Summary of Changes

I. CTEP Amendment Review Letter dated 11/20/25, Comments Requiring a Response – Major Issues:

#	Section	Comments
1	*7.1.1.2 Radium-223*	Due to a recent change in CTEP policy, protocols should no longer include the CAEPR for Standard of Care agents or regimens being used per FDA label. Please remove the Radium-223 CAEPR from the protocol. In place of the CAEPR, provide a list of those adverse events most likely to occur on the study and refer the reader to the package insert for the comprehensive list of adverse events. The ICD risk list should be updated using the list for your agent found here: https://dctd.cancer.gov/research/ctep-trials/trial-development/side-effects. If your agent is not on the list, please send an email to NCICTEPComments@mail.nih.gov to request they provide you with the risk list. **PI Response:** The change has been made as requested.

II. CTEP Request for Rapid Amendment (RRA), dated October 21, 2025:

Please note that this amendment does not update the AE Reporting Tables as they were updated with the previous amendment.

#	Section	Comments
1	*Header*	Updated "Version Date" in the header.
2	*Protocol Title Page*	Updated version and amendment date.

3	*7.1.1.1 Olaparib (AZD2281, NSC 747856)*	Added revised CAEPR (Version 2.7, July 9, 2025) as requested in the RRA.
		• Added New Risk:
		  • Rare but Serious: Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia (AIHA)); Blood and lymphatic system disorders - Other (pure red cell aplasia (PRCA)); Hepatobiliary disorders - Other (drug-induced liver injury (DILI))
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Rare but Serious: Vascular disorders - Other (venous thromboembolism)

		• Changed to Rare but Serious from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Lymphocyte count decreased
		
		• Decrease in Risk Attribution:
		  • Changed to Less Likely from Likely: Abdominal pain; Anorexia; Diarrhea
		  • Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Less Likely: Abdominal distension; Edema Limbs; Mucositis oral; Muscle cramp; Rash maculo-papular; Urinary tract infection
		
		• Deleted Risk:
		  • Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Bone pain; Flushing; Hypermagnesemia; Hypothyroidism; Renal and urinary disorders - Other (decreased glomerular filtration rate)
		
		• Provided Further Clarification:
		  • Footnote #2 is now added as "Autoimmune hemolytic anemia (AIHA) and Pure red cell aplasia (PRCA) have been reported in clinical trials as potential and identified risks when Olaparib is used in combination with durvalumab."
		  • Footnote #3 is now added as "Venous thromboembolism includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis."
		  • Footnote #4 is now added as "Rash includes exfoliative rash, generalized erythema, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic."

NCI Protocol #: 10096

Local Protocol #: TBD

ClinicalTrials.gov Identifier: NCT03317392

Title: A Phase 1/2 Study of **C**ombination **O**laparib and **Rad**ium-223 in Men with Metastatic Castration-Resistant Prostate Cancer with Bone Metastases (COMRADE)

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LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agent: Olaparib (AZD2281) NSC# 747856

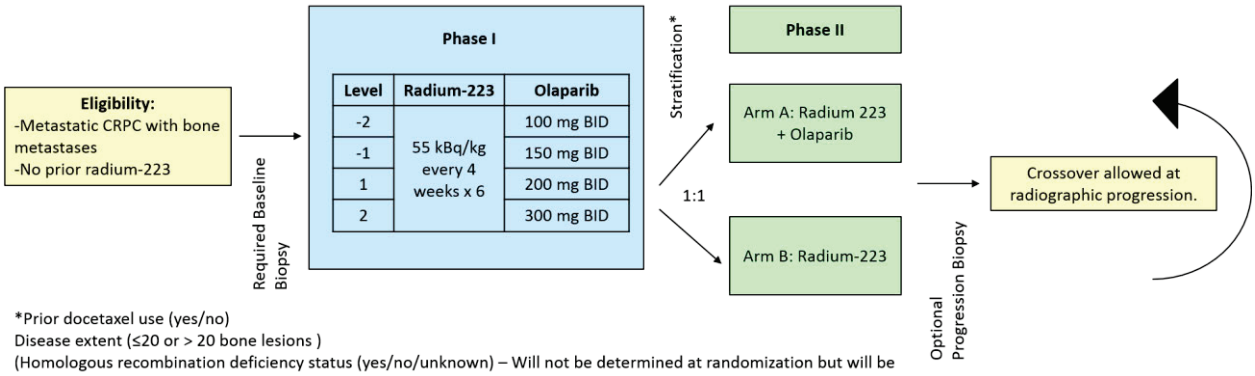
Other Agent: Radium-223, Commercial

IND #: [redacted]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Amendment /Version# 17 / *December 5*, 2025 (resubmission)

SCHEMA



*Prior docetaxel use (yes/no)
Disease extent (≤20 or > 20 bone lesions)
(Homologous recombination deficiency status (yes/no/unknown) – Will not be determined at randomization but will be retrospectively assessed)

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1. OBJECTIVES AND DESIGN

1.1 Primary Objectives

1.1.1 Phase 1: Determine the maximum tolerated dose (MTD) of olaparib in combination with radium-223.

1.1.2 Phase 2: Evaluate the radiographic progression-free survival (rPFS).

1.2 Secondary Objectives

1.2.1 Evaluate safety and tolerability as assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

1.2.2 To evaluate rPFS as stratified by disease extent (≤20 or > 20 bone lesions) and prior docetaxel use (yes or no).

1.2.3 Evaluate rPFS in patients harboring or lacking evidence of homologous recombination deficiency (HRD). HRD will be defined by the presence of homozygous deletion AND/OR putative deleterious mutation in a gene reported to be involved in homologous recombination DNA repair as determined by next generation sequencing.

1.2.4 Evaluate rPFS in patients based on prior abiraterone and/or next generation androgen receptor (AR) antagonist (enzalutamide, apalutamide, darolutamide or other agent) use (yes versus no) for either hormone sensitive or castration resistant prostate cancer (CRPC).

1.2.5 Evaluate prostate specific antigen (PSA) response rate as defined by ≥50% decline in PSA from baseline.

1.2.6 Evaluate total alkaline phosphatase response defined as a reduction of ≥30% from the baseline value, confirmed ≥4 weeks later.

1.2.7 Evaluate time to PSA progression as defined by Prostate Cancer Clinical Trials Working Group (PCTWG) 3 criteria.(1)

1.2.8 Evaluate radiographic objective response rate as defined by Response Evaluation Criteria In Solid Tumor (RECIST) version 1.1.(2)

1.2.9 Evaluate time to increase in the total alkaline phosphatase (ALP) level defined as an increase of ≥25% from baseline at ≥12 weeks, in patients with no decrease from baseline, or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline.

1.2.10 Evaluate time to first subsequent anti-cancer therapy (including AR signaling agents, cytotoxic chemotherapy, immunotherapy, or investigational agents) or death.

1.2.11 Evaluate time to first symptomatic skeletal event (SSE).

1.2.12 Evaluate overall survival (OS).

1.3 Exploratory Objectives

1.3.1 Evaluate impact on quality of life (QOL) as determined by Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and Brief Pain Inventory (BPI).

1.3.2 Estimate the frequency of mutations in the DNA repair pathway in patients with metastatic CRPC as determine by Oncopanel testing and by whole exome sequencing (WES).

1.3.3 Characterize changes in RNA expression of DNA repair genes and immune markers by whole transcriptome sequencing (WTS) in each arm.

1.3.4 Characterize changes in immune cell, T-cell receptor (TCR), and B-cell (BCR) receptor repertoire at baseline, during treatment, and at progression in each arm.

1.3.5 Evaluate changes in lactate dehydrogenase (LDH) in patients each treatment arm.

1.3.6 Assess the prevalence of germline mutations in homologous recombination genes in all enrolled patients.

1.3.7 Correlate homologous recombination gene germline mutation status with PSA response by treatment arm.

1.3.8 Evaluate family history of cancers in the study population and correlate family cancer history with germline mutation status.

1.3.9 Correlate presence or absence of RAD51 with somatic and germline homologous recombination gene mutation status, PSA response, and PFS between treatment arms.

1.3.10 Evaluate the changes in whole genome sequencing (WGS) of plasma cell-free circulating DNA (cfDNA) based patient-tumor specific signature at baseline, on treatment, and at progression.

1.3.11 Evaluate tumor mutation burden (TMB) and tumor mutational signature in plasma cfDNA at baseline and correlate to tumor tissue TMB and mutational signature.

1.4 Study Design

This is a phase 1/2 study evaluating the dosing, safety and efficacy of olaparib in combination with radium-223 in men with CRPC with bone metastases. Eligible patients will undergo a mandatory baseline metastasis biopsy. Patients will remain on treatment until evidence of radiographic progression as determined by PCWG3 for bone metastases and RECIST version 1.1 for non-bone metastases, unacceptable toxicity, intercurrent illness, or other reason. Patients will undergo an optional metastasis biopsy at time of treatment discontinuation. The second biopsy will not be obtained in patients who remain on therapy for less than three cycles. Tumor tissue will be subjected to Oncopanel testing to evaluate the presence of homologous recombination deficiency as defined by the presence of homologous deletion AND/OR putative deleterious mutation in a gene reported to be involved in homologous recombination DNA repair. Disease assessments will consist of computed tomography (CT) imaging and radionuclide bone scans every 12 weeks.

Phase 1:
For the phase 1 component of the study, a standard 3 + 3 dose escalation design will be employed with fixed dosing of radium-223 and four planned dose levels for olaparib. The starting dose of olaparib will be 200 mg by mouth twice daily continuously with one dose escalation to 300 mg by mouth twice daily continuously and two-dose de-escalation to 150 mg and 100 mg by mouth twice daily continuously. Dose escalation schema is described in section 5.2.

Phase 2:

The phase 2 component of the trial will be an open-label, randomized study designed to evaluate the combination of olaparib and radium-223 compared to radium-223 alone in men with metastatic CRPC with bone metastases. Patients with CRPC with bone metastases will be randomized with 1:1 allocation to receive olaparib and radium-223 or radium-223 alone using permuted blocks methods, stratified prospectively by prior docetaxel status (either for CRPC or hormone sensitive disease yes/no) and disease extent (≤20 or > 20 bone lesions on radionuclide bone scan). Homologous recombination deficiency status (yes/no/unknown) will be retrospectively determined on collectively tissue after randomization and included as an additional stratification factor for the primary endpoint rPFS analysis. For patients randomized to combination olaparib and radium-223, treatment with olaparib alone will continue after completion of up to six doses of radium-223 until evidence of radiographic progression, unequivocal clinical progression, unacceptable side effects, withdrawal of consent, or death as in the TOPARP study. For patients randomized to radium-223 alone, following completion of up to six doses of radium-223, patients will not receive any additional CRPC therapy and will be followed until evidence of radiographic progression, unequivocal clinical progression, unacceptable side effects, withdrawal of consent, or death as in the TOPARP study. Treatment will continue beyond PSA and ALP progression as encouraged by PCWG3 criteria.

Cross over will be allowed for patients randomized to radium-223 alone at time of radiographic progression. If patients have not yet received all six doses of radium-223, patients will be allowed to continue treatment with radium-223 to receive a total of six doses and olaparib. If all six doses of radium-223 have been received, then patient will receive single agent olaparib at time of cross-over. Optional progression tumor biopsy must take place prior to initiation of olaparib in patients who crossover.

2. BACKGROUND

2.1 Prostate Cancer

Prostate cancer is the most common solid organ malignancy in men and is the third leading cause of cancer related deaths in men. In the United States, an estimated 26,730 deaths per year are attributed to prostate cancer, and many of these occurred in patients with metastatic castration resistant prostate cancer (CRPC).(3) Data suggest that 10-20% of patients with metastatic prostate cancer develop CRPC within 5 years of follow-up and that median survival from the occurrence of castration resistance is approximately 14 months (range 9-30 months).(4, 5)

The backbone of systemic treatment for metastatic hormone sensitive prostate cancer androgen deprivation therapy (ADT) which suppresses circulating testosterone. Levels decline to the castrate range, which corresponds to a serum measurement of less than 50 ng/dL. In response, a decrease in cancer cell proliferation occurs with subsequent induction of apoptosis. However, despite the anti-proliferative response to ADT, cancer cells eventually develop resistance and most cases will manifest signs and/or symptoms of progression. At the point at which measurable progression of disease is present in the setting of castrate levels of testosterone, in the form of

either sequential rises in PSA or imaging findings, the term "castration resistant" prostate cancer is applied.

The management of metastatic CRPC has evolved over the past decade. Before 2010, the only agent shown to improve OS for patients with metastatic CRPC was docetaxel. More recently, several large randomized trials have led to the approval of multiple new agents for CRPC to include second generation hormonal agents, chemotherapy, immunotherapy, and also radiopharmaceuticals (Table 1). However, despite treatment, prolonged durable responses are limited and resistance ultimately develop. Thus, novel combinatorial and sequential treatment strategies are warranted to improve outcomes for patients.

Approach	Indications	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overall survival benefit
Abiraterone (6, 7)	Pre or post docetaxel	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 months Chemotherapy naive: 5.2 months
Enzalutamide (8, 9)	Pre or post docetaxel	Oral, daily	Not required	–	Seizures	Yes	4.8 months
Sipuleucel-T (10)	Pre or post docetaxel	IV, every 2 weeks x 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GMCSF; liver metastases	No	4.1 months
Docetaxel (11)	Metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 months
Cabazitaxel (12)	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 months
Radium-223 (13)	Symptomatic bone metastases with no known metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 months

2.2 Olaparib

Olaparib inhibits various isoforms of Poly(ADP-ribose)polymerase (PARP) (PARP-1, -2, -3) with an IC_{50}=1.94 nM. It has been shown to decrease *in vitro* and *in vivo* tumor growth in models of human cancer.(14) Furthermore, *in vitro* studies have demonstrated that olaparib-induced cytotoxicity involves trapping of PARP-DNA complexes preventing DNA repair, replication, and transcription resulting in cell death.(15)

A proof-of-concept clinical trial of olaparib, a potent oral inhibitor of PARP1 and PARP2, established 400 mg capsule formulation twice daily as the MTD.(16) Drug exposure increased proportionally with doses up to 100 mg twice daily, with less-marked increases above this threshold, and pharmacodynamics effects plateaued at doses >60 mg twice daily. However, further clinical trials in breast and ovarian *BRCA* mutated cancer suggested a dose–response relationship, supporting use of the MTD of olaparib over a minimal biologically effective dose.(17-19) In a randomized Phase II study in patients with platinum-sensitive recurrent ovarian cancer, olaparib maintenance therapy improved PFS and patients with *BRCA* mutations were most likely to benefit from treatment.(20, 21) In December 2014, the capsule formulation of olaparib received European Union and United States approval. To receive the approved 400 mg twice daily capsule dose, patients need to take 8 x 50 mg capsules twice daily. To improve dosing constraints of the capsule formulation, a meltextrusion tablet formulation with improved bioavailability was developed. An open-label, multicenter, multistage, Phase I trial compared the pharmacokinetics, efficacy and tolerability of different doses and scheduling of the olaparib capsule and tablet formulations to determine an optimal tablet dosing strategy for Phase III studies of olaparib.(22) Following multiple dosing, steady-state exposure with olaparib tablet 300 mg matched or exceeded that of the olaparib 400 mg capsule. Efficacy in relation to tumor shrinkage was similar between olaparib 300 and 400 mg tablet and 400 mg capsule doses; tolerability was better with olaparib 300 mg twice daily tablet formulation. The recommended monotherapy dose of olaparib tablet for Phase III trials was 300 mg twice daily, simplifying drug administration from 16 capsules to four tablets per day. Furthermore, a phase III trial in germline *BRCA* mutated, platinum-sensitive, relapsed ovarian cancer patients treated with olaparib tablets (300 mg twice daily) compared with placebo in the maintenance setting demonstrated a significant improvement in PFS.

The efficacy of olaparib has been investigated in prostate cancer in the TOPARP study.(23) In this single-center, single-arm, phase II study, patients with metastatic CRPC were treated with olaparib tablets 400 mg twice daily continuously. The primary endpoint was response rate, defined either as an objective response according to (RECIST version 1.1, at least 50% reduction in PSA level, or a confirmed reduction in the circulating tumor cell (CTC) count from ≥5 cells/7.5 mL blood to <5 cells/7.5 mL blood. Of the 50 patients enrolled, all had received prior docetaxel, 98% had received prior abiraterone or enzalutamide, and 58% had received prior cabazitaxel. 16 of 49 patients who could be evaluated had a response (33%) with 12 patients remaining on therapy for >6 months. Post hoc analysis to explore potential biomarkers of response in prospectively collected biopsies, demonstrated that 14 of 16 patients who were biomarker positive, demonstrated a response to single agent olaparib. With regards to safety, the grade 3-4

adverse events including anemia (20%), fatigue (12%), leukopenia (6%), thrombocytopenia (4%), neutropenia (4%). Overall, 13 patients (25%) required a dose reduction of olaparib to 300 mg twice daily and anemia was the most common indication for the dose reduction. 3/13 patients required a second dose reduction to 200 mg twice daily. Olaparib was permanently discontinued in 3 patients (6%) because of adverse events. These data support the hypothesis that tumors deficient in homologous recombination are susceptible to PARP inhibition. Additionally, the TOPARP study provides evidence for continuous dosing of olaparib. In this study, the starting dose of olaparib will be 200 mg twice daily with dose escalation to 300 mg twice daily and dose de-escalation to 100 mg twice daily.

In January 2016, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation for olaparib for the monotherapy treatment of *BRCA1/2* or *ATM* gene mutated metastatic CRPC in patients who have received a prior taxane-based chemotherapy and at least one newer hormonal agent (abiraterone or enzalutamide). This designation was based on the results of the above TOPARP-A Phase II trial.

Please refer to the currently olaparib investigators brochure for more information.

2.3 Radium-223

Radiopharmaceuticals have emerged as a treatment strategy for patients with CRPC and symptomatic bone metastases. These compounds are systemically administered agents that localize to sites of bone metastases and deliver focal radiation through β-emission (strontium-89, samarium-153) or α-emission (radium-223).(24) Strontium-89 and samarium-153 are currently used for the palliation of pain in patients with CRPC with symptomatic bone metastases. Despite the beneficial palliative effect observed with strontium-89 and samarium-153, these agents have had relatively limited clinical use, likely related to logistics of administration, myelotoxicity, availability of alternative treatment strategies, and other factors.

Radium-223 is a radioisotope that acts as a calcium-mimic with natural bone-seeking proclivity.(24) In contrast to β-particles, α-particles provide ionizing radiation in a more narrow range resulting in low myelotoxicity and they induce DNA double-strand breaks (DSB) leading to cancer cell death at all stages of the cell cycle.(25) The efficacy of radium-223 in metastatic CRPC was demonstrated in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial.(13) This phase III, double-blinded trial randomized 922 men with metastatic CRPC with bone metastases to radium-223 plus best supportive care or placebo plus best supportive care. Eligible patients had either received prior docetaxel or were unfit for docetaxel chemotherapy. Patients were randomized 2:1 to receive six injections of radium-223 (50 kBq/kg) at 4-week intervals. The phase II study of radium-223 tested four injections of radium-223 (50 kBq/kg).(26) Given limited toxicity and benefit related to duration of treatment, the treatment period was extended to six doses in the ALSYMPCA trial. The primary endpoint of the ALSYMPCA trial was OS. Updated analysis of 921 patients confirmed that radium-223 significantly improved OS (14.9 months versus 11.3 months, $p<0.001$). Additionally, radium223 prolonged to the time to first SSE (median 15.6 versus 9.8 months, $p=0.0037$).(27) The ALSYMPCA study also evaluated the benefit of radium-223 on patient reported outcomes and specifically used the

FACT-P questionnaire, a validated relevant tool used for assessing the health-related quality of life in men with prostate cancer.(28, 29) QOL data from ALSYMPCA demonstrated that improved survival with radium-223 is accompanied by significant QOL benefits, including a higher percentage of patients with meaningful QOL improvement and a slower decline in QOL over time in patients with CRPC.(30) With regards to safety, overall no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups. All grade anemia, thrombocytopenia and neutropenia were 31%, 12%, and 5% with radium-223 and no different when compared to placebo. Grade 3-5 hematologic adverse events, included anemia (13%), thrombocytopenia (6%), neutropenia (3%). The positive impact of radium-223 on OS in men with metastatic CRPC is a landmark development that may expand the utility of radiopharmaceuticals for this disease.

The activity of radium-223 can be measured in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST)-traceable radium-223 reference material. The NIST standard reference material, upon which NISTtraceable reference material is based, was re-evaluated in 2015. The results indicate that an approximately 10% difference exists between activity values obtained using the new standard (NIST 2015) and those obtained based on the former primary standardization published in 2010. The use of the updated NIST 2015-traceable reference material results in a numerical change of the labeled radioactivity of radium-223: an increase of the nominal value for the radioactivity from 1000 kBq/mL to 1100 kBq/mL and a corresponding increase in patient dose, from 50 kBq/kg body weight to 55 kBq/kg body weight (or an increase from 1.35 uCi (microcurie)/kg body weight to 1.49 uCi (microcurie)/kg body weight) However, the change does not reflect a change in the actual product radioactivity or in the amount of radioactivity given to the patient and therefore does not impact the safety and efficacy of radium-223. The dosing of radium-223 recommended in this study is 55 kBq/kg every 4 weeks x 6 doses.

2.4 Rationale

A common characteristic of radiation used in the clinical treatment of cancer is the induction of various types of DNA damage, including single-strand breaks (SSB) and DSB directly leading to tumor cell kill.(31) A key determinant of cell survival following radiation is the ability of tumor cells to repair DNA damage through efficient and faithful repair mechanisms. PARP-1 can be inhibited pharmacologically by PARP inhibitors (PARPi). By combining radiation with PARPi, the SSB induced by radiation go unrepaired by PARP-associated base-excision repair, leading to cell death and delay in tumor growth.(32) Preclinical studies have demonstrated that the ratio of SSB/DSB from alpha emitters is on the order of 0.5-8.(33, 34) Unfortunately, no preclinical studies have been conducted with the combination of radium-223 and olaparib.

In vitro studies in several different cancer models have confirmed the synergistic effects of PARP inhibition and radiation therapy.(32) Lui and colleagues demonstrated the ability of the PARPi veliparib to radiosensitize human prostate and non-small cell lung cancer cells under euoxic and hypoxic conditions.(35) Additionally, Schiewer and colleagues demonstrated similar effects with veliparib in both hormone sensitive and CRPC cells exposed to genotoxic insult with ionizing radiation and docetaxel in a dose dependent manner.(36) Furthermore, a growing body of

evidence has demonstrated the *in vivo* activity of PARPi combined with radiation.(32) Studies in head and neck, colon, lung, and glioblastoma xenograft models have demonstrated the antitumor activity of combination radiation therapy and PARPi compared to radiation therapy alone.(37-40) Given encouraging preclinical data, clinical studies are currently underway exploring the safety and efficacy of the combination of PARPi with radiation therapy in several cancer types including breast, esophageal, head and neck, and lung cancer. Though limited studies have been completed and reported, the safety of veliparib and low-dose fractionated whole abdominal radiation therapy in patients with peritoneal carcinomatosis was demonstrated in a phase I study of escalating doses of veliparib.(41) These data highlight the role of PARPi as radiosensitizing agents and provide the rationale for combining olaparib with radium-223 in men with metastatic CRPC.

Summary of Phase 1 Results:

The phase 1 enrolled a total of 12 subjects from 2/2019 – 8/2020. Initially 3 patients were allocated to dose level 1. There were no DLTs or dose reductions and therefore the study proceeded to dose level 2. There were 6 subjects enrolled at dose level 2. While there were no DLTs in the 6 subjects enrolled at dose level 2, five of six subjects required dose reductions and reasons for dose reductions were listed below:

○ Patient 4 – Start cycle 7. Grade 2 nausea. ○ Patient 5 – Start cycle 4. Grade 2 neutropenia. ○ Patient 6 – Start cycle 3. Grade 2 fatigue and grade 2 nausea. ○ Patient 7 – Mid cycle 2. Grade 3 anemia (not classified as a DLT). ○ Patient 8 – Start cycle 3. Grade 2 neutropenia.

After review by study safety committee, the decision was made that dose level 2 (300 mg by mouth twice daily) was not the optimal dose and the phase 1 would continue with enrollment of another 3 subject at dose level 1 for a total of 6 subjects to dose level 1. After all subjects completed the two month DLT window, safety analysis was performed for those subjects on dose level 1. There were no DLTs observed and no patient required a dose modification of therapy.

To summarize the treatment related adverse events, 10/12 (83%) of subjects had any grade treatment related adverse events (5 in dose level 1; 5 in dose level 2). Four of 12 patients (33%) had grade 3-4 treatment related adverse events. AT dose level 1, two subjects experienced grade 3 anemia that was not classified as a dose limiting toxicity. At dose level 2, 1 subject had grade 3 anemia and grade 4 lymphocyte count decrease and 1 subject had a grade 3 stroke. There were no grade events.

After review of all the safety data for the phase 1 study, the recommended phase 2 dosing of olaparib was 200 mg by mouth twice daily when combine with radium-223 and recommend radium-223 dosing remains fixed at 55 kBq/kg.

Summary of Rationale for Combination of Olaparib and Radium-223:

1. Radium-223 is an α-emitting radioisotope which induces DNA DSBs leading to cell death and has demonstrated improvement in OS in men with metastatic CRPC.
2. PARPi, which prevent repair of SSBs inducted by ionizing radiation, have demonstrated efficacy as radiosensitizing agents in preclinical models.

3. Approximately 30% of patients with advanced metastatic CRPC harbor mutations in the DNA repair pathway.
4. Olaparib has demonstrated anti-tumor activity in advanced metastatic CRPC patients harboring mutations in the DNA repair pathway and there is rationale for use in CRPC given crosstalk between the AR pathway and DNA repair pathway.

Therefore, the combination of radium-223 with olaparib may demonstrate anti-tumor activity in patients with metastatic CRPC irrespective of underlying homologous recombination deficiency status.

2.5 Correlative Studies Background

In this study, patients will undergo next generation sequencing of metastatic prostate tumors to evaluate for aberrations in the DNA repair pathway. Tumor tissue will be subjected to Oncopanel testing to evaluate the presence of homologous recombination deficiency as defined by the presence of homologous deletion AND/OR putative deleterious mutation in a gene reported to be involved in homologous recombination DNA repair. Oncopanel surveys exonic DNA sequencing of >400 cancer genes and analyzes mutations in >100 DNA repair genes including *BRCA1, BRCA2, CHK2, FANCA, FANCC, FANCD2, FANCF, FANCG, ATM, RAD54,* and *PALB2*.(42)
Outcomes of patients will be evaluated based on the presence or abscess of homologous recombination deficiency as determined by Oncopanel testing. Additionally, WES and WTS will be performed on tumor tissue and in order to perform this analysis WES will also be performed on germline DNA. Lastly, the tumor immunologic microenvironment will be characterized via assessment of tumor infiltrating lymphocytes and expression of co-stimulatory and co-inhibitory molecules.

In addition to tumor tissue, whole blood will be collected at baseline and on treatment at predefined intervals to perform next-generation sequencing on plasma derived cfDNA to establish baseline tumor signature for response assessment, to assess cfDNA-based microsatellite instability (MSI) status, TMB, mutational signatures, and to assess early response prediction with Foundation Medicine Inc. (FMI) proprietary bioinformatics algorithm.

Aberration in the DNA Repair Pathway in Prostate Cancer:
To provide a systematic analysis of the genomic landscape of CRPC and its potential relevance for patient care, the Stand Up To Cancer (SU2C)-Prostate Cancer Foundation (PCF) International Dream Team pursued WES and WTS of 150 biopsies from metastatic CRPC. Compelling data from this comprehensive analysis identified that aberrations in *BRCA2*, *BRCA1*, and *ATM* were observed in 19.3% of individuals overall, including 5.3% (8 of 150) harboring germline *BRCA2* mutations with a subsequent somatic event resulting in bi-allelic loss.(43) Aberrations in an expanded set of DNA repair genes were identified in at least 34 of 150 patients (22.7%). Interestingly, the type and frequency of these mutations was not found in The Cancer Genome Atlas analysis of primary prostate cancers, suggesting that selection for these defects occurs either during the development of castration resistance and/or the process of metastasis.(44) Additionally, data from a phase II study (TOPARP) evaluating the efficacy of olaparib in patients with metastatic CRPC reported that next-generation sequencing identified homozygous deletions,

deleterious mutations, or both in DNA repair genes (including *BRCA1*, *BRCA2*, *ATM*, Fanconi's anemia genes, and *CHEK2*) in 33% of patients (16 of 49).(23)

Furthermore, recently Pritchard and colleagues reported on the germline DNA analysis of 692 men with documented metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis.(45) Germline DNA was isolated and multiplex sequencing assays were used to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes. These genes included: *ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, cHek2, FAM17A, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, XRCC2*. A total of 84 germline DNA-repair gene mutations that were presumed to be deleterious were identified in 82 men (11.8%); mutations were found in 16 genes, including *BRCA2* (37 men [5.3%]), *ATM* (11 [1.6%]), *CHEK2* (10 [1.9% of 534 men with data]), *BRCA1* (6 [0.9%]), *RAD51D* (3 [0.4%]), and *PALB2* (3 [0.4%]). Mutation frequencies did not differ according to whether a family history of prostate cancer was present or according to age at diagnosis. Overall, the frequency of germline mutations in DNA-repair genes among men with metastatic prostate cancer significantly exceeded the prevalence of 4.6% among 499 men with localized prostate cancer ($P<0.001$), including men with high-risk disease. These data highlight the increased prevalence of both germline and somatic DNA repair aberrations in men with CRPC.

Crosstalk between the AR pathway and DNA Repair Pathway in Prostate Cancer: A growing body of evidence has revealed that DNA repair extends beyond the canonical signaling pathways to include crosstalk with the AR.(36, 46) PARP is a multifunctional enzyme which has a well-characterized role in single-strand DNA repair.(47) Schiewer and colleagues demonstrate that PARP-1 is recruited to sites of AR action and PARP-1 enzymatic activity is critical for AR function in hormone sensitive and castration resistant prostate cells.(36) In models of advanced CRPC, studies demonstrate that PARP-1 activity is enhanced.(36) Furthermore, *in vivo* studies demonstrate that ablation of PARP-1 activity is sufficient to suppress AR function, decrease tumor growth, and delay the onset of castration resistance.(36) These data highlight the dual functions of PARP-1 in DNA damage repair and transcription factor regulation. Taken together, targeting of PARP-1 can be leveraged to suppress critical pathways in prostate cancer cell survival and progression. These data provide rationale for PARP inhibition in unselected patients with CRPC. Additionally, these data provide rationale for continuous dosing of olaparib in men with CRPC.

Immunomodulatory Effects of Radium-223:
Despite the confirmed efficacy of radium-223 in CRPC, resistance is universal. Novel tolerable combinations are imperative to improve outcomes in CRPC. The last several years have witnessed a resurgence of interest in mobilizing the immune system to combat cancer. The programmed death (PD) PD-1 pathway is a promising target. PD-1 is an inhibitory receptor expressed on activated T and B lymphocytes. It regulates T cell antigen-specific signaling and modulates T cell activation, inactivation, and survival.[28] Interaction with its two known ligands, PD-L1 and PD-L2, inhibit T cell activation, apoptosis, and memory responses.[29, 30] Tumor cells can express PD-L1 and other immune-inhibitory ligands, which may attenuate the effects of antitumor cytotoxic T cells and stymie production of essential immune stimulating

cytokines.[31-33] PD-L1 may be constitutively expressed on tumor cells or can arise as a consequence of adaptive immunity in response to stressors such as the cytotoxic interferon-γ secreted by TILs in the tumor microenvironment and treatment with other anticancer agents.[3440] It is hypothesized that tumor cell killing with radium-223 will release tumor-associated antigens (TAAs). Dendritic cells will take up these antigens, process them, and present them to naïve T cells. These T cells will mature into tumor-specific effector cells that will proliferate and ultimately hone in on the cancer. The addition of PD-1 blockade may reverse any potential anergy of these PD-1+ infiltrating anti-tumor immune cells. Tumor heterogeneity and the dynamic nature of PD-L1 expression on tumor cells and PD-1 and PD-L1 expression on immune cells in the tumor microenvironment provides further rationale for this approach even in the absence of high PD-L1 expression upfront. Theoretically, if the TAAs released by radiuminduced tumor killing stimulate higher numbers of tumor specific T cells, this may induce adaptive upregulation of PD-L1 by the tumor in response to IFN-γ secreted by these cells. The immunomodulatory effects of radium-223 and potential for combinatorial treatment strategies of radium-223 with PD-1 pathway blocking agents provides rationale for assessment of the immune response in the tumor microenvironment.

DNA Damage Response and the Immune System:
A tight interplay exists between the DNA damage response and immune signaling. Initially, Studies have shown that triggering of DNA damage response apical kinases ATM and ATR leads to transcriptional upregulation of natural-killer group 2, member D (NKG2D) ligands in both normal cells as well as malignant cells.(48-51) NKG2D is an activating immune receptor initially identified in natural killer (NK) cells, but is also expressed in humans by all CD8+ T cells, and subsets of γδ+ T cells as a co-stimulatory receptor. Several lines of evidence suggest that NKG2D ligand expression is related with tumor surveillance.(52, 53) Human tumors overexpressing NKG2D ligands are more sensitive to recognition and killing by NK cells and activated T-cells.(49) Additionally, the persistent activation of the DNA damage response favors the secretion of inflammatory cytokines, including IL-6 and IL-8.(54)

Mutational Load and the Immune System:
The seminal work by Alexandrov *et al* has indicated a great variability in the prevalence of somatic mutations among neoplasms ranging from 0.001 per megabase to more than 400 mutations per megabase.(55) Theoretically, these mutations may create peptide epitopes— normally absent from the human genome—that are presented by the major histocompatibility complex (MHC) on the surface of malignant cells. Subsequent recognition of these epitopes by T lymphocytes in the tumor environment facilitates rejection of the malignant cells by the immune system. These peptides are called neoantigens.

Therefore, in malignancies with increased mutation load, there is an increased likelihood that more neoantigens will be present and thus increased likelihood of response to immunotherapeutic approaches. Established immunotherapeutic agents—anti- cytotoxic Tlymphocyte-associated protein 4 (CTLA-4) and anti-PD-1 antibodies—have shown greater efficacy in malignancies with higher mutational burden, namely melanoma and non-small cell lung carcinomas.(56-61)

Additionally, patients with tumors characterized from microsatellite instability have excellent response to immune checkpoint inhibitors.(57). In this study, patients were treated with the anti-PD1 antibody pembrolizumab and the response to treatment was statistically significantly associated with the mutational load.(57) Analogous conclusions were drawn for melanoma patients that were treated with the anti-CTLA4 antibody ipilimumab(62) and non-small cell lung carcinoma patients treated with pembrolizumab(63). In both these studies the quantity of predicted neoantigen epitopes was also correlated with the number of nonsynonymous mutations per tumor.

cfDNA WGS for early response prediction, MSI status, mutational load and signatures:
Foundation Medicine, Inc. (FMI) has been developing a next generation sequencing-based WGS assay of cfDNA from blood collected at baseline and 3-4 weeks into treatment to predict response to treatment. Initial studies in a cohort of patients with mainly advanced stage breast and non-small cell lung cancer starting on a new treatment regimen (immune checkpoint inhibitor with and without chemotherapy, chemotherapy, targeted or endocrine therapy) show that the assay predicts with high specificity (>95%) the progression >4 weeks before imaging.(64)

In addition, FMI platform allows for exploring whether the MSI status, TMB and mutational signature of tumor tissue can be captured in plasma cfDNA at baseline. High MSI and TMB and some mutational signatures show correlation to better response to immune checkpoint inhibitors and determining these features in cfDNA from plasma will provide a more convenient and dynamic assessment.(65)

2.5.1 Oncopanel – Dr. Neal Lindeman, Brigham and Women's Hospital, Integrated Biomarker

Sample will be analyzed using OncoPanel, a CLIA certified, next-generation sequencing test that examines over 400 genomic loci for single nucleotide variants, small insertions or deletions, and copy number variants (Appendix A) as previously described.(66) OncoPanel achieved 98% sensitivity and 100% specificity for the detection of single-nucleotide variants, and 84% sensitivity and 100% specificity for the detection of insertions and deletions compared with single-gene assays and mass spectrometry–based genotyping. Copy number detection achieved 86% sensitivity and 98% specificity compared with array comparative genomic hybridization.
The sensitivity of structural variant detection was 74% compared with karyotype, fluorescence in situ hybridization, and polymerase chain reaction. Sensitivity was affected by inconsistency in the detection of FLT3 and NPM1 alterations and IGH rearrangements due to design limitations.
Limit of detection studies demonstrated 98.4% concordance across triplicate runs for variants with allele fraction greater than 0.1 and at least 50× coverage.

Samples are aligned using the PICARD pipeline (http://broadinstitute.github.io/picard/commandline-overview.html) to GRCh37p13. Mutect20,21 and indelocator (http://www.broadinstitute.org/cancer/cga/indelocator) were used to call single nucleotide variations and insertions/deletions, respectfully.

As tumor DNA was tested without paired germline DNA, additional informatics steps are taken to remove common single nucleotide polymorphisms (SNPs). SNP are removed if they were present at >0.1% in Exome Variant Server, NHLBI GO Exome Sequencing Project (https://esp.gs.washington.edu/drupal/), or present in dbSNP and appeared less than two times in Cosmic. Following computational filtering, manual mutation review was performed by a molecular pathologist accounting for tumor purity, ploidy and estimated allele fraction at each site, along with contextual information such as tumor type.

Copy number changes based on log2 ratios were calculated using a normalized depth of coverage against a median from a panel of normal (non-cancer) samples.

Fresh tumor biopsy collected at study entry will be utilized for Oncopanel testing. If tumor not evaluable, archival tissue will be utilized for analysis for exploratory purposes.

2.5.2 Whole Exome/Transcriptome Sequencing – Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Exploratory Biomarkers

The Molecular Characterization Laboratory (MoCha) is a CLIA-certified laboratory and part of the Cancer Diagnosis Program (CDP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute operating at Frederick National Laboratory for Cancer Research. MoCha is responsible for performing genetic sequencing and gene expression profiling.

Sequencing is performed utilizing the Illumina HiSeq 2500, is an ultra-high-throughput sequencing system that allows RNA and whole exome sequencing of samples using Illumina's SBS (sequencing by synthesis) technology. Samples are sequenced using the HiSeq v4 high output run parameters.

The Standard Operating Procedures for sequencing of Libraries on the Illuminia HiSeq 2500 at MoCha Laboratory are described in the ETCTN Biospecimen Workflow Laboratory Manual: https://ctep.cancer.gov/protocolDevelopment/docs/ETCTN_BMCI_Lab_Manual.pdf

2.5.3 Immune Sequencing of Peripheral T-cell and B-Cell Receptor to Profile Immune Response – Dr. Christina Jamieson/University of California, San Diego, Exploratory Biomarker

Peripheral Blood Mononuclear Cell Phenotyping:
Multicolor flow cytometry analysis will be performed on cryopreserved peripheral blood mononuclear cells (PBMC) as previously described.(67) Specimens will be collected on the first 52 patients enrolled on the phase 2.

PBMCs will be stained for 30 minutes at 4°C with CD3-V450, CD8-FITC or APC, HLA-DRPerCPCy5.5, CD25-PECy7, CD45RA-PerCP-Cy5.5, CD62L-FITC, CD127-V450, CCR7-PECy7, Tim-3-AF700, CD4-APC-Cy7, CTLA-4-FITC, and FOXP3-APC (BD Biosciences). For NK cells, CD3-V450, CD16-APC-Cy7, and CD56-PE-Cy7 were used. For myeloid-derived suppressor cells (MDSC), CD33-PE, CD11b-APC-Cy7, HLA-DR-PerCP-Cy5.5, CD14-V450, and CD15-APC will be used.

FACS data recording and analysis will be performed in the University of California Moores Cancer Center Flow Cytometry Shared Resource and operated by Dennis Young, Technical Specialist. A total of 1×10^5 cells will be acquired on FACS Aria, a triple-laser, multiparameter flow cytometer using up to 11-color fluorescence signals, along with forward and side-angle light scatter https://healthsciences.ucsd.edu/research/moores/shared-resources/flowcytometry/Pages/service-details.aspx. Data will be analyzed using FlowJo software (Tree Star Inc.). The appropriate isotype controls will be used, and dead cells will be excluded from the analysis.

Peripheral T-cell and B-Cell Receptor Sequencing:

The adaptive immune system uses imprecise somatic DNA recombination to generate a rich and diverse array of antigen-specific receptors on BCR and TCR. The TCR protein is a heterodimer composed of an α chain and a β chain. TCR genes undergo somatic DNA rearrangements to generate the diversity of T cell binding specificities needed for effective immunity. Rapid advances in high-throughput DNA sequencing over past decades have opened the way for increasingly robust and extensive BCR and TCR repertoire studies.

We will be performing TCR and BCR immunosequencing at The Jamieson Laboratory at The University of San Diego. The amplification and sequencing of the BCR and TCR repertoire will be performed using Adaptive Biotechnologies as previously described.(68)

There is potential for combinatorial treatment with radium-223, olaparib, and a checkpoint inhibitor. In this work, we will characterize the TCR and BCR to evaluate the anti-tumor immune response. We will evaluate the presence of an exhausted or activated immune response to inform the utility of adding checkpoint inhibition to the combination.

Additionally, RNA will be extracted from whole blood in The Jamieson Laboratory at the University of California San Diego using the Illumina Globin-Zero Gold Kit (https://www.illumina.com/content/dam/illuminamarketing/documents/products/appnotes/globin-zero-application-note-770-2014-049.pdf) . RNA sequencing will be performed at the University of California San Diego Institute Genomic Medicine Genomics Core.

2.5.4 cfDNA Assay – Foundation Medicine, Inc. (FMI), San Diego, CA

Samples will be processed and analyzed in FMI's laboratory in San Diego, CA. Whole blood will be collected in two 10 ml Streck tubes supplied by FMI in a collection kit at baseline (prior to treatment start), cycle 2/day 1, cycle 4/day 1 and every 12 weeks thereafter corresponding to imaging assessment timepoints. Samples will be shipped at ambient temperature to FMI within 24 to 72 hours from time of collection. Whole blood will be separated to plasma and buffy coat with centrifugation, buffy coat will be frozen at -80c, plasma will undergo DNA extraction and DNA will be stored at -20c. In batches, libraries will be created and sequenced on Novaseq 6000 up to a depth of 40x.

Bioinformatics pipeline will be applied to the sequence data for quality control evaluation, alignment, whole genome feature extraction and at baseline establishing the "tumor signature" that will be used in follow-up to calculate response prediction. In addition, the baseline sequence data will be used to explore the determination of MSI status, TMB and mutational signature in cfDNA and correlating to data from tumor tissue.

2.5.5 RAD51 Assay – Center for DNA Damage and Repair, Dana-Farber Cancer Institute, Exploratory Biomarker

Homologous recombination mediated DNA damage repair is a pathway that repairs DNA double strand breaks with high accuracy and is predominantly active during replication i.e. the S-phase of the cell cycle. Homologous recombination is a multi-step process a key step in the pathway is the generation of single stranded DNA at double-strand breaks by nucleases. The singlestranded DNA thus generated is initially coated by hetero-trimeric replication protein A (RPA) complexes that protect this highly vulnerable single-stranded DNA. RPA is next exchanged for RAD51 by a process that involves BRCA2 among other proteins. Multiple molecules of RAD51 are deposited on the single stranded DNA resulting in the formation of a proteo-nucleo filament. These filaments can be detected as sub-nuclear foci using antibodies specific to RAD51. Presence of RAD51 sub-nuclear foci is a surrogate functional measure of HR proficiency of the tumor sample.

The Center for DNA Damage and Repair at Dana-Farber Cancer Institute in Boston MA has developed an immunohistochemistry based assay that can identify RAD51-foci in cryo-sections or sections of Formalin-fixed paraffin embedded tumor biopsies.

PDX model	Subtype	BRCA_status	Cycles_chemo	HR_status by RAD51	Olaparib_response
DF09	HGSOC	wild type	0	Proficient	resistant
DF14	HGSOC	wild type	5	Proficient	resistant
DF20	HGSOC	wild type	0	Proficient	resistant
DF59	HGSOC	BRCA1 5385InsC	7	Proficient	resistant
DF68	HGSOC	BRCA1 Q563X	5	Proficient	resistant
DF83	HGSOC	wild type	4	Deficient	sensitive
DF86	HGSOC	BRCA1 del exons 21-214	5	Proficient	resistant
DF101	HGSOC	BRCA1 187delAG	2	Proficient	resistant
DF106	HGSOC	wild type	1	Proficient	resistant
DF118	HGSOC	wild type	1	Proficient	resistant
DF149	HGSOC	wild type	0	Proficient	resistant
DF172	Mixed	wild type	2	Proficient	resistant
DF181	HGSOC	wild type	7	Proficient	resistant
DF216	Adenocarcinoma	wild type	2	Proficient	resistant

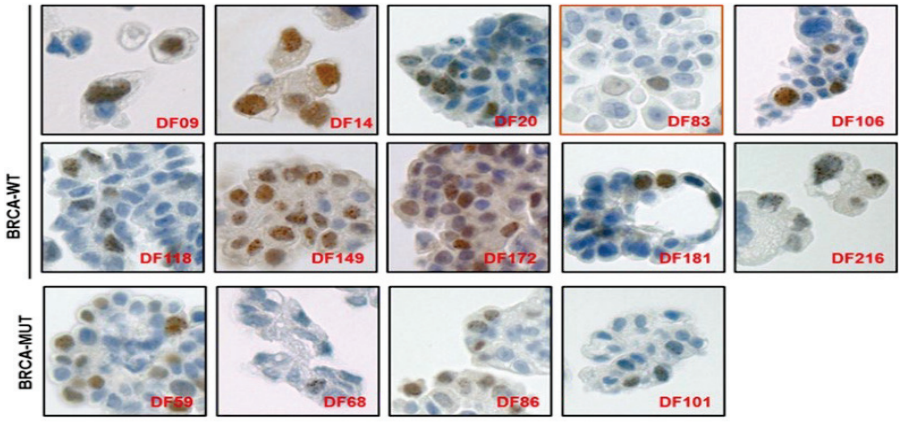


Figure 1. Presence of RAD51 foci tracks with PARP inhibitor response in ovarian cancer models. Sensitivity to olaparib, a PARP inhibitor, and the presence of RAD51 foci was determined in a cohort of 14 PDX models derived from ovarian cancers. Characteristics of eadch PDX model are shown in the table and images of RAD51 in the FFPE sections of ascitesderived cells is shown. Note that DF83 is the only model that was sensitive to olaparib, and this model lacks RAD51 foci

Multiple studies have established the synthetic-lethal relationship between homologous recombination

deficiency and sensitivity to inhibitors of PARP. Therefore, presence of RAD51foci is expected to correlate with PARP inhibitor resistance. Conditions for the assay have been developed and validated in a panel of 14 patient-derived xenograft models of high-grade serous ovarian cancer, where 10 samples were BRCA1/2 wild-type and 4 samples carried mutations in BRCA1.

In-vivo testing of Olaparib response of these models showed that 13 models were resistant to Olaparib, including the BRCA1 mutant models, while a BRCA1/2 wild-type model, DF83, was sensitive. Genomic analysis of DF83 revealed that the promoter of another HR pathway gene, RAD51C, was hyper-methylated resulting in HR-deficiency and PARP inhibitor sensitivity. In correlation with PARP inhibitor response, all models except DF83 had sub-nuclear RAD51-foci (Figure 1).

The RAD51 stains and Geminin stains (that constitute the RAD51-assay) work equally well on the control cell line (MDAMB468, irradiated and unirradiated) embedded in OCT (Figure 2).

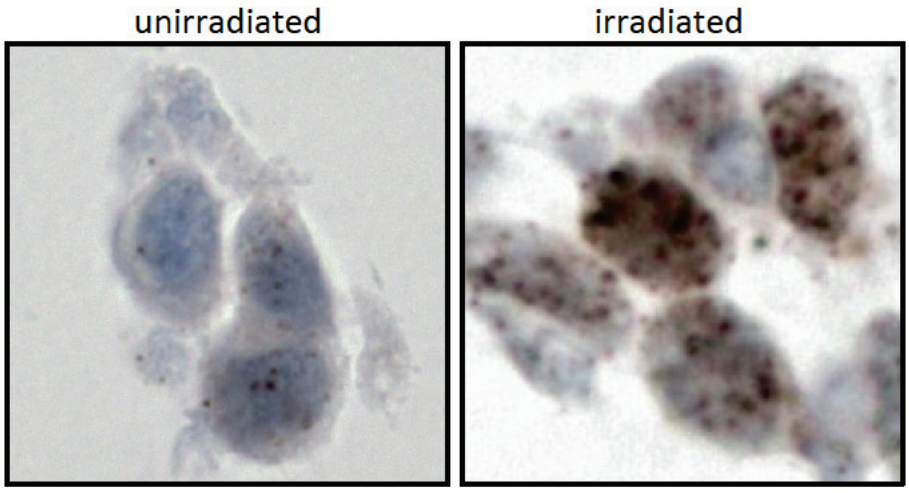


Figure 2: Cultures of unirradiated and irradiated MDA-MB-468 cells were collected 3 hour post irradiation, washed in saline and embedded in histogel. The histogel cores were frozen in OCT and cryo-sectioned. Sections were fixed in 10% normal buffered formalin and rinsed in saline prior to staining using the standardized RAD51 IHC protocol (the de-paraffinization and rehydration steps were not performed).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must be male aged ≥ 18 years of age.

3.1.2 Participants must have histologically or cytologically confirmed adenocarcinoma of the prostate.

3.1.3 Participants must have castrate levels of serum testosterone < 50 ng/dL.

3.1.4 Participants without orchiectomy must be maintained on luteinizing hormone releasing hormone (LHRH) agonist/antagonist. Participants receiving prior docetaxel, abiraterone,

or next generation AR antagonist (enzalutamide, apalutamide, or darolutamide) for hormone sensitive disease are permitted.

3.1.5 Participants must have progressive disease as defined by any of the following:
- Castrate resistant disease as defined by PCWG-3 criteria. Participants must have a rise in PSA on two successive determination at least one week apart and PSA levels ≥ 2 ng/mL (only the screening PS needs to be ≥ 2 ng/mL) and serum testosterone < 50 ng/dL.
- Soft tissue progression as defined by RECIST version 1.1.
- Bone disease progression as defined by PCWG-3 criteria including the development of two or more new lesions on bone scan.

3.1.6 Participants must have ≥2 bone metastases by radiographic imaging and at least 1 lesion which has not been treated with prior radiation therapy.

3.1.7 Participants must have tumor accessible for biopsy and be agreeable to baseline tumor biopsy. A metastatic focus is preferred but if not available and prostate is still intact prostate biopsy can be performed.

3.1.8 Availability at the study site of formalin-fixed, paraffin-embedded (FFPE) archival tumor specimens, when available.

3.1.9 ECOG performance status ≤1 (Karnofsky ≥80%, see Appendix B).

3.1.10 Patients must have normal organ and marrow function measured within 28 days prior to administration of study treatment as defined below:
- White blood cell count (WBC) ≥3,000/mcL.
- Absolute neutrophil count (ANC) ≥1,500/mcL.
- Platelets ≥100,000/mcL.
- Hemoglobin ≥10 g/dL (transfusions permitted).
- Total bilirubin ≤1.5 x the institutional upper limit of normal (ULN). For subjects with Gilbert's disease ≤ 3.0 mg/dL.
- Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤3 x institutional ULN.
- Creatinine clearance ≥ 51 ml/min as defined by Cockcroft-Gault equation.

3.1.11 Participants should be receiving an osteoclast targeting agent including either bisphosphonates or denosumab except in patients with contraindications as determined by the treating investigator including:
- Hypocalcemia
- Hypophosphatemia
- Renal impairment including those with a glomerular filtration rate < 35 mL/min using the Cockcroft-Gault equation
- Hypersensitivity to drug formulation

– Dental condition or need for dental intervention that per the investigator would increase the risk of osteonecrosis of the jaw

Use of osteoclast targeted therapy or reason against use needs to be recorded in the electronic case report forms (eCRF). Additionally reason for discontinuation of osteoclast targeted therapy needs to be appropriately documented in the eCRF.

3.1.12 The effects of olaparib and radium-223 on the developing human fetus are unknown. For this reason, men treated or enrolled on this protocol must agree to use two highly effective forms of contraception and avoid sperm donation prior to the study, for the duration of study participation, and six months after discontinuation of olaparib and radium-223 administration.

3.1.13 HIV-positive with negative viral loads on stable antiretroviral regimen and CD4 count >250 are eligible.

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making who have a legal guardian (e.g., spouse) able to make informed decisions on behalf of the patient are eligible.

3.1.15 Patients must be able to tolerate oral medications by mouth and not have a gastrointestinal illness that would preclude absorption of olaparib.

3.2 Exclusion Criteria

3.2.1 Pathology consistent with small cell carcinoma of the prostate.

3.2.2 Presence of visceral metastases (liver, lung, brain, etc.) or malignant lymphadenopathy exceeding 4 cm in short diameter.

3.2.3 Prior treatment with radium-223.

3.2.4 Prior treatment with olaparib or other PARPi.

3.2.5 Treatment with abiraterone, apalutamide, or darolutamide within 2 weeks of treatment initiation. Treatment with cytotoxic chemotherapy within 3 weeks of treatment initiation. Treatment with investigational prostate cancer directed therapy within 4 weeks of treatment initiation. Treatment with enzalutamide within 4 weeks of treatment initiation.

3.2.6 Prior hemibody external radiotherapy.

3.2.7 Palliative radiation therapy to the bone or other sites within 2 weeks of treatment initiation.

3.2.8 Participants who are receiving any other investigational agents.

3.2.9 Imminent or established spinal cord compression based on clinical and/or imaging findings.

3.2.10 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring need for intravenous anti-microbials, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Clinically significant medical condition defined as:

- Cerebral infarction within 6 months of study treatment.
- Transient ischemic attack within 3 months of study treatment.
- Myocardial infarction within 6 months of study treatment.
- Uncontrolled angina within 3 months of study treatment.
- Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months of the screening visit results in a left ventricular ejection fraction that is ≥ 45%.
- History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).
- Prolonged corrected QT interval by the Fridericia correction formula on the screening electrocardiogram (ECG) > 470 msec (as determined on 2 or more time points within a 24 hour period if the first ECG demonstrates a prolonged corrected QT interval) or family history of long QT syndrome.
- History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
- Uncontrolled hypertension as indicated by a resting systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at the screening visit.
- History of hypertensive emergency or encephalopathy within 6 months of study treatment.
- Deep venous thrombosis or pulmonary embolism within 3 months of study treatment.

3.2.12 Major surgery within 4 weeks of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

3.2.13 History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.

3.2.14 Patient unable to swallow orally administered medication.

3.2.15 History of bowel obstruction within 1 month of study treatment.

3.2.16 History of abdominal fistula, intra-abdominal abscess, or gastrointestinal perforation within the 3 months of study treatment.

3.2.17 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib or radium-223.

3.2.18 Participants receiving strong CYP3A4/5 inducers or inhibitors are ineligible. Dihydropyridine calcium-channel blockers are permitted for management of hypertension. The required washout period prior to starting olaparib is 2 weeks for CYP3A inhibitors. The required washout period prior to starting olaparib is 4 weeks for enzalutamide or phenobarbital and 3 weeks for other CYP3A inducers.

3.2.19 Patients with known active hepatitis (i.e. hepatitis B or C) infection.

3.2.20 Patients with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML.

3.2.21 Patient having received prior allogenic bone marrow transplant or double umbilical cord blood transplantation.

3.2.22 Individuals with a history of a different malignancy are ineligible except for the following circumstances: 1) individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years and are deemed by the investigator to be at low risk for recurrence of that malignancy, or 2) individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: superficial bladder cancer, basal cell or squamous cell carcinoma of the skin.

3.3 Inclusion of Women and Minorities

Women are not eligible for this study given that women anatomically lack a prostate. Every effort will be made to include men from minority populations. The enrollment of minority men will reflect the proportion of minority participants at the sites participating in the trial.

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0

Asian	0	7	0	2	9
Native Hawaiian or Other Pacific Islander	0	3	0	1	4
Black or African American	0	5	0	2	7
White	0	60	0	13	73
More Than One Race	0	5	0	2	7
Total	0	80	0	20	100

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	7	0	2	9
Native Hawaiian or Other Pacific Islander	0	3	0	1	4
Black or African American	0	5	0	2	7
White	0	60	0	13	73
More Than One Race	0	5	0	2	7
Total	0	80	0	20	100

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and • Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO), and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of the screen ○ Enter the protocol number in the search field at the top of the protocol tree, or ○ Click on the By Lead Organization folder to expand, then select LAO-CT018, and protocol number 10096,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For #10096 Site Registration:

- ETCTN Specimen Tracking Training ○ All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal. ○ The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking system may require new training. ○ This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com), Theradex phone: 609-799-7580.
- A Site Initiation Visit will need to be completed before the first patient is enrolled at a given site. Please contact the PI, Rana McKay, at rmckay@ucsd.edu to schedule the Site Initiation Visit at your site. Contact information for

Participating Site study personnel including site PI will need to be provided for coordination of study teleconferences.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

Site's registration status may be verified on the CTSU website.

- Click on Regulatory at the top of the screen,
- Click on Site Registration, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web

Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

4.3.2 Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

Patient has met all eligibility criteria within the protocol stated timeframes, and

All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Two stratification factors will be utilized as part of randomization including: prior docetaxel status (either for CRPC or hormone sensitive disease yes/no) and disease extent (≤20 or >20 bone lesions on radionuclide bone scan).

4.3.3 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

The following information will be requested:

- Protocol Number
- Investigator Identification ○ Institution and affiliate name ○ Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
    - ○ Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but**

not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Sites should reserve participant slots prior to enrollment via Open/IWRS and pending availability of slots will receive confirmation that the participant slot has been approved. Enrollment can only preceded following approval of reserved participant slot.

Following registration, patients should begin protocol treatment within 14 days. Biopsy should be performed following confirmation of eligibility prior to initiation of protocol therapy. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Project Manager should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

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. Administration of LHRH agonist/antagonists is required in patients not having undergone bilateral orchiectomy.

Phase 1:

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Radium-223	None	55 kBq/kg	IV	Day 1 (+/-7 days) of Cycle 1-6*	28 Days

Olaparib	Take with or without food. Tablets should be taken whole. Do not crush, chew or dissolve tablets.	For Phase 1 dosing is as per dose escalation schema below.	Oral	Twice Daily (continuous dosing)	
*After completion or discontinuation of radium-223 therapy, participants in phase 1 will continue treatment with olaparib monotherapy.					

Phase 1 Olaparib Dosing Schema:

Dose Level	Radium-223	Olaparib	Cycle Length
-2	Fixed dose at 55 kBq/kg every 4 weeks (+/- 7 days) x 6 maximum cycles	100 mg by mouth twice daily, continuously	28 Days
-1		150 mg by mouth twice daily, continuously	
1: Starting dose level		200 mg by mouth twice daily, continuously	
2		300 mg by mouth twice daily, continuously	

Phase 2 Arm A:

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Radium-223	None	55 kBq/kg	IV	Day 1 (+/-7 days) of Cycle 1-6*	28 days
Olaparib	Take with or without food. Tablets should be taken whole. Do not crush, chew or dissolve tablets.	200 mg by mouth twice daily, continuously	Oral	Twice Daily (continuous dosing)	
*After completion or discontinuation of radium-223 therapy, participants in Arm A will continue treatment with olaparib monotherapy.					

Phase 2 Arm B:

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Radium-223	None	55 kBq/kg	IV	Day 1 (+/-7 days) of Cycle 1-6	28 days

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle of treatment (Appendix C).

Patient initially assigned to Arm B will have the option to cross over to arm A at radiographic progression. If patients have already completed all 6 infusions of radium, they will receive monotherapy with olaparib. If they have not yet completed all 6 radium-223 infusion, they will continue radium-223 infusion until completion and receive concurrent treatment with olaparib.

Phase 2 Crossover of Arm B participants to Arm A:

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Radium-223	None	55 kBq/kg	IV	Day 1 (+/-7 days) of Cycle 1-6*	28 days
Olaparib	Take with or without food. Tablets should be taken whole. Do not crush, chew or dissolve tablets.	200 mg by mouth twice daily, continuously	Oral	Twice Daily (continuous dosing)	
*After completion or discontinuation of radium-223 therapy, participants who crossover to from Arm B to Arm A will continue treatment with olaparib monotherapy.					

5.1.1 Olaparib

Olaparib at the appropriate dose level will be given orally continuously twice daily, with doses taken at the same times each day approximately 12 hours apart. The correct number of 100 mg or 150 mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. Tablets can be taken with or without food. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the

study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

5.1.2 Radium-223

Radium-223 55 kBq/kg (1.49 microcurie/kg) will be administered as a bolus intravenous injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles (+/- 7 days). Before administration of study drug, the participant must be well hydrated; the participant should be instructed to drink ad libitum.

5.2 Definition of Dose-Limiting Toxicity

The CTCAE scale (version 5.0) will be used to grade toxicities. Dose-limiting toxicities include the following:

- Grade 4 neutropenia lasting > 7 days.
- Grade 3 or 4 neutropenia with fever > 38.5°C.
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with active bleeding.
- Grade 4 anemia.
- Grade 3 electrolyte or biochemical disturbances considered related to drug therapy that cannot be treated and recover to ≤ grade 2 within 48 hours.
- Grade 3 or 4 non-hematologic toxicity considered related to drug therapy. Only includes diarrhea, nausea or vomiting when optimal prophylactic measures have been prescribed.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. DLT is defined above.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients 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 patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients 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 patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose (RP2D).

The MTD is defined as the highest dose studied at which no more than one of six subjects has experienced a DLT in cycle 1 and 2. The observation period for the phase 1 is the first two cycles. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved.

All patients who receive at least one dose of study treatment will be evaluable for toxicity and DLT.

5.3 Phase 2

Once the RP2D is reached, enrollment on the phase 2 portion of the trial will begin. For the randomized phase 2, patients will continue to be monitored for safety and toxicity as determined by CTCAE version 5. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into

Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a serious adverse event (SAE) has occurred.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of olaparib and radium-223 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, overthe-counter medications, or alternative therapies. If there are questions or concerns regarding concomitant medications, please contact the PI and study team. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix D (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

No formal clinical drug interaction studies have been performed with radium-223. Subgroup analyses indicate that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of radium-223 in the randomized clinical trial.(13) Refer to prescribing information for more detailed data.

Olaparib is primarily metabolized by CYP3A. In patients (n=57), co-administration of itraconazole, a strong CYP3A inhibitor, increased AUC of olaparib by 170%. A moderate CYP3A inhibitor, fluconazole, is predicted to increase the AUC of olaparib by 121%. **Avoid concomitant use of strong CYP3A inhibitors** such as itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, or telaprevir with concurrent olaparib use. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

Avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice given they are CYP3A inhibitors with concurrent olaparib use.

In patients (n=22), co-administration of rifampicin, a strong CYP3A inducer, decreased AUC of olaparib by 87%. A moderate CYP3A inducer, efavirenz, is predicted to decrease the AUC of olaparib by approximately 60%. Avoid concomitant use of strong CYP3A inducers such as phenytoin, rifampicin, carbamazepine, and St. John's Wort with concurrent olaparib use.

Conventional multivitamins and minerals, such as calcium and vitamin D supplementation, are permitted and must be reported in the eCRF. Concurrent use of herbal supplements (including, but not limited to, St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng) or "folk remedies" is prohibited on this study.

Administration of LHRH agonist/antagonists is required in participants not having undergone bilateral orchiectomy.

Use of osteoclast targeted therapy including either bisphosphonates or denosumab is mandated on this study except in patients with contraindications as determined by the treating investigator, including:

- Hypocalcemia
- Hypophosphatemia
- Renal impairment including those with a GFR < 35 mL/min using the CockcroftGault equation or acute renal impairment
- Hypersensitivity to drug formulation
- Dental condition or need for dental intervention that per the investigator would increase the risk of osteonecrosis of the jaw.

Use of osteoclast targeted therapy or reason against use needs to be recorded in the eCRF. Additionally, reason for discontinuation of osteoclast targeted therapy need to be appropriately documented in the eCRF.

Anticoagulation with low molecular weight heparin, direct oral anticoagulant (such as dabigatran, apixaban, or rivaroxaban), or warfarin is permitted. Use of antiplatelet agents including clopidogrel and aspirin is permitted. If warfarin is used, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly thereafter if the INR is stable if patients are receiving olaparib.

Palliative radiation therapy is not permitted during the phase 1 portion. During the phase 2, palliative radiation therapy is permitted, however patients enrolled in Arm A will require olaparib to be held 3 days prior to initiation of radiation therapy until completion of radiation therapy.

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal agents including antiandrogens, androgen synthesis inhibitors such as abiraterone), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (by radiographic criteria)
- Intercurrent illness that prevents further administration of treatment

- Bone marrow findings consistent with MDS/AML.
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the patient's condition render the participant unacceptable for further treatment in the judgment of the investigator
- Unequivocal clinical progression (as determined by the judgment of the treating investigator)
- Participant non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.6 Duration of Follow Up

Participants removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Participants will be followed for 2 years after removal from study or until death, whichever occurs first. Participants will be followed for subsequent lines of therapy, including line of agent, name of agent, PSA kinetics, and radiographic progression following study drug discontinuation. This information will be updated every 6 months. The research team will collect this information during patient clinic visits, by phone, or via medical record review.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. Toxicity assessments will be done using CTCAE (version 5) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Treatment with radium-223 or olaparib may be held independently of one another depending on toxicities.

Dose Level	Olaparib Dose	Dose Reduction 1	Dose Reduction 2

-2	100 mg orally twice daily, continuously	Off treatment	Off treatment
-1	150 mg orally twice daily, continuously	100 mg orally twice daily, continuously	Off treatment
1: Starting dose (Phase 2 Starting Dose Level)	200 mg orally twice daily, continuously	150 mg orally twice daily, continuously	100 mg orally twice daily, continuously
2	300 mg orally twice daily, continuously	200 mg orally twice daily, continuously	150 mg orally twice daily, continuously

During the phase 1 portion of the study, radium-223 will be administered at a fixed dose at 55 kBq/kg every 4 weeks (+/- 7 days) x 6 maximum cycles. Patients are not required to re-meet eligibility criteria prior to day of each cycle.

Radium-223:
Radium-223 dose level adjustment is not permitted. Study visits during the treatment period should occur at 4 weeks intervals (within a window of +/- 7 days). Dosing delays may be instituted under the following circumstances:

Myelosuppression:
Treatment-related changes in hematology parameters may occur. If a patient experiences CTCAE version 5.0 grade 3 or 4 neutropenia, thrombocytopenia, or anemia the administration of study drug should be delayed until recovery to grade 2 or better. If a patient experiences CTCAE version 45.0 grade 3 or 4 neutropenia, thrombocytopenia, or anemia lasting > 6 weeks, further study drug administrations must be discontinued. Blood transfusion is acceptable between study drug administrations.

Gastrointestinal events:
Diarrhea should be treated as per local practice. A further dose of study medication should not be given before diarrhea is recovered to CTCAE version 5.0 grade 2 or baseline levels. If a patient experiences persistent grade 3 or 4 diarrhea refractory to medical management lasting > 6 weeks, further study drug administrations must be discontinued. Nausea or vomiting should be treated as per local practice. A further dose of study medication should not be given before nausea or

vomiting is recovered to CTCAE version 5.0 grade 2 or baseline levels. Refer to Appendix E for Patient Guide on Diarrhea.

Spinal Cord Compression:
If the patient experiences spinal cord compression during the treatment period, the patient should be treated for the event, and may receive further study drug administration if adequately recovered.

Surgical Intervention:
If surgery is required, the patient should continue with study treatment, if this is considered safe in the treating investigator's opinion. The surgeon needs to be notified that the patient has been given radioactive drug, and needs to follow the guidelines for radioactive protection.

Non-pathological fractures:
For traumatic fractures in weight-bearing bones during treatment phase, the study drug administration should be delayed for 2-4 weeks from the time of fracture.

Pathological fractures:
Pathological fractures may occur as the result of either progressive disease or increased physical activity associated with significant pain palliation. Pathologic fractures are to be treated in a manner that attempts to maintain the best functional status and quality of life. Study treatment may continue as planned. Palliative radiation therapy is not permitted during the phase 1 portion. During the phase 2, palliative radiation therapy is permitted, however patients enrolled in Arm A will require olaparib to be held 3 days prior to initiation of radiation therapy until completion of radiation therapy.

Other Radium-223 related toxicities:
If a patient experiences CTCAE version 5.0 grade 3 or 4 toxicity related to radium-223, the administration of study drug should be delayed until recovery to grade 2 or better. If a patient experiences CTCAE version 5.0 grade 3 or 4 toxicity related to radium-223 lasting > 6 weeks, further study drug administrations must be discontinued.

Olaparib:
In the presence of any olaparib related toxicities > grade 2, olaparib will initially be held. Once toxicity resolves to grade 1 or better, olaparib can be resumed at the next dose de-escalation level. No dose reduction below dose level -2 is allowed. If olaparib is held for more than 6 weeks, patients will be discontinued permanently from protocol treatment. Doses will not be reescalated once reduced unless reason for dose reduction was isolated asymptomatic, nonclinically significant laboratory abnormalities including grade 3 elevation of amylase or lipase. If a participant has toxicity related to olaparib and therapy needs to be held, this does not affect the every 4-week schedule of radium-223. If radium-223 cannot be administered for toxicity or another issue, the drugs should be administered independently of one another. Doses will not be escalated beyond the initial starting dose level.

Neutropenia, leukopenia, thrombocytopenia:

Neutropenia, Leukopenia, Thrombocytopenia	**Management/Next Dose for Olaparib**
Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this
Neutropenia, Leukopenia, Thrombocytopenia	**Management/Next Dose for Olaparib**
	should be for a maximum of 6 weeks; appropriate supportive treatment and causality investigation.
Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 6 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **first dose reduction** as a first step and **second dose reduction** as a second step.

Febrile neutropenia:

Febrile Neutropenia	**Management/Next Dose for Olaparib**
Grade 3	Hold until neutropenia ≤ Grade 1 and temperature ≤ 38.0°C. Resume at one dose level lower, if indicated.
Grade 4	Permanently discontinue protocol treatment unless it is determined that the patient is unequivocally deriving clinical benefit. In this case, upon recovery to ≤ Grade 1 or baseline and temperature ≤ 38.0°C, the participant may be re-treated at a reduced dose after discussion with the Principal Investigator.

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug as above.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Anemia:

Anemia	**Management/Next Dose for Olaparib**
≤ Grade 1	No change in dose
Grade 2	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 6 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If Hb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* dose interrupt (for maximum of 6 weeks) and upon recovery dose reduction may be considered.
Anemia	**Management/Next Dose for Olaparib**
	If Hb**< 9** *but* **≥ 8 g/dl**, dose interrupt (for maximum of 6 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered.
Grade 3	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 6 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to **first dose reduction** as a first step and to **second dose reduction** as a second step in the case of repeat Hb decrease.
Grade 4	Permanently discontinue protocol treatment unless it is determined that the patient is unequivocally deriving clinical benefit. In this case, upon recovery to ≤ Grade 1 or baseline, the participant may be re-treated at a reduced dose after discussion with the Principal Investigator.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions.

Management of Prolonged Hematologic Toxicities:
If a patient develops prolonged hematologic toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence (≥ weekly blood transfusions)

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 109/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets < 50 x 109/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Bone marrow or blood cytogenetic analysis may be performed according to standard hematologic practice for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

Management of Non-Hematological Toxicities:
Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the principal investigator must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of Liver Dysfunction:
For patients meeting the definition of Hy's Law including all of the following:

- Alanine aminotransferase elevation > 3 x ULN.
- Total bilirubin > 2 x ULN.
- No other explanation of liver injury (including but not limited to viral hepatitis, alcohol ingestion, congestive heart failure, metastases) Permanently discontinue study treatment.

Management of New or Worsening Pulmonary Symptoms:
If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and

further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the principal investigator.

Management of Nausea and Vomiting:
Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (e.g. dopamine receptor antagonist, antihistamines or dexamethasone).

Interruptions for Intercurrent Non-Toxicity Related Events:
Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the principal investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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 AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

7.1.1 CAEPRs for CTEP IND Agent.

7.1.1.1 Olaparib (AZD2281, NSC 747856)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4499 patients.* Below is the CAEPR for Olaparib (AZD2281).

> **NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, July 9, 2025[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 4499]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia (AIHA))[2]	
		Blood and lymphatic system disorders - Other (pure red cell aplasia (PRCA))[2]	
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea Vomiting			***Nausea (Gr 3)*** ***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 4499]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Hepatobiliary disorders - Other (drug-induced liver injury (DILI))	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Creatinine increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	
VASCULAR DISORDERS			
	Vascular disorders - Other (venous thromboembolism)[3]		

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Autoimmune hemolytic anemia (AIHA) and Pure red cell aplasia (PRCA) have been reported in clinical trials as potential and identified risks when Olaparib is used in combination with durvalumab.

[3]Venous thromboembolism includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.

[4]Rash includes exfoliative rash, generalized erythema, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

Adverse events reported on Olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INFECTIONS AND INFESTATIONS - Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus; Rash[4]
VASCULAR DISORDERS - Arterial thromboembolism; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 Radium-223

The following list includes the most commonly reported adverse drug reactions and their incidences associated with Radium-223. For a complete listing and additional details, please refer to the current package insert.

Adverse reactions reported in adults.

Greater than 10%:

- Cardiovascular: Peripheral edema (13%)
- Gastrointestinal: Diarrhea (25%; grades 3/4: 2%), nausea (36%; grades 3/4: 2%), vomiting (19%; grades 3/4: 2%)
- Hematologic & oncologic: Anemia (93%; grades 3/4: 6%), leukopenia (35%; grades 3/4: 3%), lymphocytopenia (72%; grades 3/4: 20%), neutropenia (18%; grades 3/4: 1% to 3%), thrombocytopenia (31%; grades 3/4: 1% to 6%)

Between 1% and 10%:

- Endocrine & metabolic: Dehydration (3%)
- Hematologic & oncologic: Pancytopenia (2%; grades 3/4: 1%)
- Local: Injection-site reaction (1%; including erythema at injection site, pain at injection site, swelling at injection site)
- Renal: Renal insufficiency (3%; including renal failure syndrome)

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 that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **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 Expedited Adverse Event Reporting

7.3.1 Rave-CTEP-AERS Integration

7.3.2 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eappsctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.3 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.4 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL SAEs</u> that meet the above criteria **<u>MUST</u>** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

<u>Expedited AE reporting timeframes are defined as:</u>

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 7.1.

8.1 Olaparib

8.1.1 Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4fluorophenyl)methyl]phthalazin-1(2*H*)-one

8.1.2 Other Names: AZD2281; KU-0059436; CO-CE 42

8.1.3 Classification: PARP inhibitor

8.1.4 CAS Registry Number: 763113-22-0

8.1.5 Molecular Formula: $C_{24}H_{23}FN_4O_3$; M.W.: 434.46

8.1.6 Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range.

8.1.7 Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

8.1.8 Description: crystalline solid

8.1.9 How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

8.1.10 Storage: Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability

8.1.11 Stability: Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

8.1.12 Route and Method of Administration: Oral. Take tablets without regard to meals.

8.1.13 Agent Ordering and Agent Accountability

8.1.13.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and

Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Study agent must be ordered after patient is registered to the combination arm. No starter supplies are available for this study. Clinical drug requests can be expedited Monday – Thursday when sites provide courier information.

8.1.13.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.14 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.15 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/ • NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov • PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eappsctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Radium-223

8.2.1 Product Description

Radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug. Radium-223 is supplied as a clear, colorless, isotonic, and sterile solution to be administered intravenously with pH between 6 and 8. Each milliliter of solution contains 1,000 kBq radium-223 dichloride (27 microcurie), corresponding to 0.53 ng radium 223, at the reference date. Radium is present in the solution as a free divalent cation. Each vial contains 6 mL of solution (6,000 kBq (162 microcurie) radium223 dichloride at the reference date). The inactive ingredients are 6.3 mg/mL sodium chloride USP (tonicity agent), 7.2 mg/mL sodium citrate USP (for pH adjustment), 0.2 mg/mL hydrochloric acid USP (for pH adjustment), and water for injection USP.

The molecular weight of radium-223 dichloride, 223RaCl2, is 293.9 g/mol. Radium-223 has a half-life of 11.4 days. The specific activity of radium-223 is 1.9 MBq (51.4 microcurie)/ng. The six-stage-decay of radium-223 to stable lead-207 occurs via shortlived daughters, and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 - 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

8.2.2 Solution Preparation

Personnel should use appropriate protective clothing and equipment during syringe handling to prevent contamination with the radioactive solution (medical gloves / protective glasses). The dose will delivered in a ready-to-use prefilled syringe with a certified activity. The activity in the syringe will be assayed in the dose calibrator according to standard institutional practice and guidelines for administration of therapeutic radiopharmaceuticals to patients.

Do not store above 40°C (104°F). If the syringes have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a patient. Store radium-223 in the original container or equivalent radiation shielding. This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

8.2.3 Dose Administration

Aseptic technique should be used in the administration of radium-223. The syringe should be handed over to the individual who will perform the injection. The study medication will be administered as a bolus IV injection (up to 1 minute or longer depending on local institutional standards). After administration, the equipment used in connection with the preparation and administration of drug is to be treated as radioactive waste and should be disposed in accordance with local procedure for the handling of radioactive material.

8.2.4 Instructions for Handling

Radium-223 should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal radium-223 are subject to the regulations and/or appropriate licenses of the competent official organization.

Radium-223 should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

The administration of radium-223 is associated with potential risks to other persons (e.g., medical staff, caregivers and patient's household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations. For drug handling, follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of radium-223, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diaminetetraacetic acid (EDTA) solution is recommended to remove contamination. For patient care, whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with radium223 or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations. The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of radium-223 and the detection of contamination with standard instruments.

8.2.5 Agent Ordering

Radium-223 will be commercially supplied.

Please refer to FDA-approved package labeling for more information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Please refer to section 2.5 which details the rationale for correlative testing to be completed and specific details of each correlative biomarker.

9.1 Summary Table for Specimen Collection

Time Point	Specimen	Shipping Parameters	Send Specimens To:
Archival			
	• Formalin-fixed paraffinembedded (FFPE) tumor tissue block (preferred) If a block is not available, then submit: • 1 H&E stained slide • 20 unstained, uncharged, unbaked slides	Room Temperature	EET Biobank

Baseline			
	• 6 OCT-embedded tumor cores[1, 2] •	Frozen on Dry Ice	EET Biobank
	• 20 mL blood in cfDNA Streck (2 x 10 mL) (Germline DNA)	Room Temperature	EET Biobank
Phase I: Pretreatment C1D1, C1D15, C2D1, C2D15, C4D1, C7D1, C8D1, C10D1, every 12 weeks thereafter, and end of study **Phase II: Pretreatment C1D1, C4D1, C7D1, every 12 weeks thereafter, and end of study**			
	• 20 mL blood in EDTA (2 x 10 mL), frozen whole in 1mL aliquots (Blood Biomarker)	Frozen on Dry Ice	Jamieson Laboratory
Phase II: Pretreatment C1D1, C2D1, C4D1, C7D1, C10D1, every 12 weeks thereafter, and end of study			
	• 20 mL blood in cfDNA Streck (2 x 10 mL) (cfDNA WGS)	Room Temperature	FMI
Phase II: Pretreatment C1D1, C4D1, C7D1, every 12 weeks thereafter, and end of study			
	• 20 mL blood in Heparin vacutainer tubes (2 x 10 mL) (PBMC)[4, 5]	Room Temperature	Jamieson Laboratory
Off-Study			
	• 6 OCT-embedded tumor cores[1, 2] (Phase I and II)	Frozen on Dry Ice	EET Biobank
	• 20 mL blood in EDTA (2 x 10 mL), frozen whole in 1-	Frozen on Dry Ice	Jamieson Laboratory
	mL aliquots (Phase I and II) •		
	• 20 mL blood in Heparin vacutainer tubes (2 x 10 mL) (PBMC) (Phase II only)[4, 5]	Room Temperature	Jamieson Laboratory

	• 20 mL blood in cfDNA Streck (2 x 10 mL) (cfDNA WGS) (Phase II only)	Room Temperature	FMI

[1]For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave.
[2]For new biopsies, a copy of the radiology and operative reports from the tissue removal procedure must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology reports to Rave.
[3]If 6 cores are not available to send, then a minimum of 3 cores is requested.
*[4]Requires shipment **same day of collection at room temperature**.*
[5]To be collected on the first 52 patients enrolled on the phase II.

Phase I Specimen Calendar:

Specimen	Baseline	C1D1	C1D15	C2D1	C2D15	C4D1	C7D1	C8D1	C10D1	Every 12 Weeks	End of Study
Archival Tissue	X										
Fresh Tumor Tissue	X										X
Research Blood – cfDNA Streck tubes (Germline DNA)	X										
Research Blood – EDTA tubes (Blood Biomarker)		X	X	X	X	X	X	X	X	X	X

Phase II Specimen Calendar:

Specimen	Baseline	C1D1	C2D1	C4D1	C7D1	C10D1	Every 12 Weeks	End of Study
Archival Tissue	X							
Fresh Tumor Tissue	X							X
Research Blood – cfDNA Streck Tubes (Germline)	X							
Research Blood – EDTA		X		X	X	X	X	X
Tubes (Blood Biomarker)								

Research Blood – Heparin Tubes (PBMC)		X		X	X	X	X	X
Research Blood – cfDNA Streck Tubes (cfDNA WGS)		X	X	X	X	X	X	X

9.2 Specimen Procurement Kits and Scheduling

9.2.1 Specimen Shipping Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: (https://ricapps.nationwidechildrens.org/KitManagement/).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the EET Biobank. Institutional supplies must be used for all other specimen collection and processing.

Foundation Medicine Collection Kit:

Kits for the blood collection and shipment of specimens to FMI can be ordered via email: clinical.operations@foundationmedicine.com. Please ensure an appropriate supply of kits is maintained. FMI collection kits include priority overnight FEDEX pre-labeled clinical paks for return shipment to FMI.

9.2.2 Scheduling of Specimen Collections

Frozen tissue may be collected, processed and shipped to the EET Biobank on Monday through Thursday, since the Biorepository does not need to perform additional processing. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -80°C.

Blood in Streck tubes may be collected and shipped to the EET Biobank and FMI Monday through Thursday. If Streck tubes cannot be shipped immediately, then they should be stored at room temperature until shipment.

9.3 Specimen Collection

9.3.1 Archival Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Tissue

1. If previously-collected FFPE tissue will be submitted.
2. Submitted archival tumor specimens should contain adequate viable tumor tissue and be overall representative of the whole tumor. Confirmation of availability of archival tumor specimens should be received to the lead institution prior to Cycle 1 Day 1. Formalin-fixed paraffin-embedded tumor tissue blocks are preferred and should contain tumor areas that measure at least 1 cm in aggregate. The optimal block is at least 70% tumor. If an existing block cannot be submitted, the following are requested if available:
    a. One (1) H&E slide
    b. Twenty (20) 4 um unstained, uncharged, unbaked slides
3. Surgical specimens are preferred with order of preference being 1) radical prostatectomy and 2) metastectomy specimens. If surgical specimens are not available, then core-needle biopsy specimens are acceptable. Fine-needle aspiration, brushings, cell pellet from pleural effusion, and bone marrow aspirate are not acceptable.

9.3.2 Biopsy Collection Procedure

9.3.3 The tissue/tumor collections will occur via an image-guided (CT scan or US-guided) needle biopsy of a soft tissue or bone lesion. Biopsy of soft tissue is preferred when possible. A metastatic focus is preferred but if not available and prostate is still intact prostate biopsy can be performed. Blood samples will be drawn within 2 weeks of the biopsy to document an acceptable coagulation profile as per institutional standard procedures. Heparin, low molecular weight heparin, aspirin, and other anti-platelet agents should be discontinued as per institutional standard procedures.

The baseline biopsy will take place following confirmation of eligibility and prior to administration of treatment on Cycle 1/Day 1. Off-study biopsy is optional and should be conducted within 21 days of study discontinuation prior to initiation of next line systemic treatment for prostate cancer. For patients who crossover from radium-223 alone to radium-223 and olaparib, the optional biopsy must take place prior to initiation of treatment with olaparib.

Important:
For each tissue collection procedure, the intent is to acquire up to 6 needle cores for rapid freezing in OCT medium. Size of these biopsy cores can be variable (0.1-1.0 cm). While larger cores are preferable to optimize tumor capture, cores of any size should be processed. A minimum of 3 cores is preferred. If feasible, the optional off-study biopsy should be taken from the same tumor lesion as the baseline biopsy.

9.3.3.1 Bone Biopsies

Bone biopsies will be performed per institutional standards and/or operator preference. Bone biopsies should not be performed on irradiated lesions. Preferred bone sites include the lumbar vertebrae, pelvic bones and long bones. Use of the OnControl® Biopsy System is preferred when safe and appropriate (pelvic bones). Given lower yield on bone biopsy special attention should be given to the following parameters which may correlate with tumor yield on bone biopsy:

- Size
- Degree of sclerosis
- Distance from the skin to the lesion
- Distance from the cortex to the lesion
- Presence of a bone scan correlate
- Area to target for biopsy (center versus periphery of the lesion)

9.3.3.2 Soft Tissue Biopsies

Soft tissue biopsies will be performed per institutional standards and/or operator preference. Preferred soft tissue biopsy sites include lymph nodes, exophytic soft tissue components associated with bone lesions. Participants with visceral metastases are not eligible for this study. An 18 gauge or larger is preferred for soft tissue biopsies.

9.3.3.3 Pre-Biopsy Labeling of Tubes and Cryomolds

Research staff should communicate with the interventional radiology team in advance of the biopsy to ensure that requested specimens are collected according to the laboratory manual. Coordination efforts with the interventional radiology and pathology teams will vary depending on the institution. It is advised to *arrive at the biopsy collection site at least 15 minutes ahead of the scheduled time to allow sufficient time to set up laboratory supplies and ensure rapid transport of specimens to the laboratory after collection.*

1. Number cryomolds 1-8 to identify which biopsy core was taken 1st, 2nd, 3rd, and etc. Refer to section 9.4.1.2 for tissue labeling requirements.

9.3.3.4 OCT-embedding Tissue Biopsies

*This procedure should be performed within **20-30 minutes** of biopsy collection. Please keep the time from biopsy to freezing to within 30 minutes. Procedures may vary depending on the institution. Bone and soft tissue biopsies will be processed by the same procedure as detailed below.*

1. Fill a cryomold with a thin layer of pre-chilled OCT.
2. Transfer freshly collected needle biopsy with the sterile needle or tweezers at one end and place the core on the bottom of the metal mold as flat as possible.

3. Fill the metal mold with prechilled OCT medium ensuring no air bubbles are present near the tissue.
4. Immediately transfer the mold to the pre-chilled metal plate on dry ice and wait for complete freezing.
5. Repeat procedure for each separate biopsy (sequentially from #1 to #5).
6. After the OCT solidifies, cut the edge of the cryomold to fit into the pre-labeled cassette before storage, if needed. Make sure to match the # on the mold with the pre-labeled cassette.

9.3.3.5 Storing of Biopsy Specimens

Return to the sample processing laboratory with the specimens, transfer cryopreserved biopsy specimens to a -80°C freezer. **Note any deviations from the laboratory manual in the Specimen Tracking System.** Please ship frozen tissue on dry ice.

9.3.4 Blood Collection

Refer to section 9.4.1.1 for Blood Specimen Labeling Instructions.

9.3.4.1 Collection of Blood in cfDNA Streck Tube – To EET Biobank

1. Label two 10 mL cfDNA Streck tubes with Rave generated specimen ID (which includes the protocol number and Universal Patient ID), patient study ID, specimen type (blood), and collection date.
2. Collect 10 ml of blood into each pre-labeled tube and gently invert to mix. Note: blood must be thoroughly mixed to ensure preservation of specimen.
3. After collection, **blood in cfDNA Streck tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.

9.3.4.2 Collection of Whole Blood in EDTA – To Jamieson Laboratory

1. Label two 10 mL EDTA tubes with Rave generated specimen ID (which includes the protocol number and Universal Patient ID), patient study ID, specimen type (blood), and collection date.
2. Collect 10 mL of blood in each of two EDTA tubes (2 x 10 mL). Gently invert tubes 8-10 times.
3. Place EDTA tube on ice or 4°C and IMMEDIATELY aliquot.
4. Transfer total of 20 mL of blood into labeled cryovials, 1.0 mL per cryovial.
5. Freeze these vials immediately in a -80 °C freezer. Make sure to complete Blood Requisition Form (Append F).

9.3.4.3 Collection of Whole Blood in Heparin Vacutainer Tubes for PBMC Isolation – To Jamieson Laboratory

1. Label two 10 mL Heparin Vacutainer tubes with Rave generated specimen ID (which includes the protocol number and Universal Patient ID), patient study ID, specimen type (blood), and collection date.
2. Collect 10 mL of blood in each of two 10 mL Heparin Vacutainer tubes (2 x 10 mL).
3. Immediately after draw, invert the tube gently 8-10 times. DO NOT SPIN DOWN THE TUBE.
6. Specimens require shipment **same day of collection at room temperature.** Make sure to complete Blood Requisition Form (Append F).

9.3.4.4 Collection of Whole Blood in cfDNA Streck Tube for WGS – To FMI

1. Using an FMI kit (see Section 9.2.1) collect 20 mL of blood into each of the two provided and pre-labeled cfDNA Streck tubes (2 x 10 mL) and gently invert to mix. Note: blood must be thoroughly mixed to ensure preservation of specimen.
2. Place tubes back into the provided foam insert with the completed packing slip.
3. Store at room temperature for up to 24 to 72 hours from time of collection until shipment to FMI for processing (see Section 9.7). After collection, **blood in cfDNA Streck tubes should never be refrigerated**.

9.4 Specimen Tracking System Instructions

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tacking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

9.4.1 Specimen Labeling

9.4.1.1 Blood Specimen Labeling

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

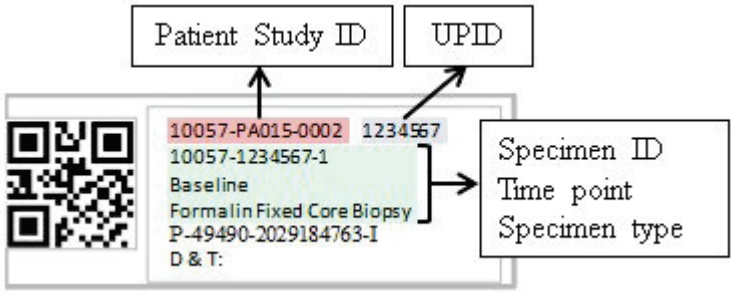
9.4.1.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only) • Collection date (to be added by hand)

9.4.1.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-

2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:
1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (e.g., for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.4.2 Overview of Process at Treating Site

9.4.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:
1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

9.4.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:
- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.
- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 9.3.2.5 and 9.3.3.

- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have PHI data like name, mailing address, medical record number or SSN redacted. Do not redact SPID, block number or relevant dates.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

9.5 Shipping Specimens from Clinical Site to the EET Biobank

Blood collected in cfDNA Streck tubes should be shipped as one shipment at ambient temperature, whenever possible. The same box sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

For OCT-embedded biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, then the surgical and/or radiology report must be uploaded to the ETCTN specimen tracking system and included in the package, or the specimen will not be processed.

9.5.1 Specimen Shipping Instructions

9.5.1.1 Shipping Blood in an Ambient Shipper

1. Before packaging specimens verify that each specimen is labeled according to the instructions above.
2. Place specimens into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
3. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
4. Place the specimen and a copy of the shipping manifest into the shipping box. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container, to prevent specimens from freezing.
5. Close the box and attach a shipping label to the top.
6. Place an Exempt Human Specimen sticker to the side of the container.
7. Ship specimens via overnight courier to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.1.2 Packaging Frozen Specimens in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.

8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.2 EET Biobank Shipping Address

Ship to the address below. Ship fresh blood specimens the same day of specimen collection. Saturday delivery is only available for ambient blood. Do not ship specimens the day before a holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
E-mail: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per specimen shipment to the EET Biobank, utilizing the site screening and base intervention payments.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

9.5.3 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
PH: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

9.6 Shipping of Specimens to Jamieson Laboratory

9.6.1 Specimen Shipping Instructions for Shipment of Whole Blood in ETDA

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Samples should be batch shipped

every 5 patients who complete the study on dry ice. Please include Blood Requisition Form (Appendix F) with shipment. Shipping reservations must be made to allow delivery within 24 hours of shipment prior to 2:00 pm the next day. Do not ship on Thursday or Friday. Avoid weekend or holiday delivery as specimens cannot be received on these days. Please notify The Jamieson Laboratory as below prior to shipping to confirm plan for receipt.

Attention: NCI Protocol 10096 Olaparib/Radium-223
The Jamieson Laboratory
University of California, San Diego
Christina Jamieson/ Michelle Muldong
Moores Cancer Center, Room 4359, Bay 4KK
3855 Health Sciences Drive
La Jolla, CA 92093
Telephone: (858) 534-2921
Fax: (858) 822-6288
Email: CAMJamieson@ucsd.edu
Email: mmuldong@ucsd.edu

At least one week prior to shipment email the receiving laboratory to confirm plan for receipt: Christina Jamieson at CAMJamieson@ucsd.edu and Michelle Muldong at mmuldong@ucsd.edu.

Include the FedEx tracking number and electronic copy of Blood Requisition Form in the email.

9.6.2 Specimen Shipping Instructions for Shipment of Whole Blood for PBMC

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Ship tubes on the **same day of collection at room temperature** via **FedEx Priority Overnight**. Specimens must be received to The Jamieson Laboratory at the University of California, San Diego within 24 hours of collection from patient. Please include Blood Requisition Form (Appendix F) with shipment. Ship specimens Monday through Thursday only. If samples are collected on Thursday, they MUST be delivered by noon on Friday. Avoid weekend or holiday delivery as specimens cannot be received on these days. Current shipper and institutional procedures must be followed. Biologic specimens (Category B, UN3373) will be in leak-proof primary and secondary receptacles with puncture resistant packaging and absorbent material. Shipments are to be preceded with Email contact to the receiving lab to assure the shipment will be met and processed promptly.

Attention: NCI Protocol 10096 Olaparib/Radium-223 - PBMC
The Jamieson Laboratory
University of California, San Diego
Christina Jamieson/ Michelle Muldong
Moores Cancer Center, Room 4359, Bay 4KK

3855 Health Sciences Drive
La Jolla, CA 92093
Telephone: (858) 534-2921
Fax: (858) 822-6288
Email: CAMJamieson@ucsd.edu
Email: mmuldong@ucsd.edu

At least one week prior to shipment email the receiving laboratory to confirm plan for receipt: Christina Jamieson at CAMJamieson@ucsd.edu and Michelle Muldong at mmuldong@ucsd.edu.

Include the FedEx tracking number and electronic copy of Blood Requisition Form in the email.

9.7 Shipping of Specimens (cfDNA Streck tubes for WGS) to FMI

Samples need to be shipped **same or next day of collection at room temperature** to FMI. Do not ship with cool packs.

FMI collection kits include priority overnight FEDEX pre-labeled clinical paks for return shipment to FMI. Ship specimens Monday through Thursday only. Avoid weekend or holiday delivery as specimens cannot be received on these days.

On day of shipment, email the receiving laboratory at san.accessioning@foundationmedicine.com and include:

- Protocol Number: NCI10096
- FedEx tracking number

Specimens ship to:

Attention: Clinical Trial 10096 Foundation Medicine Inc.
11010 Torreyana Road
San Diego, CA 92121
Email: san.accessioning@foundationmedicine.com

Note: for UCSD only – call The Messenger Company at 858-514-8866 account number 5510 for pick-up and delivery before 5PM or before 9am the following morning (Mon-Friday only).

9.8 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Point(s)	Laboratory performing Assay
1	Brigham and Women's Hospital Center for Advanced Molecular Diagnostics	Tumor Oncopanel	Integrated	M	DNA from OCTembedded tumor tissue at baseline and off-treatment DNA from archival tumor, if available	Brigham and Women's Hospital
2	ETCTN Biobanking and Molecular Characterization Initiative	Tumor and Germline Whole Exome Sequencing	Exploratory	M	DNA from OCTembedded tumor tissue at baseline and off-treatment Germline DNA from Blood in cfDNA Streck tubes at baseline	NCI MoCha Lab
3	ETCTN Biobanking and Molecular Characterization Initiative	Tumor Whole Transciptome Sequencing	Exploratory	M	RNA from OCTembedded tumor tissue at baseline and off-treatment	NCLN Genomics Laboratory Or NCI MoCha Lab
4	Center for DNA Damage and Repair Dana Farber Cancer Institute	RAD51-foci assay	Exploratory	M	Two 4-5 um serial sections of the tumor sample derived from baseline, offtreatment or archival tissue	Center for DNA Damage and Repair Dana Farber Cancer Institute
Priority	**Biomarker Name**	**Biomarker Assay**	**Biomarker Type and Purpose**	**M/O**	**Specimen(s) and Time Point(s)**	**Laboratory performing Assay**

	Immune Sequencing of Peripheral TCell and B-Cell Receptor	TCR, BCR DNA and RNA sequencing	Exploratory	M	Frozen blood at: Phase 1: C1D1 (pretreatment), C1D15, C2D1, C2D15, C4D1, C7D1, C8D1, C10D1, then every 12 weeks, and Offtreatment Phase 2: C1D1, C4D1, C7D1, then every 12 weeks, and Off-treatment	Jamieson Laboratory at University of California, San Diego
	Phenotyping of PBMCs	Multicolor flow cytometry analysis	Exploratory	M	Whole blood in Heparin Vacutainer tubes Phase 2: C1D1 (pretreatment), C4D1, C7D1, then every 12 weeks, and Off-treatment	Jamieson Laboratory at University of California, San Diego
	Patient-tumor specific signature, MSI status, TMB and mutational signature	Plasma derived cfDNA WGS	Exploratory	M	Whole blood in cfDNA Streck tubes Phase 2: C1D1 (pretreatment), C2D1, C4D1, and every 12 weeks, Offtreatment	FMI

The EET Biobank will receive tumor specimens for processing and short- and long-term storage. Minimum percent tumor tissue needed is approximately 10%. Nucleic acids will be prioritized in the following order:

1. Oncopanel (Brigham and Women's Hospital)
    a. Minimum DNA content – 50 ng (1 ug/uL)
    b. Optimal DNA content – 200-250 ng (1 ug/uL)

2. Whole exome sequencing (MoCha)
    a. Minimum DNA content – 75 ng
    b. Optimal DNA content – 150 ng

3. Whole transcriptome sequencing (NCLN Genomics Laboratory or MoCha Laboratory)
    a. Minimum RNA content – 60 ng
    b. Optimal RNA content – 200 ng

4. RAD51 Assay (Dana Farber Cancer Institute)
    a. Two 4-5 um serial sections of the tumor sample

5. All remaining tissue and nucleic acid will banked.

9.9 Integrated Correlative Studies

9.9.1 Oncopanel – Dr. Neal Lindeman, Brigham and Women's Hospital, Integrated Biomarker

9.9.1.1 Specimens and Processing at the EET Biobank

OCT-embedded tumor tissue collected at baseline time point will be used for this assay. Formalin-fixed paraffin-embedded archival tumor tissue may also be used, if submitted. A slide from each OCT-embedded tissue core will be cut and H&E stained for pathology quality control review to assess tumor content. After removing the OCT, DNA and RNA will be co-extracted from the biopsies.

For archival tumor, the H&E slide will be used for pathology quality control review to assess tumor content. Unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction.

DNA will be extracted from blood collected in cfDNA Streck tubes at the baseline time point following plasma processing.

All nucleic acids will be stored in a -80°C freezer until distribution for testing.

Tumor and germline DNA will be shipped on dry ice in batches to Michele Baltay:

Attention: NCI Protocol 10096 Olaparib/Radium-223; Michele Baltay
Brigham and Women's Hospital
Center for Advanced Molecular Diagnostics
SH-5030
75 Francis Street
Boston, MA 02115
Email: Baltay@BWH.Harvard.edu

9.10 Exploratory/Ancillary Correlative Studies

9.10.1 Whole Exome Sequencing – Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research; Whole Transcriptome Sequencing, National Clinical Laboratory Network Genomics Laboratory, or Mocha Laboratory, Exploratory Biomarkers

9.10.1.1 Specimens and Processing at the EET Biobank

OCT-embedded tumor tissue collected at baseline time point will be used for this assay. Formalin-fixed paraffin-embedded archival tumor tissue may also be used, if submitted. A slide from each OCT-embedded tissue core will be cut and H&E stained for pathology quality control review to assess tumor content. After removing the OCT, DNA and RNA will be co-extracted from the biopsies.

For archival tumor, the H&E slide will be used for pathology quality control review to assess tumor content. Unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction.

DNA will be extracted from blood collected in cfDNA Streck tubes at the baseline time point following plasma processing.

All nucleic acids will be stored in a -80°C freezer until distribution for testing.

Tumor DNA and germline DNA will be shipped on dry ice in batches to the Molecular Characterization (MoCha) Frederick National Laboratory for Cancer Research:

MoCha Lab, Frederick National Laboratory for Cancer Research
Fort Detrick
Building 433 Room 302
Frederick, MD 21702
Leidos Biomedical Research, Inc.
Phone: 301 620 3914
Email: vivekananda.datta@nih.gov

Tumor RNA will be shipped on dry ice in batches to the National Clinical Laboratory Network Genomics Laboratory or the MoCha Laboratory.

9.10.2 Immune Profiling and Sequencing of Peripheral T-cell and B-Cell Receptor to Profile Immune Response – Dr. Christina Jamieson/University of California, San Diego, Exploratory Biomarker

Whole blood collected in heparin vacutainer tubes will need to be shipped **same day of collection at room temperature** to the Jamieson Laboratory of cryopreservation of PBMCs. Multicolor flow cytometry analysis will be performed on cryopreserved PBMC for immune cell phenotyping.

Additionally, whole blood will be batch shipped every 5 patients who complete the study on dry ice to the Jamieson Laboratory for TCR/BCR sequencing.

Attention: NCI Protocol 10096 Olaparib/Radium-223
The Jamieson Laboratory
University of California, San Diego

Christina Jamieson/ Michelle Muldong
Moores Cancer Center, Room 4359, Bay 4KK
3855 Health Sciences Drive
La Jolla, CA 92093
Telephone: (858) 534-2921
Fax: (858) 822-6288
Email: CAMJamieson@ucsd.edu
Email: mmuldong@ucsd.edu

9.10.3 cfDNA Assay – FMI, San Diego, CA

Samples will be processed and analyzed in FMI's laboratory in San Diego, CA. Whole blood will be collected in two 10 ml Streck tubes supplied by FMI in a collection kit. Samples will be shipped at ambient temperature to FMI within 24 to 72 hours from time of collection. Whole blood will be separated to plasma and buffy coat with centrifugation, buffy coat will be frozen at -80c, plasma will undergo DNA extraction and DNA will be stored at -20c. In batches, libraries will be created and sequenced on Novaseq 6000 up to a depth of 40x.

Bioinformatics pipeline will be applied to the sequence data for quality control evaluation, alignment, whole genome feature extraction.

Attention: Clinical Trial 10096 Foundation
Medicine Inc.
10355 Science Center Dr. #150
San Diego, CA 92121
Email: san.accessioning@foundationmedicine.com

9.10.4 RAD51 Assay – Center for DNA Damage and Repair, Dana-Farber Cancer Institute, Exploratory Biomarker

OCT-embedded tumor tissue collected at baseline and progression time point will be used for this assay. Formalin-fixed paraffin-embedded archival tumor tissue may also be used (if available). To perform the assay, two 4-5 um serial sections of the tumor sample will be stained independently for RAD51 and the cell cycle S-phase marker Geminin. The IHC staining will be performed at the CLIA/CAP certified pathology core at the Brigham and Women's Hospital and the interpretation of the stains will be performed at the Center for DNA Damage and Repair.

Interpretation of the staining will be based on the following criteria:

1. There must be more than 3 (>3) sub-nuclear RAD51 foci to call a cell RAD51-foci positive.

2. There must be 4 or more 40X fields of tumor cells with at least one RAD51-foci positive cell to call homologous recombination proficient.
3. If the percentage of Geminin positive cells is greater than 3 (i.e. >3%) and there are no RAD51-foci positive cells in at least 4 40X fields, the sample is homologous recombination deficient.
4. If the percentage of Geminin positive cells is less than 3 (i.e. <3%) and there are no RAD51 foci positive cells in 4 40X fields, the assay is not informative. This is because homologous recombination is restricted to S-phase of the cell cycle and the rate of tumor proliferation is low.

Slides will be shipped at room temperature in batches to Bose Kochupurakkal:

Attention: NCI Protocol 10096 Olaparib/Radium-223
Bose Kochupurakkal
Department of Radiation Oncology
Dana-Farber Cancer Institute
HIM331/324
4 Blackfan Circle
Boston, MA 02115
Office Phone: 617-632-4172
Email: Bose_kochupurakkal@dfci.harvard.edu

10. STUDY CALENDAR

CALENDAR FOR PHASE I SUBJECTS								
Study Evaluation Cycle = 28 days	Baseline	Cycle 1-2		Cycles 3-6	Cycles 7+			Follow-Up[10]
	Screening period is -28 days	Day 1 ± 3 days (± 7 days labs)	Day 15 ± 3 days (± 7 days labs)	Day 1 ± 3 days (± 7 days labs)	Day 1 ± 3 days (± 7 days labs)	Every 12 weeks ± 7 days	End of Study Visit	Every 6 months x 2 years
TREATMENT EXPOSURE[1]								
Radium-223		X		X				
Olaparib		X----------					X	
REQUIRED ASSESSMENTS[2]								
Informed Consent	X							
Medical History	X							X
Diagnosis and Staging	X							

Physical Exam	X	X	X	X	X			
Vital signs and ECOG Performance Status	X	X	X	X	X			
AEs & concomitant medications	X	X----------X						
CALENDAR FOR PHASE I SUBJECTS								
Study Evaluation Cycle = 28 days	Baseline	Cycle 1-2		Cycles 3-6	Cycles 7+			Follow-Up[10]
	Screening period is -28 days	Day 1 ± 3 days (± 7 days labs)	Day 15 ± 3 days (± 7 days labs)	Day 1 ± 3 days (± 7 days labs)	Day 1 ± 3 days (± 7 days labs)	Every 12 weeks ± 7 days	End of Study Visit	Every 6 months x 2 years
ECG[3]	X							
LABORATORY ASSESSMENTS[4]								
Complete Blood Cell Count with Differential (CBC)	X	X	X	X	X			
Comprehensive Metabolic Profile (CMP)	X	X	X	X	X			
PT/INR and aPTT	X							
Testosterone	X							
PSA	X	X		X	X			
LDH	X	X		X	X			
DISEASE ASSESSMENT[5]								
CT of chest[5]	X					X		
CT or MRI of abdomen and pelvis[5]	X					X		
Technetium-99m-MDP bone scintigraphy[5]	X					X		
MRI or CT Brain[5]	X							
QUESTIONNAIRES[11]								
FACT-P		X				X	X	
BPI		X				X	X	
Family History Questionnaire		X						
SPECIMEN COLLECTION								
Tumor Biopsy[6]	X						X	
Research Blood Sample - Germline DNA[7]	X							

Research Blood Sample – Blood Biomarkers[8]		X	X	X	X	X	X	
Archival Tissue[9]	X							

Key to Footnotes:
1: Radium-223 will be administered on Day 1 of Cycles 1-6 ± 3 days. Olaparib will be dosed continuously during treatment.
2: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, body weight (kg) and height (cm). Height at SCREENING ONLY. Documentation of analgesics including both narcotics and non-narcotics will be required.
3: 12-lead ECGs will be obtained after patient has rested in a supine position according to institutional standard practice.
4: Laboratory assessments may be completed up to 7 days prior to Day 1 and Day 15 for cycles 1 and 2, and up to 7 days prior to Day 1 for all subsequent cycles. Hematology testing to include full CBC with hemoglobin, red blood cells, platelets, mean cell volume, mean cell hemoglobin concentration, mean cell hemoglobin, white blood cell count, absolute white blood cell differential counts (preferred, percentages acceptable if not available) including neutrophils with band forms, lymphocytes, monocytes, eosinophils and basophils. Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, AST, ALT, ALP, total bilirubin. Gamma glutamyltransferase may be performed when clinically indicated.
5: Radiology imaging at screening to include: Diagnostic CT chest and CT or MRI of the abdomen and pelvis. MRI or CT of the brain is only necessary if clinically indicated at baseline. Imaging assessments at baseline can be performed up to 42 days prior to registration. Radiology assessments during treatment will occur every 12 weeks ± 7 days
6: The baseline biopsy will take place following confirmation of eligibility and prior to administration of treatment on Cycle 1/Day 1. Off-study biopsy is optional and should be conducted within 21 days of study discontinuation prior to initiation of next line systemic treatment for prostate cancer.
7: Blood for germline DNA analysis collected once between screening to prior to treatment on Cycle 1/Day 1.
8: Blood samples for blood based biomarkers will be collected at the following time points pretreatment Cycle 1/Day 1, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 2/Day 15, Cycle 4/Day 1, Cycle 7/Day 1, Cycle 8/Day 1, Cycle 10/Day 1, then every 12 weeks, end of study visit ± 7 days. If end of study collection is within 2 weeks of prior collection, research samples for blood biomarkers do not need to be collected.
9: Archival tissue is mandatory when available. The archival specimen must contain adequate viable tumor tissue. The specimen may consist of a tissue block (preferred and should contain the highest grade of tumor) or at least 20 unstained serial sections. Fine-needle aspiration, brushings, cell pellet from pleural effusion, bone marrow aspirate are not acceptable.
10: Long term follow-up for survival and initiation of a new anti-cancer treatment will occur every 6 months (± 14 days) until death or 2 years after end of treatment visit whichever comes first. This follow up may be via phone calls and through review of medical records.
11: QOL assessments will take place at pretreatment C1D1, every 12 weeks ± 7 days, and at end of study visit.

CALENDAR FOR PHASE II SUBJECTS						
Study Evaluation Cycle = 28 days	Baseline	Cycle 1-6	Cycles 7+			Follow-Up[12]

	Screening period is -28 days	Day 1 ± 3 days (± 7 days labs and radium-223)	Day 1 ± 3 days (± 7 days labs)	Every 12 weeks ± 7 days	End of Study Visit	Every 6 months x 2 years
TREATMENT EXPOSURE[1]						
Radium-223		X				
Olaparib		X----------X				
REQUIRED ASSESSMENTS[2]						
Informed Consent	X					
Medical History	X					X
Diagnosis and Staging	X					
Physical Exam	X	X	X			
Vital signs and ECOG Performance Status	X	X	X			
AEs & concomitant medications	X	X----------X				
ECG[3]	X					
LABORATORY ASSESSMENTS[4]						
Complete Blood Cell Count with Differential (CBC)	X	X	X		X	
Comprehensive Metabolic Profile (CMP)	X	X	X		X	
PT/INR and aPTT	X					
PSA	X	X	X		X	
Testosterone	X					
LDH	X	X	X		X	
QUESTIONNAIRES[13]						
FACT-P		X		X	X	
BPI		X		X	X	
Family History Questionnaire		X				
DISEASE ASSESSMENT[5]						
CT of chest[5]	X			X		
CT or MRI of abdomen and pelvis[5]	X			X		
Technetium-99m-MDP bone scintigraphy	X			X		
MRI or CT Brain[5]	X					

SPECIMEN COLLECTION						
Tumor Biopsy[6]	X				X	
Research Blood Sample - Germline DNA[7]	X					
Research Blood Sample – Blood Biomarker[8]		X		X	X	
Research Blood Sample – PBMC[9]		X		X	X	
Research Blood Sample – WGS cfDNA[10]		X		X	X	
Archival Tissue[11]	X					

Key to Footnotes:

1: Radium-223 will be administered on Day 1 of Cycles 1-6 ± 7 days for patients in both arms. Olaparib will be dosed continuously during treatment for patients randomized to combination therapy with radium-223 and olaparib. Cross-over will be allowed for patient randomized to radium-223 alone at time of radiographic progression on radium-223 alone.

3: 12-lead ECGs will be obtained after patient has rested in a supine position according to institutional standard practice.

2: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, body weight (kg) and height (cm). Height at SCREENING ONLY. Documentation of analgesics including both narcotics and non-narcotics will be required.

4: Laboratory assessments may be completed up to 7 days prior to Day 1 of each cycle. Hematology testing to include full CBC with hemoglobin, red blood cells, platelets, mean cell volume, mean cell hemoglobin concentration, mean cell hemoglobin, white blood cell count, absolute white blood cell differential counts (preferred, percentages acceptable if not available) including neutrophils with band forms, lymphocytes, monocytes, eosinophils and basophils. Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, AST, ALT, ALP, total bilirubin. Gamma glutamyltransferase may be performed when clinically indicated.

5: Radiology imaging at screening to include: Diagnostic CT chest and CT or MRI of the abdomen and pelvis. MRI or CT of the brain is only necessary if clinically indicated at baseline. Imaging assessments at baseline can be performed up to 42 days prior to registration. Radiology assessments during treatment will occur every 12 weeks ± 7 days.

6: The baseline biopsy will take place following confirmation of eligibility and prior to administration of treatment on Cycle 1/Day 1. Off-study biopsy is optional and should be conducted within 21 days of study discontinuation prior to initiation of next line systemic treatment for prostate cancer. For patients who crossover from radium-223 alone to radium-223 and olaparib, optional biopsy must take place prior to initiation of treatment with olaparib.

7: Blood for germline DNA analysis collected once between screening to prior to treatment on Cycle 1/Day 1.

8: Blood samples for blood based biomarkers will be collected once between screening to prior to treatment Cycle 1/Day 1, pretreatment Cycle 4/Day 1, pretreatment Cycle 7/Day 1, every 12 weeks, end of study visit ± 7 days. If end of study collection is within 2 weeks of prior collection, research samples for blood-based biomarkers do not need to be collected.

9: Blood samples for PBMC collection and analysis will be collected pretreatment Cycle 1/Day 1, pretreatment Cycle 4/Day 1, every 12 weeks thereafter, and end of study visit ± 7 days. If end of study collection is within 2 weeks of prior collection, research samples for PBMC analysis do not need to be collected. Specimens will be collected on the first 52 patients enrolled on the phase 2.

10: Blood samples for whole blood for cfDNA WGS collection and analysis will be collected pretreatment Cycle 1/Day 1, pretreatment Cycle 2/day 1, pretreatment Cycle 4/Day 1, every 12 weeks thereafter, and end of study visit ± 7 days. If end of study collection is within 2 weeks of prior collection, research samples for cfDNA WGS samples do not need to be collected.

11: Archival tissue is mandatory when available. The archival specimen must contain adequate viable tumor tissue. The specimen may consist of a tissue block (preferred and should contain the highest grade of tumor) or at least 20 unstained serial sections. Fine-needle aspiration, brushings, cell pellet from pleural effusion, bone marrow aspirate are not acceptable.
12: Long term follow-up for survival and initiation of a new anti-cancer treatment will occur every 6 months (± 14 days) until death or 2 years after end of treatment visit whichever comes first. This follow up may be via phone calls and through review of medical records.
13: QOL assessments will take place at pretreatment C1D1, every 12 weeks ± 7 days, and at end of study visit for patients on both study arms.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. Imaging assessment will be time-based and not cycle-based. All patients will be followed with same imaging techniques to determine response and progression. This includes:

- Technetium-99m bone scintigraphy
- CT chest
- CT or MRI abdomen and pelvis

Alternative imaging modalities to including but not limited to F-18 NaF PET/CT, 68Ga-PSMA PET/CT will not be utilized to assess disease response and progression.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST version 1.1 and for bone metastases PCWG3.(1, 2)

The ALSYMPCA study did not mandate baseline staging or regular monitoring of antitumor activity by imaging. Thus, the use of radiological examinations in patients receiving radium-223 has not been fully characterized. Similar to other therapies for metastatic prostate cancer, a flare phenomenon with increase of bone metastases-related pain, or increase in apparent number of bone metastases on imaging studies, may be noted during the first three treatment cycles, and should not be interpreted as disease progression.(71) As such, PCWG-3 criteria will be used to define progression of bone metastases. Per PCWG-3 criteria, progression of bone metastases will be defined as(72):

- Exclude pseudo-progression in the absence of symptoms or other signs of progression.
- At least two new lesions on first post-treatment scan with at least two additional lesions on the next scan (2+2 rule).
- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented.
- For scans after the first post-treatment scan, 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.
- Changes in intensity of uptake alone do not constitute either progression or regression.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with radium-223 and/or olaparib.

Evaluable for objective response. Only those patients 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 response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) 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 are not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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 nonnodal 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 Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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 (≥1 cm) 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 slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for 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.

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 date 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 at 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 Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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.

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 FDGPET 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.

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 (<1 cm).

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 (0.5 cm). (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-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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 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 Patients 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/NonPD	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: Patients 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 Patients 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 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).

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.

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 Radiographic Progression-Free Survival (rPFS)

rPFS is defined as the duration of time from randomization to time of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is determined by PCWG3 for bone metastases and RECIST version 1.1 for non-bone metastases. Patients who are alive and progression free will be censored at last disease assessment. rPFS will analyzed by arm in the total population and will also be stratified by disease extent (≤20 or > 20 bone lesions), prior docetaxel use (yes or no), and HRD status (yes/no/unknown).

11.2 Other Response Parameters

11.2.1 PSA Response

PSA response is defined by ≥50% decline in PSA from baseline. PSA will be monitored by cycle.

11.2.2 Time to PSA progression

Time to PSA progression is defined as time from randomization to PSA progression by PCWG 3 criteria. Patients who do not experience PSA progression will be censored at their last PSA assessment.

11.2.3 ALP response

ALP response is defined as ≥ 30% reduction of the blood level, compared to the baseline value and confirmed ≥4 weeks later.

11.2.4 Time to ALP progression

Time to ALP progression is defined as the time from randomization to the date of first ALP progression. ALP progression is defined as an increase of ≥25% from baseline at ≥12 weeks, in patients with no decrease from baseline; or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline.

11.2.5 Time to first subsequent therapy

Time to first subsequent systemic therapy is defined as the time from randomization to the date of initiation of first subsequent systemic therapy or death due to any cause.

11.2.6 Time to first SSE

Time to SSE is defined as time from randomization to the occurrence of the first SSE, such as pathologic bone fracture, spinal cord compression, hypercalcemia of malignancy or radiation therapy or surgery to bone, as described by the US Food and Drug Administration (FDA). Patients who do not reach the endpoint will be censored at their last assessment.

11.2.7 OS

OS is defined as time from randomization to the date of death due to any cause. Patients who are alive will be censored at last follow up date.

12. STUDY OVERSIGHT AND 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 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported

adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/deescalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

For the Phase 2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements:

    - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type, ○ Rave Investigator role, must be registered as an Non-Physician Investigator

(NPIVR) or Investigator (IVR), and ○ Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.

- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. Onsite audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informaticsresources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family

member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be

delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design and Primary Endpoint

Phase I

The primary objective of the phase I study is to evaluate the safety of the combination of olaparib and radium-223 and to determine the MTD level in men with metastatic CRPC. The observation period is the first two cycles of the combination therapy.

A standard 3+3 dose escalation scheme will be employed with four planed dose levels of olaparib as described in section 5.1. Three patients will be entered at the starting dose level 1. If no DLT is observed in the first three patients, escalation will proceed. If two or three DLTs are observed in the first three patients, escalation stops and three patients will be entered at the lower dose level -1. If one DLT is observed in the first three patients, an additional three patients will be entered. If no additional DLTs are observed in the three additional patients, escalation proceeds. If any DLTs are observed among the three additional patients (>1 DLT among six patients), escalation stops. MTD is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1 and 2. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved.

Up to July 2019, dose level 1 has been evaluated with 3 patients in cohort 1; no DLT was reported. There was one 1 grade 3 anemia reported out of the DLT window during the end of cycle 3 for a patient with concurrent disease progression. Dose level was escalated to level 2 (the highest dose level for this study). Given the observation period for DLT determination is the first two cycles of the therapy (56 days), the waiting time for next 3 patients would be long if we use traditional 3+3 design for dose level 2. We proposed a cohort of 6 patients for dose level 2 evaluation. This larger group size would help us avoid having to pause and then restart enrollment to the same dosing level several months later, given need to have 6 patients evaluated

at the MTD. If anytime we observe >1 DLT during the first two cycles of treatment from cohort 2, dose level 2 will be determined to have unacceptable toxicity. If ≤1 DLT out of 6 patients is observed, dose level 2 will be chosen as MTD level and the study will move to phase II part.

Patients will be followed with serial imaging at baseline and every 12 weeks to include CT chest, CT or MRI of abdomen and pelvis, and technetium-99m-MDP bone scintigraphy.

Phase II

This is a randomized, open-label phase II trial to evaluate whether combination of olaparib and radium-223 can prolong rPFS time compared to radium-223 alone in men with metastatic CRPC. The primary endpoint rPFS is defined in section 11.1.6. Participants will be randomized with 1:1 allocation to receive radium-223 +/- olaparib using permuted blocks methods. Randomization will be stratified by prior docetaxel status (either for CRPC or hormone sensitive disease yes/no) and disease extent (≤20 or > 20 bone lesions on radionuclide bone scan). Homologous recombination deficiency status (yes/no/unknown) will be retrospectively determined on collectively tissue after randomization and included as an additional stratification factor for the primary endpoint rPFS analysis.

Patients will be followed with serial imaging at baseline and every 12 weeks to include CT chest, CT or MRI of abdomen and pelvis, and technetium-99m-MDP bone scintigraphy.

13.2 Sample Size/Accrual Rate

Phase I

Approximately 6-18 patients may be enrolled in Phase I portion of the study.

Phase II

rPFS was not defined in the phase III ALSYMPCA study. However, based on a treatment period of six months and rPFS estimates from all the large phase III studies conducted in patients with metastatic CRPC (excluding sipuleucel-T), and a retrospective series of patients treated with radium-223 which reported a rPFS of 6.1 months (Challapalli et al, Presented at Genitourinary Cancers Symposium, 2016), we estimate a median of 6 month rPFS for the radium-223 arm. Additionally, rPFS in the phase II TOPARP study ranged from 9.8 months in biomarker positive patients to 2.7 months in biomarker negative patients.(23)

Phase III Metastatic CRPC Landmark Trials	Patients	Treatment Arms	Median rPFS (months)
TAX-327	1006	Docetaxel vs. Mitoxantrone	Not Reported

TROPIC	755	Cabazitaxel vs. Mitoxantrone	2.8 versus 1.4
COU-301	1195	Abiraterone vs. Placebo (PostChemo)	5.6 versus 3.6
COU-302	1088	Abiraterone vs. Placebo (Pre-Chemo)	16.5 versus 8.3
AFFIRM	1199	Enzalutamide vs. Placebo (Pre-Chemo)	8.3 versus 2.9
PREVIAL	1717	Enzalutamide vs. Placebo (PostChemo)	Not reached vs. 3.7

This study is designed to have adequate power to detect a 43% reduction in the rPFS hazard rate (from 0.1155 to 0.0660) on the olaparib and radium-223 arm, corresponding to a hazard ratio of 0.57. This difference corresponds to an improvement in median rPFS from 6 to 10.5 months on the combination arm under the exponential distribution assumption. There will be 88% power to detect this rPFS difference assuming that 120 men are uniformly enrolled over 12 months with 7 months of additional follow-up (a total of study duration of 19 months) at one-sided alpha of 0.10. Full information under the alternative hypothesis will occur at 80 rPFS events.

Following activation of the phase 2 portion of the study it was determined that the patients 13-25 underwent off-randomization enrollment given error in the electronic randomization algorithm. Given the randomization design of the phase 2, we will expand enrollment to 133 patient to ensure enrollment of 120 evenly randomized patients for analysis.

The study will be monitored for futility with one interim analysis, planned at approximately 50% information (i.e. 40 rPFS events, approximately 11 months after the first participant randomized). The decision for stopping the trial for futility will be guided by a hazard ratio boundary using the spending function of Lan and DeMets with O'Brien-Fleming parameter to adjust the boundary for the actual interim analysis time. If conducted precisely at 50% information, the cut-off hazard ratio is 1.05 corresponding to a z-scale value of 0.149. If the estimated hazard ratio (experimental/control) lies above 1.05, the study may be stopped early for lack of efficacy. The boundary crossing probability is 0.441 under the null hypothesis and is 0.028 under the alternative hypothesis. East version 6 (Cytel Inc.) is used for sample size and interim monitoring considerations.

The study design does not consider dropout rate, but we anticipate early dropout rate would be low as this study will include patients with end-stage disease and both arms will receive active treatment up to 6 mouth and be routinely followed per protocol. In addition, the final analysis for the primary endpoint rPFS will be driven by number of events, not by a fixed calendar time. If the study conduct does not follow the original design (e.g. occurrence of early drop out, slow or

non-uniform accrual), the required follow-up time for final rPFS analysis would be longer than projected (19 months from study initiation) to achieve the full information (i.e. 80 rPFS events).

Efforts to facilitate uniform enrollment will include timely site activation of participating sites, monthly study calls to encourage enrollment at participating sites, understand barriers to enrollment at participating sites, and developing strategies to overcome these barriers. Additionally, accrual holds will be limited. The protocol is designed to allow for continuous enrollment on the phase II with only one pre-planned interim analysis to assess futility.

13.3 Analysis of Primary Endpoints

Patients will be followed with serial imaging at baseline and every 12 weeks to include CT chest, CT or MRI of abdomen and pelvis, and technetium-99m-MDP bone scintigraphy. Radiographic progression is determined by PCWG3 for bone metastases and RECIST version 1.1 for non-bone metastases. Patients who are alive and progression free will be censored at last disease assessment. rPFS distributions will be estimated using the Kaplan-Meier method by treatment arm. The primary analysis is a superiority test of rPFS, performed using a stratified logrank test at one-sided 0.10 significance level. A stratified Cox proportional hazards regression model will estimate the rPFS treatment hazard ratio with 80% 2-sided confidence intervals (CIs). Stratification factors used in randomization as well as homologous recombination deficiency status (yes/no/unknown) determined on prospectively collectively tissue after randomization will be included in the stratified test for the rPFS analysis.

13.4 Analysis of Secondary Endpoints

Treatment comparison in rPFS will be conducted in pre-defined subgroups, including homologous recombination deficiency status (yes/no/unknown), disease extent (≤ 20 or >20 bone lesions) and prior docetaxel (yes or no). Cox regression hazard ratios (for treatment comparison) along two-sided 80% CI will be provided for each subgroup.

PSA response, ALP response and tumor response by RECIST 1.1 criteria are defined in section 11.1 & 11.2. Response rate by different criteria will be summarized as number and percentage of participants by treatment arm with two-sided 80% CI and compared between groups using Fisher's exact tests. Distributions of time to PSA progression, time to ALP progression, time to SSE and OS (see section 11.2 for detailed definitions) will be estimated using the method of Kaplan-Meier and compared between treatment arms using the stratified log-rank test. From the ALSYMPCA trial, median time to first SSE was 15.6 months compared to 9.8 months (HR 0.66, 95% CI 0.52-0.83, p<0.001). The ALSYMPCA trial did not report the 6-month SSE rate, however estimating from the Kaplan-Meier curves, the rate appears to be 22% for patients in the radium-223 arm.
The primary analysis for OS will be conservatively conducted using the intention-to-treat approach, where two treatment groups will be compared regardless of cross-over or any subsequent therapy post progression. Two additional sensitivity analyses may be conducted to evaluate the effect of cross-over on OS: a) presenting separate Kaplan-Meier curves for patients

randomized to radium-223 alone who have and have not crossed over; b) conducting a timevarying covariate for the exposure in a survival model. Other complex models will not be used given OS as a secondary endpoint and limited sample size in this study.

For toxicity reporting, all adverse events will be graded and analyzed using CTCAE version 5. The worst grade will be used if any toxicity event is reported multiple times on the same participant. Adverse events will be summarized according to grade, overall and by treatment arm, as number and percentage of participants. All adverse events resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized by treatment arm.

13.5 Analysis of Correlative Endpoints

The levels of serum LDH will be summarized at baseline and each cycle with descriptive statistics. Percent change from baseline or status change (e.g. from normal to abnormal defined by institution upper limit level) will be reported and compared between treatment arms at selected timepoints using Wilconxon rank sum test or Fisher's exact test as appropriate.

Frequency of mutations in the DNA repair pathway will be determined by Oncopanel testing. Gene mutation frequencies and mean ± SD of quantitative biomarkers will be summarized by arm and in overall population at baseline and/or at time of progression. It is anticipated that we will have samples assayed in about 80% of participants (approximately N=100) at baseline and in 25% (N=30) at progression. With a total of 100 samples, the 90% exact binominal CI width is 0.11 and 0.16 with the observed mutation rate of 0.1 and 0.3 respectively. Assuming 30 patients with paired (pre- and post-treatment) biopsy available, there is 80% power to detect a 0.53 SD mean change in quantitative biomarkers between time points using a paired t-test (two-sided α=0.05). Fresh tumor biopsy collected at study entry will be utilized for Oncopanel testing. If tumor not evaluable from biopsy, archival tissue will be utilized for analysis for exploratory purposes.

Homologous recombination deficiency will be defined by the presence of homozygous deletion AND/OR putative deleterious mutation in a gene reported to be involved in homologous recombination DNA repair as determined by next generation sequencing. Cox regression or logistic regression will be conducted to explore the association of rPFS or treatment response (PSA or tumor response) with homologous recombination gene mutation status.

The prevalence of germline mutations in homologous recombination genes will also be assessed in all participants. Their correlation with family history of cancers as determined by the Family History Questionnaire (Appendix G) and PSA response will be evaluated using Fisher's exact test or logistic regression as appropriate in all patients and/or by treatment arm as exploratory analyses.

13.6 Analysis of QOL endpoints

The QOL will be measured using the FACT-P questionnaire and BPI. The questionnaires will be administered at baseline, during treatment and at treatment discontinuation.

The BPI (Short Form) is a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of pain on the patient's daily functioning on a 10 point scale (Appendix H). Pain severity score at its worst, least and average pain and pain interference score will be summarized by time points. This tool has been previously validated.(73) Proportion of patients with pain progression (defined as an increase in scores of 30% or greater from baseline or using other established cutoffs) on the BPI at selected time points will be summarized.

The FACT-P is a multidimensional, self-report QOL instrument specifically designed for use with prostate cancer patients (Appendix I). It consists of 27 core items which assess patient function in four domains: Physical, Social/Family, Emotional, and Functional well-being and a supplemental 12-item prostate cancer subscale (PCS). Each item is rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QOL score (transformed on a 0–100 scale, with higher values representing a more favorable healthrelated QOL). This tool has been previously validated and used in the phase III ALSYMPCA study.(13)
For each treatment group, calculated QOL scores will be summarized at baseline and each time point. Changes from baseline will be graphically presented. The effect of treatment will be evaluated using a repeated measures model to incorporate assessments across time into a single analysis, using model contrasts to compare treatment groups at selected time points.

13.7 Reporting and Exclusions

The following Analysis Populations are planned for this study:

Full analysis set (FAS): The FAS will include all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received or any dosing error. Patients who were randomised but did not subsequently receive treatment are included in the FAS. The FAS will be used for all efficacy analyses.

Safety analysis set: The safety population will include all patients who received at least one dose of study treatment. Patients will be analysed in the treatment group according to the study treatment they actually received. The safety population will be used for the analysis of safety data in this study.

Please also refer to section 11.1.1 for Population Evaluable for toxicity and Population Evaluable for Measurable and Non-measurable Response used in this protocol. Unevaluable patients will be included in the analysis of response as non-responders assuming they were eligible and received study drug.

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69. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
70. Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATION SOC.

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APPENDIX A ONCOPANEL GENE LIST

ABCB11	BUB1B	CTNNB1	FAM175A	H3F3B
ABL1	C17ORF70	CUX1	FAM46C	HABP2
ACVR1	C19ORF40	CXCR4	FAN1	HELQ
AKT1	C1ORF86	CYLD	FANCA	HFE
AKT2	CALR	DAXX	FANCB	HIST1H3B
AKT3	CARD11	DCLRE1C	FANCC	HIST1H3C
ALK	CASP8	DDB1	FANCD2	HMBS
APC	CBFA2T3	DDB2	FANCE	HNF1A
AR	CBFB	DDR2	FANCF	HOXB13
ARAF	CBL	DICER1	FANCG	HRAS
ARHGAP35	CBLB	DIS3	FANCI	ID3
ARHGEF12	CCND1	DIS3L2	FANCL	ID4
ARID1A	CCND2	DKC1	FANCM	IDH1
ARID1B	CCND3	DMC1	FAS	IDH2
ARID2	CCNE1	DNMT3A	FAT1	IGF1R
ASXL1	CD274	DOCK8	FBXW7	IGF2
ATM	CD79B	EGFR	FGFR1	IKZF1
ATR	CDC73	EGLN1	FGFR2	IL7R
ATRX	CDH1	ELANE	FGFR3	ITK
AURKA	CDH4	EME1	FGFR4	JAK1
AURKB	CDK12	ENG	FH	JAK2
AXIN2	CDK4	EP300	FLCN	JAK3
AXL	CDK6	EPCAM	FLT1	JAZF1
B2M	CDK8	ERBB2	FLT3	KAT6A
BABAM1	CDKN1A	ERBB3	FLT4	KAT6B
BAP1	CDKN1B	ERBB4	FOXA1	KCNQ1
BARD1	CDKN1C	ERCC1	FOXL2	KDM5A
BCL11B	CDKN2A	ERCC2	FUS	KDM5C
BCL2	CDKN2B	ERCC3	GALNT12	KDM6A
BCL2L1	CDKN2C	ERCC4	GATA2	KDR
BCL2L12	CEBPA	ERCC5	GATA3	KEAP1
BCL6	CHEK1	ERCC6	GATA4	KIF1B
BCOR	CHEK2	ERG	GATA6	KIT
BCORL1	CIC	ESR1	GBA	KLF2
BLM	CIITA	ETV1	GEN1	KLF4
BMPR1A	COL7A1	ETV4	GLI1	KLLN
BRAF	CREBBP	ETV5	GLI2	KMT2A
BRCA1	CRKL	ETV6	GNA11	KMT2D
BRCA2	CRLF2	EWSR1	GNAQ	KRAS
BRCC3	CRTC1	EXO1	GNAS	LIG4
BRD3	CSF3R	EXT1	GPC3	LMO1

BRD4	CTCF	EXT2	GREM1	LMO2
BRE	CTLA4	EZH2	H19	MAF
BRIP1	CTNNA1	FAH	H3F3A	MAFB

MAP2K1	NKX3-1	PRKDC	SBDS	TERT
MAP2K2	NOTCH1	PRSS1	SDHA	TET1
MAP2K4	NOTCH2	PTCH1	SDHAF2	TET2
MAP3K1	NOTCH3	PTEN	SDHB	TFE3
MAPK1	NPM1	PTK2B	SDHC	TLX3
MAX	NR0B1	PTPN11	SDHD	TMEM127
MBD4	NRAS	PTPN14	SERPINA1	TMPRSS2
MCL1	NRG1	PVRL4	SETBP1	TNFAIP3
MCM8	NSD1	QKI	SETD2	TOPBP1
MDM2	NT5C2	RAC1	SF3B1	TP53
MDM4	NTHL1	RAD21	SH2B3	TP53BP1
MECOM	NTRK1	RAD50	SH2D1A	TRAF3
MED12	NTRK2	RAD51	SLC25A13	TRAF7
MEF2B	NTRK3	RAD51C	SLC34A2	TRIM37
MEN1	OGG1	RAD51D	SLX1A	TSC1
MET	PALB2	RAD52	SLX1B	TSC2
MGA	PARK2	RAD54B	SLX4	TSHR
MITF	PAX5	RAF1	SMAD2	U2AF1
MLH1	PAXIP1	RARA	SMAD4	UBE2T
MLH3	PBRM1	RASA1	SMARCA4	UIMC1
MPL	PDCD1LG2	RB1	SMARCB1	UROD
MRE11A	PDGFRA	RBBP8	SMARCE1	USP28
MSH2	PDGFRB	RBM10	SMC3	USP8
MSH6	PHF6	RECQL4	SMO	VEGFA
MTA1	PHOX2B	REL	SOCS1	VHL
MTAP	PIK3C2B	RELA	SOS1	WAS
MTOR	PIK3CA	RET	SOX2	WHSC1
MUS81	PIK3R1	RHBDF2	SOX9	WHSC1L1
MUTYH	PIM1	RHEB	SPOP	WRN
MYB	PML	RHOA	SRSF2	WT1
MYBL1	PMS1	RHOH	SRY	XPA
MYC	PMS2	RHOT1	SS18	XPC
MYCL1	PNKP	RICTOR	STAG2	XPO1
MYCN	POLB	RIF1	STAT3	XRCC1
MYD88	POLD1	RINT1	STAT6	XRCC2
NBN	POLE	RIT1	STK11	XRCC3
NEIL1	POLH	RMRP	SUFU	XRCC4
NEIL2	POLQ	RNF43	SUZ12	XRCC5
NEIL3	POT1	RNF8	TAL1	XRCC6
NF1	PPARG	ROS1	TAL2	YAP1
NF2	PPM1D	RPA1	TAZ	ZNF217
NFE2L2	PPP2R1A	RPTOR	TCEB1	ZNRF3
NFKBIA	PRDM1	RSPO2	TCF3	ZRSR2

NFKBIE	PRF1	RSPO3	TCF7L2
NFKBIZ	PRKAR1A	RUNX1	TDG
NKX2-1	PRKCI	RUNX1T1	TERC

DNA Repair Genes

ATM	EME1	HELQ	PMS2	SLX4
ATR	ERCC1	ID4	POLB	TDG
BABAM1	ERCC2	LIG4	POLD1	TOPBP1
BAP1	ERCC3	MBD4	POLE	TP53
BARD1	ERCC4	MCM8	POLQ	TP53BP1
BLM	ERCC5	MLH1	PPM1D	UBE2T
BRCA1	ERCC6	MRE11A	PRKDC	UIMC1
BRCA2	EXO1	MSH2	PTEN	USP28
BRCC3	FAM175A	MSH6	RAD50	WRN
BRE	FAN1	MUS81	RAD51	XPA
BRIP1	FANCA	MUTYH	RAD51C	XPC
C17ORF70	FANCB	NBN	RAD51D	XRCC1
C19ORF40	FANCC	NEIL1	RAD52	XRCC2
C1ORF86	FANCD2	NEIL2	RAD54B	XRCC3
CDH4	FANCE	NEIL3	RBBP8	XRCC4
CDK12	FANCF	NR0B1	RIF1	XRCC5
CHEK1	FANCG	NTHL1	RINT1	XRCC6
CHEK2	FANCI	OGG1	RNF8	
DCLRE1C	FANCL	PALB2	RPA1	
DDB1	FANCM	PAXIP1	SLX1A	
DMC1	GEN1	PIK3CA	SLX1B	

APPENDIX B 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 C PATIENT STUDY DRUG DIARY

Today's Date: _____
Participant Name: _____
Participant Study ID: _____
Cycle Number: _____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle (28 days).
2. You will take ____ tablets each day by mouth with approximately 240 mL of water. Tablets can be taken with or without food. Tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the comments column.
5. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Otherwise, do not make up the dose. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.
6. Please bring your pill bottle and this form to your physician when you go to your next appointment.

Date	Day	# of 100 mg	# of 150 mg	AM Time	PM Time	Comments	Date	Day	# of 100 mg	# of 150 mg	AM Time	PM Time	Comments
	1							15					
	2							16					
	3							17					
	4							18					
	5							19					
	6							20					
	7							21					
	8							22					
	9							23					
	10							24					
	11							25					

	12							26					
	13							27					
	14							28					

Participant's Signature: _____ Date: _____

Physician's office will complete this section:
Date participant started protocol treatment: _____
Participant's planned daily dose: _____
Total number of pills taken this month: _____
Physician/Nurse/Data Manager's Signature: _____ Date: _____

APPENDIX D PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINCIAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10096

Study Drug(S): Olaparib

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

NIH NATIONAL CANCER INSTI

EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

NIH NATIONAL CANCER INSTI

Tell your doctors before you start or stop any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

Avoid concomitant use of strong CYP3A inhibitors or inducers.

NIH NATIONAL CANCER INSTI NIH NATIONAL CANCER INSTI

DRUG INT :RACTIONS

Carry this card with you at all times enzyme
Olaparib interacts with a specifi your liver and must be with used very carefully ther medicines.

Your healthcare providers should be aware of any medicines that are strong CYP3A inhibitors or inducers. Avoid grapefruit, grapefruit juice, Seville oranges, or Seville orange juice as they may increase concentratio s of olaparib.

Study Drug(S):		**Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a list of **drugs to avoid** or contact your study doctor. Version mmm/yyyy	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX E PATIENT GUIDE ON DIARRHEA MANAGEMENT

Diarrhea is defined as three or more loose or watery stools/bowel movements in one day.

- It may cause an urgent need to go to the bathroom and you want not be stop yourself from having a bowel movement.
- Diarrhea may also cause stomach cramps, bloating, restlessness, sore skin in your rectal area, and (when your body does not have enough liquids). Dehydration can result in thirst, dry mouth, dark yellow urine or need to urinate less frequently.

If you have these symptoms, **call your doctor or nurse**. It is important for you and your doctor to try to manage diarrhea as soon as it begins. As your doctor or nurse if you can be treated with over-the-counter medications.

If you have diarrhea, these tips may also help:

- **Drink lots of liquid** – Diarrhea can cause dehydration. Drinking more will not stop your diarrhea, but it will help make up for the liquids you lose. ○ Drink an extra cup of liquid for every watery bowel movement you have. ○ Drink small amounts many times during the day.
    - Drink liquids slowly. ○ Warm or room temperature liquids may be easier to drink.
    - Avoid drinks with artificial sweetener (like chewing gum, candy, cough drops and "diet" drinks"), when you have diarrhea. These sweeteners may make your gas and diarrhea worse.

- **Diet** – There is no particular food or group of foods that is best while you have diarrhea. However, adequate nutrition is important when having diarrhea. Individuals vary in their tolerance to foods.
    - Eat many small meals and snacks instead of 2 or 3 large meals.
    - Eat slowly, take small bites and chew food well.

- **Plan for outings** – Sometimes diarrhea can cause an urgent need to get to a bathroom. Plan ahead so you can feel more comfortable leaving home. Find the nearest bathroom before you need it when you go out.

- **Take care of your skin** – When you have diarrhea, the skin around your rectal area can get damaged and be painful. To avoid infection or feeling uncomfortable, use these tips to take care of your skin:
    - Take a sitz bath. A sitz bath is a warm, soothing soak for your perineal or rectal area.
    - Leave your bottom open to the air as much as possible. ○ Wear cotton underwear with no elastic around the leg holes.
    - Your health care team may give you an ointment or cream to protect open skin and prevent infections.

- Tell your health care team if your skin is painful, swollen, bleeding a lot or you notice it leaking liquids other than clear or white.

Hydration and Diet Suggestions to Ease Diarrhea

Drinks to help ease diarrhea	**Food to help ease diarrhea**
Water, clear juice, ice chips or popsicles Flat non-fizzy, non-caffeinated drinks Broth, strained clear soup Milk, if your body tolerates it Low lactose milk if you are lactose intolerant Ask your health care team about oral rehydration solutions (a mix of water, salt and sugar that keeps you hydrated)	Fruit like peeled pears, apples, apricots, bananas and canned fruit like apple sauce and peaches Vegetables like cooked and peeled squash, carrots, potatoes, sweet potatoes and turnips Breads and low fiber cereals like oatmeal, cold rice cereal, pasta, white rice and tapioca Protein from foods like eggs, meat, chicken, yogurt and smooth peanut butter
Drinks you should limit	**Foods you should limit**
× Caffeine × Prune juice, fruit juice with pulp × Pop and fizzy drinks × Alcohol × Limit milk and dairy products if they make your diarrhea worse	× Dried and seedy fruits, like prunes, raisins and berries × Spicy foods × Corn, broccoli, chickpeas, lentils, beans, cabbage, onion, garlic × Greasy and fried meats, eggs, sausage, bacon and salami × Whole wheat breads, high fiber cereals and grains × Brown rice, wild rice, quinoa × Raw vegetables and fresh fruits like papaya × Gravy and rich sauces × Sweets and heavy desserts

Blood Requisition Form

A Phase 1/2 Study of Olaparib in Combination with Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer with Bone Metastases

Date:		Protocol Number:	NCI10096
Site Contact Name:		Phone Number:	
Fax Number:		Email Address:	
Institution:		Site PI Name:	
Patient ID:			
Date of Collection:		Time of Collection:	(HH:MM)
Whole Blood for Blood Based Biomarkers □			
Time point (Cycle X/Day X):			
Time Frozen (HH:MM):		# of Vials:	
Initials of individual aliquoting and freezing:			
Whole Blood for PBMCs □			
Time point (Cycle X/Day X):			
Time Frozen (HH:MM):		# of Vials:	
Initials of individual aliquoting and freezing:			

Comments/Deviations from Laboratory Manual:

APPENDIX G FAMILY HISTORY QUESTIONNAIRE

Today's Date: _____
Participant Name: _____
Participant Study ID: _____
Date of Birth: _____

*Please complete this form by listing all family members (**blood relatives**) known to you with a cancer diagnosis. Please identify your relatives using their first name, and first letter of their last name only.*

Relative	Cancer(s) – What Type(s)?	Approximate Age at Diagnosis
Mother		
Father		
Children		
Grandchildren		
Mother's Mother (grandmother)		
Mother's Father (grandfather)		
Father's mother (grandmother)		
Father's father (grandfather)		
Brothers **Example:** John C.	Prostate Cancer	58

Sisters		
Nieces (female children of brothers/sisters)		
Nephews (male children of brothers/sisters)		
Other Relatives on Mother's side **Describe how related:** **Example:** Mary S. Maternal aunt	Ovarian Cancer	67
Other Relatives on Father's side **Describe how related:**		

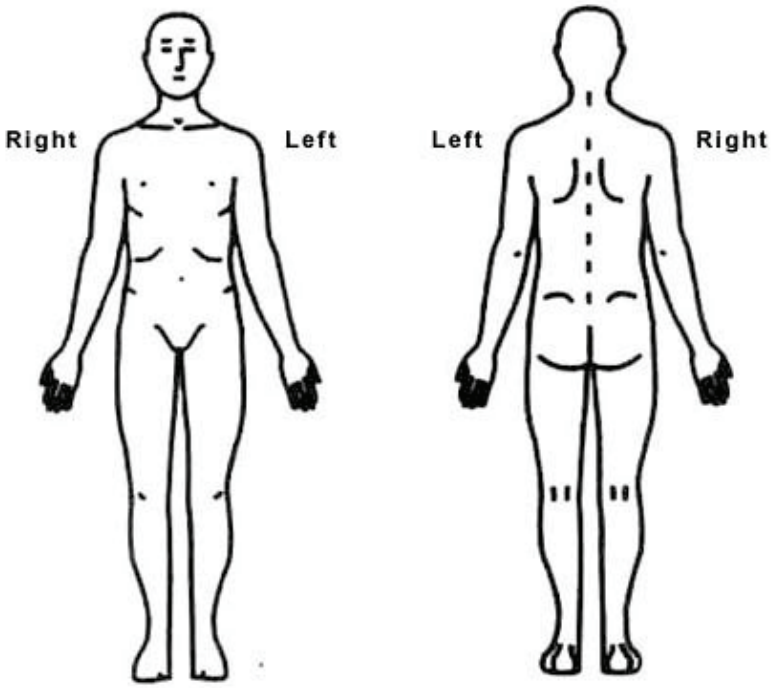
APPENDIX H BRIEF PAIN INVENTORY (SHORT FORM)

Today's Date: _____ Participant Study ID: _____
Participant Name: _____ Cycle Number: _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where your feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the past 24 hours, how much relief have pain treatment or medications provided? Please circle the one percentage that most shows how much RELIEF you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No relief — Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your: A. General activity:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework):

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life:

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

APPENDIX I FACT-P

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1						
GP2	I have a lack of energy	0	1	2	3	4
GP3	I have nausea	0	1	2	3	4
GP4	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP5	I have pain	0	1	2	3	4
	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING **Not at all**	**A little bit**	**Some- what**	**Quite a bit**	**Very much**
GS1					
GS2	I feel close to my friends	0	1	2	3	4
GS3	I get emotional support from my family	0	1	2	3	4
	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.					
Q1 GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1						
GE2	I feel sad	0	1	2	3	4
GE3	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE4	I am losing hope in the fight against my illness	0	1	2	3	4
	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING **Not at all**	**A little bit**	**Some- what**	**Quite a bit**	**Very much**
GF1					
	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

<u>ADDITIONAL CONCERNS</u> **Not at A little Some- Quite Very all bit what a bit much**

C2						
C6	I am losing weight	0	1	2	3	4
P1	I have a good appetite	0	1	2	3	4
P2	I have aches and pains that bother me	0	1	2	3	4
	I have certain parts of my body where I experience pain	0	1	2	3	4
	My pain keeps me from doing things I want to do	0	1	2	3	4
P3	I am satisfied with my present comfort level	0	1	2	3	4
P4	I am able to feel like a man	0	1	2	3	4
P5	I have trouble moving my bowels	0	1	2	3	4
P6	I have difficulty urinating	0	1	2	3	4
P7	I urinate more frequently than usual	0	1	2	3	4
BL2	My problems with urinating limit my activities	0	1	2	3	4
P8 BL5	I am able to have and maintain an erection	0	1	2	3	4