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PROTOCOL SYNOPSIS

Protocol Title: Phase II Trial of PARP Inhibitor Niraparib for Men with Unfavorable Intermediate or High Risk Prostate Cancer and DNA Damage Response Defects

Protocol Number: UCDCC#279

Phase of Development: II

Investigational Product: Niraparib (Zejula®) will be supplied as 100 mg capsules for oral administration.

Primary Objective: To assess the impact of neoadjuvant niraparib therapy prior to radical prostatectomy (RP) on pathologic tumor stage, frequency of lymph node metastases and positive margin rates for patients undergoing radical prostatectomy for unfavorable intermediate or high-risk, clinically localized prostate cancer with alterations in DNA repair pathways. Key pathologic endpoints include complete response (PCR) defined as no tumor identified on H&E sections; and minimal residual disease (MRD) defined as <0.5 cc tumor clusters confined to the prostate gland (<pT3).

Secondary Objectives: To assess 5-year biochemical recurrence in subjects with unfavorable intermediate or high-risk prostate cancer and DNA-damage response defects after prostatectomy.

Exploratory Objectives:

- To assess the 5-year biochemical progression-free survival (bPFS), bPFS rate, disease progression, disease-free survival (DFS), and overall survival (OS).
- To evaluate the safety and tolerability of neoadjuvant niraparib prior to surgery for unfavorable intermediate or high-risk patients undergoing radical prostatectomy.
- To assess the impact of neoadjuvant niraparib on time to clinically apparent local disease recurrence and metastatic disease in unfavorable intermediate or high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer.

Study Design: This is a Phase II, open-label study to assess the efficacy and safety of once daily dosing of 200 mg niraparib in male subjects ≥ 18 years with unfavorable intermediate or high-risk, clinically localized prostate cancer and alterations in DNA-repair pathways who have selected radical prostatectomy as the primary treatment for treatment of prostate cancer.

Treatment will be for 12 weeks (3 cycles, where 1 cycle = 4 weeks) prior to radical prostatectomy. Prostatectomy will be scheduled ≤ 6 weeks after last treatment with niraparib. Prostatectomy specimens will be analyzed after surgery for staging. Tumor volume will be estimated, and responses defined as complete, minimal residual disease (<0.5 cc, organ confined), or none. Interim analysis for fertility will be conducted once 11 participants undergo radical prostatectomy (see section 12.4 for details).

All subjects will be monitored for safety during the study period, and up to 30 days after the last dose of study drug. Subjects will be followed for 5 years for bPFS, bPFS rate, disease progression, disease-free survival, and OS.

Study Population and Sample Size: The study will enroll about 30 subjects. Unfavorable intermediate, high or very high risk clinically localized prostate cancer defined by National Comprehensive Cancer Network (NCCN) criteria in men eligible for radical prostatectomy with >10 -year life expectancy. Men must have clinically negative staging studies with CT/MRI and bone scan and must have not been previously treated.

Endpoints:

Primary Endpoint

The primary output is pathologic response rate (pRR) at the time of radical prostatectomy, and the study is powered to assess this. We will assess the impact of neoadjuvant niraparib therapy prior to radical prostatectomy (RP) on pathologic tumor stage, frequency of lymph node metastases and positive margin rates for patients undergoing radical prostatectomy for unfavorable intermediate or high-risk, clinically localized prostate cancer with alterations in DNA repair pathways. Pathologic complete response (PCR) defined as no tumor identified on H&E stained sections will be assessed; minimal residual disease (MRD) will be defined as tumor clusters limited to <5 mm and confined to prostate gland.

The pRR will be compared to a null rate of 0.001 using a one-sided exact binomial test. Exact 95% confidence intervals for pRR and other binary outcomes will be calculated using the Clopper-Pearson method. Response rates will be compared between patients with biallelic and monoallelic loss using Fisher's Exact Test.

Secondary Endpoint

Biochemical (PSA) progression free survival at 5 years.

Median bPFS and quartiles (when reached) will be calculated from Kaplan-Meier estimates, and 95% confidence intervals will be calculated using Greenwood's formula.

Exploratory Endpoints

- To assess the 5-year biochemical progression-free survival (bPFS) rate, bPFS, disease progression, disease-free survival, and overall survival (OS)
- To evaluate the safety and tolerability of neoadjuvant niraparib prior to surgery for unfavorable intermediate or high-risk patients undergoing radical prostatectomy

- To assess the impact of neoadjuvant niraparib on time to clinically apparent local disease recurrence and metastatic disease in unfavorable intermediate or high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer

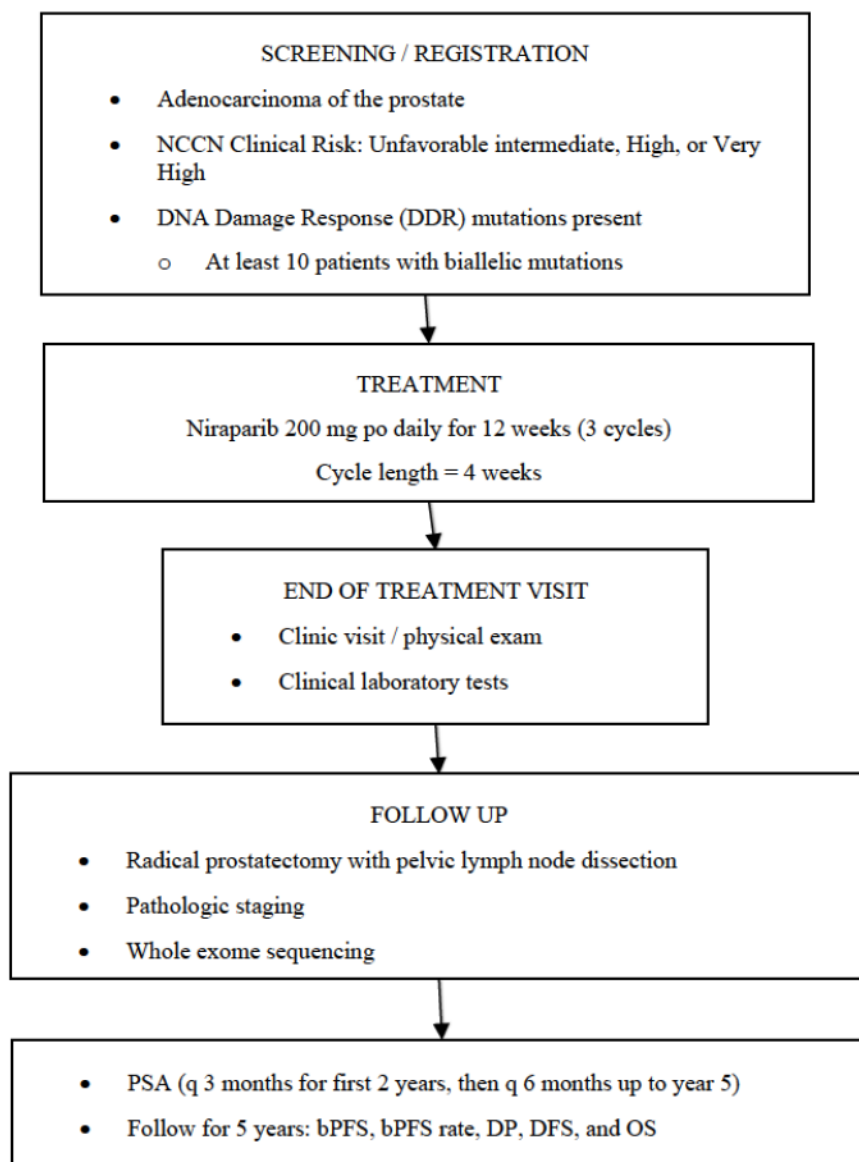
Time to event outcomes will be analyzed as for median bPFS.

Duration of Study and Follow-up: 6 ½ years

Statistical Considerations:

Sample Size Determination

For the purposes of sample size calculations, we assume an underlying pathologic response rate pRR of 0.001 with surgery alone and an underlying pRR of 15% with surgery plus PARP inhibitor in marker-positive subjects. Based on the above, 30 marker-positive subjects would be required to provide 80% power for the test that the pRR is greater with the addition of the PARP inhibitor. To assess response differences in patients with biallelic versus monoallelic loss of DNA repair genes, we will enroll at least 10 patients with biallelic loss. (Calculations are based on an alpha level of 0.025 to compensate for using a one-sided test).

STUDY SCHEMA

LIST OF ABBREVIATIONS AND TERMS

Abbreviation/ Term	Definition/Explanation
°C	degrees Celsius
μM	micromolar
AE	adverse event
ANC	absolute neutrophil count
ALT	alanine transaminase
AST	aspartate transaminase
bPFS	biochemical progression-free survival
BSA	body surface area
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	curriculum vita
DDR	DNA damage response
DFS	disease-free survival
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DP	disease progression
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DOB	date of birth
ECOG	Eastern Cooperative Oncology Group
ECT	enteric-coated tablet
FDA	Food and Drug Administration
FDG	Fludeoxyglucose (¹⁸ F)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation/ Term	Definition/Explanation
GLP	Good Laboratory Practice
ht	height
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous
Ki	inhibitory constant
lbs	pounds
LDH	lactate dehydrogenase
m ²	square meters
mg	milligram
Min	minute
mL	milliliter
mm ³	cubic millimeters
mmol	millimole
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
Ng	nanogram
nM	nanomole
OCR	Office of Clinical Research
OS	overall survival
PARP	poly-ADP Ribose Polymerase
PD	progressive disease
PET	positron emission tomography
PET	Probablility of early termination
PFS	progression-free survival
PI	principal investigator
PIC	powder-in-capsule

Abbreviation/ Term	Definition/Explanation
PR	partial response
pRR	pathological response rate
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SRC	Scientific Review Committee
UCD	University of California, Davis (UC Davis)
UCDCC	UC Davis Cancer Center
US	United States
USP	United States Pharmacopeia
w/w	weight-to-weight ratio
wt	weight

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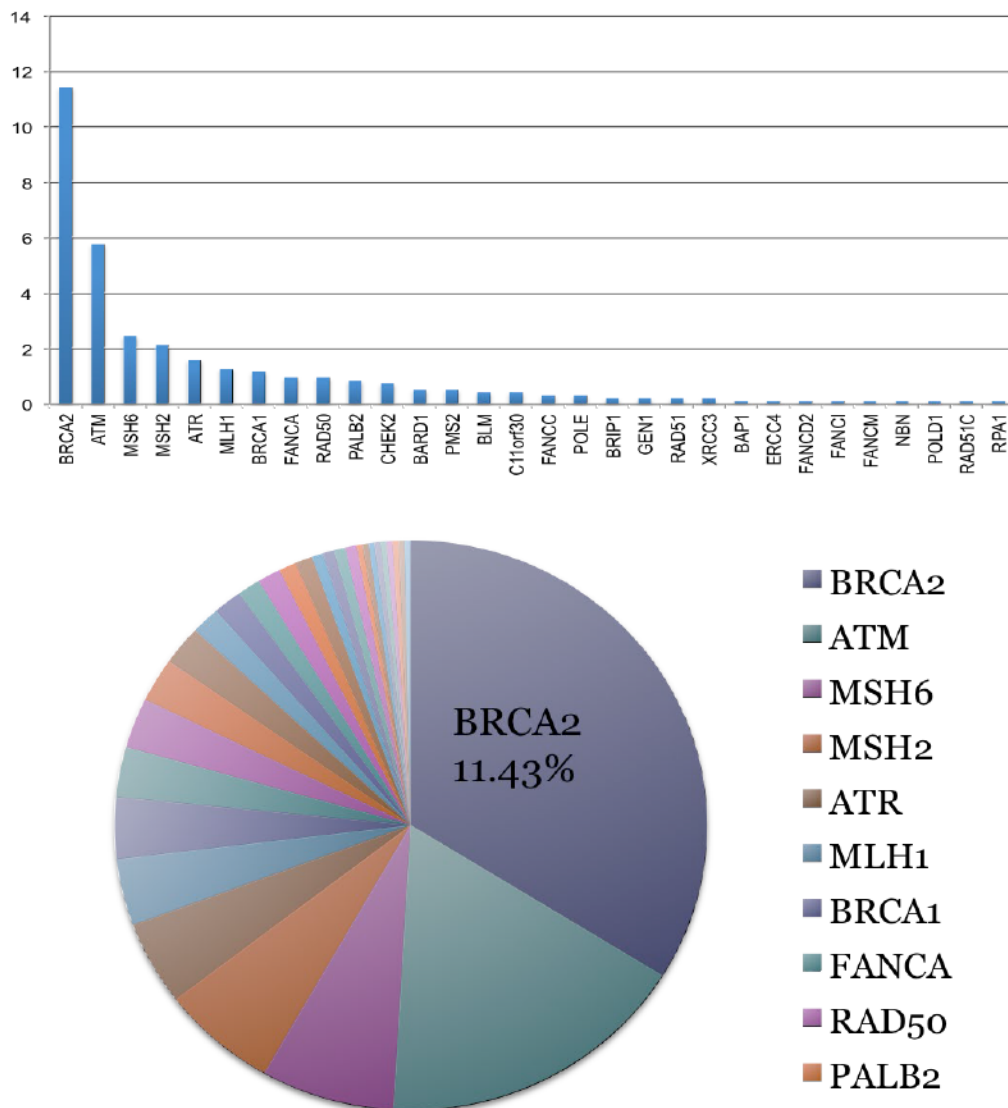
1. INTRODUCTION

1.1 Disease

High risk, clinically localized prostate cancer continues to present a therapeutic challenge. Up to 50% of men may have micro-metastatic disease at diagnosis and are destined to fail with single modality, prostate directed therapy such as radiation or radical prostatectomy (1, 2). Multimodal therapy for localized, high-risk disease strives to improve cure rates and overall survival (OS) during an earlier stage of disease. Several studies have been performed with cytotoxic chemotherapy or hormonal axis agents in the neoadjuvant setting with limited response (3-5). Neoadjuvant trials for high-risk, localized prostate cancer have primarily focused on androgen deprivation, next generation androgen axis inhibitors, or chemotherapy. To date no trial has demonstrated a clinical benefit and standard of care is to proceed with radical prostatectomy and provide adjuvant or salvage therapy as indicated over time.

Inhibition of poly-ADP Ribose Polymerase (PARP) especially in the setting of defective DNA repair mechanisms provides a novel therapeutic approach in prostate cancer (6, 7). PARP inhibition has shown efficacy in the metastatic, castrate resistant setting especially in tumors with BRCA2 or other known DNA repair gene mutations (8). The PARP inhibitor niraparib (ZEJULA®) appears well tolerated with activity against tumors, particularly ovarian cancer, with DNA repair gene defects (9, 10). The Phase 2 TOPARP-A trial demonstrated an overall cohort response rate to the PARP inhibitor olaparib of 33% in men with metastatic castration resistant prostate cancer (11). Treatment response was defined by radiographic response according to RECIST v1.1 criteria, >50% decline in PSA, or decline in measurable circulating tumor cells (CTC) to <5 cells/7.5 cc. There was a dramatic treatment response in men with germline defects in DNA damage repair genes of 88%, most of which included patients with biallelic loss of BRCA2. In contrast, only 6% of the patients without DNA damage repair gene defects showed any response. This trial was the first to show response with PARP inhibition in men with advanced, heavily pre-treated forms of prostate cancer.

PARP inhibition however has not been studied in the setting of castrate sensitive, early stage prostate cancer. The Cancer Genome Atlas (TCGA) molecular taxonomy of prostate cancer describes multiple important recurring genomic alterations in prostate cancer including genes involved with DNA repair (12), DNA repair pathway genes are noted to be altered in up to 20% of primary tumors with higher frequencies noted in paired metastatic samples. In a recent study we performed of a large prostate cancer targeted sequencing dataset with over 900 samples including primary prostate and metastatic tumors, we found defects in DNA repair genes in up to 20% of prostate tumors. The most commonly mutated genes in the DNA repair pathways are: BRCA2 (11.43%), ATM (5.77%), MSH6 (2.46%), MSH2 (2.14%), ATR (1.60%), MLH1 (1.28%), and BRCA1 (1.18%) (Figure 1). In a separate cohort of men presenting with untreated high risk, localized or metastatic castrate sensitive prostate cancer, we found a higher incidence (31%) of DNA repair gene defects including known mutations and variants in BRCA2, ATM, BRIP1, MUTYH and Fanconi anemia genes. These data suggest that neoadjuvant PARP inhibition may provide a novel and effective therapeutic pathway for men with high-risk prostate cancer to improve overall response rates and survival after radical prostatectomy.

Figure 1. List of DNA repair genes with frequency of mutation in prostate cancer

1.1.1 Treatment Options

Men with localized prostate cancer typically face two treatment options. Radical prostatectomy with pelvic lymph node dissection is performed to remove the cancerous prostate and provide complete pathologic staging. Adjuvant and salvage therapy is delivered as indicated. The second option is primary radiation therapy with neoadjuvant and concurrent androgen deprivation therapy.

1.2 Study Rationale

In multiple tumor types, impairment of DNA repair mechanisms is important for tumor initiation and progression but may also provide therapeutic value. Poly-ADP-ribose-polymerase (PARP) inhibition with multiple agents in cells with already impaired DNA repair mechanisms seem leads to insurmountable DNA damage even for a transformed cell, a concept known as synthetic

lethality. Cells with defects in genes important in homologous recombination including BRCA1/2, ATM, and Fanconi genes seem particularly sensitive to PARP inhibition and knock out of this second repair pathway (6). This pathway therefore may provide a novel therapeutic target outside of the traditional androgen axis for men with prostate cancer who harbor either germline or acquired somatic alterations in DNA repair. PARP inhibition has been studied in men with progressive, castration resistant prostate cancer with dramatic responses in those tumors with deficient DNA repair. We propose to study the effect of PARP inhibition with Niraparib in men with localized, unfavorable intermediate or high-risk prostate cancer undergoing radical prostatectomy that typically has a 50% risk of disease recurrence with need for additional treatment.

1.3 Correlative Studies

Tissue will be collected from diagnostic biopsy and at the time of prostatectomy for whole exome sequencing. Responses will be stratified by type of DNA repair alterations as well as for 'BRCAness', i.e., molecular features that are shared with BRCA-deficient tumors. Genes that are known to be important in DNA repair pathways are shown in Table 1. Blood will be collected at screening and banked for future studies.

Table 1. Genes Known to be Important in DNA Repair Pathways

ATM	C12orf48	FANCA	FEN1	PALB2	POLE4	RAD54L
ATR	CHEK2	FANCB	GEN1	PCNA	POLH	RAD54L2
BAP1	DNA2	FANCC	HELQ	PMS2	RAD50	RBBP8
BARD1	EME1	FANCD2	MAD2L2	POLD1	RAD51	RECQL
BLM	EME2	FANCE	MLH1	POLD2	RAD51AP1	RECQL4
BRAP	ERCC1	FANCF	MRE11A	POLD3	RAD51B	RECQL5
BRCA1	ERCC4	FANCG	MSH2	POLD4	RAD51C	REV1
BRCA2	EXO1	FANCI	MSH6	POLE	RAD51D	REV3L
BRIP1	FAM175A	FANCL	MUS81	POLE2	RAD52	RMI1
C11orf30	FAN1	FANCM	NBN	POLE3	RAD54B	RMI2
WRN	XRCC2	XRCC3	ZRANB3	ZSWIM7	RPA1	RPA2
RPA3	RPA4	RTEL1	SHFM1	SLX1A	SLX4	SYCP3
TOP3A						

2. STUDY OBJECTIVES

2.1 Primary Objective

To assess the impact of neoadjuvant niraparib therapy prior to radical prostatectomy (RP) on pathologic tumor stage, frequency of lymph node metastases and positive margin rates for patients undergoing radical prostatectomy for unfavorable intermediate or high-risk, clinically localized prostate cancer with alterations in DNA repair pathways. Key pathologic endpoints include complete response (PCR) defined as no tumor identified on H&E sections; and minimal residual disease (MRD) defined as <0.5 cc tumor clusters confined to the prostate gland (<pT3).

2.2 Secondary Objective

To assess 5-year biochemical recurrence in subjects with unfavorable intermediate or high-risk prostate cancer and DNA-damage response defects after prostatectomy.

2.3 Exploratory Objectives

- To assess the 5-year biochemical progression-free survival (bPFS), bPFS rate, disease progression, disease-free survival (DFS), and overall survival (OS).
- To evaluate the safety and tolerability of neoadjuvant niraparib prior to surgery for unfavorable intermediate or high-risk patients undergoing radical prostatectomy.
- To assess the impact of neoadjuvant niraparib on time to clinically apparent local disease recurrence and metastatic disease in unfavorable intermediate or high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer.

3. STUDY DESIGN

This is a Phase II, open-label study to assess the efficacy and safety of once daily dosing of 200 mg niraparib in male subjects ≥ 18 years with unfavorable intermediate or high-risk, clinically localized prostate cancer and alterations in DNA-repair pathways who have selected radical prostatectomy as the primary treatment for treatment of prostate cancer.

Unfavorable intermediate, high, or very high risk clinically localized prostate cancer defined is by National Comprehensive Cancer Network (NCCN) criteria in men eligible for radical prostatectomy with ≥ 10 -year life expectancy. Men must have clinically negative staging studies with CT/MRI and bone scan and must have not been previously treated. Patients will be screened for alterations in genes involved in DNA repair, primarily in the homologous recombination pathway. Patients will be screened with targeted gene sequencing utilizing the Tempus platform which analyzes both germline and somatic gene alterations. This is already being done for patients at high risk of failure after local therapy, and patients will not be billed for this service.

Treatment will be for 12 weeks (3 cycles, where 1 cycle = 4 weeks) prior to radical prostatectomy. Prostatectomy will be scheduled ≤ 6 weeks after last treatment with niraparib. Prostatectomy specimens will be analyzed after surgery for staging. Tumor volume will be estimated, and responses defined as complete, minimal residual disease (<0.5 cc, organ confined), or none. Tissue will be collected from diagnostic biopsy and at the time of prostatectomy for whole exome sequencing. Responses will be stratified by type of DNA repair alterations as well as for 'BRCAness' i.e., molecular features that are shared with BRCA-deficient tumors.

The study will enroll approximately 30 subjects. All subjects will be monitored for safety during the study period, and up to 30 days after the last dose of study drug using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Interim analysis for fertility will be conducted once 11 participants undergo radical prostatectomy (see section 12.4 for details).

Subjects will be followed for 5 years for bPFS, bPFS rate, disease progression, disease-free survival, and OS.

4. SUBJECT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

1. Ability to understand and willingness to sign an informed consent form.
2. Ability to adhere to the study visit schedule and other protocol requirements.
3. Men ≥ 18 years of age.
4. Patients must have histologically or cytologically confirmed prostate cancer that is clinically localized as defined by negative cross-section imaging and/or bone scan, and classified as unfavorable intermediate, high, or very high risk per NCCN guidelines (Appendix 7).
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 (Appendix 1).
6. Life expectancy ≥ 10 years.
7. Men who have selected radical prostatectomy as the primary treatment for their prostate cancer.
8. Prostate cancer tumors with alterations in key DNA repair genes. This will include at least one alteration in a gene involved in DNA repair primarily through the homologous recombination pathway including BRCA1/2, ATM, CHEK1/2, FANCA, FANCD2, FANCL, GEN1, NBN, PALP2, RAD51, RAD51c, and BRIP1. Mutations will be selected that are known or likely pathogenic. Mean allele frequencies will be assessed to estimate mono versus biallelic loss of function. Patients with biallelic deletions or mutations will be prioritized for inclusion to make up at least 30% of the enrollment (i.e., 10 patients) to gauge response in this group over monoallelic loss. Final inclusion will be determined by the principal investigator.
9. Must be able to swallow whole capsules.
10. To avoid risk of drug exposure through the ejaculate, male subjects (even if they have undergone a successful vasectomy) must agree while on study therapy (including during dose interruptions) and for 3 months following the last dose of study drug to:
 - a. Use a condom during sexual activity or practice complete sexual abstinence,
 - b. Not donate sperm
11. The following laboratory results obtained ≤ 14 days of the first study treatment:

- a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin ≥ 9 g/dL (may have been transfused)
- b. Liver function tests meeting the following criteria: total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range and AST and ALT levels $\leq 2.5 \times$ ULN.
- c. INR and aPTT $\leq 1.5 \times$ ULN (for patients on anticoagulation they must be receiving a stable dose for at least 1 week prior to randomization)
- d. Creatinine clearance ≥ 30 mL/min by Cockcroft-Gault formula (or local institutional standard method).

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

12. Any condition that would prohibit the understanding or rendering of informed consent.
13. Prior treatment for prostate cancer.
14. Prior treatment with a PARP inhibitor.
15. Prior treatment with androgen deprivation therapy (LHRH agonist/antagonist), anti-androgen (e.g., bicalutamide, nilutamide, enzalutamide, apalutamide), or androgen synthesis inhibitor (e.g., abiraterone, orteronel).
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
17. Uncontrolled concomitant disease that in the opinion of the investigator would interfere with the patient's safety or compliance on trial, including:
 - a. Presence of uncontrolled HTN (SBP ≥ 160 or SBP ≥ 100).
18. Severe infection that in the opinion of the investigator would interfere with the patient's safety or compliance on trial within 4 weeks prior to enrollment.
19. Known allergies, hypersensitivity, or intolerance to niraparib or its excipients (refer to Investigator's Brochure).
20. Known disorder affecting gastrointestinal absorption.
21. Corrected QT interval by the Fridericia correction formula (QTcF) on the screening ECG >450 msec.

22. Receiving concomitant medications that prolong QTc and are unable to discontinue use while receiving study drug (see Appendix 3).
23. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes).
24. Known HIV positive subjects with 1 or more of the following:
 - a. Not receiving antiretroviral therapy
 - b. A change in antiretroviral therapy within 6 months of the start of screening (except if, after consultation with the sponsor on exclusion criterion 14.c, a change is made to avoid a potential drug-drug interaction with the study drug)
 - c. Receiving antiretroviral therapy that may interfere with the study drug (consult the PI for review of medication prior to enrollment)
 - d. CD4 count <350 at screening
 - e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening
25. History or current diagnosis of MDS/AML.

5. DOSAGE AND ADMINISTRATION

For the purpose of this study, ‘study drug’ refers to niraparib. All dosing information must be recorded in the case report form (CRF). The 200 mg once daily dose was chosen based on the PK, pharmacodynamics, clinical activity, safety, and tolerability profiles of niraparib seen in two Phase 3 studies in subjects with ovarian and breast cancer.

5.1 Study Drug Administration

The study drug, niraparib 200 mg, will be provided as capsules (2 x 100 mg) for once daily oral administration. The capsules must be swallowed whole. Subjects should take their dose in the morning (with or without food).

A treatment cycle is defined as 28 days, irrespective of missed doses. Subjects will begin taking study drug on Day 1 of Cycle 1. Sufficient study drug for each treatment cycle will be distributed on the first day of each cycle. If subjects miss a dose, then that dose should be replaced if the subject remembers within an approximate 12-hour window. Otherwise, subjects should take the next dose the following day. If a dose is missed, an additional dose should not be taken if more than 12 hours from prior dose and the patient should resume dosing with the next scheduled daily dose. If subject vomits after taking a dose, they should not repeat the dose. Subject should contact the study investigator and resume dosing at the time of the next scheduled dose (i.e., next day). Missed doses should be recorded in the CRF.

5.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Study treatment will use a cycle length of 28 days. For a new cycle of treatment to begin, subjects must meet the following criteria ≤ 14 days of Cycle 1 Day 1 and ≤ 3 days prior to the start of Day 1 of Cycles 2 and 3:

- All non-hematologic toxicities as described in Section 5.3.1 must have resolved to Grade ≤ 1 or baseline.
- Grade ≥ 3 anemia must have resolved to Grade < 3
- All other hematologic toxicities as described in Section 5.3.2 as described in Section 5.3.2 must have resolved to Grade ≤ 1 or baseline

Patients who do not meet the above criteria for initiation of the next cycle of treatment, dosing should be delayed 7 days. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. For dosing recommendations upon recovery, refer to Section 5.3.

5.3 Dose Modification and Management of Toxicity

All dose interruptions and dose reductions (including missed doses) and the reason for the interruption/reduction are to be recorded in the CRF. For procedures while on treatment, dose interruption of up to 28 days is allowed. Once the dose of study drug is reduced, any reescalation must be discussed in advance with the Principal Investigator.

5.3.1 Non-hematologic Toxicities

Treatment must be interrupted for any non-hematologic toxicity of Grade 3 or 4 at least possibly related to study drug. If the toxicity resolves to Grade 1 or less ≤ 28 days of interruption, then the subject may restart treatment with a reduced dose level according to Table 2. If the event recurs at a similar or worse grade, then treatment should be discontinued. No more than 1 dose reduction will be permitted.

A subject must permanently discontinue study drug for the following non-hematologic toxicity if:

- The non-hematologic toxicity requiring dose interruption has not resolved to Grade 1 or less, within the 28-day dose interruption period.
- Permanently discontinue study drug for any of the following: Drug-induced liver injury defined as:
 - ALT $>8 \times$ ULN at any time, if total bilirubin is $<2 \times$ ULN.
 - ALT $>5 \times$ ULN for >2 weeks, if total bilirubin is $<2 \times$ ULN.
 - ALT $>3 \times$ ULN and total bilirubin $>2 \times$ ULN or INR >1.5 (i.e., meets the definition of Hy's law).
 - Symptoms of drug-induced hepatitis.
 - Exclusion of other etiologies (e.g., infection, cholestasis).
- QTcF ≥ 500 ms or QTcF prolongation >60 ms above baseline.

Table 2. Dose Reduction for Non-hematologic Toxicities

Event	Dose
Starting Dose 200 mg QD	200 mg QD
First dose reduction for Grade 3 or 4 treatment-related SAE/AE 100 mg QD	100 mg QD
Continued Grade 3 or 4 treatment-related SAE/AE for ≥ 28 days	Discontinue

AE=adverse event; QD=once daily; SAE=serious adverse event

5.3.2 Hematologic Toxicities

Niraparib dose interruption/modification criteria for platelet and neutrophil counts will be based on the criteria outlined in Table 3. For the management of anemia, supportive measures such as blood transfusions may be performed as deemed necessary by the investigator per institutional standard-of-care. If more than 1 blood transfusion is given within 4 weeks, the Principal Investigator should be notified. For Grade ≥ 3 anemia, niraparib should be interrupted until resolution to Grade <3 .

The site should consider discontinuation of niraparib if:

- Hematologic toxicity has not recovered to Grade 1 or baseline after >28 days of dose interruption.

Niraparib must be discontinued if a diagnosis of MDS/AML is confirmed by a hematologist.

Table 3: Niraparib/Placebo Dose Modification/Reductions for Platelet and Neutrophil Counts

Toxicity Grade	Dose of Niraparib
Grade 1	No Change, consider weekly monitoring.
Grade 2	At least weekly monitoring and consider interrupting until Grade ≤ 1 or baseline and then resume at same dose with recommendation of weekly monitoring for 28 days after restart.
Grade ≥ 3	<p>Interrupt until Grade ≤ 1 or baseline, then:</p> <ul style="list-style-type: none"> • Resume at 200 mg or 1 dose-level reduction (at the discretion of the investigator). • If subject was already on reduced dose at 100 mg, (because of non-hematologic toxicity), discuss with PI prior to resuming treatment. <p>Weekly monitoring is required until resolution to Grade 1 or baseline. Weekly monitoring is recommended for 28 days after restarting dose.</p>
Second occurrence Grade ≥ 3	<p>Interrupt until Grade ≤ 1 or baseline and restart at 1 dose-level reduction. Weekly monitoring is required until resolution to Grade 1 or baseline. Weekly monitoring is recommended for 28 days after restarting dose.</p> <p>If subject was already on 100 mg, permanently discontinue.</p>

Notes:

1. For subjects with a platelet count $\leq 10,000$ cells/ μ L, prophylactic platelet transfusion per guidelines may be considered. For subjects taking anti-coagulant or anti-platelet therapy, consider the risk/benefit of interrupting these drugs or prophylactic transfusion at an alternative threshold such as $\leq 20,000$ cells/ μ L.
2. Weekly monitoring and/or interruption are not required if at baseline grade, e.g., subject with baseline Hgb 9.1 (Grade 2 anemia) does not need to be monitored weekly for Grade 1 or 2 anemia.
3. If subject requires platelet transfusion or has neutropenic fever or neutropenia requiring granulocyte-colony stimulating factor for Grade ≥ 3 AE deemed to be related to niraparib toxicity, interrupt study drug and restart at 1 dose-level reduction after resolution to Grade 1 or baseline. If the subject was previously dose-reduced for the same hematologic toxicity, discontinue niraparib.

6. STUDY TREATMENT DISCONTINUATION AND SUBJECT COMPLETION/ WITHDRAWAL

6.1 Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he discontinues study drug. Subjects who discontinue study drug should complete the End of Treatment (EoT) visit within 30 days of the last dose of study drug. Subjects should ordinarily be maintained on study treatment unless not tolerated. Although serial PSA's will be measured on this study, change in PSA values is not considered a reliable measure of disease progression within the time frame of treatment, and should not be used as an indication to discontinue study therapy (13). However, a subject's study treatment must be discontinued for the following:

- Study drug-related toxicity as defined in Section 5.2.
- Unequivocal clinical progression defined as:

- Deterioration in ECOG PS to Grade 3 or higher.
- Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease):
 - Alternative anticancer therapy for prostate cancer.
 - The use of external beam radiation therapy to relieve skeletal symptoms.
 - The need for tumor-related orthopedic surgical intervention.
- The investigator believes it is in the best interest of the subject to discontinue study drug.
- Withdrawal of consent for continued treatment (subject's decision to discontinue for any reason).

Note: subjects who discontinue study treatment for any reason remain on study and must follow all study evaluations described in Section 9 and outlined in the Study Calendar.

6.2 Withdrawal from the Study

A subject will be considered withdrawn from the study (i.e., treatment phase and follow-up phase) for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent for subsequent data collection
- Study is terminated

If a subject is lost to follow up, effort must be made by the study-site personnel to contact the subject and determine endpoint status and the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. The informed consent will stipulate that even if a subject decides to discontinue the study drug, he will agree to be contacted periodically by study personnel to assess endpoint status. This can be done by telephone or by chart review. If the subject withdraws consent for all study-related procedures, then no further contact is permitted by the investigator, study personnel, or Janssen.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw prior to prostatectomy will be replaced in order to meet target sample size.

6.3 Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7. CONCOMITANT MEDICATION

Concomitant therapies must be recorded throughout the study beginning with the signing of the main study informed consent to 30 days after the last dose of study drug. All therapies different

from the study drug must be recorded. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and indication. Concurrent enrollment in another investigational drug or device study is prohibited during the Treatment Phase.

7.1 Prohibited Therapy

The Principal Investigator must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered:

1. Chemotherapeutic, biologic, hormonal (exception: subjects must continue GnRHa during the course of the study if not surgically castrate), or other agents with antitumor effect against prostate cancer.
2. Drugs known to cause QT prolongation or torsades de pointes (see Appendix 3).
3. Live virus vaccines. An increased risk of infection by the administration of live virus vaccines has been observed with conventional chemotherapy. Effects with niraparib are unknown and therefore live virus vaccines should not be administered. Note that inactivated bacterial and virus vaccines are permitted.

7.2 Restricted Therapy

Niraparib has the potential to induce CYP1A2; therefore, caution should be used with drugs metabolized by CYP1A2 or drugs that are inhibitors of P-glycoprotein (see examples in Appendix 2).

8. STUDY CALENDAR

Study Calendar Treatment Cycle/Title:	Screening ¹	Cycle 1				Cycle 2		Cycle 3	Surgery	End of Treatment Visit ¹⁵	Follow-up ¹⁶
	Day	C1D1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1	≤6 wks Post Last Dose	30 days Post Last Dose	q3 mos for 2 yrs, then q6 mos
Scheduling Window (Days):	≤28 days Prior to First Dose	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 2 weeks
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X										
Treatment Administration ²		Daily									
Physical Examination ³	X	X				X		X		X	
Vital Signs ⁴	X	X	X	X	X	X	X	X		X	
ECOG Performance Status	X	X				X		X		X	
CT or MRI; Bone scan (^{99m} Tc) ⁵	X										
ECG ⁶	X	X				X		X		X	
Hematology (CBC with Differential) ⁷	X	X	X	X	X	X	X	X		X	

Study Calendar Treatment Cycle/Title:	Screening ¹	Cycle 1				Cycle 2		Cycle 3	Surgery	End of Treatment Visit ¹⁵	Follow-up ¹⁶
	Day	C1D1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1	≤6 wks Post Last Dose	30 days Post Last Dose	q3 mos for 2 yrs, then q6 mos
Scheduling Window (Days):	≤28 days Prior to First Dose	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 2 weeks
Serum Chemistry ⁸	X	X				X		X		X	
Serum PSA ⁹	X	X				X		X		X	X
Testosterone	X										
Urinalysis	X										
Coagulation Panel (PT/INR, aPTT)	X										
CD4+ Count ¹⁰	X										
Prostatectomy ¹¹									X		
Tumor Measurement ¹²									X		
Review Adverse Events ¹³		Ongoing									
Archival or Newly Obtained Tissue Collection ¹⁴	X								X		
Correlative Studies Blood Collection ¹⁴	X										

AE=adverse event; CBC=complete blood count; CT=computed Tomography; MRI=magnetic resonance imaging; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; PSA=prostate specific antigen; 99mTc=technetium-99m

1. Screening: Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. Imaging will be accepted up to 8 weeks prior to Cycle 1 Day 1. Screening clinical laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed ≤ 14 days of Cycle 1.
2. Treatment administration: will begin at Cycle 1 Day 1 and will continue for 3 cycles (1 cycle = 28 days); treatment will be for 12 weeks (3 cycles) prior to scheduled radical prostatectomy (RP). However, the niraparib treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided.
3. Physical Examination: A complete physical examination will be performed at screening. During the treatment phase and at the EoT visit, limited symptom-directed physical examination and weight assessment is required.
4. Vital Signs: Vital signs include body temperature, heart rate, and blood pressure. Body temperature measurement is only needed at screening, at Day 1 of every cycle, and at the EoT visit. Vital signs can be measured in the clinic or self-administered at home and reported to the study team.
5. CT or MRI; Bone scan: Abdomen, and pelvis CT or MRI scans and whole-body bone scans (99mTc) must be evaluated at screening. Scans performed ≤ 8 weeks of Cycle 1 Day 1 are allowed and may serve as screening scans.
6. ECGs: ECGs will be performed at every cycle and at the EoT visit. ECGs must be performed at approximately the same time of day (± 3 hours) at each cycle, and any known electrolyte imbalance should be treated prior to performing the ECG. See Section 9.9 for details of ECG collection.
7. Hematology panel (includes CBC [hemoglobin, white blood cell count, platelets, absolute lymphocyte count (ALC), and absolute neutrophil count (ANC)]) needs to be performed weekly during Cycle 1, every 2 weeks during Cycle 2, during Cycle 3, and as clinically indicated.
8. Serum Chemistry Panel (includes sodium, lactate dehydrogenase, potassium, calcium, creatinine, glucose, magnesium, uric acid, inorganic phosphorus, gamma glutamyltransferase, total protein, chloride, blood urea nitrogen); Liver function tests (AST, ALT, total bilirubin [if above normal, measure direct bilirubin]). To be performed at screening, at every cycle, at EoT, and as clinically indicated.
9. Serum PSA: PSA will be measured at screening, at every cycle of treatment, at EoT, and during Follow up (every 3 months ± 2 weeks from the date of prostatectomy for two years and then every 6 months (± 2 weeks) up to year 5).
10. CD4+ counts: to be performed during screening only for known HIV-positive subjects only.
11. Prostatectomy: Subjects will undergo radical prostatectomy following completion of study treatment (≤ 6 weeks post last dose). Administer anti-thrombotic prophylaxis during the peri-operative period per standard of care.
12. Tumor Measurement: Final pathologic stage and grade will be determined at time of prostatectomy.
13. Adverse Events: If dose interruption or modification is required at any point on study due to hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until AE resolution per section 5.3. Adverse Events collection will begin from the time patient has received at least one dose of study treatment until 30 days after the last dose of study drug. Adverse events will be coded as per CTCAE v5.0.
14. Tissue and Blood: Archival tissue will be collected from diagnostic biopsy (if available) ≤ 90 days prior to Cycle 1 Day1 and at the time of prostatectomy for whole exome sequencing. Blood will be collected at screening and banked for future correlative studies (see Section 10 for details).
15. End of Treatment: The EoT visit must be scheduled ≤ 30 days (± 3 days) after the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. The EoT visit may occur after radical prostatectomy. Subjects who discontinue study drug should complete the EoT visit ≤ 30 days of the last dose of study drug.
16. Follow up: Subjects will be followed for 5-years for biochemical progression-free survival (bPFS), bPFS rate, disease progression (DP), disease-free survival (DFS), and overall survival (OS). PSA will be measured every 3 months ± 2 weeks from the date of prostatectomy for two years and then every 6 months up to year 5 (± 2 weeks for all time points). Survival follow-up will be performed at 3 months and then every 6 months (± 2 weeks) either via clinic visits, telephone interview, chart review, or other methods.

9. STUDY EVALUATIONS

9.1 Study Procedures

The Study Calendar summarizes the frequency and timing of efficacy, biomarker, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECGs first, vital signs second, and any other type of blood draw last. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF.

9.2 Screening Phase

All biomarker-positive subjects must sign the main study ICF prior to the conduct of any study-related procedures in the Screening Phase. During this phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the Study Calendar.

Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. Imaging will be accepted up to 8 weeks prior to Cycle 1 Day 1. Screening clinical laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed ≤ 14 days of Cycle 1.

9.3 Treatment Phase

The Treatment Phase will begin at Cycle 1 Day 1 and will continue for 3 cycles (1 cycle = 28 days). The last measurements taken on Day 1 of Cycle 1 before administration of the study drug or at screening (whichever value was last) will be defined as the baseline values. Visits for each cycle will have a ± 3 -day window, unless otherwise specified. Study visits will be calculated from the Cycle 1 Day 1 date, irrespective of any treatment interruptions. Refer to the Study Calendar for treatment visits and assessments during the Treatment Phase.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Study drug treatment will continue for 3 cycles (12 weeks), or until unacceptable toxicity, death, or the sponsor terminates the study. Once the subject discontinues study drug, the subject must complete the End of Treatment (EoT) visit ≤ 30 days after the last dose of study drug, and enter the Follow-up Phase.

9.4 Radical Prostatectomy

Subjects will undergo radical prostatectomy following completion of study treatment (≤ 6 weeks post last dose). Radical prostatectomy may occur before or after the EoT visit.

Administer anti-thrombotic prophylaxis during the peri-operative period per standard of care.

9.5 End of Treatment Visit

An End of Treatment (EoT) visit must be scheduled within 30 days after the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. If a subject is unable to return to the site for the EoT visit, the subject should be contacted to collect AEs that occurred within 30 days after the last dose of study drug.

9.6 Follow-up Phase

Patients will be followed for 5 years for biochemical progression-free survival (bPFS), bPFS rate, disease progression, disease-free survival, and overall survival (OS). PSA will be measured every 3 months (± 2 weeks) from date of prostatectomy for two years and then every 6 months up to year 5.

Survival follow-up will be performed at 3 months and then every 6 months (± 2 weeks) either via clinic visits, telephone interview, chart review, or other methods.

9.7 Efficacy

9.7.1 Evaluations

Efficacy evaluations will be conducted as specified in the Study Calendar. Unscheduled assessments should be considered if clinically indicated, and results collected in the CRF. The efficacy evaluations include the following.

- Tumor measurements: Final pathologic stage and grade at prostatectomy
- Serum PSA
- Survival status

9.7.2 Criteria

Initial tumor response will be gauged by pathologic findings at the time of radical prostatectomy. Further evaluation of treatment response by PSA will be assessed. Initial PSA will be at 3 months after surgery and then monitored every 3 months for the first two years and then every 6 months up to year 5. PSA recurrence is defined by PSA >0.2 ng/mL and rising after surgery.

9.8 Correlatives

Tissue will be collected from diagnostic biopsy and at the time of prostatectomy for whole exome sequencing. Responses will be stratified by type of DNA repair alterations as well as for 'BRCAness' or molecular features of BRCA deficient tumors.

Blood will be collected at screening (4 ml whole blood into an EDTA tube, in 4 x 1 ml aliquots). and banked for future correlative studies. Blood will be stored within our IRB approved institutional biorepository.

9.9 Assessments

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs (12-lead), physical examinations, clinical laboratory tests, ECOG PS, and other safety evaluations at specified time points as described in the Study Calendar. Any clinically significant abnormalities persisting at the EoT visit will be referred to appropriate specialist for management.

9.9.1 Adverse Events

Potential adverse events (AE) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the

study, and investigators will determine if the events are recorded as AEs. AEs will be followed by the investigator as specified in Section 13.4.

9.9.2 Clinical Laboratory Tests

Blood samples to assess the safety of study drug will be collected. The investigator must review laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. For each laboratory abnormality reported as an AE, toxicity grades should be reported.

Required laboratory tests must be performed within ± 3 days of the scheduled visit. In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Principal Investigator. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to World Health Organization (WHO) criteria (14) and other sample testing reports related to MDS/AML. Data from the report will be entered on the appropriate CRF pages and the site must keep a copy of the report with the subject's study file.

The following tests will be performed as outlined in the Study Calendar:

- **Hematology Panel:** CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC) needs to be performed weekly during Cycle 1, every 2 weeks during Cycle 2, and once during Cycle 3.
- **Serum Chemistry Panel:** sodium, lactate dehydrogenase, potassium, calcium, creatinine, glucose, magnesium, uric acid, inorganic phosphorus, gamma glutamyltransferase, total protein, chloride, blood urea nitrogen. Liver Functions Tests: AST, ALT, total bilirubin (if above normal, measure direct bilirubin).
- **Other Laboratory Tests:** testosterone (screening only), serum PSA, albumin, alkaline phosphatase, CD4 count for HIV-positive subjects only (screening only), urinalysis, thyroid function, and coagulation panel.

9.9.3 Electrocardiogram (ECG)

ECGs (12-lead) will be recorded at the time points outlined in the Study Calendar. ECGs must be performed at approximately the same time of day (± 3 hours) at each cycle and any known electrolyte imbalance should be treated prior to performing the ECG. ECGs should be recorded on the same device, if at all possible, to avoid ECG device variability. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. Subjects are to reside in a quiet setting without distractions (e.g., television, cell phones, and staff talking) at each scheduled time point for ECG measurements. Subjects should rest in a supine position for at least 10 minutes before ECG collection and should refrain from talking or moving arms or legs. Clinically significant abnormalities noted at the time of

screening will be documented in the subject's medical history and recorded on the CRF. Clinically significant abnormalities noted during the treatment phase and at the EoT visit will be recorded on the Adverse Event section of the CRF.

9.9.4 Vital Signs

Body temperature, heart rate, and blood pressure will be recorded at the time points outlined in the Study Calendar.

9.9.5 Physical Examination

A complete physical examination will be performed at screening. During the treatment phase and at the EoT visit, limited symptom-directed physical examination and weight assessment is required.

9.9.6 ECOG Performance Status

The ECOG PS scale (see Appendix 1) will be used to grade changes in the subject's daily living activities. The frequency of ECOG PS assessment is provided in the Study Calendar.

9.10 Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. Refer to the Study Calendar for the timing and frequency of all sample collections.

10. CORRELATIVES

10.1 Tissue

Tissue will be collected from diagnostic biopsy and at the time of prostatectomy for whole exome sequencing. Prostate cancer tissue will be collected from FFPE blocks processed by the standard protocols of the Department of Pathology. A board-certified pathologist will identify tumor on the clinical H&E slides. Paraffin sections and cores will be prepared by the Biorepository shared resource. We will request 5 FFPE slides sectioned at 5 microns or 3mm X 5mm cores (if possible) based on tumor volume. No other patient identifiers will be shared with lab running sequencing.

Responses will be stratified by type of DNA repair alterations as well as for 'BRCAness' i.e., molecular features that share the BRCA-deficient tumors. At the of prostatectomy, post procedure additional tissue will be collected as before labelled and placed on ice as well and delivered to the McPherson Lab to harvest DNA and for whole exome sequencing.

10.2 Blood

One 10 mL EDTA tube of whole blood will be collected at screening and processed by the MPSR. Whole blood will be centrifuged at 2000 x g for 15 minutes to separate plasma from buffy coat and red blood cells (RBC). Plasma will be discarded, and buffy coat will be collected ~2 mL and mixed well and placed into 2 x 1 mL cryotubes, stored at -80C until delivery to Dr. McPherson's lab. Tubes will be labelled with study, study ID, date and time of collection.

10.3 Sample Retention

Stored samples will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research. Details of the sample retention for research are presented in the main ICF.

11. STUDY DRUG INFORMATION

11.1 Physical Description of Study Drug

The niraparib capsule supplied for this study contains 100 mg of niraparib. It will be manufactured and provided by Janssen. Refer to the Investigator's Brochure for a list of excipients.

11.2 Packaging

Niraparib 100 mg capsules (90 capsules per bottle) will be packaged in high-density polyethylene bottles with child-resistant closures.

11.3 Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Although niraparib is a marketed product, it is not currently approved for the indication under study.

11.4 Preparation, Handling, and Storage

The study drug must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Subjects should be advised to keep the study drug out of reach and sight of children.

Niraparib may have adverse effects on a fetus in utero. It is not known whether niraparib is present in, or has transient effects on the composition of semen. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug.

11.5 Safe Handling of Drug

Caregivers should wear gloves if they need to touch the niraparib capsules. Any caregivers should be notified of this information, to ensure the appropriate precautions are taken.

11.6 Drug Accountability

Responsibility for drug accountability is on the investigator and the assigned pharmacist or designee. Drug supply will be disposed of according to institutional standard operating procedures. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

11.6.1 Ordering / How Supplied

Niraparib will be supplied by Janssen at no cost to study participants.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

Unfavorable intermediate, high, or very high risk clinically localized prostate cancer defined by National Comprehensive Cancer Network (NCCN) criteria in men eligible for radical prostatectomy with >10-year life expectancy. Men must have clinically negative staging studies with CT/MRI and bone scan and must have not been previously treated.

Men will be screened for alterations in genes involved in DNA repair, primarily in the homologous recombination pathway. Patients will be screened with targeted gene sequencing utilizing an FDA-approved assay.

Prostatectomy specimens will be analyzed after surgery for staging. Tumor volume will be estimated, and responses defined as complete, minimal residual disease (<0.5 cc, organ confined), or none. Tissue will be collected from diagnostic biopsy and at the time of prostatectomy for whole exome sequencing. Responses will be stratified by type of DNA repair alterations as well as for 'BRCAness' i.e., molecular features that are shared with BRCA-deficient tumors.

12.2 Endpoints

12.2.1 Primary Endpoints

The primary output is pathologic response rate (pRR) at the time of radical prostatectomy, and the study is powered to assess this. We will assess the impact of neoadjuvant niraparib therapy prior to radical prostatectomy (RP) on pathologic tumor stage, frequency of lymph node metastases and positive margin rates for patients undergoing radical prostatectomy for unfavorable intermediate or high-risk, clinically localized prostate cancer with alterations in DNA repair pathways. Pathologic complete response (PCR) defined as no tumor identified on H&E-stained sections will be assessed; minimal residual disease (MRD) will be defined as tumor clusters limited to <5 mm and confined to prostate gland.

The pRR will be compared to a null rate of 0.001 using a one-sided exact binomial test, adjusted for the two-stage Simon design as described by Koyama and Chen (15). Exact 95% confidence intervals for pRR and other binary outcomes, adjusted for the two-stage design, will be calculated as described by Koyama and Chen (15, 16). Response rates will be compared between patients with biallelic and monoallelic loss using Fisher's Exact Test.

12.2.2 Secondary Endpoints

Secondary endpoint is biochemical (PSA) progression free survival at 5 years.

Median bPFS and quartiles (when reached) will be calculated from Kaplan-Meier estimates, and 95% confidence intervals will be calculated using Greenwood's formula (17).

12.2.3 Exploratory Endpoints

- To assess the 5-year biochemical progression-free survival (bPFS) rate, bPFS, disease progression, disease-free survival, and overall survival (OS)

- To evaluate the safety and tolerability of neoadjuvant niraparib prior to surgery for unfavorable intermediate or high-risk patients undergoing radical prostatectomy
- To assess the impact of neoadjuvant niraparib on time to clinically apparent local disease recurrence and metastatic disease in unfavorable intermediate or high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer

Time to event outcomes will be analyzed as for median bPFS.

12.3 Sample Size Determination

The study uses a modification of an optimal Simon 2 stage design. We will enroll 11 participants and assess pathologic response rate (pRR). If 0 patients have pRR, then we will stop the study for futility. Otherwise, we will continue the study and enroll 19 more patients. At the end of the study, if 2 or more participants have overall response, we will deem this treatment strategy acceptable.

Probabilities of early termination are summarized in 12.4. The probability of proceeding to the second stage then observing at least 2 out of 30 responses and deeming the treatment strategy acceptable is summarized for different response probabilities in the table below:

pRR Probability	Probability of Deeming Treatment Acceptable
0.001	0.000
0.01	0.018
0.05	0.268
0.10	0.593
0.15	0.795

To assess response differences in patients with biallelic versus monoallelic loss of DNA repair genes, we will enroll at least 10 patients with biallelic loss. All calculations are based on an alpha level of 0.025 to compensate for using a one-sided test.

12.4 Planned Interim Analyses

We plan to conduct one interim analysis for futility. Following a modification of an optimal Simon 2 stage design, we will enroll 11 participants and assess pathologic response rate (pRR). Enrollment will be paused once the 11th participant is enrolled. If the 11th participant does not undergo radical prostatectomy, then enrollment would re-open to allow another participant to replace the participant that did not undergo radical prostatectomy during the study.

If 0 patients have pRR during interim analysis, then we will stop the study for futility. Otherwise, we will continue the study and enroll 19 more patients. At the end of the study, if 2 or more participants have pRR, then we will deem this treatment strategy acceptable. Probabilities of deeming this treatment strategy acceptable are summarized in section 12.3.

The probability of early termination (PET) is shown for different underlying pRR below:

pRR Probability	PET
0.001	0.989
0.01	0.895
0.05	0.569
0.10	0.314
0.15	0.167

Once the 11th participant undergoes radical prostatectomy, the data team will provide the relevant pathological response information to the study team and DSMC. The Principal Investigator, UCD Data Safety Monitoring Committee (DSMC), and other investigators/ members of the study team (as their schedule allows) will discuss pRR outcomes once the 11th participant undergoes radical prostatectomy. pRR will be assessed per section 12.2.1 for all 11 participants. Ultimately, the DSMC must elect to stop the study for futility or continue to enroll participants based on the predetermined rules described above.

13. SAFETY AND REPORTING REQUIREMENTS

13.1 Overview

As the sponsor of the Study, UC Davis Comprehensive Cancer Center (UCDCCC) and the Principal Investigator (PI) 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 adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The UCDCCC and the PI will provide safety information to Janssen on adverse events, special situations including pregnancies and product quality complaints as defined within this protocol.

Interim analysis for futility will be conducted once 11 participants undergo radical prostatectomy (see section 12.4 for details).

13.1.1 Management of Safety Data

This study has been designated as an interventional study. As such, all adverse events for Johnson & Johnson Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Johnson & Johnson 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 (SAE) will be reported for 30 days after the last dose of study drug. Safety events that require special reporting are described in Section 13.3.

For the purposes of this study, the Johnson & Johnson medicinal product is: Niraparib.

13.2 Definitions

13.2.1 Adverse Event (AE)

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. (Definition per International Council for Harmonisation [ICH]). 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.

13.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

- | | |
|-----------------------------|---|
| Mild (Grade 1): | The event causes discomfort that affects normal daily activities. |
| Moderate (Grade 2): | The event makes the subject unable to perform normal daily activities or significantly affects his/her clinical status. |
| Severe (Grade 3): | The event makes the subject unable to perform normal daily activities or significantly affects his/her clinical status. |
| Life-threatening (Grade 4): | The subject was at risk of death at the time of the event. |
| Fatal (Grade 5): | The event caused death. |

13.2.3 Causality (Attribution) of Adverse Events

The investigator is to assess the causal relation of all AEs (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

- | | |
|---------------------|--|
| Not Related: | Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible. |
| Unlikely: | The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely. |

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Related: The AE is clearly related to use of the investigational product.

13.2.4 Individual Case Safety Report (ICSR)

A valid ICSR must contain the 4 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 Johnson & Johnson medicinal product
- An adverse event, outcome, or certain special situations

The minimum information required is:

- Suspected Johnson & Johnson 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)
- Gender
- Age at AE onset
- Reporter ID
- Adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

13.2.5 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
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*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.

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

13.2.6 Adverse Events of Special Interest

Adverse events of special interest (AESI) are events that Janssen is actively monitoring as a result of a previously identified signal (even if non-serious). For niraparib, the adverse events of special interest are the following if Grade ≥ 3 :

- Grade 3-4 Thrombocytopenia
- Grade 3-4 Neutropenia
- Grade 3-4 Anemia
- Hypertension
- Acute Myeloid Leukemia
- Myelodysplastic Syndrome

Any Adverse Event of Special Interest that is to be reported to Janssen should be recorded on a Serious Adverse Event Report Form and be reported to Janssen **within 24 hours of knowledge of the event**.

13.3 Special Reporting Situations

Safety events of interest for a Johnson & Johnson medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Johnson & Johnson medicinal product
- Exposure to a Johnson & Johnson medicinal product from breastfeeding
- Suspected abuse/misuse of a Johnson & Johnson medicinal product
- Inadvertent or accidental exposure to a Johnson & Johnson medicinal product

- Medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson 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 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 should be recorded on a Serious Adverse Event Report Form and be reported to the Janssen within 24 hours of becoming aware of the event.

13.4 Procedures for Reporting Adverse Events

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Johnson & Johnson medicinal product (i.e., Niraparib) are to 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 a Johnson & Johnson medicinal product (i.e., Niraparib).

All (serious and non-serious) adverse events reported for a Johnson & Johnson medicinal (i.e., Niraparib) product should be followed up in accordance with clinical practice.

Any patient enrolled in the trial who signed the consent form and received at least one dose of study treatment will be eligible for adverse event reporting. Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 5.0 for adverse event reporting.

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

13.4.1 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The UCDCCC and the PI 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 Janssen's request.

13.4.2 Serious Adverse Events, Adverse Events of Special Interest 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)

The UCDCCC and the PI will transmit all SAEs, adverse events of special interest and special situations following exposure to a Janssen product (i.e., Niraparib) under study within 24-hours of becoming aware of the event(s).

The following methods are acceptable for transmission of safety information to Janssen:

- Electronically via Janssen 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 Janssen.

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 must be reported directly by the PI, **within 24 hours of becoming aware**, to Janssen using Janssen's Serious Adverse Event Report or FDA MedWatch form.

All available clinical information relevant to the evaluation of a related SAE, adverse events of special interest, serious adverse drug reaction (ADR), or special situation is required.

- The UCDCCC and/or PI are/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 follow the same timeline as initial reports.
- 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 (i.e., Niraparib) under study, are to be provided to Janssen **within 24 hours of such report or correspondence being sent to applicable health authorities**.

13.4.3 Pregnancy

Because the Johnson & Johnson medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Johnson & Johnson medicinal product will be reported by the PI within 24 hours of their knowledge of the event using the Serious Adverse Event Form or

FDA MedWatch form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

13.4.4 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 or for <24-hour observation)
- 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.)

13.4.5 Life-Threatening Conditions

The cause of death of a subject in a study within 30 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.

13.4.6 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.

13.4.7 Product Quality Complaint (PQC)

A product quality complaint 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., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

13.4.8 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Johnson & Johnson Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non- Johnson & Johnson medicinal product under study, the PI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

13.5 Product Quality Complaints (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 the Janssen, and are mandated by regulatory agencies worldwide. Janssen 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 Johnson & Johnson medicinal product under study must be reported to Janssen by the PI **within 24 hours after being made aware of the event**. The Janssen contact will provide additional information/form to be completed.

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

13.6 Safety Reporting Requirements for IND Exempt Studies

For Investigator Sponsored IND Exempt Studies there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

13.6.1 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

14. ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

14.3 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. Eligibility must be confirmed by the Investigator. After verifying the eligibility, the OCR coordinator will register the patient onto the study and assign a patient accession number. Administration of study drug may not be initiated until the patient is registered.

14.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

14.5 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD OCR. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.6 Protocol Compliance and Deviations

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR. Any departures from the protocol must be fully documented in the source documents.

14.7 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator and/or Janssen, there is sufficient reasonable cause.

If the study is prematurely terminated, then the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB). Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Refer to section 6 for details regarding treatment discontinuation procedures for participants on study treatment.

14.8 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

14.9 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan. Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

14.10 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 12.4, this protocol is also subject to the UC Davis Comprehensive Cancer Center's (UCDCCC) Data and Safety Monitoring Plan. The UCDCCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCCC to fulfill its mission in conducting high quality clinical cancer research.

As per UCDCCC Office of Clinical Research (OCR) standard operating procedures: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events, and to determine if dose escalation is warranted, when applicable.

According to the UCDCCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCCC Scientific Review Committee (SRC) determines if a UCDCCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information, and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

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16. APPENDICES**Appendix 1: ECOG and Karnofsky Performance Status Scores^{1,2}**

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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Appendix 2: Substrates of CYP1A2 and Inhibitors of P-glycoprotein**16.1.1 Substrates of CYP1A2**

Niraparib has the potential to induce CYP1A2; therefore, caution should be used with drugs metabolized by CYP1A2 and subjects should be monitored for decreased efficacy.

amitriptyline	ondansetron
clomipramine	propranolol
clozapine	riluzole
cyclobenzaprine	ropivacaine
duloxetine	tacrine
estradiol	theophylline
fluvoxamine	tizanidine
haloperidol	triamterene
imipramine N-DeMemexiletine	verapamil
nabumetone	(R)warfarin
naproxen	zileuton
olanzapine	

Source: Indiana University Department of Medicine: P450 Drug Interaction Table.
<http://medicine.iupui.edu/CLINPHARM/ddis/main-table>

16.1.2 Inhibitors of P-glycoprotein

Example inhibitors of P-glycoprotein transporters include the following:

- Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil

Source: FDA: Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. Available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>.

Appendix 3: Prohibited Medications That Could Potentially Cause QT Prolongation or Torsades De Pointes

Note that the following list of drugs is not a complete list. New medications may be approved and should be considered carefully. When in doubt, contact the sponsor.

Drug Class	Drug Name
Typical antipsychotics	Thioridazine, haloperidol, chlorpromazine, pimozide, loxapine
Atypical antipsychotics	Ziprasidone, iloperidone, quetiapine, ziprasidone, olanzapine, risperidone, paliperidone, aripiprazole, asenapine, clozapine, brexpiprazole, lurasidone,
SSRIs (selective serotonin reuptake inhibitors)	Citalopram, escitalopram, paroxetine, fluoxetine, sertraline, fluvoxamine
TCAs (tricyclic antidepressants) and TeCAs (tetracyclic antidepressants)	Amitriptyline, imipramine, maprotiline, nortriptyline, desipramine, clomipramine, trimipramine, doxepin
SNRIs (serotonin norepinephrine reuptake inhibitors)	Venlafaxine, duloxetine, desvenlafaxine, levomilnacipran, milnacipran
Other antidepressants	Mirtazapine, bupropion, vortioxetine, vilazodone, trazodone
Antiarrhythmics	Amiodarone, sotalol, quinidine, procainamide, dofetilide, ibutilide, disopyramide, dofetilide
Antimicrobials	Levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin, clarithromycin, erythromycin, ketoconazole, itraconazole, fluconazole, voriconazole
Oncology	Sunitinib, nilotinib, dasatinib
Others	Cisapride, sumatriptan, zolmitriptan, dolasetron, methadone, ondansetron, ranolazine, furosemide, hydrochlorothiazide, chlorthalidone

Appendix 4: Cockcroft-Gault Estimation of Creatinine Clearance

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

(Males)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

(Females)

Appendix 5: Data Collection Forms

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

Appendix 6: Pill Diary

Patient Name: _____ Medical Record #: _____

Cycle#: _____ Start Date: _____ Dose: _____

Instructions to Patients: In the table below, please provide time, date, and number of pills for each dose taken. If a dose is missed, then that dose should be replaced within a 12-hour window. Otherwise, take the next dose the following day without double dose and leave cell blank; confirm with study coordinator upon return of pill diary.

Niraparib will be provided as 100 mg capsules for oral administration. The capsules must be swallowed whole. Subjects should take their dose in the morning with or without food.

Day	1	2	3	4	5	6	7
	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____
	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____
Day	8	9	10	11	12	13	14
	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____
	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____
Day	15	16	17	18	19	20	21
	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____
	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____
Day	21	22	23	24	25	26	28
	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____	Date: _____
	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____	# Pills: _____

Patient Signature: _____ Date: _____

Date Returned	# of pills left	Collector's Initials	Returned to Pharmacy
			Yes or N/A

Appendix 7: NCCN Guidelines Version 4.2018 – Risk Stratification for Prostate Cancer

Risk group	Clinical/pathologic features
Very low ^g	<ul style="list-style-type: none"> • T1c AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density <0.15 ng/mL/g
Low ^g	<ul style="list-style-type: none"> • T1-T2a AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL
Favorable intermediate ^g	<ul style="list-style-type: none"> • T2b-T2c OR • Gleason score 3+4=7/grade group 2 OR • PSA 10–20 ng/mL AND • Percentage of positive biopsy cores <50%
Unfavorable intermediate ^g	<ul style="list-style-type: none"> • T2b-T2c OR • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR • PSA 10–20 ng/mL
High	<ul style="list-style-type: none"> • T3a OR • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR • PSA >20 ng/mL
Very high	<ul style="list-style-type: none"> • T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Gleason score 8–10/ grade group 4 or 5
Regional	Any T, N1, M0
Metastatic	Any T, Any N, M1

Source: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer. Version 4.2018 - August 15, 2018.

- g. For asymptomatic patients with life expectancy ≤5 years, no further workup or treatment is indicated until the patient becomes symptomatic.