DF/HCC Protocol #: *21-086*

TITLE: A Phase Ia/Ib study of talazoparib in combination with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC)

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SUMMARY OF CHANGES

Protocol changes

Section	Change
Header, Title Page	Updated version number and version date
4.1, 13.2	Added "Subjects enrolled to phase 1b who do not initiate protocol therapy can be replaced."
5.7, 10	Added a window of +/- 2 weeks to survival follow up schedule

SCHEMA

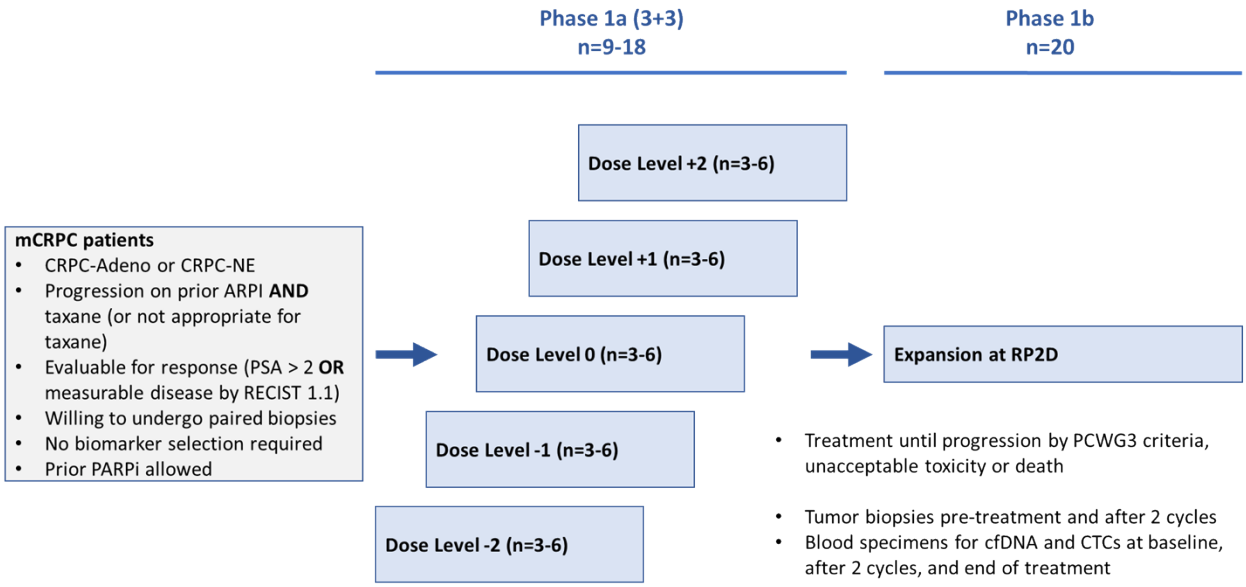

Phase 1a (3+3)
n=9-18
Phase 1b
n=20
mCRPC patients
• CRPC-Adeno or CRPC-NE
• Progression on prior ARPI AND taxane (or not appropriate for taxane)
• Evaluable for response (PSA > 2 OR measurable disease by RECIST 1.1)
• Willing to undergo paired biopsies
• No biomarker selection required
• Prior PARPi allowed
Dose Level +2 (n=3-6)
Dose Level +1 (n=3-6)
Dose Level 0 (n=3-6)
Dose Level -1 (n=3-6)
Dose Level -2 (n=3-6)
Expansion at RP2D
• Treatment until progression by PCWG3 criteria, unacceptable toxicity or death
• Tumor biopsies pre-treatment and after 2 cycles
• Blood specimens for cfDNA and CTCs at baseline, after 2 cycles, and end of treatment

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1. OBJECTIVES

1.1 Study Design

This is a Phase 1a/1b clinical trial to assess safety, tolerability and preliminary clinical activity of the combination of talazoparib with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC). The study will take place in two parts: Phase 1a to define the recommended phase 2 dose (RP2D) and Phase 1b to better assess safety and preliminary clinical activity of the combination at the RP2D.

1.2 Primary Objective

To assess the safety and tolerability of the combination of talazoparib with tazemetostat in mCRPC patients (based on incidence of dose-limiting toxicities [DLTs] and incidence and grade of adverse events [AEs] by CTCAE version 5.0), as well as to establish the Recommended Phase 2 Dose (RP2D).

1.3 Secondary Objective

To assess preliminary clinical efficacy of talazoparib with tazemetostat at the RP2D in mCRPC patients as assessed by overall response rate (ORR; PSA reduction by ≥ 50% OR radiographic response by RECIST 1.1)

1.4 Exploratory Objectives

1) To assess preliminary clinical efficacy of talazoparib with tazemetostat at the RP2D in mCRPC patients including by duration of response (DOR), progression-free survival by prostate cancer working group 3 (PCWG3) criteria (PFS), PSA progression-free survival (PSA-PFS), and clinical benefit rate (complete response or partial response or stable disease at 6 months or PSA reduction by ≥ 50%).
2) To explore predictive biomarkers of response to talazoparib with tazemetostat in pre-treatment tumor biopsy and blood specimens including:
    a. Expression of DNA damage repair (DDR) genes in tumor tissue through immunohistochemistry (IHC) and RNA-seq (when feasible)
    b. Genetic alterations in DDR genes in tumor and circulating cell-free DNA (cfDNA) specimens
    c. RAD51 focus formation assay (to assess homologous recombination proficiency) and expression of ATM, phospho-KAP1 and γ-H2AX by IHC
    d. EZH2 expression and H3K27 trimethylation by IHC
    e. Assessment of canonical PRC2 targets through ChIP-seq, ATAC-seq and RNA-seq from pre-treatment biopsies (when feasible); methylation signatures from cfDNA, and RNA signatures from circulating tumor cells (CTCs)
    f. Assessment of androgen receptor (AR)-driven castration resistant prostate adenocarcinoma (CRPC-Adeno) vs. non-AR driven castration resistant neuroendocrine prostate cancer (CRPC-NE) phenotype / AR signaling as determined through pathology review, expression of AR and NE markers by IHC,

ChIP-seq for AR targets, methylation signatures of CRPC-NE vs. CRPC-Adeno from cfDNA, and RNA signatures of CRPC-NE vs. CRPC-Adeno from CTCs

3) To explore predicted downstream effects of EZH2 and PARP inhibition in paired pre-treatment and on-treatment tumor biopsies and blood specimens through:
    a. Modulation of expression of DDR genes predicted to be activated by EZH2i
    b. Modulation of DDR response (RAD51 focus formation, phospho-KAP1 and γ-H2AX) by IHC
    c. PRC2 target gene expression
    d. luminal/basal markers
    e. Reversal of CRPC-NE signaling and restoration of AR signaling
    f. DNA methylation profile detected in cfDNA
    g. RNA-seq from CTCs

2. BACKGROUND

2.1 Study Disease(s)

Prostate cancer is the most common non-cutaneous malignancy and second most common cause of cancer death in men in the United States.[2] The backbone of systemic treatment for metastatic prostate cancer is androgen deprivation therapy (ADT), most commonly accomplished through agonists or antagonists of luteinizing hormone releasing hormone (LHRH). However, depth and duration of response to ADT is highly variable, and eventual resistance to ADT, i.e. progression to metastatic castration-resistant prostate cancer (mCRPC), is nearly universal. Castration-resistant prostate cancers most commonly remain dependent on signaling through the androgen receptor (AR), and novel hormonal therapies (NHTs) abiraterone[3,4] and enzalutamide[5,6] have demonstrated overall survival benefit in mCRPC. Other agents that have demonstrated overall survival benefit in Phase III studies in mCRPC include the chemotherapeutics docetaxel[7] and cabazitaxel,[8] the immunotherapeutic Sipuleucel-T,[9] and the radiopharmaceutical Radium-223.[10] However, patients eventually progress through these therapies and succumb to their disease, and thus novel therapeutic approaches to treating mCRPC is a major clinical need.

The genetic landscapes of both primary prostate cancer[11] and mCRPC[12] have been characterized, and have nominated oncogenic drivers of prostate cancer and mechanisms of resistance to ADT, as well as potential therapeutic targets in mCRPC. For example, genetic alterations in the *AR* gene locus (including amplifications, point mutations, or structural variants[13]) and the presence of ligand-independent splice variants (such as AR-v7[14]) seen in mCRPC have been implicated in resistance to ADT. In addition, other genetic alterations involving the AR, PTEN/PI3K (Phosphatase and Tensin Homolog/Phosphatidylinositol 3-kinase), Wnt/β-catenin, and cell cycle pathways, as well as genes involved in DNA damage repair and epigenetic modulation are commonly seen in metastatic castration-resistant prostate cancer[12] and are enriched in mCRPC compared to primary treatment-naïve prostate cancer.[15,16]

Despite this extensive genetic characterization, clinical benefit to molecularly targeted agents other than those targeting the androgen receptor has so far been limited primarily to genetically defined subsets of patients with mCRPC with defects in DNA damage repair (DDR) pathways. The immune checkpoint inhibitor immunotherapy (CPI) pembrolizumab is approved for use in unresectable or metastatic microsatellite instability–high (MSI-H) or mismatch repair deficient

(dMMR) solid tumors progressing following prior treatment and who have no satisfactory alternative treatment options,[17] and can thus be prescribed for the subset of patients with mCRPC with this phenotype. In addition, patients with deleterious alterations in genes involved in homologous recombination repair (HRR) can respond to inhibitors of Poly (ADP-ribose) polymerase (PARP)[18,19] –the FDA has approved olaparib for patients with HRR gene mutations and rucaparib for patients with deleterious mutations involving *BRCA1* or *BRCA2*. However, only ~3% of patients with mCRPC are phenotypically MSI-H/dMMR[20], and only ~18-20% have mutations in *BRCA1*, *BRCA2* or *ATM*[15,16] – even in these subpopulations responses to pembrolizumab[20,21] and PARP inhibitors (PARPi)[18,19] are not universal. As such, alternative paradigms for molecularly targeted therapy in mCRPC warrant exploration.

One of these paradigms currently under study is pharmacologic inhibition of the epigenetic modifier Enhancer of Zeste Homolog 2 (EZH2). EZH2 is overexpressed in metastatic prostate tumors, in both AR-driven castration resistant prostate adenocarcinoma (CRPC-Adeno) and non-AR driven castration resistant neuroendocrine prostate cancer (CRPC-NE).[22-26] Beyond its canonical role in mediating trimethylation of histone H3 lysine 27 (H3K27me3) through its role in the polycomb repressive complex 2 (PRC2),[27] we previously identified a non-canonical role of EZH2 in activating AR signaling,[22] as well as in driving lineage plasticity and CRPC-NE.[28,29] EZH2 is a critical mediator of cancer progression and therapeutic resistance in prostate cancer, and EZH2 inhibitors (EZH2i) have demonstrated promising activity in preclinical CRPC models.[30,31] This activity has led to several early phase clinical trials, including an ongoing Phase 1 study of the EZH2i PF-06821497 in combination with enzalutamide in mCRPC (NCT03460977), a Phase 1b/2 trial of the EZH2i CPI-1205 in combination with potent AR-targeted therapy (NCT03480646), and a Phase 1b/2 study evaluating the EZH2i tazemetostat in combination with enzalutamide or abiraterone/prednisone in mCRPC (NCT04179864). The clinical activity of EZH2 inhibition in mCRPC, either as monotherapy or in combination with potent AR pathway inhibition, has yet to be reported.

Pre-clinical data from our group and others suggests that EZH2 directly regulates the expression of a number of genes involved in DDR, and EZH2 inhibition sensitizes cancer cells to genotoxic stress, such as that induced by PARPi. Based on this pre-clinical rationale as well as the importance of both PARP and EZH2 as therapeutic targets in prostate cancer, we are undertaking this Phase 1a/1b study to assess safety, tolerability and preliminary clinical activity of the combination of the PARPi talazoparib with the EZH2i tazemetostat in mCRPC.

2.2 IND Agents

2.2.1 Talazoparib

Talazoparib (PF-06944076, formerly BMN 673, MDV3800) is a potent, orally bioavailable, small molecule PARPi that is in development for the treatment of a variety of human cancers. PARPis exert antitumor activity via both inhibition of PARP catalytic activity (including inhibition of poly-ADP-ribosylation [PARylation]) and PARP trapping. For detailed information, please refer to the Investigator Brochure (IB) for talazoparib.

2.2.1.1 *Non-clinical experience*

In vitro pharmacology studies with talazoparib demonstrated potent and selective inhibition of PARP1 (50% inhibitive concentration [IC_{50}] = 0.7 nM) and PARP2 (IC_{50} = 0.3 nM) catalytic activity in a biochemical assay. Robust cytotoxicity following talazoparib treatment was observed in a panel of breast, prostate, pancreatic, and colorectal cancer cell lines with defects in DNA damage repair pathways, including PTEN-deficient prostate cancer cell lines LNCaP and PC-3 with IC_{50} values of 4.3 nM and 4.4 nM, respectively.

Evaluation of PARP trapping in breast and prostate cancer cell lines treated with talazoparib resulted in increased trapping in the presence of single-strand break inducing agent methyl methane sulfonate (MMS). The effects were clearly evident in the *BRCA1*-mutant MDA-MB-436 breast cancer, which is sensitive to talazoparib-induced cytotoxicity, compared to the less sensitive *BRCA1*-mutant breast cancer HCC1954 line. PARP trapping has also been shown for the *BRCA2*-mutant DU145 prostate cancer cell line. Additionally, a multiparametric DDR assay in the DU145 cell line also showed that talazoparib treatment induced S-phase cell-cycle arrest, increased S-phase specific and total double-strand DNA (dsDNA) breaks (measured by γH2AX), increased early apoptosis (measured by cleaved caspase 3 [CC3]), and decreased cell population growth, compared to vehicle treated cells. The reduced population growth and cytotoxicity observed in the DDR assays are consistent with the proposed mechanisms of action for talazoparib: catalytic activity inhibition and PARP trapping.

2.2.1.2 *Non-clinical Pharmacology*

The nonclinical toxicologic profile of talazoparib has been characterized through the conduct of studies including repeat dose toxicity in rat and dog of ≤13-week duration, genetic toxicity (*in vitro* and *in vivo*), embryo-fetal development in rat, and phototoxicity, in accordance with the ICH S9 guidelines. There were no talazoparib-related effects on respiratory or CNS parameters following a single oral administration to rat in the safety pharmacology studies, or on cardiovascular parameters (hERG potassium channel assessment and ECG evaluations following repeat-dose administration to dog). No ocular findings were observed with talazoparib in rat or dog in the repeat dose studies and talazoparib is not phototoxic *in vivo*.

Based on the cumulative evaluation of the toxicology profile of talazoparib, the primary talazoparib-related target organ findings include effects on the hematolymphopoietic system, the male reproductive system and the GI system in both rat and dog. Additional target organ findings observed in rat only include findings in the female reproductive system and liver. Talazoparib is clastogenic *in vitro* in human peripheral blood lymphocytes (HPBLs), in cancer cell lines and *in vivo* in rat. In an investigative *in vitro* bone marrow (BM) study, results were consistent with the repeat dose toxicity studies showing no lineage specific effect on blood cells and that rat BM was highly sensitive to talazoparib treatment (>2× more than human) *in vitro*. Talazoparib caused frank fetotoxicity in an embryo-fetal development study in rat. The primary nonclinical toxicology profile of talazoparib following oral administration can be largely explained by the pharmacological effects of talazoparib on rapidly dividing cells (talazoparib-

induced PARP inhibition). Talazoparib mechanism of action (cytotoxicity) is dependent on the inhibition of PARP1/2 enzyme activity (inhibition of catalytic activity) and its robust PARP trapping ability at the site of damaged DNA (causing S-phase induced dsDNA break leading to apoptosis and/or necrosis). Evaluation of the cumulative toxicological profile of talazoparib suggests that the hematolymphopoietic and testes toxicities occur at subtherapeutic clinical exposure margins, while the GI, liver and ovary findings occur in rat at higher clinical exposure margins and are potentially mediated by a combination of the catalytic activity inhibition and PARP trapping activity. However, the clastogenic potential is considered to mainly be a result of talazoparib-induced inhibition of the PARP catalytic activity. The frank embryo-fetal toxicity observed in pregnant female rats in the embryo-fetal development (EFD) study is considered to be a result of both the clastogenic and cytotoxic activities of talazoparib.

2.2.1.3 *Clinical Pharmacology*

The pharmacokinetics (PK) of talazoparib as a single agent has been evaluated in a total of 7 clinical studies. The PK of talazoparib was similar in patients with hematological malignancies and patients with solid tumors, and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib can be administered without regard to food. The plasma exposure of talazoparib is dose proportional in the dose range of 0.025 mg to 2 mg QD, suggesting linear PK. The mean t½ was approximately 4 days. Talazoparib accumulated after 1 mg QD dosing with a median Rac ranging from 2.33 to 5.15, consistent with its t½. Steady state was reached around 3 weeks after the start of talazoparib dosing. Talazoparib undergoes minimal hepatic metabolism in humans. Renal excretion of unchanged talazoparib was the major elimination pathway of talazoparib. Talazoparib is moderately bound to human plasma proteins (74%, *in vitro*). Talazoparib is evenly distributed across human blood cells and plasma compartments.

In vitro, talazoparib did not significantly interact with any of the major CYP or UGT drug metabolizing enzymes, nor was it an inhibitor of any ABC or SLC drug. At test concentrations in excess of therapeutic exposures (approximately 200-fold Cmax), talazoparib did not markedly induce or inhibit CYP enzymes. Furthermore, concentrations in excess of therapeutic exposures (approximately 20-fold Cmax) did not inhibit membrane transporter function. In addition, an *in vitro* assay demonstrated talazoparib did not inhibit any of the major UGT isoforms (1A1, 1A4, 1A6, 1A9, 2B7, and 2B15) at clinically relevant concentrations. Therefore, it is unlikely that talazoparib will demonstrate clinically significant drug-drug interactions (DDIs) when coadministered with corresponding CYP, UGT, or transporter substrates. However, talazoparib is a substrate for P-gp and BCRP, and plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Based on the high oral bioavailability observed in rats, dogs, and humans, absorption of talazoparib is not limited by these efflux transporters.

In a dedicated DDI study, coadministration of P-gp inhibitor itraconazole was shown to increase the AUCinf and Cmax of talazoparib by approximately 56% and 40%, respectively; whereas, coadministration of P-gp inducer rifampin increased talazoparib Cmax by approximately 37% but had no impact on the AUCinf of talazoparib. In a renal impairment study, talazoparib AUC0-24 at steady state increased by approximately 12.2%, 43.0%, and 163.3% with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function; and talazoparib Cmax at steady state increased by 11.1%, 31.6%, and 89.3% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. Additional ongoing Phase 1 company-sponsored clinical pharmacology study is evaluating the PK of talazoparib in patients with hepatic impairment.

2.2.1.4 *Clinical experience*

As of the talazoparib IB dated 30 September 2019, approximately 1212 patients and 18 healthy volunteers received talazoparib at doses up to 2 mg/day in company-sponsored clinical studies in hematologic malignancies and solid tumors. Aggregate safety data from 5 open-label, including 1 randomized, company-sponsored clinical studies (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14; N = 502 patients) evaluating talazoparib monotherapy in solid tumors at the proposed dose of 1 mg/QD as of 30 Sept 2019, provide the basis for the reported Treatment-emergent adverse events (TEAEs). TEAEs of all causality reported in ≥20% of patients administered single-agent talazoparib 1 mg/day are related to myelosuppression (anemia, neutropenia), GI toxicity (nausea, diarrhea, vomiting, constipation, and decreased appetite), fatigue, headache, and alopecia. TEAEs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 severity in ≥5% of patients were related to myelosuppression. The adverse events (AEs) associated with talazoparib are detectable through routine laboratory and clinical monitoring and may be managed with supportive care or dose reductions or interruptions as described in each study protocol.

In the Phase 1 first-in-human study (Study PRP-001 [C3441007]) in patients with advanced or recurrent solid tumors, a total of 110 patients were treated at a range of talazoparib doses (0.025-1.1 mg/day). Data from this study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma. In an open-label Phase 2 study (Study 673-201, [C3441008, ABRAZO]) of talazoparib in patients with germline BRCA-mutated locally advanced or metastatic breast cancer, 83 patients were treated with talazoparib 1 mg/day across 2 cohorts. Cohort 1 enrolled 49 patients (48 treated) who had a partial response (PR) or complete response (CR) to a prior platinum-containing regimen for metastatic disease with disease progression >8 weeks following the last dose of platinum. Cohort 2 enrolled 35 patients who received 3 or more prior chemotherapy regimens and no prior platinum therapy for metastatic disease. Cohort 1 had an objective response rate (ORR) of 20.8% (95% CI: 10.5, 35.0) including 2 CRs (4.2%). Cohort 2 had an ORR of 37.1% (95% CI: 21.5, 55.1). Median duration of response (DOR) was 4.9 months (interquartile range [IQR]: 2.8, 7.1) in Cohort 1 and 4.2 months (IQR: 3.2, 5.6) in Cohort 2.

In the pivotal randomized Phase 3 study (Study 673-301, [C3441009, EMBRACA]) of talazoparib versus physician's choice treatment (PCT) in patients with germline BRCA mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, 431 patients overall were randomized in a 2:1 ratio to receive talazoparib 1 mg/day (n = 287) or 1 of 4 PCTs (n = 144) reflecting the standard of care in this disease setting (capecitabine, eribulin, gemcitabine, or vinorelbine). In this study, talazoparib demonstrated significantly prolonged progression-free survival (PFS) by blinded independent central review (BICR) assessment when compared to PCT. Median PFS by BICR in the talazoparib arm was 8.6 months (95% CI: 7.2, 9.3) compared to 5.6 months (95% CI: 4.2, 6.7) in the PCT arm. This led to FDA approval for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer on 16 October 2018.

Talazoparib is currently being evaluated in mCRPC. An ongoing Phase 2 study [C3441006, TALAPRO-1] is evaluating talazoparib in men with DNA repair defects and mCRPC who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (enzalutamide and/or abiraterone acetate/prednisone). In this study,[32] talazoparib monotherapy demonstrated antitumor activity in mCRPC patients with DDR alteration who have previously received taxane therapy and NHT with a confirmed overall ORR of 26.7%, and ORR of 41.5% in patients with tumors harboring *BRCA1/2* alterations. No new safety signals were observed in this study. An ongoing Phase 3, randomized, double-blind, placebo-controlled study [C3441021, TALAPRO-2] is evaluating talazoparib in with combination enzalutamide in mCRPC patients with and without DDR deficiencies.

2.2.2 Tazemetostat

Tazemetostat (EPZ-6438) is a selective small molecule inhibitor of the histone-lysine methyltransferase (HMT) EZH2,[33] and inhibits both wild-type (WT) EZH2 and EZH2 mutated on residues Y646, A682, and A692 with half-maximal inhibitory concentrations (IC50) ranging from 2 to 38 nmol/L. The compound shows a 36-fold selectivity over the most closely related HMT, enhancer of zeste homolog 1 (EZH1), and greater than 4500 fold selectivity over other HMTs. For detailed information, please refer to the IB for tazemetostat.

2.2.2.1 *Nonclinical experience*

Tazemetostat selectively inhibits intracellular H3K27 methylation in a concentration and time-dependent manner in all cell lines tested *in vitro* to date. Incubation with tazemetostat inhibited the proliferation of genetically defined cancer cells, such as diffuse large B-cell lymphoma (DLBCL) lines bearing EZH2 mutations, malignant rhabdoid tumor (MRT) lines deficient for integrase interactor 1 (INI1), and INI1-deficient synovial sarcoma cell lines. Tazemetostat-induced effects in culture require several days of continuous treatment, consistent with a mechanism that requires inhibition of H3K27 methylation followed by reversal of an aberrant gene expression program.

Administration of tazemetostat to mice-bearing xenografts of genetically defined human cancers (1 MRT, 5 DLBCL, 3 synovial sarcoma, and 3 small cell carcinoma of the ovary hypercalcemic type [SCCOHT] models) induces significant antitumor effects, ranging from tumor growth inhibition to complete and durable tumor regressions. Tazemetostat exposure leads to dose- and time-dependent decreases in intracellular H3K27me3 in both tumor and selected nontumor tissues.

In studies conducted by Epizyme, tazemetostat dose-dependently reduced global cellular H3K27me3 levels in all prostate cancer cell lines tested and inhibited proliferation *in vitro* over the course of 14 days of treatment in the LNCaP cell line, that expresses AR and carries a mutation in the AR gene, in 22Rv1 (that expresses AR, AR-V7 splice variant and carries a mutation in the AR gene) and in a cell line of the neuroendocrine subtype (NCI-H660). No antiproliferative effect is observed in cell lines that do not express AR such as PC-3 and DU145 and that are not classified as of the neuroendocrine subtype. Combination treatment of the LNCaP and 22Rv1 cell lines with tazemetostat and enzalutamide showed synergistic antiproliferative activity. Abiraterone synergistically enhanced the *in vitro* activity of tazemetostat in the LNCaP cell line. Tazemetostat showed *in vivo* antitumor activity in a mouse xenograft model of LNCaP cell line. Combinatorial benefit was observed as tumor growth inhibition was enhanced when tazemetostat was combined with enzalutamide and abiraterone. Analysis of LNCaP tumors revealed a reduction of H3K27me3 induced by tazemetostat as a single agent and in combinations of tazemetostat with androgen signaling inhibitors.

2.2.2.2 *Non-clinical pharmacology*

No notable cardiovascular, central nervous system (CNS), or respiratory risks were identified during nonclinical safety pharmacology assessments of tazemetostat. Tazemetostat was not genotoxic in the standard battery of genotoxicity studies and showed *in vitro* phototoxic potential in BALB/c 3T3 mouse fibroblasts exposed to ultraviolet (UV) radiation, compared with a positive control (promethazine), up to the solubility limit of 100 μg/mL.

The following key tazemetostat-related findings were identified from Good Laboratory Practice (GLP) repeat-dose toxicology studies in rats and/or monkeys: T-cell lymphoblastic lymphoma (T-LBL; in rat 13-week studies but not 4-week studies), bone/teeth changes (rat), nonprogressive bile duct hyperplasia (monkey), lymphoid depletion (rat and monkey), and teratogenicity (rat and rabbit).

Tazemetostat exposures (Cmax and AUC) increased in a more than dose-proportional manner with point estimates >1 and with the lower bounds of the 90% confidence interval (CI) close to or >1. There was little to no accumulation (Cmax and AUC) of tazemetostat after multiple doses, likely due to autoinduction. Tazemetostat metabolites had minimal accumulation following multiple doses. Across all dose cohorts, <6% of unchanged drug was excreted in urine.

2.2.2.3 *Clinical pharmacology*

In population-pharmacokinetic analysis, the human absorption, distribution, metabolism and elimination (ADME) properties of tazemetostat in observed clinical data suggests low DDI potential. In ADME studies, especially metabolism and phenotyping results, suggest considerable potential for tazemetostat as a victim in the presence of cytochrome P450 (CYP)3A4 inhibitors and inducers.

Robust analysis provides sufficient evidence that tazemetostat and its major metabolite, EPZ-6930, do not cause clinically meaningful QT prolongation in subjects with advanced solid tumors or with B-cell lymphomas at clinically relevant concentrations. In pediatric subjects, systemic exposure to tazemetostat measured by mean AUC from zero time to 8 hours (AUC0-8h) decreased after repeated doses relative to a single dose in all dose cohorts. In contrast, mean AUC0-8h of EPZ-6930 increased after repeated doses of tazemetostat relative to a single dose in all dose cohorts. These results are consistent with results from adult subjects and indicate induction of CYP3A4-mediated metabolism of tazemetostat. Mean Cmax and AUC values after administration of 520 mg/m2 twice daily and greater as a suspension in pediatric subjects were comparable with or exceeded those observed after administration of 800 mg twice daily as tablets in adults. Pharmacodynamic and PK/pharmacodynamic results informed the determination of 800 mg twice daily as the tazemetostat recommended phase 2 dose (RP2D).

2.2.2.4 *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.

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

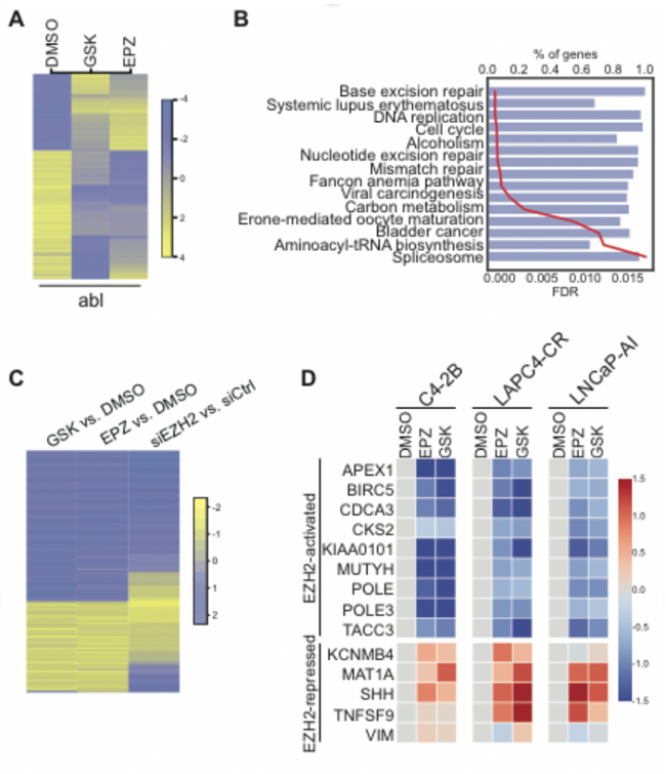
- On 23 January 2020, tazemetostat was approved for the treatment of adults and pediatric subjects aged 16 years and older with metastatic or locally advanced epithelioid sarcoma (ES) not eligible for complete resection.
- On 18 June 2020, tazemetostat was approved for the treatment of:
  - adult subjects 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.



2.3 Rationale

Multiple preclinical studies suggest that EZH2i may be synergistic with PARPi.[34,35] Unpublished work from the laboratories of Dr. Myles Brown at Dana-Farber Cancer Institute (DFCI) and Dr. Kexin Xu at University of Texas at San Antonio has demonstrated that EZH2 directly regulates the expression of a number of genes involved in DDR, particularly base excision repair (BER), such as *APEX1*, *POLE* and *MUTYH*. EZH2i using GSK126 or EPZ-6438 led to downregulation of these genes (Figure 1), and thus heightened sensitivity to genotoxic stress, such as that induced by PARPi. Dr. Brown's and Xu's laboratories demonstrated preferential synergistic activity of the EZH2 inhibitor GSK126 with the PARP inhibitor olaparib in androgen-independent LNCaP-Abl cells compared to parental androgen-dependent LNCaP cells (Figure 2), suggesting potential clinical activity in treatment-refractory prostate cancers.

Similarly, in an ovarian cancer model, EZH2 was found to regulate expression of *MAD2L2*,[35] which plays a critical role in the choice between homologous recombination (HR) and non-homologous end-joining (NHEJ)-mediated repair. EZH2 inhibition in this HR-proficient model led to a decrease in DNA end resection, leading to chromosomal abnormalities and ultimately causing mitotic catastrophe in cells simultaneously treated with a PARP inhibitor.

Importantly, in both models, the mechanism of synergy of EZH2 inhibition and PARP inhibition does not require underlying defects in the DNA damage response in the treated cancer cells. Since EZH2 is nearly universally overexpressed in treatment-resistant mCRPC (both in CRPC-Adeno and CRPC-NE), a therapeutic strategy combining EZH2 inhibition with PARP inhibition has the potential for clinical benefit in a broader population of patients than monotherapy of either agent. However, not all patients are expected to respond to this combination, so the biomarker studies proposed are critical for identifying predictors of response or resistance to this strategy. The translational studies are also critical for elucidating the downstream effects of combined EZH2 and PARP inhibition in order to credential pharmacodynamic biomarkers discovered in pre-clinical models in clinical biospecimens, and to discover novel pathways modulated by these agents in patients for further pre-clinical study.

2.4 Correlative Studies Background

2.4.1 Tissue-based biomarkers

Paired tumor biopsies will be obtained from all study participants in both parts of the study at baseline and after approximately 8 weeks of therapy.

2.4.1.1 Targeted DNA sequencing

OncoPanel is a massively parallel next-generation sequencing platform at DFCI for genomic profiling of tumor tissue. OncoPanel testing is done at the Center for Advanced Molecular Diagnostics, a CLIA-certified laboratory in the Department of Pathology at Brigham and Women's Hospital. OncoPanel version 3 interrogates 447 genes known to be involved in cancer biology, including DDR genes and *EZH2* (though *EZH2* mutations are rare in mCRPC). Genomic profiling of pre-treatment tumor specimens will allow us to explore the correlation of particular DDR gene mutations with clinical responses to therapy.

Figure 1. Differential gene expression in abl cells treated with vehicle (DMSO), 5 uM GSK126 (GSK) or 5 uM EPZ-6438 (EPZ) for 72 hrs. (B) Top overrepresented functional annotations of genes that were significantly downregulated after EZHi in abl cells from Gene Set Enrichment Analysis. Blue bars, percentage of genes in each specific functional category; red line, values of the false discovery rate (FDR) for the particular GO term. C) Differential gene expression induced by EZH2i comparing GSK or EPZ drug to vehicle or EZH2 knockdown comparing to control siRNA (siEZH2 vs. siCtrl) in abl cells.

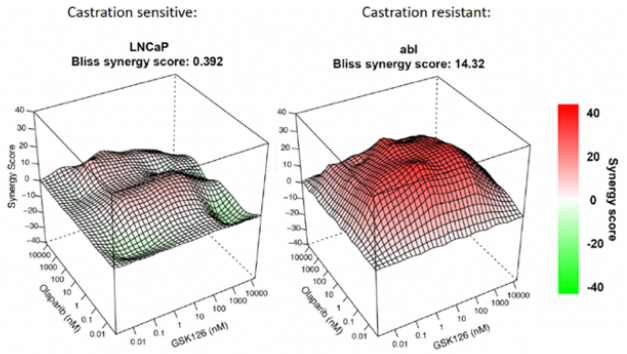


Figure 2. Synergistic effect of EZH2 inhibitor and olaparib in abl cells. Various doses of GSK126 and olaparib were combined and applied for 7 days. A matrix for synergy score was calculated based on Ianevski et al [1] and is indicated in y-axis

2.4.1.2 RNA-seq

RNA Sequencing (RNA-seq) from tumor biopsy specimens will be used to assess expression of canonical PRC2 target genes; relevant DDR genes (such as *APEX1*, *POLE*, *MUTYH*, *MAD2L2*);

AR and AR target genes (such as *KLK3, TMPRSS2*); markers of CRPC-Adeno (such as *HOXB13*, *NKX3-1*) vs. CRPC-NE (such as *CHGA*, *ASCL1*); and markers of lineage plasticity (*SOX2*). Expression of these genes in pre-treatment specimens will be explored as predictive biomarkers, and modulation of gene expression on-treatment will be explored as a pharmacodynamic marker of combined EZH2i + PARPi treatment. Gene set enrichment analysis[36] of on-treatment versus pre-treatment RNA-seq data will facilitate the identification of other expression programs up- or down-regulated in response to treatment.

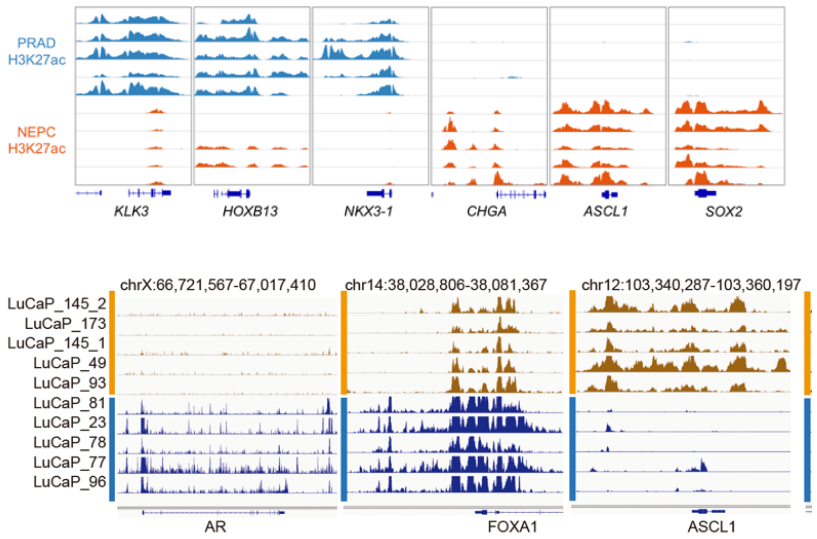


Figure 3. A. CRPC-Adeno (PRAD) and CRPC-NE (NEPC) LuCaP PDXs show distinct H3K27ac patterns consistent with activation of luminal lineage genes (KLK3, HOXB13, NKX3-1) in CRPC-Adeno and neuroendocrine (CHGA, ASCL1) and plasticity/pluritopotency genes (SOX2) in CRPC-NE. **B.** CRPC-Adeno (blue) and CRPC-NE (yellow) LuCaP PDXs show distinct ATACseq patterns consistent with open chromatin at the AR in CRPC-Adeno, ASCL1 in CRPC-NE, and FOXA1 in both.

2.4.1.3 ChIP-seq

The laboratory of Dr. Matthew Freedman has pioneered and optimized chromatin immunoprecipitation and sequencing (ChIP-seq) from the small amounts of tumor present in clinical tumor biopsy specimens. Our prior work has shown that genome-wide binding of transcription factors such as the *AR* varies across disease contexts and within disease subtypes.[37,38] As EZH2 is a transcriptional activator of the *AR*,[31] we will perform *AR* ChIP-seq prior to and during drug therapy.

ChIP-seq for acetylated histones at the H3K27 position (H3K27ac) identifies active enhancers and promoters that regulate cellular transcription programs. This technique is feasible in both frozen[37,39] as well as formalin-fixed paraffin embedded tissue,[40] and can distinguish regulatory patterns consistent with activation of luminal lineage genes (*KLK3, HOXB13, NKX3-1*) in CRPC-Adeno and CRPC-NE (*CHGA, ASCL1*) as well as plasticity/pluripotency genes (*SOX2*) in CRPC-NE (Figure 3A), and may allow the identification of *trans*-acting transcription factors mediating the cellular response to combined PARPi and EZH2i.

2.4.1.4 ATAC-seq

ATAC-seq is a more general assay of chromatin accessibility that identifies active enhancers and promoters also identified by H3K27ac marks in addition to other regulatory elements that together coordinate transcription of target genes.[41] This technique can be applied to frozen tumor tissue and identifies genomic regions of open chromatin at *AR* in CRPC-Adeno, *ASCL1* in CRPC-NE, and *FOXA1* in both (Figure

3B). Similarly to H3K27ac ChIP-seq, but more broadly based on the identification of other non-H3K27Ac marked regulatory elements, analysis of genomic sites with accessible chromatin identified by ATAC-seq may identify transcription factors modifying the cellular response to treatment with talazoparib + tazemetostat.

2.4.1.5 Immunohistochemistry (IHC)

Homologous recombination repair deficiency (HRD) confers sensitivity to PARPi and platinum-based chemotherapeutic agents, but genomic assays for HRD analyze history of the tumor rather than providing a functional assessment of HR status at the time of diagnosis. We have previously described a RAD51-based immunohistochemical (IHC) assay that identifies HR status[42] – in our previous studies, the presence or absence of RAD51 foci in cell lines and PDX models correlated with olaparib sensitivity and not with *BRCA* mutation status. γ-H2AX[43] is a marker for DNA double-strand breaks (DSBs), and IHC for γ-H2AX can be used for real-time assessment of the presence of DSBs at the time of tissue procurement.

Alterations in the Ataxia Telangiectasia Mutated (*ATM*) gene are highly enriched in mCRPC compared with locoregional prostate cancer.[15,16] While *ATM* mutations lead to defects in DNA damage repair, clinically very modest activity has been seen with PARPi monotherapy for patients with these mutations.[18,19,44] We developed an immunohistochemistry assay for ATM demonstrating in 208 primary gastric tumors that ATM expression is absent in 11% of samples with very low expression in 26% - notably higher than the rate of *ATM* mutation in this cancer type.[45] In addition we have developed an IHC assay for the phosphorylated form of the ATM substrate KAP1 (KRAB [Kruppel-Associated Box Domain]-Associated Protein 1), which is an indicator of DNA replication stress.[46,47]

We thus plan to assess for RAD51 focus formation, γ-H2AX, ATM expression, and phospho-KAP1, as well as EZH2 and H3K27me3 and markers of CRPC-Adeno (KLK3, HOXB13, NKX3-1) and CRPC-NE (CHGA, ASCL1) in pre-treatment and on-treatment biopsy specimens as possible predictive biomarkers for therapeutic response and as pharmacodynamic markers of the combined activity of PARPi and EZH2i in metastatic prostate tumors.

2.4.2 Blood-based biomarkers

Serial blood samples will be collected at baseline, on cycle 3 day 1 of therapy, and at end of treatment.

2.4.2.1 Circulating cell-free DNA

Analysis of circulation cell-free DNA (cfDNA) is a promising approach to genetic profiling as well as phenotypic assessment of a patient's tumor burden over time. Sparse whole genome sequencing at 0.1x coverage, termed ultra-low pass whole genome sequencing (ULP-WGS), can be used to identify copy number alterations (CNA) in the tumor, as well as the tumor fraction (i.e. percentage of cfDNA

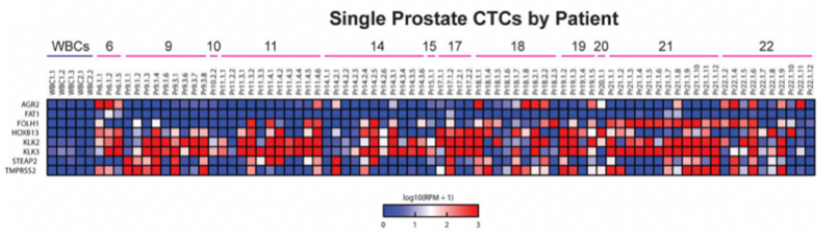


Figure 4. Single cell RNA-seq data showing expression of select genes in WBCs and single prostate CTCs isolated from men with metastatic prostate cancer

derived from tumor rather than non-cancerous tissues), using an algorithm called ichorCNA.[48] In addition, comprehensive genomic characterization can be performed through whole exome sequencing[48] and targeted sequencing panels.[49] We have designed a custom bait set specifically for prostate cancer including allowing for identification of SSNVs in all genes known to be recurrently mutated in metastatic prostate cancer,[15] genes involved in DNA damage repair, as well as sequencing of intronic and intergenic regions of genes known to be translocated or have complex structural alterations in prostate cancer (AR[13], ERG, TMPRSS2, ETV1, ETV4, SLC45A3, RAF1).

In addition, cfDNA methylation is capable of detecting CRPC-NE-associated epigenetic changes, and we previously demonstrated that a targeted set combining genomic (TP53, RB1, CYLD, AR) and epigenomic (hypo- and hyper-methylation of 20 differential sites) alterations applied to cfDNA is capable of identifying patients with CRPC-NE.[50] Dr. Freedman's laboratory has demonstrated that a technique called cfMeDIP-seq can detect the presence of tumor DNA at very low abundance[51] – training this technique on CRPC-Adeno and CRPC-NE specimens will allow us to distinguish these phenotypes from cfDNA even when tumor DNA content is sparse.

Analyses from cfDNA from pre-treatment specimens may be able to identify predictive markers of response and resistance to talazoparib + tazemetostat, and changes identified in cfDNA at the time of resistance could nominate markers of resistance - this is particularly important in cases where metastatic biopsy specimens are not amenable to the extensive characterization detailed above.

2.4.2.2 Circulating tumor cells (CTCs)

We have previously found that CTCs from men with CRPC-Adeno or CRPC-NE harbor unique phenotypic and molecular characteristics[52,53]. Liquid biopsies may therefore be exploited to identify resistance subsets and evaluate target expression non-invasively. The Miyamoto lab on our team has successfully isolated and characterized CTCs from patients with CRPC using a microfluidic device called the CTC-iChip, which is based on negative selection (thus not requiring cell surface marker).[54,55] In published work,[56,57] CTC-iChip has demonstrated that nearly all patients with metastatic prostate cancer have CTCs by this approach and this approach is feasible for single cell transcriptome profiling of CTCs **(Figure 4)** by RNA-seq and/or droplet digital PCR as well as in situ analyses, which we will apply to the current proposal to look at EZH2 expression, H3K27me3, and downstream targets.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed prostate cancer (code 10036910) with progressive disease at the time of study entry by either

- Sequence of at least 2 rising PSA values at a minimum of 1-week intervals
- Radiographic progression per RECIST1.1 for soft tissue and/or per PCWG3[58] for bone, with or without PSA progression

3.1.2 Patients must have metastatic disease by bone scintigraphy or other nodal or visceral lesions on CT or MRI with a bone or soft tissue lesion amenable to image-guided percutaneous biopsy, a castrate level of testosterone (<50ng/dL), and evaluable for disease response by either

- Baseline PSA ≥ 2.0 ng/mL OR
- Measurable disease per RECIST 1.1

NOTE: Subjects must maintain a castrate state. If they have not had an orchiectomy, they must continue to receive LHRH or GnRH agonists or antagonists unless intolerant.

3.1.3 Past progression on at least one NHT (abiraterone, enzalutamide, apalutamide, darolutamide, galeterone, orteronel, seviteronel or equivalent) in either the hormone-sensitive or castration-resistant disease setting.

3.1.4 Not a candidate for docetaxel or cabazitaxel chemotherapy due to:

a. progression within 12 months of completion or intolerance to prior taxane OR
b. refusal of taxane OR
c. contraindication to, or lack of fitness for taxane OR
d. investigator assessment that taxane is not clinically indicated or preferred

3.1.5 Age ≥18 years. Children under 18 are excluded from this study as prostate cancer is a disease of adults

3.1.6 ECOG performance status ≤1 (Karnofsky ≥70%, see Appendix A).

3.1.7 Participants must have adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- hemoglobin ≥9 g/dL (without transfusion or growth factor in prior 28 days)
- platelets ≥100,000/mcL (without transfusion of growth factor in prior 28 days)
- total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN) unless known or suspected Gilbert syndrome
- AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN
- glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2 (based on Cockcroft-Gault

formula, CKD-EPI refit formula, OR creatinine clearance based on 24 hour urine collection)

3.1.8 Human immunodeficiency virus (HIV)-infected participants on effective anti-retroviral therapy (with no known or predicted drug-drug interactions with talazoparib and/or tazemetostat) with undetectable viral load within 6 months are eligible for this trial.

3.1.9 For participants with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable. If suppressive therapy is indicated, there must be no known or predicted drug-drug interactions with talazoparib and/or tazemetostat.

3.1.10 Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if there are no known or predicted drug-drug interactions with talazoparib and/or tazemetostat and they have an undetectable HCV viral load.

3.1.11 Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants should be class 2B or better.

3.1.12 Prior treatment with a PARP inhibitor is allowed.

3.1.13 Planned to undergo core biopsy of a recurrent/metastatic lesion adequate for next generation sequencing (NGS) after trial registration but prior to cycle 1 day 1 of therapy. Confirmation of adequacy of this biopsy material for NGS is NOT required for initiation of therapy. If elective biopsies are not being performed at the treating institution due to preparations or precautions related to COVID-19, this requirement can be waived on discussion with the trial PI.

3.1.14 Willing to undergo core biopsy of a recurrent/metastatic lesion adequate for next generation sequencing (NGS) after approximately 8 weeks of study treatment.

3.1.15 The effects of talazoparib and tazemetostat on the developing human fetus are unknown. For this reason and because oral chemotherapeutic agents are known to be teratogenic, men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also not donate semen or sperm and agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of talazoparib and tazemetostat administration.

3.1.16 Ability to swallow oral medications.

3.1.17 Ability to understand and the willingness to sign a written informed consent

document.

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy, intravenous experimental agent, radiopharmaceutical therapy or radiotherapy within 4 weeks prior to planned cycle 1 day 1 of study treatment.

3.2.2 Participants who have received oral anti-neoplastic intervention such as an oral hormonal agent, PARP inhibitor, or oral experimental agent within 14 days prior to planned cycle 1 day 1 of study treatment.

3.2.3 Participants who have not recovered from clinically significant adverse events due to prior anti-cancer therapy (i.e., have clinically significant residual toxicities > Grade 1) except for stable complications of prior procedures (such as urinary incontinence or erectile dysfunction) or Grade 2 anorexia, alopecia, neuropathy, and fatigue, for which resolution is not required.

3.2.4 Participants who are receiving any other investigational agents.

3.2.5 Participants previously treated with an inhibitor of EZH2.

3.2.6 Patients with known brain metastases or leptomeningeal disease should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to talazoparib or tazemetostat.

3.2.8 Participants receiving the following concurrent medications:

- Participants receiving the P-gp inhibitors amiodarone, carvedilol, clarithromycin, itraconazole, or verapamil are ineligible. Participants receiving other P-gp inhibitors are not excluded but should be monitored for potential increased adverse reactions.
- Participants receiving BCRP inhibitors are not excluded but should be monitored for potential increased adverse reactions.
- Participants receiving any medications or substances that are strong or moderate inhibitors or inducers of CYP3A4 are ineligible.
- Precaution is warranted with concomitant use of agents with a narrow therapeutic index that are substrates of CYP3A4 and/or P-gp.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is

considering a new over-the-counter medicine or herbal product.

3.2.9 Participants with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

3.2.10 Participants with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Pregnant and nursing women are excluded from this study because they do not develop prostate cancer.

3.2.12 Arterial or venous thromboembolic event within the last 3 months.

3.2.13 Concurrent active malignancy. Patients with non-melanomatous skin cancer, superficial bladder cancer, cancer not needing active systemic therapy for at least 2 years and would not affect imaging assessments for prostate cancer, cancer for which the treating investigator deems the subject to be in remission, or any prior malignancy that was treated with curative intent (no evidence of disease for at least 3 years) are also permitted to enroll.

3.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Women are not included as they do not develop prostate cancer.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. To facilitate management of potential toxicity, at least 24 hours must pass between consecutive participants starting on trial therapy. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered. Subjects enrolled to phase 1b who do not initiate protocol therapy can be replaced.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Talazoparib and tazemetostat will be administered continuously, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Dose Escalation Schedule		
Dose Level	**Dose**	
	talazoparib	**tazemetostat**
Level +2	1 mg QD	800 mg BID
Level +1	0.75 mg QD	800 mg BID
Level 0- Starting Dose	0.75 mg QD	600 mg BID
Level -1	0.5 mg QD	600 mg BID
Level -2	0.5 mg QD	400 mg BID

Dose Level -2					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Talazoparib	Take doses approximately 24 hours apart (at least 18 hours apart) with or without food.	2 × 0.25 mg capsules	Orally	daily	28 days (4 weeks)
Tazemetostat	Take doses approximately 12 hours apart (at least 8 hours apart) with or without food.	2 × 200 mg tablets	Orally	BID	

Dose Level -1

Agent	Premedications; Precautions	Dose	Route***	Schedule	Cycle Length
Talazoparib	Take doses approximately 24 hours apart (at least 18 hours apart) with or without food.	2 × 0.25 mg capsules	Orally	daily	28 days (4 weeks)
Tazemetostat	Take doses approximately 12 hours apart (at least 8 hours apart) with or without food.	3 × 200 mg tablets	Orally	BID	

Dose Level 0					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Talazoparib	Take doses approximately 24 hours apart (at least 18 hours apart) with or without food.	3 × 0.25 mg capsules	Orally	daily	28 days (4 weeks)
Tazemetostat	Take doses approximately 12 hours apart (at least 8 hours apart) with or without food.	3 × 200 mg tablets	Orally	BID	

Dose Level +1					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Talazoparib	Take doses approximately 24 hours apart (at least 18 hours apart) with or without food.	3 × 0.25 mg capsules	Orally	daily	28 days (4 weeks)
Tazemetostat	Take doses approximately 12	4 × 200 mg tablets	Orally	BID	

	hours apart (at least 8 hours apart) with or without food.				

Dose Level +2					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Talazoparib	Take doses approximately 24 hours apart (at least 18 hours apart) with or without food. Dose should be reduced to 0.75 mg if persistent eGFR < 60 ml/min/1.73 m^2	1 × 1 mg capsule	Orally	daily	28 days (4 weeks)
Tazemetostat	Take doses approximately 12 hours apart (at least 8 hours apart) with or without food.	4 × 200 mg tablets	Orally	BID	

5.2 Pre-Treatment Criteria

Pre-treatment assessments should be performed within 72 hours of planned treatment dose. Results from the patient's complete blood counts and serum chemistry must be reviewed prior to drug dosing. Study agents 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 via by mouth will be followed. An adequate supply will be provided with instructions on home administration.

5.2.1 Cycle 1, Day 1

The patient's laboratory parameters must meet the eligibility criteria in section 3.1.7 to initiate cycle 1 day 1 of trial therapy.

5.2.2 Subsequent Cycles

Eligibility to receive subsequent doses is based on dose delay/modification criteria detailed in Section 6.

5.3 Agent Administration

5.3.1 Talazoparib

Talazoparib will be administered with or without food. The capsules should be swallowed whole, and the capsules should not be dissolved or opened.

Doses must be administered at least 18 hours apart. If a dose is missed or vomited, the dose should be skipped, and next dose administered at the regular time. All doses given, missed, and vomited, should be recorded.

5.3.2 Tazemetostat

Tazemetostat will be administered with or without food. Doses must be administered at least 8 hours apart. If a dose is missed (e.g., missed morning dose or vomited and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose.

If the subject vomits within 30 minutes of tazemetostat dosing, anti-emetics should be given (ondansetron 4 mg- 8 mg preferred) and a second fresh dose of tazemetostat given. If both talazoparib and tazemetostat are vomited, only the tazemetostat should be re-dosed. All doses given, missed, and vomited, should be recorded.

Talazoparib and tazemetostat can be administered simultaneously with either administered first and no minimum time interval required between dosing of these agents.

5.3.3 Other Modalities or Procedures

N/A

5.4 Definition of Dose-Limiting Toxicity (DLT)

A DLT will be defined as any of the following treatment-related events during the 1st cycle of study treatment:

Hematologic Toxicity

- Grade 3 thrombocytopenia associated with clinically significant bleeding and requiring platelet transfusion
- Grade 4 thrombocytopenia
- Grade ≥3 febrile neutropenia
- Grade ≥3 anemia requiring a blood transfusion
- Other Grade 4 toxicity lasting >7 days

Non-Hematologic Toxicity

- Grade ≥3 fatigue lasting >7 days
- Grade ≥3 nausea, vomiting, and diarrhea lasting >3 days
- Grade ≥3 hypertension despite maximal medical therapy
- Grade 2 pneumonitis that does not resolve to Grade ≤1 within 14 days after initiation of optimal medical management
- Grade ≥3 colitis or noninfectious pneumonitis

Other Toxicity

- ALT or AST:

>8 × ULN, if the patient does not have liver metastasis

OR

>3 × ULN with concomitant bilirubin >2 × ULN, in the absence of cholestasis

- Grade 3 bilirubin (total) level
- Grade 3 or 4 amylase or lipase that does not resolve to Grade ≤2 within 7 days after initiation of optimal medical management
- Other Grade 3 or 4 laboratory value lasting >14 days or requiring medical intervention
- Grade 5 toxicity (i.e. event that results in death)
- Toxicity otherwise deemed by the treating and/or Sponsor Investigator to be dose limiting (e.g., toxicity that is possibly related to study treatment and requires treatment discontinuation prior to completion of Cycle 1; persistent Grade >2 toxicities causing a delay of >14 days in initiating Cycle 2)

Events not considered to be a Dose-Limiting Toxicity

Hematologic Toxicity

- Grade 3 or 4 neutropenia if not associated with fever or systemic infection AND improves by at least 1 grade within 7 days
- Grade 3 or 4 lymphopenia
- Grade 3 anemia not requiring a blood transfusion

Other Toxicity

- Isolated Grade 3 electrolyte abnormalities if not associated with clinical signs or symptoms AND reversed with appropriate maximal medical intervention within 7 days
- Vitiligo or alopecia (any grade)
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency), if: the disorder is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy AND the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (such as, inflammatory reaction in the lymph nodes or at sites of metastatic disease)
- Toxicity that is clearly and directly related to the primary disease or to another etiology

Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level.

	• If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is will be considered the recommended phase 2 dose for Phase 1b expansion. At least 6 participants must be entered at the recommended phase 2 dose.

Participants who experience a DLT may continue on study treatment per the discretion of the treating investigator with dose delay/modification per section 6.

5.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of talazoparib and tazemetostat with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

The following are not permitted while on study:

- Antineoplastic therapy or other investigational therapy for the treatment of cancer
- Prophylactic use of hematopoietic colony stimulating factors is not permitted in the phase 1a (dose escalation) part of the study; if the use of granulocyte colony stimulating factors is indicated for febrile neutropenia in phase 1a then study drugs must be held. Growth factors are permitted in phase 1b per investigator discretion.
- Palliative radiation therapy to up to two symptomatic sites is permitted while the patient continues on study, in which case trial medications should be held starting the day before radiation to the day after radiation is completed. If the requirement for radiation is felt by the treating investigator to not reflect progression of disease (i.e., the sites were symptomatic prior to enrolling on study), radiation is not considered a progression event towards the PFS endpoint (section 11.1.6) – otherwise, this would be considered a progression event but patients are permitted to continue on trial therapy until they are felt to be "no longer clinically benefiting" (NLCB) (section 5.6).

5.5.1 Talazoparib

It is unlikely that talazoparib will demonstrate clinically significant drug-drug interactions (DDIs) when coadministered with corresponding CYP, UGT, or transporter substrates. However, talazoparib is a substrate for P-gp and BCRP, and plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or

BCRP inhibitors or inducers, respectively.

- Coadministration with P-gp inhibitors may increase talazoparib exposure.
    - In the clinical studies, coadministration with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil resulted in an approximate 45% increase in talazoparib exposure and an increase in the rate of talazoparib dose reduction. If coadministration of talazoparib with these P-gp inhibitors cannot be avoided, reduce the talazoparib dose by at least 25%; when the P-gp inhibitor is discontinued, increase the talazoparib dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the P-gp inhibitor.
    - Coadministration with P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in clinical studies increased talazoparib exposure by 8%. When coadministering talazoparib with these P-gp inhibitors or others not listed above (i.e. those other than amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil), monitor patients for potential increased adverse reactions.
- Coadministration with BCRP inhibitors may increase talazoparib exposure. If coadministration cannot be avoided, monitor patients for potential increased adverse reactions when coadministering.

5.5.2 Tazemetostat

The human absorption, distribution, metabolism and elimination (ADME) properties of tazemetostat in observed clinical data suggests low drug-drug interaction (DDI) potential with tazemetostat, and there has been no evidence of DDI in the clinical development program to date. However, from the pharmacologic mechanism perspective, DDIs are possible, and the following guidance is given to reduce the risk of DDIs.

- CYP3A4 Substrates: Precaution is warranted with concomitant use of agents with a narrow therapeutic index that are metabolized by CYP3A4 when co-administrating tazemetostat.
- Strong and Moderate CYP3A4 Inhibitors: Avoid coadministration of strong and moderate CYP3A4 inhibitors with tazemetostat. Reduce the dose of tazemetostat by at least 25% if coadministration of moderate CYP3A inhibitors cannot be avoided; when the inhibitor is discontinued, increase the tazemetostat dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the moderate CYP3A inhibitor.
- Strong and Moderate CYP3A4 Inducers: Avoid coadministration with tazemetostat.
- P-gp Substrates: Precaution is warranted with agents that are substrates of P-gp.

NOTE: A listing of CYP inhibitors, inducers, and substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely until one of the following criteria applies:

- Disease progression by PCWG3 criteria,[58] including clinical progression. Patients should not be discontinued from study therapy for PSA progression alone. PCWG3 criteria allow treatment beyond radiographic progression, and this protocol permits patients to continue on trial after radiation to a single site of symptomatic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy – in either case the patient will continue until felt to be "no longer clinically benefiting" (NLCB).
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.7 Duration of Follow Up

The end of treatment visit is the visit on or after the decision is made to end protocol therapy. An additional safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment. In the event subjects cannot be seen for the end treatment safety assessment at the site of enrollment due to the ongoing COVID-19 situation or other extenuating circumstances, safety assessments may be conducted at alternate locations if these assessments are deemed of adequate quality by the treating investigator.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

After end of treatment visit, follow-up for survival and adverse evaluation (only for unresolved adverse events related to study treatment) will be every 12 weeks (+/- 2 weeks) for 24 months or death, whichever is sooner. Follow-up can be performed through phone contact, medical record review, or country/region specific cancer and/or mortality registries.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Guidelines for dose modification for toxicity are provided below. The final dose reduction or delay for each subject may be determined by the investigator and sponsor. However, these guidelines provide the minimum dose reduction or delay criteria. Patients may hold both drugs up to 3 weeks – if neither drug can be safely resumed within this window then the subject must be discontinued from trial. If the patient must hold treatment for > 3 weeks due to a health issue unrelated to trial therapy, such as COVID-19 infection, resumption of treatment on study may be permitted but must be approved on a case-by-case basis by the principal investigator. If the treating investigator feels that it is unsafe to resume one of the study drugs and the patient is felt to be clinically benefiting, patients may continue on monotherapy of the other agent.

For management of **treatment-related hematologic toxicities**, refer to Tables 6-2 to 6-4. For management of **treatment-related nausea, vomiting and diarrhea** refer to Tables 6-5 to 6-7. For **dose modification of talazoparib for renal dysfunction**, refer to Table 6-8.

For the following **treatment-related non-hematologic toxicities**, treatment should be interrupted. Once the toxicity has returned to Grade 1 or lower, dosing can be resumed with 1 dose level reduction (Table 6-1).

- o Grade 3 non-hematologic toxicity (except for fatigue or nausea, vomiting, or diarrhea adequately controlled by supportive care, or asymptomatic unrelated laboratory abnormalities that would not prevent safe administration of trial therapy in the opinion of the trial investigator), after resolution to Grade 1 or lower.
- o Any Grade 2 or lower non-hematologic toxicity requiring dose delay of more than

2 weeks, once felt safe to resume trial therapy by the treating investigator.
If, after 1 dose level reduction, the above drug-related non-hematologic toxicities are subsequently observed, then dosing may be resumed with 2 dose level reductions (Table 6-1).

For **Grade 4 treatment-related non-hematologic toxicity**, treatment will be interrupted and may be resumed with 2 dose level reductions (Table 6-1) when toxicity has returned to Grade 1 or lower. If any toxicity not described results in delay in dosing in any part of the study (such as for recurrent Grade 2 toxicities requiring frequent treatment interruptions), but this section does not specifically mandate a dose reduction, then dosing may be reduced by 1 dose level or continued without dose reduction at the discretion of the investigator. If a participant experiences toxicity at DL -3 necessitating dose reduction, they must be discontinued from study treatment.

Dose re-escalation is allowed if an unrelated confounding variable that contributed to the dose reduction (for example, an AE of another agent that has since been discontinued) has resolved; dose re-escalation must be approved on a case-by-case basis by the principal investigator.

Of note, the toxicity profiles of talazoparib and tazemetostat are largely overlapping so in most cases it would be difficult to ascribe a particular adverse event to a single agent, so in most cases dose reductions will be performed per Table 6-1. However, situations in which the treating investigator ascribes an adverse event to one agent and not the other, or dose modifications are required for one agent and not the other (e.g. decreasing talazoparib dose to 0.75 mg daily for eGFR < 60 mL/min/1.73m^2), dose modifications or interruptions can be made independently from the other agent.

Table 6-1 Guidelines for Dose Modification for Toxicity

Dose Level	Talazoparib Dose	Tazemetostat Dose
+2	1 mg daily	800 mg BID
+1	0.75 mg daily	800 mg BID
0	0.75 mg daily	600 mg BID
-1	0.5 mg daily	600 mg BID
-2	0.5 mg daily	400 mg BID
-3	0.25 mg daily	400 mg BID

Table 6-2 Guidelines for Management and Dose Adjustment for Neutropenia

Neutropenia	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose, consider more frequent monitoring
Grade 3 (≤ 7 days, 1st occurrence)	Hold* until ≤ Grade 2. Resume at same dose level.
Grade 3 (> 7 days or recurrent), Grade 4 or febrile neutropenia	Hold* until ≤ Grade 2. Resume at one dose level lower per Table 6-1.**
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: Neutropenic precautions as indicated per institutional standard. In phase 1a, granulocyte colony stimulating growth factors are permitted only if indicated for	

Neutropenia	**Management/Next Dose**
febrile neutropenia while holding study drugs and are not permitted for prophylactic use. In phase 1b, granulocyte colony stimulation factors are permitted per investigator discretion.	

Table 6-3 Guidelines for Management and Dose Adjustment for Anemia

Anemia	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose, consider more frequent monitoring
Grade 3 (≤ 7 days, 1st occurrence)	Hold* until ≤ Grade 2. Resume at same dose level.
Grade 3 (> 7 days or recurrent)	Hold* until ≤ Grade 2. Resume at same dose level or at one dose level lower per Table 6-1.**
Grade 4	Hold* until ≤ Grade 2. Resume at one dose level lower per Table 6-1.**
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: Blood transfusions are not recommended during cycle 1 unless Hgb is < 7 g/dl or patient is symptomatic with ≥Grade 3 anemia. Persistent/recurrent grade 3 anemia can be managed with blood transfusions or with dose reduction per investigator discretion. Erythropoietic growth factors are not permitted in phase 1a of the study but are permitted per investigator discretion in part 1b.	

Table 6-4 Guidelines for Management and Dose Adjustment for Thrombocytopenia

Thrombocytopenia	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose, consider more frequent monitoring
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower per Table 6-1, if indicated.**
Grade 4	Hold* until ≤ Grade 2. Resume at two dose levels lower per Table 6-1, if indicated.**
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: Platelet transfusions as clinically indicated. Thrombopoietic growth factors are not permitted in phase 1a of the study but are permitted per investigator discretion in part 1b.	

Table 6-5 Guidelines for Management and Dose Adjustment for Nausea

Nausea	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower per Table 6-1, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: antiemetics (ondansetron 4 mg- 8 mg preferred)	

Table 6-6 Guidelines for Management and Dose Adjustment for Vomiting

Vomiting	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower per Table 6-1, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: antiemetics (ondansetron 4 mg- 8 mg preferred).	

Table 6-7 Guidelines for Management and Dose Adjustment for Diarrhea

Diarrhea	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower per Table 6-1, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >3 weeks should go off protocol therapy. **Participants requiring dose reduction below DL -3 should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose bowel movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Table 6-8 Guidelines for Management and Dose Adjustment Renal Dysfunction

Dose cap for talazoparib is 0.75 mg for patients with eGFR 30-59 mL/min/1.73m2. Patients can be monitored using eGFR by Cockcroft-Gault or CKD-EPI refit formula per investigator discretion.

Renal dysfunction	**Management/Next Dose for Talazoparib**	**Management/Next Dose for Tazemetostat**
eGFR 30-59 mL/min/1.73m^2 (initial finding)	No change in dose. Address reversible causes.* If patient is receiving talazoparib at 1 mg daily, recheck within 7 days, with consideration of 24 hour urine collection for calculation of creatinine clearance.	No dose adjustment required
eGFR 30-59 mL/min/1.73m^2 (confirmed)	Address reversible causes.* If patient is receiving talazoparib at 1 mg daily, reduce dose to 0.75 mg daily and consider nephrology consultation. Dose re-escalation to	

Renal dysfunction	**Management/Next Dose for Talazoparib**	**Management/Next Dose for Tazemetostat**
	1 mg is allowed if eGFR increases back to ≥ 60 mL/min/1.73m^2	
eGFR < 30 mL/min/1.73m^2 (≤ 3 weeks)	Hold talazoparib. Address reversible causes* and consider nephrology consultation. Talazoparib can be resumed with dose cap of 0.75 mg if eGFR returns to 30-59 mL/min/1.73m^2. If the patient was assigned to the 1 mg dose level, dose re-escalation is allowed if eGFR increases back to ≥ 60 mL/min/1.73m^2	
eGFR < 30 mL/min/1.73m^2 (> 3 weeks)	Permanently discontinue talazoparib.**	
*Consider IV hydration if indicated. Initial workup for reversible causes would include urinalysis, urine electrolytes to calculate fractional excretion of sodium, and imaging of the urinary tract (such as with renal ultrasound) to assess for obstruction. **The patient may continue tazemetostat monotherapy if felt to be clinically benefiting.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events Lists

7.1.1.1 Adverse Event List for Talazoparib

Very Common (>10%):

- Fatigue (57.6%)
- Anemia (50.6%)
- Nausea (44.6%)
- Neutropenia (31.1%)
- Thrombocytopenia (29.9%)
- Headache (26.9%)
- Diarrhea (22.7%)
- Vomiting (22.7%)
- Alopecia (22.3%)
- Abdominal pain (21.7%)

- Decreased appetite (20.3%)
- Leukopenia (16.3%)
- Dizziness (14.5%)
- Increased sensitivity to light (photosensitivity)

Common (1-<10%):

- Dyspepsia (8.8%)
- Dysgeusia (8.4%)
- Stomatitis (6.4%)
- Lymphopenia (6.4%)

Uncommon (<1%)

- Myeloproliferative neoplasms (MPN): As of the 30 Sept 2019 IB, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML) has been reported in 2 out of 584 (0.3%) solid tumor patients treated with talazoparib at any dose in Pfizer clinical studies. The duration of talazoparib treatment in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively. Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.
- Secondary non-hematologic primary malignancy: As of the 30 Sept 2019 IB, in the talazoparib 1 mg/day population 7 AEs of second primary malignancies were reported in 6 patients (squamous cell carcinoma of skin [2 patients], and basal cell carcinoma, glioblastoma multiforme, intraductal proliferative breast lesion, neoplasm skin, and ovarian neoplasm [1 patient each]. These second primary malignancies were mostly skin malignancies. In general, latency to diagnosis of the malignancy was relatively short, making a relationship with talazoparib unlikely, and in some cases, other risk factors were reported. None of the events were considered related to study drug by the investigator.

7.1.1.2 Adverse Event List for Tazemetostat

Very Common (>10%):

- Feeling like throwing up (Nausea) (28%)
- Extreme tiredness (Fatigue) (23%)
- Throwing up (Vomiting) (19%)
- Frequent, loose stools (Diarrhea) (18%)
- Low red blood cell count (Anemia) (18%)
- Cough (17%)
- Decreased appetite (16%)
- Lack of energy or overall physical weakness (Asthenia) (15%)
- Difficult or labored breathing (Dyspnea) (15%)
- Few, infrequent stools (Constipation) (14%)
- Decrease in the cells that help stop bleeding (Low platelet count/Thrombocytopenia) (11%)
- Stomach pain (Abdominal pain/ Abdominal pain upper) (11%)
- Cancer pain (10%)
- Back pain (10%)
- Fever or body temperature increase above normal (Pyrexia) (10%)

Common (1-<9%):
- Swelling of lower legs or hands (Peripheral edema) (9%)
- Headache (8%)
- Weight decreased (8%)
- Decreased white blood cell count (Neutropenia) (7%)
- Muscle spasm (6%)
- Infection of the nose, sinuses, throat, voice box or lungs (Upper respiratory tract infection) (6%)
- Hair loss (Alopecia) (6%)
- Change in taste (Dysgeusia) (6%)
- Inflammation of the airways that carry air to the lungs (Bronchitis) (5%)
- Leg or hand pain (Pain in extremity) (5%)
- Muscle, bone, tendon, or ligament pain (Musculoskeletal pain) (4%)
- Rash (4%)

Uncommon (<1%) [see section 2.2.2.4]
Potential for Second Primary Hematologic Malignancy:
- T-cell lymphoblastic lymphoma (T-LBL): Out of approximately 160 pediatric patients, two patients treated with tazemetostat as a single drug developed a new blood cancer called, T-LBL. Both patients had taken tazemetostat for greater than one year. T-LBL was also seen in some animals that were treated with tazemetostat.
- Myeloproliferative neoplasms (MPN): Out of more than 2,280 adult patients treated with tazemetostat as a single drug or in combination with other chemotherapy in clinical studies or with marketed tazemetostat, some (<1%) patients developed Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML) or Myeloproliferative Neoplasms (MPN).
- Some (approximately 0.1%) patients developed a new blood cancer called B-cell acute lymphocytic leukemia (B-ALL).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Serious Adverse Events: Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant 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 inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy and potential drug-induced liver injury (DILI) is not always serious by regulatory definition, these events must be reported within the SAEs timeline.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health

status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

All SAEs that occur following the subject's initial dose of study treatment through 30 days of discontinuation of dosing must be reported to the Sponsor-Investigator, Epizyme, Pfizer, and local institutional IRB per local policy (whether related or not related to study drug) within 5 calendar days of investigator awareness or within 24 hours for grade 5 events. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

7.4 Adverse Event Reporting

7.4.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Sponsor-Investigator.

7.4.2 Investigators **must** report to the Sponsor-Investigator any adverse event (AE) that meets the definition of SAE in section 7.3 or is a reportable event per the table in section 7.4.2 that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.3 Adverse Event Reporting Guidelines

In addition to the SAEs defined in section 7.3, which must be reported within 5 calendar days of investigator awareness or within 24 hours for grade 5 events, the table below indicates which events must be reported to the DF/HCC Sponsor-Investigator, Epizyme, Pfizer, and local institutional IRB per local policy.

Attribution	DF/HCC Reportable Adverse Events (AEs)				
	Gr. 3 AE Expected	**Gr. 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*

Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.4.4 Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the DF/HCC Sponsor-Investigator. However, they still must be recorded through the routine reporting mechanism (i.e. case report forms).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Blood and lymphatic system disorders	Anemia	1-4	N/A	Any	
Investigations	Neutrophil, platelet, or lymphocyte count decreased	1-4	N/A	Any	

7.5 Reporting to the Food and Drug Administration (FDA)

Since this study is IND Exempt, FDA reporting is not required.

7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Sponsor-Investigator on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, Pfizer, Inc., Epizyme, Inc., etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents

administered in this study can be found in Section 7.1.

8.1 Talazoparib

8.1.1 Description

Talazoparib (PF-06944076; MDV3800; BMN 673) is provided as the 4-methylbenzenesulfonate (tosylate) salt. Talazoparib tosylate has the chemical name ((8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one 4-methylbenzenesulfonate (1:1).

8.1.2 Form

The drug product is a capsule formulation composed of a blend of talazoparib tosylate drug substance and silicified microcrystalline cellulose (SMCC) filled into a hypromellose capsule. Capsules are provided as 0.25 mg, opaque white, size 4; and 1 mg, opaque flesh (light pink), size 4 capsules in high-density polyethylene (HDPE) bottles, with heat induction-sealed closures, containing 30 drug product capsules of a single strength.

8.1.3 Storage and Stability

The drug product is stored at room temperature (15°C–30°C; 59°F–86°F) or per approved local label. Any temperature excursions must be reported to GCSTempExcursionSupport@Pfizer.com

Talazoparib 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.

8.1.4 Compatibility

N/A

8.1.5 Handling

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Patients should be advised that oral anticancer agents are toxic substances and that caregivers (other than the patient) should always use gloves when handling the capsules.

8.1.6 Availability

Talazoparib 0.25 mg and 1 mg capsules will be supplied for this study by Pfizer, Inc.

8.1.7 Preparation

N/A

8.1.8 Administration

Talazoparib will be administered with or without food. The capsules should be swallowed whole, and the capsules should not be dissolved or opened. Doses must be administered at least 18 hours apart. If a dose is missed or vomited, the dose should be skipped and next dose administered at the regular time. All doses given, missed, and vomited, should be recorded.

8.1.9 Ordering

Drug supply for talazoparib will be requested through the cybergrants.com/pfizer/loi portal by filling out the Drug / Compound Supply Request Impact Report. Pfizer should be provided with 6 months notification of resupply.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return

The investigative site will monitor the expiration status of all supplies of Pfizer-provided talazoparib, ensure that Study subjects only receive talazoparib that is within its expiration dating, and provide Pfizer with sufficient notice if resupply is needed because of pending expiration of existing supplies. Unless otherwise instructed by Pfizer in writing, the investigative site will destroy any supplies of talazoparib that expire during the term of this study, as well as all supplies that remain unused at the termination of this study. The investigative site will destroy these materials in accordance with all applicable law and institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Tazemetostat

8.2.1 Description

Tazemetostat (also known as EPZ-6438 and E7438, NSC # 791066), chemical name [1,1'-Biphenyl]-3-carboxamide, N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2Hpyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-, hydrobromide (1:1), is a selective and

reversible oral small-molecule inhibitor of enhancer of zeste homolog 2 (EZH2), a histone methyltransferase (HMT).

The molecular weight of tazemetostat is 572.75 for the free base ($C_{34}H_{44}N_4O_4$) and 653.66 for the hydrobromide salt ($C_{34}H_{44}N_4O_4$·HBr). Tazemetostat is an off-white solid, soluble in 0.1 N hydrochloride (HCl) solution and slightly soluble in water, ethanol, and phosphate buffered saline.

8.2.2 Form

Tazemetostat film-coated tablets contain 200 mg of drug substance with respect to the free base. Lactose monohydrate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate are the excipients used for core tablets. Opadry® 03F45063 RED, a mixture of 20ypromellose 2910, talc, polyethylene glycol 8000, titanium dioxide, and ferric oxide (red), has been chosen as the film-coating agent. The 200 mg tablets are red, round, and biconvex with a diameter of approximately 10 mm.

Tablets are packaged in a white, high-density polyethylene bottle with a desiccant and a child-resistant, tamper-evident polypropylene screw cap.

8.2.3 Storage and Stability

Tazemetostat film-coated tablets are not to be stored at temperatures above 30°C (86°F). The expiration date is printed on the label. Store in the original package.

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.

8.2.4 Compatibility

N/A

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS). A MSDS describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Epizyme, Inc. upon request.

8.2.6 Availability

Tazemetostat 200 mg tablets will be supplied for this study by Epizyme, Inc.

8.2.7 Preparation

N/A

8.2.8 Administration

Tazemetostat will be administered with or without food. Doses must be administered at least 8 hours apart. If a dose is missed (e.g., missed morning dose or vomited and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose. If the subject vomits within 30 minutes of dosing, anti-emetics should be given and a second fresh dose of study treatment given. All doses given, missed, and vomited, should be recorded.

8.2.9 Ordering

When requesting Study Drug, Sponsor shall submit a completed the Product Order Form to be provided by Epizyme Medical Affairs. When planning for and requesting Product, please allow at least 30 business days for processing the first shipment and 10 business days for each additional shipment. Please note that Epizyme cannot guarantee arrival of Epizyme Study Drug on or before a requested date if Epizyme is given less than the required time.

8.2.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.11 Destruction and Return

Unused or expired tazemetostat will be destroyed by the investigative site. Destruction will be documented in the Drug Accountability Record Form. Destruction certificates for tazemetostat should be sent to Epizyme, Inc. on an on-going basis.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

	At registration	**Cycle 1, Day 1**	**Week 8 +/- 7 days (tissue)[1] Cycle 3, Day 1 (blood)**	**End of Treatment[2]**

Tissue specimens				
Tumor biopsy Paraffin Frozen in OCT	 2 cores 2 cores		 2 cores 2 cores	
	Blood specimens - Number and volume of tubes to draw			
Whole Blood (CTCs) EDTA (purple top)		2 x 10 mL	2 x 10 mL	2 x 10 mL
Plasma (cfDNA) EDTA (purple top)		2 x 10 mL	2 x 10 mL	2 x 10 mL
Whole Blood (germline DNA) EDTA (purple top)	1 x 10 mL			

1. Window for the on-treatment biopsy can be extended per PI discretion if the patient required dose interruption(s) prior to the biopsy to allow for treatment resumption at time of biopsy.
2. End of treatment samples may be collected and submitted up to 30 days after end of treatment prior to any intervening treatment. If end of treatment is within 14 days of prior collection, research samples do not need to be collected.

9.2 Laboratory Correlative Studies

9.2.1 Tumor Biopsy Specimens

9.2.1.1 Collection of Specimen(s)

Patients will undergo biopsy of an accessible metastatic site after registration and prior to C1D1, and again after 8 weeks (+/- 7 days) of treatment on trial (window for the on-treatment biopsy can be extended per PI discretion if the patient required dose interruption(s) prior to the biopsy to allow for treatment resumption at time of biopsy). Biopsies will be performed by an interventional radiologist under CT guidance (ultrasound guidance is allowed if preferred by the interventional radiologist.) Blood samples will be drawn within 28 days of the biopsy to document an acceptable coagulation profile (INR < 1.5, PTT < 45, platelets >50,000). Aspirin and/or Plavix should be discontinued 5 days prior to the biopsy, though aspirin up to 81 mg daily may be continued per discretion of IR at the performing institution. On the day of the biopsy, a short physical exam will be performed by the radiologist including assessing the patient's general ASA score and airway rating. Informed written consent will be obtained following discussion of the risks (bleeding, infection, adjacent tissue injury, and pain) and benefits of the procedure. Biopsies will be performed using standard coaxial techniques under CT (or ultrasound) guidance without the administration of intravenous contrast. Conscious sedation will be administered by a trained radiology nurse using small doses of Versed and fentanyl titrated to the patient's level of discomfort. Following the biopsy, patients will be observed for 2 hours following their last dose of conscious sedation for any complications (severe pain, hematoma, neurologic deficit) prior to

departing with a chaperone.

The study investigator and interventional radiologist will decide on appropriate biopsy site likely to yield tissue amenable to NGS analysis[59] while exposing the patient to acceptable risk. Large bore core biopsies will be performed per institutional standards.

9.2.1.2 Handling of Specimens(s)

Specimen size requirement is as follows:

- Surface area of 25mm^2 is optimal. Minimum is 5mm^2.
- Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3

At least 4 biopsy cores should be obtained – 2 fresh frozen and at least 2 placed in formalin. They should be apportioned as follows.

a) 1st core placed in OCT and frozen for ChIP-seq and ATAC-seq
b) 2nd core placed in OCT and frozen for RNA-seq
c) 3rd core placed in formalin for immunohistochemistry
d) 4th core placed in formalin for pathology review/OncoPanel
e) Any additional cores placed in formalin

9.2.1.3 Shipping of Specimen(s)

A clinical research coordinator will be present at the time of biopsy to apportion the biopsy specimens. They will be processed, stored and shipped per the laboratory manual. These samples may also be stored for possible future use.

9.2.1.4 Site(s) Performing Correlative Study

Dana-Farber Cancer Institute

9.2.2 <u>Blood collection for ctDNA</u>

9.2.2.1 Collection of Specimen(s)

Collect blood in EDTA tube at the following time points:

- 1 × 10 mL pre-treatment for genomic DNA
- 2 × 10 mL at C1D1 and C3D1 visits for cfDNA
- 2 × 10 ml at end of treatment (EOT) for cfDNA

9.2.2.2 Handling and Shipping of Specimens(s)

Blood specimens in EDTA tubes will be labeled with the patient's trial ID and time point (pre-treatment, C1D1, C3D1, or EOT) and sent immediately to the Gelb Center laboratory for processing. Germline DNA will be isolated from pre-treatment specimen, and plasma for cfDNA will be isolated from subsequent specimens as detailed in the laboratory manual. Frozen germline DNA(pre-treatment) and plasma (C1D1, C3D1, end of treatment) will be stored at the Gelb Center Blood Biorepository.

9.2.2.3 Site(s) Performing Correlative Study
Dana-Farber Cancer Institute and Broad Institute of MIT and Harvard.

9.2.3 Whole blood for Circulating Tumor Cells

9.2.3.1 Collection of Specimen(s)
Collect 2 × 10 mL of blood in EDTA tube at the following time points:

- At C1D1 and C3D1 visits
- At end of treatment (EOT)

9.2.3.2 Handling and Shipping of Specimens(s)
Blood specimens will be labeled with the patient's trial ID and time point (C1D1, C3D1 or EOT), and shipped immediately by courier to the laboratory of Dr. David Miyamoto at Massachusetts General Hospital, where they will be processed to CTCs per published protocols.

9.2.3.3 Site(s) Performing Correlative Study
Massachusetts General Hospital

10. STUDY CALENDAR

Pre-study (screening) laboratory testing, imaging studies, and EKG must be done ≤4 weeks prior to the start of therapy. Packed red blood cell (PRBC) and/or platelet transfusions and growth factors are not permitted within 28 days of screening. Pre-treatment assessments should be performed within 72 hours of planned treatment dose. Results from the patient's complete blood counts and serum chemistry must be reviewed prior to drug dosing. The patient's laboratory parameters must meet the eligibility criteria in section 3.1.7 to initiate cycle 1 day 1 of trial therapy; eligibility to receive subsequent doses is based on dose delay/modification criteria detailed in Section 6. The acceptable window for start of day 1 of a cycle is 28 days +/- 4 days in relation to day 1 of the prior cycle. The acceptable day 15 lab assessment window is +/- 4 days. Administration outside of these windows may be permitted for weather or other emergencies after discussing with the principal investigator.

	Baseline	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Subsequent cycles	End of treatment[e]	Follow-Up[e]	EDC Timepoints
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1			
Talazoparib		A	A	A	A	A	A	A	A	A	A			Day 1 of every Cycle
Tazemetostat		B	B	B	B	B	B	B	B	B	B			Day 1 of every Cycle
Informed consent	X													N/A
Demographics	X													Baseline
Medical history	X													Baseline
Concurrent Medications			X----------X											Baseline, Day 1 of every Cycle, End of Treatment
Physical exam	X	X		X		X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
Vital signs	X	X		X		X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
Height	X													Baseline
Weight	X	X		X		X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
Performance status	X	X		X		X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment
PSA	X	X		X		X	X	X	X	X	X	X		Baseline, Day 1 of every Cycle, End of Treatment, Follow-Up
Testosterone	X													Baseline
EKG (only if clinically indicated)	X													Baseline only if clinically indicated – If an EKG is performed during any Cycle, at Off Treatment, or during Follow-Up visits, it must be captured in InForm.
Adverse Event Evaluation				X----------X[e]										During all visits
Radiologic Evaluation[b]	X			Radiologic measurements should be performed every 8 weeks for the first								X		Baseline, C3D1, C5D1, C7D1, C10D1

	Baseline	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Subsequent cycles	End of treatment[e]	Follow-Up[e]	EDC Timepoints
				24 weeks of the study, then every 12 weeks thereafter.										and every 3 cycles thereafter. If a Radiologic Evaluation is performed during any other Cycle, it must be captured in InForm.
Tumor biopsy[c]	X					X								Baseline, C3D1
gDNA/cfDNA[d]	X	X				X						X		C1D1, C3D1, End of Treatment
CTCs		X				X						X		C1D1, C3D1, End of Treatment
Survival				X----------									----------X	During all visits

A: Talazoparib daily
B: Tazemetostat BID
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine (with estimated glomerular filtration rate), glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Cross-sectional imaging of Chest, Abdomen and Pelvis as well as bone scintigraphy, to be performed as scheduled every 8 or 12 weeks (+/-7 days) even if investigational drug doses are held or delayed.
c: Tumor biopsy is performed after trial registration but prior to C1D1; then again after 8 weeks on treatment +/- 7 days. Window for the on-treatment biopsy can be extended per PI discretion if the patient required dose interruption(s) prior to the biopsy to allow for treatment resumption at time of biopsy.
d: Pre-study genomic DNA sample can be drawn any time between and including screening and C1D1; cfDNA samples are drawn on C1D1, C3D1 and end of study (before or after drug dosing)
e: The end of treatment visit is the visit on or after the decision is made to end protocol therapy. The end of treatment research blood collection can happen during this visit, or any time between discontinuing protocol therapy and starting a new treatment. An additional safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment. After end of treatment visit, follow-up for survival and adverse evaluation (only for unresolved adverse events related to study treatment) will be every 12 weeks (+/- 2 weeks) for 24 months or death, whichever is sooner. Follow-up can be performed through phone contact, medical record review, or country/region specific cancer and/or mortality registries.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks for the first 24 weeks of the study, then every 12 weeks thereafter, to be performed as scheduled (+/- 7 days) even if investigational drug doses are held or delayed. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using Prostate Cancer Working Group 3[58] modifications of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the modified RECIST criteria. Response and progression of osseous disease by bone scintigraphy will be per Prostate Cancer Working Group 3 criteria.[58]

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as

possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a

pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Refer to section 11.2

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Osseous Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Osseous Disease by Bone scintigraphy per PCWG3 criteria[58]

Osseous disease will be monitored by bone scintigraphy. The bone scan performed at 8 weeks will serve as the baseline for assessment of radiographic progression of osseous disease. Bone scan progression will be defined as the appearance of at least two new lesions relative to the first post-treatment scan, confirmed on a subsequent

scan. Date of progression is the date of the scan that first documents the second lesion (and not the date of the confirmatory scan). Changes in intensity of uptake alone do not constitute either progression or regression.

11.1.4.4 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Radiographic Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from protocol treatment initiation to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from protocol treatment initiation to the earlier of progression by PCWG3 criteria[2] or death due to any cause. PCWG3 progression is defined as radiographic or clinical/symptomatic progression (i.e. not PSA progression alone). However, PCWG3 criteria allow treatment

beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy (compared to other available treatments or no treatment) until the patient is "no longer clinically benefiting" (NLCB). Participants alive without disease progression are censored at date of last disease evaluation.

11.2 PSA Response and Progression

Evaluable for PSA response
Only those patients with PSA ≥ 2.0 ng/mL at baseline, have received at least one cycle of therapy, and have had their PSA re-measured will be evaluable for PSA response.

Biochemical (PSA) Response[60]
The laboratory will utilize a consistent method to check serum PSA at baseline, on treatment as per the study calendar, and at study termination.
A PSA response will be defined as any PSA decline ≥50% from baseline during trial therapy.

Percent change in serum PSA[61]
The percent change (rise or fall) from baseline at 12 weeks, and separately, the maximal change (rise or fall) at any time will be recorded using a waterfall plot.

PSA Progression-Free Survival (PSA-PFS)
PSA Progression-Free Survival is defined as the time from protocol treatment initiation to the first PSA failure (two consecutive increases in PSA of 25% and ≥2 ng/mL above nadir) or death, or it is censored at date of last PSA test for participants alive without PSA progression.

Duration of PSA response
The duration of PSA response is measured from the time of PSA response till the PSA progression, or it is censored at date of last PSA test.

11.3 Overall Response

Overall response rate (ORR) of this study is defined by PSA reduction by ≥ 50% OR radiographic response by RECIST 1.1.

Clinical Benefit Rate (CBR) is defined as the proportion of patients with a BOR of CR or PR, or SD ≥6 months by RECIST 1.1 or achieve PSA reduction by ≥ 50%.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a Phase 1a/1b clinical trial to assess safety, tolerability and preliminary clinical activity of the combination of talazoparib with tazemetostat in mCRPC patients.

Metastatic CRPC patients with progression on at least one novel hormonal therapy (NHT) and taxane (or not a candidate for taxane) will be enrolled. Patients must have disease amenable to biopsy and consent to pre-treatment and on-treatment biopsies. Due to the fact that the proposed mechanism of synergy between these two agents does not require genetic alteration in the DNA damage repair pathway, we will accrue a biomarker-unselected population of patients, and prior treatment with a PARP inhibitor will be allowed.

The study will take place in two parts: Phase 1a to define the recommended phase 2 dose (RP2D) and Phase 1b to better assess safety and preliminary clinical activity of the combination at the RP2D. The Phase 1a will be conducted as a standard 3+3 dose escalation study with starting dose (dose level 0) of talazoparib 0.75 mg daily and tazemetostat 600 mg BID. We will monitor for dose-limiting toxicities (DLTs) during the first cycle of therapy and escalate or de-escalate dose

per section 5.4. If DLTs are seen in 0-1 of 6 patients at dose level +2 (tazemetostat 800 mg BID with talazoparib 1 mg daily), then this will be the RP2D; otherwise the maximally tolerated dose (MTD) will be the RP2D.

After 6 patients are treated at the RP2D, phase 1b will open to enroll an additional 20 patients in the expansion cohort (for a total of 26 patients treated at RP2D) to assess preliminary clinical efficacy by overall response rate (ORR; defined as PSA reduction by ≥ 50% OR radiographic response by RECIST 1.1). Exploratory efficacy endpoints include duration of response (DOR), progression-free survival by the PCWG3 criteria (PFS), PSA progression-free survival (PSA-PFS), and clinical benefit rate at 6 months (as defined in section 11.1.5, 11.1.6, 11.2 & 11.3).

In both Phase 1a and Phase 1b, the patient will be treated until disease progression by Prostate Cancer Working Group 3 criteria,[62] unacceptable toxicity or death.

Paired tumor biopsies will be obtained from all patients in both parts of the study at baseline and after approximately 8 weeks of therapy, and serial blood samples will be collected at baseline, on cycle 3 day 1 of therapy, and at end of treatment for the biomarker studies detailed in Section 2.4 (exploratory biomarker endpoints were described in section 1.4).

13.2 Sample Size, Accrual Rate and Study Duration

The sample size of the phase 1a (dose escalation) part of the study is between 9 and 18 patients, and the sample size of the expansion cohort is 20 patients for a total sample size of up to 38 patients. Subjects enrolled to phase 1b who do not initiate protocol therapy can be replaced.

For the secondary endpoint of ORR, with a sample size of 26 (6 patients from dose escalation and 20 from expansion cohort treated at RP2D), we deem talazoparib+tazemetostat effective if 5 or more responses are recorded. The probability of concluding that the treatment strategy effective is 0.11 if its true response rate is 10% and at least 0.93 if the true response rate exceeds 30%.

To assess the safety of the combination at the RP2D, we deem the toxicity profile of talazoparib+tazemetostat is acceptable if 6 or less suffer a DLT out of 26 patients treated at PR2D (i.e. observed rate ≤23%). The probability of accepting talazoparib+tazemetostat is 0.20 if its true DLT rate is 33% and at least 0.86 if its true DLT rate is 17% or less.

We anticipate an accrual rate of 2 patients per months in the Phase 1a portion, which will complete within 6-9 months of activation. In the Phase 1b (dose expansion) part, we anticipate an accrual rate of 2-3 patients per month, to complete accrual to the entire trial within 18 months. The secondary endpoint of preliminary clinical efficacy will be assessed at 20-24 months.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino		+	4	=	4
Not Hispanic or Latino		+	34	=	34

Ethnic Category: Total of all subjects	0	+	38	=	38
Racial Category					
American Indian or Alaskan Native		+	0	=	0
Asian		+	3	=	3
Black or African American		+	5	=	5
Native Hawaiian or other Pacific Islander		+	0	=	0
White		+	30	=	30
Racial Category: Total of all subjects	0	+	38	=	38

13.3 Analysis of Primary Endpoints

For the primary endpoint of the study, dose escalation will follow a 3+3 design. Dose-limiting toxicities (DLTs) are defined using criteria in section 5.4 and assessed by the investigator, based on toxicity grade (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), clinical significance, and possible relationship to either study drug. DLTs are defined for the combination treatment at each dose level. The MTD for the study drug combination is defined as the maximum dose combination at which < 33% of patients experience a DLT during Cycle 1 (the DLT-evaluation period). If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue until at least 2 of the 3 to 6 patients treated at a dose level experience a DLT or until the maximum dose to be evaluated is reached, whichever occurs first. If the end of dose escalation is reached due to DLTs, the next lower dose will then be considered the MTD. If DLTs are seen in 0-1 of 6 patients at dose level +2 (tazemetostat 800 mg BID with talazoparib 1 mg daily), then this will be the RP2D; otherwise the maximally tolerated dose (MTD) will be the RP2D.

13.4 Analysis of Secondary Endpoint

For the secondary endpoint of ORR, 26 patients (6 from the dose escalation part and 20 from the expansion) will be analyzed. ORR will be summarized with the two-sided 80% exact binomial confidence interval (CI). The minimum number of responses (NR) necessary to declare the combination provisionally effective is determined using the 80% lower confidence bound (LCB) for response of the drug at the RP2D.[63]

13.5 Analysis of Exploratory Endpoints

For exploratory endpoints, time to event endpoints (PFS, PSA-PFS, duration of response) will be estimated with the Kaplan Meier methodology. Clinical benefit rate would be reported with the two-sided 80% exact binomial CI. The tissue and blood-based biomarkers are exploratory in nature and are not statistically justified within the small sample size of the study. Biomarkers will be quantified using the appropriate methods for each assay and binary variables will be categorized as present/absent (e.g. for presence or absence of a mutation in a DDR gene) or proficient/deficient (e.g. for homologous recombination proficiency by RAD51 focus formation assay) and assessed for association with clinical outcomes. For continuous variables (e.g. EZH2

expression) without known cut points from clinical specimens, specimens will be characterized as above or below the median and assessed for association with clinical outcomes. For comparison of on-treatment vs. pre-treatment specimens, the relevant biomarkers will be quantified as percent change from baseline – percent change from baseline above or below the median will be assessed for association with clinical outcomes.

13.6 Reporting and Exclusions

13.6.1 Evaluation of DLT

The DLT evaluable population is defined as patients who received 75% or more of planned doses of study drugs in Cycle 1 or had experienced a DLT before receiving 75% of planned doses in Cycle 1. Patients who received less than 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation and will be replaced.

13.6.2 Evaluation of Toxicity

Evaluation of toxicity will be done in the safety population, which will include all patients who received at least one dose of study treatment. Patients will be analyzed in the treatment group according to the dose of study treatments they actually received. Participants who do not receive study drug will be excluded from toxicity and efficacy analyses.

13.6.3 Evaluation of the Efficacy Endpoints

The Efficacy Analysis Set will include all patients in the dose escalation part of the study and the dose expansion part of the study who initiated treatment at the RP2D. The Efficacy Analyses Set will be used for the primary efficacy endpoint of objective response rate. Response unevaluable patients or early death from any causes prior to response evaluation will be included in the analysis of the response rate as non-responders, and will not be excluded from the analysis.

13.6.3 Evaluation of the Biomarker Endpoints

The Biomarker Analysis Set will include all patients in the dose escalation part of the study and the dose expansion part of the study who initiated study treatment and had blood and/or tissue collected at any time point for biomarker analyses.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be 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. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The participant _____ is enrolled on a clinical trial using the experimental agents talazoparib and tazemetostat. This form is addressed to the participant, but includes important information for others who care for this participant.

Talazoparib and tazemetostat can interact with many drugs that can affect how they are processed in your body. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

- The level of talazoparib in your body can be affected by the activity of certain proteins of the cell membrane that pump many foreign substances out of cells.
    - The pumps in question are P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).
    - Talazoparib must be used very carefully with other medicines that affect the functioning of these pumps.
    - Substances that decrease the pump's activity ("inhibitors") could result in high levels of talazoparib, increasing the chance of harmful side effects.
- Tazemetostat interacts with a certain specific enzyme in your liver.
    - The enzyme(s) in question is CYP3A4. Tazemetostat is broken down by this enzyme in order to be cleared from your system.
    - Tazemetostat must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
    - Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inhibitors of P-gp" and "strong inducers/inhibitors of CYP3A4".
- Your prescribers should look at this web site

http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking the study drugs.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is:

_____

and he or she can be contacted at

_____