PLATPARP: A Phase II Single-Arm Trial of Niraparib in Platinum-Sensitive Castration-Resistant Prostate Cancer with DNA Repair Defects

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This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including (including 21 CFR Part 312 and *Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH)).*

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Study Summary

Title	**PLATPARP: A Phase II Single-Arm Trial of Niraparib in Platinum-Sensitive Castration-Resistant Prostate Cancer with DNA Repair Defects**
Short Title	Niraparib in Platinum-Sensitive CRPC
IRB Number	834752
Protocol Number	21819
Phase	Phase 2
Methodology	Single-arm, open-label, phase II clinical trial
Study Duration	Approximately 36 months
Study Center(s)	Single-center
Objectives	Primary Objective To evaluate the efficacy of maintenance niraparib by assessment of the 6-month radiographic progression-free survival (rPFS) rate in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects. Secondary Objectives 1. To assess the effects of maintenance niraparib on PSA response rates (PSA30: ≥30% decline and PSA50: ≥50% decline) in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects. 2. To assess the effects of maintenance niraparib on the time to PSA progression (as defined by first PSA increase that is >25% and an absolute increase of ≥ 2 ng/ml from nadir) in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects. 3. To evaluate the safety of maintenance niraparib in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects. 4. To estimate overall survival (OS) following maintenance niraparib therapy in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.
Number of Subjects	18 patients

Main Inclusion and Exclusion Criteria	**Inclusion** 1. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma (mixed histology will be acceptable, but pure small cell histology is to be excluded). 2. ≥ 18 years of age. 3. No prior therapy with PARP inhibitor therapy. 4. Patients must have received at least three 21- or 28-day treatment cycles or a minimum of 9 weeks (regardless of number of cycles) of platinum-based chemotherapy for the treatment of mCRPC as the proximal treatment regimen prior to study screening. Patients must not have evidence of clinical or radiographic disease progression (per Investigator assessment) and should have adequately recovered from chemotherapy-related toxicities (at least 4 weeks following completion of chemotherapy, with treatment-related toxicities ≤ grade 1 per CTCAE version 5.0). 5. ECOG performance status of ≤ 2. 6. Documented evidence of a pathogenic or likely pathogenic DNA repair aberration in *BRCA1/2*, ATM, FANCA, CDK12, RAD51B, RAD54L, PALB2, CHEK2, HDAC2, or BRIP1 through either somatic or germline testing from a CLIA certified laboratory. 7. Radiographic evidence for metastatic disease. Measureable disease (per RECIST) is not required for enrollment. (i.e. bone-only metastatic disease is permitted). 8. History of brain metastases if off systemic corticosteroids for at least 2 weeks. 9. Clinical evidence for castration resistance. 10. Adequate organ function 11. Projected life expectancy of at least 3 months. **Exclusion** 1. Prior PARP inhibitor therapy. 2. Clinically significant cardiovascular disease 3. Known, significant immunodeficiency 4. Clinically significant active infections 5. Known allergy to niraparib or its components 6. Prostate cancer with histologic evidence of pure small cell histology (mixed histology and/or treatment emergent neuroendocrine differentiation are allowable) 7. History or current diagnosis of MDS/AML.
Investigational Product	Niraparib 200 mg daily by oral administration
Statistical Methodology	The primary study endpoint will be the radiographic PFS rate at 6 months (rPFS6), as determined by Kaplan-Meier analysis. rPFS will be defined as the time from the start of study therapy to the first occurrence of radiographic disease progression (using RECIST v1.1 for soft tissue disease, PCWG2 criteria for osseous metastatic disease, or clinical deterioration) as assessed by the investigator, or death from any cause. The null hypothesis is that the rPFS6 rate is 30%, and the alternative hypothesis is that the rPFS6 rate has been increased to 50%.
Safety Evaluations	Toxicity assessment as per CTCAE version 5.0.
Data and Safety Monitoring Plan	The study PI will be responsible for monitoring the data quality and the ongoing safety of subjects. This study will utilize a monitoring plan in accordance with the University of Pennsylvania Abramson Cancer Center's Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan.

1 BACKGROUND AND STUDY RATIONALE

1.1 Study Rationale

Metastatic castration-resistant prostate cancer (mCRPC) represents the lethal phase of the disease, with a median overall survival (OS) of approximately 2-3 years. [1] Although several systemic agents, including androgen signaling inhibitors, taxane chemotherapies, and radiopharmaceuticals are available for the treatment of mCRPC, each is associated with variable response rates of modest duration and an improvement in the median OS of only 3-5 months. [2] Furthermore, while mCRPC exhibits marked interpatient heterogeneity, clinically- or molecularly-defined predictive markers are sorely lacking for commonly used systemic therapies. Therefore, novel treatment strategies in defined patient populations are critically important.

1.2 Background and Relevant Literature

1.2.1 Platinum-based Chemotherapy Yields Moderate Response Rates of Short Duration in Advanced Prostate Cancer

Platinum-based chemotherapy, either as monotherapy or in combination with taxanes, has long been studied in the treatment of advanced prostate cancer. Platinum compounds exert their cytotoxic activity through the formation of covalent adducts with cellular DNA, thereby resulting in DNA damage. [3] While no platinum-based treatment has yet received regulatory approval for prostate cancer, platinum remains a useful treatment option in CRPC patients refractory to available systemic therapies. Indeed, pooled analysis of > 70 clinical trials of platinum-based therapy in molecularly unselected advanced prostate cancer patients demonstrates moderate anti-tumor activity (ORR or ~10 – 40%; PSA decline ≥ 50% of ~ 20 – 70%).[3,4] Although a randomized phase III trial of the orally available platinum derivative satraplatin failed to meet its primary endpoint of OS improvement, satraplatin did result in significant improvements in progression-free survival (PFS), PSA response, pain response, and quality of life. [5] Furthermore, platinum-based therapy has an established role in the management of clinically-defined aggressive variant prostate cancers, as well as disease with high-grade neuroendocrine differentiation. [6] However, these observed responses with platinum-based therapy are often of limited duration and may be limited by cumulative treatment-related toxicities (including fatigue, cytopenias, and neuropathy). As a result, novel strategies enabling more durable treatment responses are highly desired.

1.2.2 DNA Damage Repair Aberrations Are Common in mCRPC and may be Therapeutically Targeted

Next-generation sequencing studies of advanced prostate cancer have identified enrichment of mutations in DNA repair genes among patients with mCRPC. [7] Indeed, the prevalence of aberrations in key DNA repair genes in mCRPC is estimated at 20-30%, most commonly as alterations in homologous recombination (HR)-mediated repair genes (including *BRCA2* and ATM). [7-9] Based on the established biologic concept of synthetic lethality, PARP inhibition was hypothesized to result in clinical responses in mCRPC lacking HR repair capacity. Importantly, this hypothesis was tested in the TOPARP-A trial, in which antitumor activity of the PARP inhibitor olaparib was strongly associated with the presence of mutations or homozygous deletions in DNA repair genes. [9]

In addition, the identified prevalence of DNA repair defects in advanced prostate cancer, as well as the demonstrated responses to platinum therapies in HR-deficient (HRD) breast, ovarian, and pancreatic cancers, has re-invigorated the investigation of platinum therapies in mCRPC. Retrospective series have reported longer benefit from carboplatin in prostate cancer cases with HR defects. Similarly, small case series have reported marked tumor responses to carboplatin in mCRPC patients with biallelic *BRCA2* loss.[10] As a result, several prospective trials are currently evaluating carboplatin-based chemotherapy regimens in advanced prostate patients selected for DNA damage repair defects (NCT02598895, NCT02985021).

1.2.3 Platinum Sensitivity May Predict Improved Clinical Outcomes with PARP inhibition in mCRPC

Based on the observed prevalence of DNA repair defects in breast and ovarian malignancies, as well as the observed responses among HRD selected patients to both PARP inhibitors and platinum chemotherapy, cross-sensitivity between platinum agents and PARP inhibitors has been hypothesized. Indeed, in platinum-sensitive metastatic ovarian cancer, maintenance therapy with the PARP inhibitors niraparib or olaparib has demonstrated significant improvements in median PFS relative to placebo. [11,12] While this clinical benefit has been reported regardless of germline *BRCA* mutation or HRD status, platinum-sensitive ovarian cancer patients with a deleterious *BRCA* mutation (germline or tumor) have demonstrated the greatest likelihood of benefiting from such PARP inhibitor maintenance treatment. [13,14] These findings demonstrate that PARP inhibitor maintenance strategies in platinum-sensitive advanced cancer patients are both feasible and effective. Indeed, this concept is planned to be tested in advanced prostate cancer patients unselected for DNA repair defects (NCT03263650).

This background therefore provides the rationale for an open-label phase II study to evaluate the preliminary clinical benefit of maintenance niraparib in a biomarker-defined platinum-sensitive mCRPC patient population. We hypothesize that maintenance niraparib, a well-tolerated oral agent, will consolidate and prolong tumor responses to platinum-based chemotherapy among mCRPC patients harboring germline or somatic DNA repair defects.

1.3 Name and Description of the Investigational Product

Niraparib is an orally available, potent, and highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)1 and PARP2 inhibitor. Based on the concept of synthetic lethality, niraparib exhibits anti-tumor activity in tumors containing *BRCA* mutations or other evidence for homologous recombination deficiency (HRD) by commercially available testing.

Niraparib is currently being developed as a therapy for tumors with defects in the homologous recombination DNA repair pathway including ovarian cancer, triple-negative breast cancer (TNBC), non-small cell lung cancer, and prostate cancer (either as a monotherapy or in combination with immunotherapy or androgen receptor-targeted therapies). Thus far, niraparib, at a dose of 300 mg once daily, has achieved clinical indication for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response or partial response following platinum-based chemotherapy.

1.3.1 Nonclinical Data

Refer to the Niraparib IB for detailed nonclinical data.

Anti-tumor/Pharmacodynamic Effects

Niraparib functions as an inhibitor of DNA repair processes to selectively kill tumor cells, particularly in the context of HRD and consequent synthetic lethality.

Although PARP1 and PARP2 have been functionally linked to several DNA repair mechanisms, PARP1 and PARP2 activity is most tightly linked to the base excision repair (BER) pathway and the repair of single-strand breaks (SSBs) in DNA. Niraparib was evaluated in biochemical assays to determine its potency and selectivity against PARP enzymes. Biochemical assays showed that niraparib was selective for PARP1 and PARP2 with an IC50 of <4 nM and displayed a >100-fold window over other PARP family members. The primary circulating metabolite, M1, did not inhibit PARP1 or PARP2. A mechanism of action proposed for niraparib involves the trapping of PARP onto SSBs by inhibiting auto-PARylation and PARP release from the DNA. Trapping of PARP/niraparib complexes on damaged DNA inhibits the recruitment of DNA repair proteins and, thus, the repair of SSBs.

In addition to its role in the BER pathway, PARP also functions in the nucleotide excision repair (NER) pathway, in the restart of stalled replication forks, and in double stranded break (DSB) repair. Inhibition of PARP1 and PARP2 results in the accumulation of DSBs and, in an HRD cell, necessitates the use of alternative DNA repair pathways, including the more error-prone non-homologous end-joining (NHEJ).

Over-dependence upon the NHEJ pathway leads to subsequent genomic instability and ultimately cell death.

Several *in vivo* pharmacology studies have been conducted with niraparib as monotherapy demonstrating anti-tumor activity. In a cell line-derived human xenograft murine model of ovarian cancer with a functional *BRCA1* mutation, continual niraparib administration demonstrated substantial tumor regression and supported a rationale for continuous dosing of niraparib. In a study to evaluate the potential therapeutic effect of single-agent niraparib monotherapy on HRD-positive high-grade serous ovarian cancers, a response rate of 52% (10 out of 19) was observed in treatment-naïve mice PDX models demonstrating HRD (by the Myriad myChoice HRD test). These results supported that tumors with *BRCA* mutations or HRD-positive/*BRCA*wt status demonstrated higher response rate and greater tumor inhibition than HRD-negative tumors.

Pharmacokinetic Effects
The absorption, distribution, metabolism, and elimination (ADME) of niraparib in nonclinical species, demonstrated rapid and high absorption, with extensive distribution to the tissues. Niraparib was concentrated in tumor relative to plasma, and exhibits moderate protein binding (approximately 83% bound to human plasma proteins, mainly human serum albumin). Cytochrome P450s (CYPs) play a minimal role in niraparib metabolism. The major, primary metabolite is the carboxylic acid (M1), which is subsequently converted to the glucuronide (M10). Elimination occurred primarily via the renal and fecal routes in the nonclinical species as well as in humans.

Toxicology
A comprehensive toxicology program was conducted that supported the oral administration of niraparib in humans. Oral repeat-dose toxicity studies of up to 3 months of daily dosing were performed in rats and dogs. The results obtained from the general toxicity studies were similar in both species and indicate that the bone marrow and the testes are the target organs of niraparib. The no-observed-adverse-effect-level (NOAEL) in rats after 1 or 3 months of dosing was 10 mg/kg/day. The NOAEL in dogs after 1 month of dosing in male animals was 3 mg/kg/day and 6 mg/kg/day in females. After 3 months of dosing, the NOAEL in male dogs was 4.5 mg/kg/day and 12 mg/kg/day in female dogs.

Bone marrow suppression affected cells in the leukocytic, erythrocytic, and megakaryocytic lineages. Spermatogenic epithelium was decreased in both species. These adverse findings are considered to reflect the pharmacology of niraparib. The findings can be monitored, are dose-related, and are reproducible across studies and species. All findings were reversible or trended toward reversibility during recovery in both species.

1.3.2 Clinical Data to Date

Human Pharmacokinetics
The PK profile of niraparib has primarily been investigated in 3 clinical studies performed in patients with cancer and 1 additional food effect sub-study.

Niraparib is rapidly absorbed following oral dosing, with time to maximum plasma concentration (tmax) occurring within 3 hours. The absolute bioavailability of niraparib is approximately 73%. Systemic exposure to niraparib (Cmax and area under the plasma concentration time curve [AUC]) following oral doses over the range of 30 to 400 mg is dose proportional.

Having a high-fat meal (defined as 800 to 1,000 calories with approximately 50% of total caloric content of the meal derived from fat) prior to the time of dosing did not significantly affect the PK of niraparib. The average t½ of niraparib ranges from 32.8 to 46.0 hours over the 60- to 400-mg dose range.

Hepatobiliary clearance and renal excretion are the major routes of elimination for niraparib in humans. In pooled samples collected over 6 days, unchanged niraparib accounted for 11% and 19% of the administered dose recovered in urine and feces, respectively. Collectively, these data suggest minimal long-term body retention of niraparib and its metabolites.

Age, race/ethnicity, and mild to moderate renal impairment had no clinically significant effect on the PK of niraparib.

1.3.3 Clinical Studies in Adults

Clinical Safety

The Pooled Safety Population for niraparib is derived from 14 studies conducted prior to and following its approval. These studies vary in phase (1 through 3) and dose level, and the full Pooled Safety Population consists of a total of 1,379 patients who have received any amount of niraparib as monotherapy or in combination therapy as of 19 August 2018. Single-agent niraparib (30 to 400 mg QD) was administered in 10 studies (1,168 patients), and niraparib in combination with pembrolizumab, TSR-042, or bevacizumab was evaluated in 4 studies (211 patients).

In the Pooled Safety Population, over 98% of niraparib-treated patients reported at least 1 TEAE. Approximately 72% of patients experienced an event that was Grade 3 or higher in severity. TEAEs leading to treatment discontinuation occurred in approximately 18% of patients. TEAEs leading to death occurred in 29 of 1,379 (2.1%) patients.

The most frequently reported TEAEs (≥20%) were primarily gastrointestinal (e.g., nausea, vomiting, and constipation), constitutional (e.g., fatigue and decreased appetite), hematological (e.g., anemia and thrombocytopenia), neurological (e.g., headache), or psychiatric (e.g., insomnia) in nature. The events were generally considered related to study drug but were mostly mild (Grade 1) to moderate (Grade 2) in severity. Grade 3 or higher TEAEs consisted primarily of hematological events (e.g., anemia, thrombocytopenia, and neutropenia) and investigations (e.g., platelet count decreased and neutrophil count decreased), followed by gastrointestinal events (nausea, vomiting, and abdominal pain).

In terms of serious AEs only serious thrombocytopenia and serious anemia were considered to be drug-related by the investigator in 2% or more of niraparib-treated patients. Serious vomiting, neutropenia, and nausea were considered related to study drug in ≥1% but <2% of patients.

In the Pooled Safety Population, 29 patients (2.1%) have experienced a serious TEAE that resulted in death. Three serious TEAEs leading to death, acute myeloid leukemia (AML), gastric hemorrhage, and acute respiratory distress syndrome, were considered related or likely related to study drug.

Clinical Efficacy

Efficacy data are available from 2 clinical studies of niraparib monotherapy.

NOVA Study

The efficacy of niraparib as maintenance treatment in patients with platinum-sensitive, recurrent OC was demonstrated in the NOVA study, a randomized, double-blind, placebo-controlled Phase 3 trial to assess the importance of biomarker-based patient selection for maintenance treatment with a PARP inhibitor in this patient population. The PFS was significantly longer for patients who received niraparib compared to those who received placebo in both cohorts. Within the g*BRCA*mut cohort, the median PFS was 21.0 months with niraparib versus 5.5 months with placebo (HR, 0.27; 95% CI, 0.173 to 0.410; p <0.001) and in the non-g*BRCA*mut cohort, the median PFS was 9.3 months with niraparib versus 3.9 months with placebo (HR, 0.45; 95% CI, 0.338 to 0.607; p <0.001). PFS was also significantly longer with niraparib than with placebo in the HRDpos group of the non-g*BRCA*mut cohort (median, 12.9 months versus 3.8 months; HR, 0.38; 95% CI, 0.243 to 0.586; p <0.001).

Secondary endpoints, including CFI, TFST, time to second subsequent therapy, and PFS2, demonstrated a persistent treatment effect in favor of the niraparib treatment arm in the g*BRCA*mut and the overall non-g*BRCA*mut cohorts, and no detrimental impact of niraparib treatment on OS was observed. The robustness of the results was supported by sensitivity analyses that were consistent with the primary efficacy analyses. Importantly, dose reductions had no impact on PFS outcomes.

Quadra Study
The efficacy of niraparib as a monotherapy was evaluated in QUADRA, a Phase 2, open-label, single-arm study in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 3 or more previous chemotherapy regimens. The primary analysis population was a subset of the intent-to-treat (ITT) population and consisted of 47 patients who received 3 or 4 prior lines of treatment, had HRDpos tumors, were sensitive to platinum-based therapy, and were PARP inhibitor (PARPi)-naïve. The study met its primary endpoint in this population, with a RECIST objective response rate (ORR) of 27.7% (95% CI, 15.6% to 42.6%, p=0.0005). The results were similar in the response evaluable population (defined as all ITT patients with at least 1 evaluable post-baseline tumor scan); ORR was 30.2% (95% CI, 17.2% to 46.1%, p=0.0002).

Results for secondary efficacy variables in the 47 patients in the primary analysis population were median duration of response of 9.2 months, disease control rate of 68.1%, median PFS of 5.5 months, and median TFST of 8.6 months. Median OS was not reached (95% CI, 18.5, NE).

Clinical benefit was observed as a continuum along the *BRCA* and HRD status and platinum response status. ORR was highest in patients with *BRCA*mut tumors (28.6%), followed by HRDpos tumors (15.3%). While ORR was 2.7% in patients with HRDneg tumors, the clinical benefit rate at 16 and 24 weeks in this group was 23.7% and 14.0%, respectively, and the median OS was 15.5 months (95% CI, 11.6 to 19.0).

1.4 Dose Rationale

The approved dose of niraparib as maintenance treatment for recurrent ovarian, fallopian tube, or primary peritoneal cancer is 300 mg once daily. The proposed trial population is relatively similar in nature to this approved population. Patients must have received at least three 21- or 28-day treatment cycles or a minimum of 9 weeks (regardless of number of cycles) of platinum-based chemotherapy for the treatment of mCRPC as the proximal treatment regimen prior to study screening. Patients must not have evidence of clinical or radiographic disease progression (per Investigator assessment) and should have adequately recovered from chemotherapy-related toxicities (at least 4 weeks following completion of chemotherapy, with treatment-related toxicities ≤ grade 1 per CTCAE version 5). However, as men with prostate cancer are often prone to hematologic toxicities of therapy, owing to prior systemic chemotherapy and pelvic radiation therapy with resultant bone marrow toxicity, particular attention to hematologic toxicity is warranted for this study. Notably, a reduced dosing strategy for niraparib or 200 mg daily has been utilized in patients at risk for hematologic toxicity.[15] This reduced dose strategy will be used in this protocol. This niraparib dosing has been demonstrated to have a favorable risk:benefit profile, with clear clinically meaningful benefit. The most commonly reported adverse drug reactions occurring in 10% or more of the patients in clinical trials were as follows: nausea, vomiting, constipation, anemia, thrombocytopenia, neutropenia, fatigue, platelet count decreased, white blood cell count decreased, neutrophil count decreased, decreased appetite, and headache.

The occurrence of these adverse events is consistent with the mechanism of action of niraparib. These adverse events are readily manageable with established dose modifications.

2 Study Objectives

2.1 Primary Objective

To evaluate the efficacy of maintenance niraparib by assessment of the 6-month radiographic progression-free survival (rPFS) rate in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.

2.2 Secondary Objectives

1. To assess the effects of maintenance niraparib on PSA response rates (PSA30: ≥30% decline and PSA50: ≥50% decline) in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.

2. To assess the effects of maintenance niraparib on the time to PSA progression (as defined by first PSA increase that is >25% and an absolute increase of ≥ 2 ng/ml from nadir) in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.

3. To evaluate the safety of maintenance niraparib in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.

4. To estimate overall survival (OS) following maintenance niraparib therapy in patients with platinum-sensitive mCRPC harboring germline or somatic DNA repair defects.

3 Investigational Plan

3.1 General Design

This is a single-institution, open-label phase II study to evaluate the preliminary clinical benefit of maintenance niraparib in a biomarker-defined platinum-sensitive mCRPC patient population. We hypothesize that maintenance niraparib, a well-tolerated oral agent, will consolidate and prolong tumor responses to platinum-based chemotherapy among mCRPC patients harboring germline or somatic DNA repair defects. Eligible subjects will include patients with mCRPC who have recently received at least three treatment cycles or a minimum of 9 weeks of platinum-based chemotherapy for the treatment of mCRPC. Following completion of chemotherapy, subjects without evidence of clinical or radiographic disease progression (including those patients with stable disease) and who have adequately recovered from chemotherapy-related toxicities (at least 4 weeks following completion of chemotherapy) will be eligible for enrollment and study treatment with maintenance niraparib at a planned starting dose of 200 mg daily. The primary objective will be to evaluate the progression-free survival rate at 6 months (PFS6) in 18 treated subjects.

3.1.1 Screening Phase

All patients will undergo screening assessments within 28 calendar days prior to the first dose of study therapy. AEs that occur after signing of the informed consent form and before administration of the first dose of study therapy will also be collected during this period.

Screening assessments will include demographics and medical history, prior treatments for prostate cancer, prior and current medications and procedures, 12-lead electrocardiogram (ECG), ECOG performance status, hematology, serum chemistry, physical examination, vital signs, weight and height measurements, adverse events, and radiological assessments. There is an optional submission of a tumor tissue specimen where available (from newly-obtained or archived tissue) will be requested for planned correlative analyses. Written consent will be obtained before screening procedures are initiated.

3.1.2 Study Intervention Phase

Following completion of screening procedures and confirmation of study eligibility, the treatment phase will begin with niraparib 200 mg daily as maintenance treatment following platinum-based chemotherapy. Treatment will continue on 28 calendar day cycles (28 calendar days = 1 treatment cycle).

During the treatment phase, patients will be monitored for both safety and efficacy. All patients receiving study drug will be evaluated for study objectives. Assessments during the treatment phase will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, 12-lead ECG (only if clinically indicated), hematology and serum chemistry, serum PSA, and blood collection for storage for correlative analyses.

Patients will be assessed for disease status per RECIST v1.1 for soft tissue disease and PCWG3 criteria for bone metastases every 12 weeks (± 7 calendar days) from the first study treatment. Treatment will continue until documented progression, unmanageable toxicity, or subject or treating investigator decision to discontinue for any reason.

Patients will be monitored continuously for safety. The Data and Safety Monitoring Committee (DSMC) of the University of Pennsylvania (Penn) Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) will evaluate safety and efficacy in compliance with a charter.

3.1.3 Follow Up Phase

Treatment Discontinuation
Upon treatment discontinuation, all patients will return to the clinic for an End of Treatment (EOT) visit. Assessments at this visit will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, hematology and serum chemistry, serum PSA, blood sample for correlative analyses, and disease status assessment.

Follow-up
All patients will have a 30 calendar day (±7 days) follow-up period for AEs following the last dose of study therapy. This follow-up visit may be combined with the EOT visit as scheduling allows.

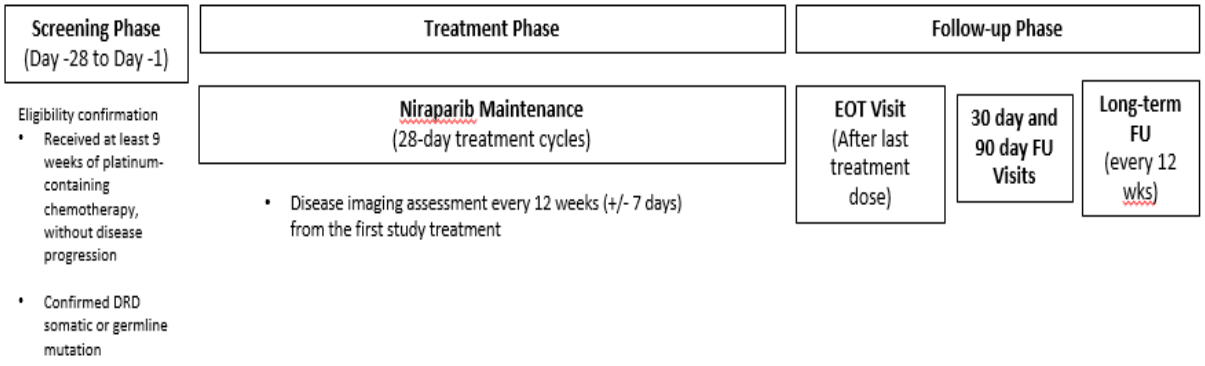
All patients will also have a 90-day (± 3 weeks) follow-up evaluation (either via telephone call or site visit) for AEs following the last dose of study therapy. If a telephone call is performed for this 90-day follow-up evaluation, a subsequent site visit may be requested in case any concerns are noted during the telephone call.

After the 90-day follow-up visit, patients will be followed for survival every 12 weeks (± 3 weeks) until death, loss to follow-up, withdrawal of consent, or study closure.

For patients who discontinue treatment without evidence for documented progression, patients will continue to be assessed for disease status per RECIST v1.1 for soft tissue disease, PCWG3 criteria for bone metastases, and serum PSA, every 12 weeks (±7 calendar days) from the first study treatment (until documented progression, initiation of new anti-cancer therapy, or withdrawal of consent).

End of Study
The trial will be completed when all enrolled patients have discontinued study treatment or have experienced progressive disease.

3.1.4 Study Schema



3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary study endpoint will be the radiographic PFS rate at 6 months (rPFS6), as determined by Kaplan-Meier analysis. rPFS will be defined as the time from the start of study therapy to the first occurrence of radiographic disease progression (using RECIST v1.1 for soft tissue disease, PCWG2 criteria for osseous metastatic disease, or clinical deterioration) as assessed by the investigator, or death from any cause.

3.2.2 Secondary Study Endpoints

Secondary study endpoints will include:

- PSA30, defined as the proportion of patients achieving a ≥30% decline in PSA following the initiation of niraparib maintenance therapy.
- PSA50, defined as the proportion of patients achieving a ≥50% decline in PSA following the initiation of niraparib maintenance therapy.
- Time to PSA progression, defined by the time until the first PSA increase that is >25% (and an absolute increase of ≥ 2 ng/ml) from the nadir PSA value following the initiation of niraparib maintenance therapy.
- Safety, as defined by the frequency and severity of adverse events (AEs), as assessed by CTCAE version 5.0 following the initiation of niraparib maintenance niraparib therapy.
- Overall survival (OS), defined as the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma (mixed histology will be acceptable, but pure small cell histology is to be excluded).
2. ≥ 18 years of age.
3. No prior therapy with PARP inhibitor therapy.
4. Patients must have received at least three 21- or 28-day treatment cycles or a minimum of 9 weeks (regardless of number of cycles) of platinum-based chemotherapy for the treatment of mCRPC as the proximal treatment regimen prior to study screening. Patients must not have evidence of clinical or radiographic disease progression (per Investigator assessment) and should have adequately recovered from chemotherapy-related toxicities (at least 4 weeks following completion of chemotherapy, with treatment-related toxicities ≤ grade 1 per CTCAE version 5.0).
5. ECOG performance status of ≤ 2.
6. Documented evidence of a pathogenic or likely pathogenic DNA repair aberration in *BRCA1/2*, ATM, FANCA, CDK12, RAD51B, RAD54L, PALB2, CHEK2, HDAC2, or BRIP1 through either somatic or germline testing from a CLIA certified laboratory.
7. Radiographic evidence for metastatic disease. Measureable disease (per RECIST) is not required for enrollment. (i.e. bone-only metastatic disease is permitted).
8. Patients with history of treated brain metastases are eligible if off systemic corticosteroids for at least 2 weeks.

9. Clinical evidence for castration-resistance, with total testosterone < 50 ng/dL. Patients who have not undergone bilateral orchiectomy must plan to continue ongoing androgen deprivation therapy for the duration of the trial therapy.

10. Patients must have adequate organ function, as confirmed by laboratory values obtained ≤ 14 calendar days prior to the first day of study therapy:

    Hematologic: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

    Hepatic: Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver). (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)

    Renal: Serum creatinine < 2 times the ULN (or estimated creatinine clearance ≥ 45 mL/min using Cockcroft Gault formula).

11. Patients must have a projected life expectancy of at least 3 months.

4.2 Exclusion Criteria

1. Prior therapy with a PARP inhibitor.

2. Presence of clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

3. Presence of known significant immunodeficiency, as determined by the treating investigator.

4. Presence of clinically significant active infections, as determined by the treating investigator.

5. Known allergy to niraparib or any of its components.

6. Prostate cancer with histologic evidence for pure small cell histology (mixed histology and/or treatment emergent neuroendocrine differentiation are allowable)

7. History or current diagnosis of MDS/AML.

4.3 Subject Recruitment

Subjects will be recruited for the study from investigator and sub-investigator clinical practices, referring physicians, and through public notification via clinicaltrials.gov. Patients will be enrolled over a planned period of approximately 24 months.

4.4 Total Number of Subjects and Sites

18 patients will be enrolled at the University of Pennsylvania. It is expected that approximately 30 patients will be screened in order to enroll 18 patients.

4.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. As the study population is men with castration-resistant prostate cancer, women are not allowed to participate in this study.

5 Study Intervention

Niraparib 200 mg by mouth daily (2 x 100 mg pills)

5.1 Description

The niraparib drug substance is a crystalline tosylate monohydrate salt. This salt is a nonhygroscopic, white to off-white powder. The niraparib drug product is provided as either 100-mg capsules filled with a dry blend of 159 mg niraparib tosylate monohydrate (equivalent to 100 mg free base), lactose monohydrate, and magnesium stearate in a hard gelatin capsule, or as film-coated tablets manufactured to facilitate individual tablet strengths that contain either 159, 319, or 478 mg niraparib tosylate monohydrate drug substance, equivalent to 100, 200, or 300 mg of niraparib free base, respectively, as the active ingredient.

5.2 Intervention Regimen and Dose Modifications

Treatment will entail niraparib 200 mg PO (2 x 100 mg pills) self-administered daily on 28-day treatment cycles (28 calendar days = 1 treatment cycle). Patients will be encouraged to take their dose (200 mg) of niraparib at approximately the same time each day. Doses can be taken with or without food. In the case of a missed dose of niraparib, patients will be instructed to take their next dose at its regularly scheduled time. Patients will complete study drug diaries below. Treatment will continue until documented progression, unmanageable toxicity, or subject or treating investigator decision to discontinue for any reason. Niraparib should be discontinued for a diagnosis of MDS/AML confirmed by a hematologist.

Table 1 Niraparib Dose Levels for Dose Reductions

Dose Level	Niraparib Dose
Level 0	200 mg daily
Level -1	100 mg daily

Table 2 Suggested Dose Modifications for Treatment-Related Toxicity

Hematologic Toxicity	Suggested Management
Grade 1 and Grade 2	No requirement for dose interruption or reduction
Grade ≥ 3 anemia, neutropenia, or thrombocytopenia	• Hold niraparib and monitor weekly until resolves to baseline hemoglobin, ANC ≥ 1500/ul, PLT ≥ 75,000 • Consider reducing niraparib by 1 dose level • Permanently discontinue if toxicity lasting > 4 weeks without adequate recovery to baseline
Non-Hematologic Toxicity	**Suggested Management**
Grade 1 and Grade 2	No requirement for dose interruption or reduction
Grade ≥ 3	• Consider interruption of niraparib until toxicity is ≤ Grade 1 or at subject's baseline. • Consider reducing niraparib by 1 dose level.

5.3 Receipt

Supply of the study drug niraparib will be provided by Janssen as the funding supporter for this investigator-initiated study. Study drug will be dispensed as per the Abramson Cancer Center investigational drug service (IDS).

5.4 Storage

Niraparib will be stored in accordance with directions provided in the Pharmacy Manual. Prior to dispensing, niraparib will be stored in a securely locked area, accessible to authorized study personnel only.

5.5 Preparation and Packaging

Both niraparib 100 mg capsules and niraparib tablets (100, 200, and 300 mg) are packaged in high-density polyethylene (HDPE) bottles fitted with child-resistant plastic closures (CRC).

5.6 Subject Compliance Monitoring

Documentation of dosing will be recorded in a study specific dosing diary. Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency, and the number of tablets to be taken for each dose. Patients will be instructed to record dosing information for niraparib taken at home in the dosing diary and to bring the dosing diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Every effort will be made to ensure patients complete the dosing diary and return their study drug containers at the end of each treatment cycle.

5.7 Return or Destruction of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed on-site in accordance with standard policies for the destruction of investigational agents.

6 Study Procedures

All study procedures are listed in the Schedule of Events. Details on specific events are outlined within this section.

6.1 Screening

Following written informed consent, and unless otherwise specified, the following assessments will be performed during the 28-day period prior to the first dose of study therapy. Assessments performed within this window, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard or care.

- Informed Consent
- Medical/Oncologic history, including date of cancer diagnosis, prior treatments and any surgical or radiation therapy procedures
- Prior and concomitant medications
- Confirmation of a pathogenic DNA repair aberration through either somatic or germline testing from a CLIA certified laboratory
- Demographic information (birth date, race, ethnicity)
- Physical examination, including height and weight
- Vital signs (blood pressure, heart rate, temperature)
- ECOG performance status
- 12-lead ECG
- AE monitoring
- Hematology (hemoglobin, WBC and differential [with ANC], and platelet count)
- Serum chemistry (albumin, creatinine, BUN, total bilirubin, ALKP, ALT, AST, glucose, sodium, potassium, chloride, CO2, calcium)
- Total testosterone
- Serum PSA
- Tumor assessments, including clinical examination, and appropriate imaging (including CT C/A/P, nuclear bone scan). MRI imaging may be substituted for CT abdomen/pelvis imaging, per

investigator discretion. Efforts should be made to use the same methods used to detect lesions at Screening to follow the same lesions throughout the clinical study.
- Optional submission of an FFPE archival tissue sample or at least 10 (5 µm) unstained slides, if available, for correlative research studies

6.2 Study Intervention Phase

Participants will be asked to come in every 28 calendar days (±3 days) after the first treatment day (Cycle 1, Day 1). The starting dose of niraparib is 200 mg PO daily (2 x 100 mg pills). The specific tests and procedures for each visit day are listed herein.

In addition to the visit procedures below, CBC must be performed weekly for the first month of treatment, then monthly thereafter, including within 30 days of the last dose of the study drug. Additionally, blood pressure and heart rate must be monitored weekly for the first two months of treatment, then monthly thereafter.

6.2.1 Cycle 1, Day 1 (Baseline Visit, Study Treatment Initiation)

Following confirmation of study eligibility criteria, the patient will initiate maintenance treatment with niraparib. Specific tests and procedures for this visit are listed below, including administration of niraparib of 200 mg PO daily (2 x 100 mg pills). Patients also will be instructed on how to complete the dosing diary. The following assessments will be performed on Cycle 1, Day 1:

- Medical history and concomitant medications and procedures
- Physical examination including weight
- Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed weekly during Cycles 1 and 2
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology (if not performed within the preceding 14 calendar days)
    - CBC must be performed weekly during Cycle 1
- Serum chemistry (if not performed within the preceding 14 calendar days)
- Serum PSA (if not performed within the preceding 14 calendar days)
- Research blood samples
- Dispense niraparib
- Instruct patient on drug dosing diary use/adherence

6.2.2 Cycle 1, Day 15 (± 3 days)

The patient will return for toxicity assessment on day 15 (± 3 days) of Cycle 1 of study treatment. The following assessments will be performed at this visit.

- Medical history and concomitant medications and procedures
- Physical examination including weight
- Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed weekly during Cycles 1 and 2
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology
    - CBC must be performed weekly during Cycle 1

- Serum chemistry
- Review of study drug diary
- Tablet count

6.2.3 Cycles 2 and 3 (± 3 days)

The following procedures will be performed for all patients for Cycles 2 and 3.

- Medical history and concomitant medications and procedures
- Physical examination including weight
- Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed weekly during Cycle 2 and then monthly during Cycle 3
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology
    - CBC must be performed monthly
- Serum chemistry
- Serum PSA
- Review of study drug diary
- Tablet count
- Research blood samples **(Cycle 2 only)**

6.2.4 Cycle 4 and all Subsequent Cycles (± 3 days)

The following procedures will be performed for all patients every 28 calendar days (± 3 days).

- Medical history and concomitant medications and procedures
- Physical examination including weight
- Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed monthly during Cycles 4 and beyond
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology
    - CBC must be performed monthly
- Serum chemistry
- Serum PSA
- Review of study drug diary
- Tablet count
- Research blood samples **(Cycle 4 only)**
- Disease Imaging
    - Disease Imaging assessment will continue every 12 weeks (± 7 calendar days) from the first study treatment while patient remains on study therapy

Treatment will continue until documented progression, unmanageable toxicity, or subject or treating investigator decision to discontinue for any reason.

6.3 Follow Up Phase of the Study

6.3.1 End of Treatment (EOT) Visit

The following procedures will be performed for all patients as soon as possible upon treatment discontinuation. The EOT Visit procedures may be combined with the 30 Day Follow-up Visit procedures, as circumstances allow.

- Medical history and concomitant medications and procedures
- Physical examination including weight
- Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed if not done within the last 4 weeks.
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology
    - CBC must be performed within 30 days of last dose of study drug
- Serum chemistry
- Disease Imaging should be performed if treatment was discontinued for reason other than radiologic disease progression and if not performed within the preceding 8 weeks.
- Research blood samples

6.3.2 30 Day Follow-up Visit (± 7 days)

The following procedures will be performed for all patients at 30 calendar days (± 7 days) after the last dose of study therapy. The 30 Day Follow-up Visit procedures may be combined with the EOT Visit, as circumstances allow.

- Medical history and concomitant medications and procedures
- Physical examination including weight
    - Vital signs (blood pressure, heart rate, temperature)
    - Blood pressure and heart rate must be performed
- ECOG performance status
- 12-lead ECG – Only if clinically indicated
- AE monitoring
- Hematology
    - CBC must be performed within 30 days of last dose of study drug
- Serum chemistry
- Serum PSA

6.3.3 90 Day Follow-up Visit (± 3 weeks)

The following procedures will be performed for all patients at 90 calendar days (± 3 Weeks) after the last dose of study therapy.

- AE monitoring
- Overall survival information

This 90-day follow-up can be performed via a telephone call, with a subsequent site visit requested in case any concerns are noted during the telephone call.

6.3.4 Long-Term Follow-up Every 12 weeks (± 3 weeks)

Following the 90-day follow-up evaluation, the following procedures will be performed for all patients every 12 weeks (± 3 weeks) until death, loss to follow-up, withdrawal of consent from the study, or closure of the study.

- Overall survival information
- For patients who discontinued treatment without evidence of documented progression, patients will continue to be assessed for disease status per RECIST v1.1 for soft tissue disease, PCWG3 criteria for bone metastases, and serum PSA, every 12 weeks (± 7 calendar days) from the first study treatment (until documented progression, initiation of new anti-cancer therapy, or withdrawal of consent)

This long-term follow-up can be performed via a telephone call, with a subsequent site visit requested in case any concerns are noted during the telephone call. Public databases and subject next-of-kin may be queried as needed for survival follow-up information.

6.4 Subject Withdrawal

Subjects may withdraw their consent from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Principal Investigator for lack of adherence to intervention or study procedures or visit schedules or toxicity. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety, or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

Some specific reasons for withdrawal include, but are not limited to the following:

- Patient decision. The patient is at any time free to discontinue treatment.
- AE including SAE and AESI
- Progression of disease as defined by RECIST v1.1.
- Unacceptable toxicity
- Protocol non-compliance
- Pregnancy
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), or diagnosis of MDS/AML confirmed by a hematologist
- Any new primary malignancy
- Study termination

6.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who would like to withdraw consent to participate in the study will be asked to attend one final visit 30 calendar days (± 7 days) following the last dose of study drug in order to collect the investigational study drug and to follow up regarding AEs. In the event of an ongoing AE, regardless of withdrawal, the subject will continue to be followed until resolution of the AE (of improvement to ≤ grade 1). They will be asked for permission to have the study team look into their survival status via publically available means.

Table 3 Schedule of Events

Study Assessment	Screening	Treatment Phase (Cycle = 28 Calendar Days)										EOT Visit[h, n]	30 Calendar Day Post-Treatment Follow-Up[n]	90 Calendar Day Post-Treatment Follow-Up	Long-Term Follow-Up[h] Every 12 weeks
		Cycle 1				Cycle 2				Cycle 3	Cycles 4+ D1				
		C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1					
PROCEDURES	≤ 28 calendar days	± 1 day								± 3 days			± 7 days	± 3 weeks	
Informed Consent	X														
Medical History and Concomitant Medications	X	X		X		X				X	X	X	X		
Documentation of pathogenic or likely pathogenic DNA repair aberration	X														
Demographics	X														
Physical Exam incl. Weight, and Height[a]	X	X		X		X				X	X	X	X		
Blood pressure and heart rate	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X	X	X	X		
Temperature	X	X		X		X				X					
ECOG Performance Status	X	X		X		X				X	X	X	X		
12-lead ECG[m]	X														
AE Assessment	X	X		X		X				X	X	X	X	X	
Safety and Survival Status Follow-up														X[b,c]	X[b,c,h]
LABORATORY															
Hematology[g] (Table 4)	X	X		X		X				X	X	X	X		
Serum Chemistry (Table 4)	X	X		X		X				X	X	X	X		
Serum PSA[h, l] (Table 4)	X	X				X				X	X		X		
Total Testosterone (Table 4)	X														
Additional Lab: CBC[g]		X[g]	X[g]	X[g]	X[g]	X[g]				X[g]	X[g]	X[g]			
IMAGING															
CT chest, abdomen, pelvis[d, h, f]	X										X[f]	X[e]			
Bone scan[h, f]	X										X[f]	X			
TREATMENT															
Niraparib Administration[k]		Daily													
RESEARCH SAMPLES															
Tissue Block/Unstained Slides - Optional (Section 7.8)	X[l]	X[l]		X[l]		X[l]				X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Research Blood (Section 7.8)		X[j]				X[j]					X[j]	X[j]			

a. Height only needs to be performed at the screening visit. Subsequent visits can include only weight.
b. Extended safety follow-up beyond 30 calendar days after the last study drug administration may be performed either via a site visit or via a telephone call with a subsequent site visit requested in case any concerns are noted during the telephone call.
c. All patients discontinued from treatment, regardless of reason, should be followed for survival every 12 weeks (± 3 weeks) until death, loss to follow-up, withdrawal of consent, or study closure. Follow-up can be performed via telephone.
d. MRI abdomen/pelvis imaging may be substituted for CT abdomen/pelvis imaging, per Principal Investigator discretion.
e. End of treatment tumor imaging assessments should be performed if treatment was discontinued for reason other than radiologic disease progression and if not performed within the preceding 8 weeks.
f. Disease imaging assessments will be performed at Screening and every 12 weeks (± 7 calendar days) from the first study treatment.
g. CBC must be performed weekly for the first month of treatment, then monthly thereafter, including within 30 days of the last dose of study drug.
h. Patients who discontinue treatment without documented evidence of progression will continue to be assessed for disease status per RECIST v1.1 for soft tissue disease, PCWG3 criteria for bone metastases, and serum PSA, every 12 weeks (± 7 calendar days) from the first study treatment (until documented progression, initiation of new anti-cancer therapy, or withdrawal of consent).
i. Serum PSA not collected on C1D15
j. Research blood drawn at C1D1, C2D1, C4D1, and EOT only.
k. Dosing of niraparib is 200 mg PO (2 x 100 mg pills) unless dose reduced per Section 5.2. Tablet counts will be completed by study personnel at all study visits after C1D1.
l. Archival tissue will be obtained, if available. Tumor tissue that is obtained for clinical purposes during the study period that is banked may be used for future research analyses.
m. ECG at Screening visit only, unless clinically indicated, whereby it should occur at every study visit.
n. EOT Visit procedures may be combined with the 30 Day Follow-up Visit procedures, as circumstances allow.
o. Blood pressure and heart rate must be monitored weekly for the first two months of treatment, then monthly thereafter.

7 Study Evaluations and Measurements

7.1 Medical Record Review

The following information will be extracted from the medical record of each subject prior to the first dose of study therapy.

- Medical/Oncologic history, including date of cancer diagnosis, prior treatments, and any surgical or radiation therapy procedures

7.2 Physical Examination

Physical examination will include all of the major body systems. Physical examinations will be performed at screening (complete) and at selected study visits (limited as appropriate).

Height will be measured during the Screening visit only. Weight will be measured at each study visit.

7.3 Vital Signs

Vital signs will include blood pressure (automated or manual), heart rate, and body temperature.

7.4 ECOG Performance Status

ECOG performance status will be assessed at Screening, during selected Study Intervention Phase visits, and at End of Treatment and 30-day Post-Treatment Follow-up visits. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

7.5 12-lead Electrocardiogram

For all patients, 12-lead ECGs will be performed at Screening. During the Study Intervention Phase, ECGs will be performed as clinically indicated. All 12-lead ECGs will be analyzed locally.

7.6 Laboratory Evaluations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. The investigator will comment on out of range parameters and assess clinical significance. Clinical significant abnormalities, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE. The panels of laboratory tests to be performed are shown in **Table 4**.

Table 4 Laboratory Tests

Category	Tests
Hematology	Hemoglobin, platelet count, WBC with differential
Serum Chemistry	SGOT/AST, SGPT/ALT, Total Bilirubin, alkaline phosphatase, albumin, glucose, creatinine, BUN, sodium, chloride, CO2, calcium
Total Testosterone	Total testosterone
Serum PSA	PSA

CBC must be performed weekly for the first month of treatment, then monthly thereafter, including within 30 days of the last dose of study drug. These labs can be drawn at the following locations: Quest, LabCorp, or Penn and Penn Affiliates.

7.7 Efficacy Evaluations

7.7.1 Imaging Assessments

Tumor assessments will be performed at Screening and every 12 weeks (± 7 calendar days) from the start of study therapy during the Study Intervention Phase. Tumor assessments should also be performed at the End of Treatment visit if treatment was discontinued for reason other than radiologic disease progression and if not performed within the preceding 8 weeks. For such patients who have treatment discontinuation for reason other than radiologic disease progression and no evidence of disease progression at the End of Treatment evaluation, tumor assessments should continue to be performed every 12 weeks (±7 calendar days) until evidence of disease progression, initiation of alternative anti-cancer therapy, withdrawal of consent, loss to follow-up, or study closure. Timing of imaging assessment should follow calendar days, and should not be adjusted for delays in treatment cycle starts.

Tumor assessments should include clinical examination, and appropriate imaging techniques (including CT scans of the chest, abdomen, and pelvis). CT contrast material can be administered at the discretion of the Principal Investigator. MRI abdomen/pelvis imaging may be substituted for CT abdomen/pelvis imaging, per Principal Investigator discretion.

Efforts should be made to use the same methods used to detect lesions at baseline to follow the same lesions throughout the clinical study.

Soft tissue disease (including nodes, viscera, and prostate/prostate bed) tumor response will be interpreted using RECIST Version 1.1 for CT/MRI imaging (as assessed per Investigator). Bone disease will not be considered as non-target lesions assessed by RECIST Version 1.1, but will be assessed as per PCWG3 criteria for bone scan imaging, as assessed per Investigator.

An objective response is defined as a best overall response of CR or PR per RECIST Version 1.1 and must be confirmed on repeat imaging (at least 4 weeks after initial response documentation). Disease progression in bone metastatic disease must be confirmed at least 6 weeks later (as per PCWG3).

7.7.2 Serum PSA

Blood will be collected at the time points described in the Schedule of Events and analyzed as per local laboratory protocol for serum PSA.

7.8 Research Blood and Tissue (Banked Biospecimens)

Banked biospecimens (research blood and archived FFPE tumor tissue of primary tumor and/or metastatic lesions, if available) will be collected for exploratory research relating to the study therapy at the time points described in the Schedule of Events. Additionally, tumor tissue that is obtained for clinical purposes during the study period, will be collected, as well, and may be banked for future research analyses. Collection of tumor tissue, whether archived or obtained for clinical purposes, is optional for participants. Research blood collection is not optional.

These specimens will be handled in a manner that protects each patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study ID, and all data generated by such biospecimens will be indexed by this study ID.

As described in the Schedule of Events the following blood samples will be collected:

- Blood samples (6 mL whole blood) will be collected before, during, and at the end of treatment and processed for RNAseq in order to assess the level of expression of genes in peripheral blood.

- Blood samples (20 mL whole blood for processing to plasma and Buffy coat) will be collected before, during, and at the end of treatment for isolation and analysis of cell free DNA and germline sequencing as needed.

- An additional blood sample (20 mL whole blood) will be collected and banked for future research before, during, and at the end of treatment for isolation and analysis of cell free DNA and germline sequencing as needed.

Details of correlative testing will depend on available funds and samples.

7.9 Safety Evaluations

Toxicity and adverse event monitoring will occur at Screening, at each Treatment Phase study visit, at the End of Treatment visit, and at the 30-day Follow-up Visit. AEs will be graded as per CTCAE Version 5.0.

8 Statistical Plan

8.1 Primary Endpoint

The primary study endpoint will be the radiographic PFS rate at 6 months (rPFS6), as determined by Kaplan-Meier analysis. rPFS will be defined as the time from the start of study therapy to the first occurrence of radiographic disease progression (using RECIST v1.1 for soft tissue disease, PCWG2 criteria for osseous metastatic disease, or clinical deterioration) as assessed by the investigator, or death from any cause.

8.2 Secondary Endpoints

Secondary study endpoints will include:

- PSA30, defined as the proportion of patients achieving a ≥30% decline in PSA following the initiation of niraparib maintenance therapy.

- PSA50, defined as the proportion of patients achieving a ≥50% decline in PSA following the initiation of niraparib maintenance therapy.

- Time to PSA progression, defined by the time until the first PSA increase that is >25% (and an absolute increase of ≥ 2 ng/ml) from the nadir PSA value following the initiation of niraparib maintenance therapy.

- Safety, as defined by the frequency and severity of adverse events (AEs), as assessed by CTCAE version 5.0, following the initiation of niraparib maintenance niraparib therapy.

- Overall survival (OS), defined as the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.

8.3 Statistical Methods

This is a single-arm, single-stage Phase II study to evaluate radiologic progression-free survival at 6 months (rPFS6) in 18 eligible subjects with platinum-sensitive mCRPC harboring a pathogenic DNA repair defect. All patients receiving at least one dose of study therapy will be evaluable for rPFS. The null hypothesis is that the PFS6 rate is 25%, and the alternative hypothesis is that the PFS6 rate has been increased to 50%. Assuming one-sided alpha of 0.05, 24 months of enrollment and an additional 6 months of follow-up prior to statistical analysis, a sample size of 18 subjects will provide power of 0.77 for a one-sample test of this hypothesis. This analysis assumes that all patients will be followed for a minimum of 6 months or until documented disease progression within 6 months.

The primary study endpoint will be the radiographic PFS rate at 6 months (rPFS6), as determined by Kaplan-Meier analysis. rPFS will be defined as the time from the start of study therapy to the first occurrence of radiographic disease progression (using RECIST v1.1 for soft tissue disease, PCWG2 criteria for osseous metastatic disease, or clinical deterioration) as assessed by the investigator, or death from any cause. All patients receiving at least one dose of study drug will be eligible for analysis for the primary study endpoint. If a subject withdraws from study participation prior to receipt of study drug, then he/she will be replaced in the study sample.

We will present Kaplan-Meier curves for time-to-event endpoints including progression-free and overall survival, and time to PSA progression, for patients receiving study treatment. The 6-month PFS rate and 1-sided 95% confidence interval will be calculated to determine whether the lower bound of the confidence interval (CI) excludes the assumed historical value of 25%. A 1-sided one-sample Z test will also be conducted. The goal is to compare the PFS probability at time *t* to the historical value. The null hypothesis is H0: PFS(*t*) < 0.25 at time *t*. The alternative hypothesis is H1: PFS(*t*) > 0.50, a one-sided test. For this study, *t* = 6 months. PFS(*t*) and its standard deviation, are estimated from the Kaplan-Meier analysis.

Other statistical analyses will be primarily descriptive in nature in keeping with the study design. All baseline data, adverse events, and clinical responses will be tabulated and summarized. Exact 95% confidence intervals will be produced for adverse event and PSA30 and PSA50 response rates. For all patients treated, we will use waterfall plots to present tumor response measured using RECIST 1.1 criteria and PSA response rates.

9 Safety and Adverse Events

Overview
As the sponsor of the study, the Institution (Sponsor - University of Pennsylvania) and Principal Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this protocol, safety data includes serious adverse events, product quality complaints (PQCs), and special situations including pregnancies (see Reporting Special Situations).

Management of Safety Data
This study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this protocol will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 calendar days after the last dose of study drug.

For the purpose of this study, the Janssen medicinal product is: Niraparib

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event

A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Is a suspected transmission of any infectious agent via a medicinal product; or
- Is an important medical event*.

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious (See Reporting Special Situations for more information).

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

The cause of death of a subject in a study within 30 calendar days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For niraparib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Individual Case Safety Report (ICSR)
An ICSR is the information entered into the Form FDA 3500A. ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- sex
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English) including, but not limited to, onset date, relatedness, causality, action taken, outcome, etc.
- Janssen protocol ID 64091742PCR2006

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g. auto-injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

Reporting Special Situations
Safety events of interest for a Janssen medicinal product that require expedited reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding

- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g. name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event will be recorded and reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event**, as any other SAE would be reported.

Adverse Events of Special Interest
Adverse events of special interest are events that the Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). For niraparib, the adverse events of special interest are:

- ≥ Grade 3 Anemia
- ≥ Grade 3 Thrombocytopenia
- ≥ Grade 3 Neutropenia
- Acute Myeloid Leukemia
- Myelodysplastic Syndrome

Any adverse event of special interest will be recorded and reported to the Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.** Adverse Events of Special Interest are considered special situations that would be reported to Janssen Scientific Affairs, LLC as an SAE.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF).

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study Drug and Study Procedures

The relationship of each adverse event to the study procedures will be characterized by the PI or Sub-investigators, and the relationship will be classified as related or unrelated.

9.4 Reporting of Adverse Events and Unanticipated Problems

9.4.1 Initial Reports

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible (e.g. ethics board/IRB, DSMB, etc.), but at a minimum those events that must be reported are those that are:

- Related to study participation;
- Unexpected; and

- Serious or involve risks to subjects or others.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects, and subject complaints) will be recorded and reported with respect to institutional and federal policies.

9.4.2 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g. concomitant medication, medical history) should be submitted to the various entities to which the investigator is responsible. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.4.3 Notifying Janssen Scientific Affairs, LLC: Reporting of Serious and non-Serious AEs, Special Situations, and PQC

This study has been designated as an interventional study. As such, all adverse events for niraparib regardless of causality and special situations excluding those from subjects not exposed to a Janssen Scientific Affairs, LLC Medicinal Product and product quality complaints with or without an adverse event will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 calendar days after the last dose of study drug. Reporting requirements for AEs, SAEs, and Special Situations is outlined further in this protocol.

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to niraparib will be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to niraparib.

All (serious and non-serious) adverse events reported for niraparib should be followed-up in accordance with clinical practice.

Penn and the Principal Investigator will promptly transmit all SAEs and special situations following exposure to niraparib on Form FDA 3500A to e Janssen Scientific Affairs, LLC in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal will be promptly reported by Penn or the Principal Investigator, to the Janssen Scientific Affairs, LLC using the Form FDA 3500A.

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- Penn and/or the Principal Investigator is responsible for ensuring that these cases are complete and, if not, are promptly followed-up. A safety report is not considered complete

until all clinical details needed to interpret the case are received. Reporting of follow-up information should be completed promptly.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be promptly provided to the Janssen Scientific Affairs, LLC promptly after such report or correspondence is sent to applicable regulatory authorities.

Pregnancy

Because the Janssen Scientific Affairs, LLC medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Janssen medicinal product should be reported by the Principal Investigator **within 24 hours of their knowledge of the event**, given the pregnant partner has provided consent, using the Form FDA 3500A. Depending on local legislation this may require prior consent of the partner.

If the pregnant partner has provided consent, follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be requested.

Serious adverse events and special situations will be reported for 30 calendar days after the last dose of study drug.

SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to the Janssen Scientific Affairs, LLC by the Principal Investigator **within 24 hours after being made aware of the event.** The Janssen Scientific Affairs, LLC contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Principal Investigator must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the Janssen Scientific Affairs, LLC.

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

Maintenance of Safety Information
All safety data should be maintained in a clinical database in a retrievable format. Penn and the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the Janssen Scientific Affairs, LLC's request.

Transmission Methods
The following methods are acceptable for transmission of safety information to the Janssen Scientific Affairs, LLC:

- Electronically via Janssen Scientific Affairs, LLC SECURE Email service IIS-BIO-VIRO-GCO@its.jnj.com (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax) at 1-866-451-0371, receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by the Janssen Scientific Affairs, LLC.

SAEs Listing
At a minimum, on a semi-annual basis and at the end of the Study, Janssen Scientific Affairs, LLC will provide to the Penn and/or the Principal Investigator, a listing of all SAEs reported to the Janssen Scientific Affairs, LLC for this protocol. Sponsor and/or the Principal Investigator will review this listing and will resolve any discrepancies with the data provided by the Janssen Scientific Affairs, LLC.

Dissemination of Safety Information from Janssen Scientific Affairs, LLC to Penn and/or the Principal Investigator

The Principal Investigator will be responsible for submitting to the IRB of record in accordance with institutional and Federal regulations 21 CFR 312.66.

Janssen Scientific Affairs, LLC agrees to provide to the Principal Investigator updated safety information on the study drug until the last participating subject has completed their 30 Day Follow-up Visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

Contacting Janssen Scientific Affairs, LLC Regarding Safety
The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by the Janssen Scientific Affairs, LLC.

Final Study Report
Penn/the Principal Investigator will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the Research Funding Agreement.

9.4.4 Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 business days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

9.4.5 Notifying the Abramson Cancer Center (ACC) Data Safety Monitoring Committee (DSMC)

Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

1. Unless covered by exclusions below, Grade 3 or higher events must be reported within 10 days of knowledge.
2. All unexpected deaths within one business day of knowledge.
3. All others deaths within 30 calendar days of knowledge. Deaths of subjects off-study for greater than 30 calendar days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

SAEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Reportable Events

Exception
A one time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Director or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Director or Safety Monitoring Committee prior to submitting your exception request to the DSMC.
The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe?
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval?
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.?
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI?
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject
Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

1. Any investigator-initiated treatment study.
2. Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended. If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

Deviation
Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has **any potential** to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must

report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified? If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had **no potential** to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

9.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at the site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. Medical monitoring by an independent clinician will include a regular assessment of the number and type of serious adverse events on a periodic basis, as well as participate in decision making regarding dose modifications, exemption and deviation requests, and an ability to stop enrollment or the study for safety concerns. All SAEs will also be reviewed by the independent medical monitor.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. When a subject decides to withdraw, the investigator should ask the subject if they wish to withdraw from just receiving niraparib. If they only want to stop receiving the investigational treatment, other parts of the study may to which they've previously given consent may continue, including, but not limited to specimen and follow-up activities.

10. 2 Data Collection and Management

The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed (eCRF). CRFs will be provided for each patient. Subjects must not be identified by name on any CRFs. Subjects will be identified by their patient identification number (PID).

10.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the drug manufacturer. In such an instance, it is the responsibility of the drug manufacturer to inform the investigator/institution as to when these documents no longer need to be retained.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored in accordance with the Abramson Cancer Center's Data and Safety Monitoring Plan (DSMP). This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Janssen before commencement of this study.

12.1 Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This clinical study is funded by funds provided by Janssen.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by Janssen for the purposes of performing the study, will be published or passed on to any third party without the consent of Janssen. Any investigator involved with this study is obligated to provide Janssen with complete test results and all data derived from the study.

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