NRG ONCOLOGY

NRG-GU007
(ClinicalTrials.gov NCT #04037254) (07-APR-2020)

RANDOMIZED PHASE II TRIAL OF NIRAPARIB WITH STANDARD COMBINATION RADIOTHERAPY AND ANDROGEN DEPRIVATION THERAPY (ADT) IN HIGH RISK PROSTATE CANCER (WITH INITIAL PHASE I)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

Study Team (07APR2020)

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Niraparib	Janssen	804335	Exempt	NRG Oncology
GnRH Agonist: leuprolide, goserelin, buserelin, triptorelin	Commercial	N/A		

Participating Sites

☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History

	Version Date
Amendment 2	**April 07, 2020**
Amendment 1	June 18, 2019
Initial	April 30, 2019

NRG ONCOLOGY

NRG-GU007

Randomized Phase II Trial of Niraparib with Standard Combination Radiotherapy and Androgen Deprivation Therapy (ADT) in High Risk Prostate Cancer (With Initial Phase I)

<table>
<tr><td colspan="3">CONTACT INFORMATION: (18-JUN-2019)</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For study data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal: (Sign in at www.ctsu.org, and select Regulatory > Submission.)

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

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related),</u> contact the Study Data Manager of the Lead Protocol Organization</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU website is located at https://www.ctsu.org.</td></tr>
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PHASE I SCHEMA

Histologically confirmed adenocarcinoma of prostate at high risk for recurrence determined by Gleason score (Gleason ≥ 9, PSA ≤ 150 ng/mL, any T-stage)

↓

GnRH agonist androgen suppression therapy*
+
Niraparib**
+
Dose Escalated IMRT

*GnRH agonist androgen suppression therapy is not allowed prior to registration in Phase I.
**See Dose Level chart in Section 5.1.

PHASE II SCHEMA

Histologically confirmed adenocarcinoma of prostate at high risk for recurrence determined by Gleason score

↓

STRATIFICATION

Gleason Score:

- Gleason ≥ 9, PSA ≤ 150 ng/mL, any T-stage
- Gleason 8, PSA < 20 ng/mL, and ≥ T2
- Gleason 8, PSA ≥ 20-150 ng/mL, any T-stage
- Gleason 7, PSA ≥ 20-150 ng/mL, any T-stage

RT: Standard fractionation vs. hypofractionation

RANDOMIZE (1:1)

Arm 1*	**Arm 2***
GnRH Agonist Androgen Suppression Therapy + Dose Escalated IMRT	GnRH Agonist Androgen Suppression Therapy + Dose Escalated IMRT + Niraparib**

***See Section 5.1 for drug treatment details and Section 5.2 for radiation therapy details. GnRH agonist androgen suppression therapy can begin prior to registration in Phase II

**Dosing per Phase I results

1. OBJECTIVES

1.1 Primary Objective

1.1.1 **Phase I:** To establish the preferred dose of niraparib in combination with radiation and ADT

1.1.2 **Phase IIR:** To compare the disease-free state, defined as PSA remaining < 0.1 ng/ml at the end of ADT therapy in men with high risk prostate cancer treated with standard therapy with or without the addition of niraparib

1.2 Secondary Objectives

1.2.1 To further establish the safety and toxicity profile of standard treatment with radiation and androgen deprivation therapy specifically, two years from initiation of ADT, plus niraparib at the phase II dose

1.2.2 To compare the overall survival, prostate cancer-specific survival, local/regional or distant progression, and distant metastatic disease rates of standard therapy with or without the addition of niraparib. Although the clinical benefit of niraparib in combination with radiotherapy and ADT has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to dose, safety and tolerability.

1.3 Exploratory Objective

1.3.1 To identify genomic biomarkers of response to combination therapy with radiation, ADT and PARP inhibition

2. BACKGROUND

2.1 Rationale

High level evidence has established the use of long-term ADT with radiation therapy as standard of care for men with locally advanced prostate cancer. However, in men with the highest recurrence rates, the failure rate may exceed 50%, and a substantial number of men will still progress to life threatening complications from prostate cancer.

The control arm in this study will consist of involved field radiation therapy plus standard long-term ADT for 24 months. Prior studies have demonstrated that PSA nadir is a strong predictor of outcome in men treated with standard therapy (D'Amico 2012; Zelefsky 2013). PSA nadir values of > 0.5 ng/ml were associated with higher rates of disease-specific and all-cause mortality among men treated with radiation with or without short-term ADT (D'Amico 2012). In another study, among men treated with ADT, failure to achieve PSA < 0.3 ng/ml was highly prognostic for death related to prostate cancer (Zelefsky 2013). Thus, PSA nadir appears to be a surrogate for survival related to prostate cancer and may be considered as an intermediate marker for assessing the efficacy of novel agents in this disease context. Here, we further require that men sustain very low PSA until the end of the 2-year post-ADT therapy interval, in order to identify those likely to be in a ‘disease-free’ state.

The initial experimental arm in this study will add the potent PARP inhibitor, niraparib, to standard therapy in men with high risk prostate cancer.

2.2 Why This Trial Is Important

With current standard of care therapy, a substantial percentage of men with high risk, localized prostate cancer will ultimately progress to metastatic disease despite maximal treatment. The aim of our study is to identify additional therapeutic interventions that will improve outcomes in this patient population. The design of this trial will utilize the intermediate endpoint of PSA nadir to assess whether the addition of the PARP inhibitor niraparib appears promising. Our intent would be to rapidly advance a promising systemic agent to definitive phase 3 testing. Positive phase 3 results would alter standard of care treatment for high risk localized prostate cancer.

2.3 Pertinent Data

Neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT) with a long acting GnRH agonist improves survival when added to primary radiation therapy for men with prostate cancer at high risk for relapse. Three notable studies have established the role of long term ADT with a GnRH agonist. An EORTC trial enrolled 415 subjects with locally advanced disease and showed a 16% overall survival benefit with three years of ADT (78% vs. 62% survival at five years, $p = 0.001$) (Bolla 1997). RTOG 85-31 enrolled 977 patients and demonstrated a non-significant 4% overall survival benefit (75% vs. 71%, $p = 0.52$) at five years (Pilepich 1997) and a significant 10% overall survival benefit at 10 years (49% vs. 39%, $p = 0.002$) with the addition of indefinite ADT (Pilepich 2005). A subsequent EORTC trial was designed to demonstrate equivalence of 6 months and 3 years of ADT but instead showed a significant 5 year overall survival advantage for the longer term ADT group (15% vs. 19% mortality) (Pilepich 1997).

As a result of these studies, high level evidence strongly supports the use of long-term ADT with radiation therapy as standard of care for men with locally advanced prostate cancer. However, not all men are at similar risk of adverse outcome. Therefore, risk stratification is crucial in determining appropriate treatment for men with localized prostate cancer (Albertsen 2005; Chism 2004; D'Amico 2002; Pisansky 1997; Symon 2003). Prognostic factors include clinical stage, Gleason score, and the level of PSA (Albertsen 2005; Chism 2004; D'Amico 2002; Pisansky 1997; Symon 2003). In men with the highest recurrence rates, the failure rate with regard to PSA relapse is 40% to 65% (Albertsen 2005; Chism 2004; D'Amico 2002; Pisansky 1997; Symon 2003). Despite the addition of ADT to radiation therapy, a substantial subset of these men may progress to life threatening complications related to prostate cancer. Additional treatments at the time of definitive therapy may prevent subsequent relapse and progression.

When studied in the neoadjuvant setting with prostatectomy, standard ADT alone is not associated with improvement in PSA failure rate (Fair 1997; Klotz 1999; Meyer 1999). Pathologic complete responses are rarely observed in response to standard ADT. To explain this lack of efficacy, a leading hypothesis suggests that GnRH agonist therapy alone does not adequately suppress prostate tissue androgens (Mostaghel 2014).

Consequently, preliminary studies have studied more intensive androgen blockade. Abiraterone acetate, a CYP17 (cytochrome P450 c17) inhibitor, reduces all sources of serum androgens to undetectable or near undetectable levels. Taplin and colleagues demonstrated that in prostate tissue as well, levels of androgens were significantly lower with GnRH agonist therapy plus abiraterone than with GnRH agonist therapy alone (Taplin 2014).

Despite the lack of benefit with the combination of ADT and radical prostatectomy, there is clear demonstration of improved survival when ADT is combined with radiation. In part this may be explained by the demonstration that androgen signaling increases prostate cancer specific DNA repair, while androgen suppression inhibits DNA repair and renders prostate cancer cells preferentially more sensitive to radiation induced damage and cell death (Goodwin 2013; Polkinghorn 2013).

There is great interest in targeting DNA repair mechanisms in tumor cells. Normal cellular physiology is characterized by elaborate DNA repair mechanisms for both single and double stranded DNA breaks. Single stranded breaks in DNA are addressed by nucleotide excision, base excision and mismatch excision repair. The nuclear enzyme PARP (poly ADP-ribose polymerase) efficiently recognizes, and subsequently facilitates repair of, single stranded DNA breaks. A number of other proteins, including BRCA1, BRCA2 and ATM, are integral components of double-stranded DNA repair pathways. When the pathways for both single stranded and double stranded repair are simultaneously disrupted, the impact on cells may be profound. This notion of synthetic lethality has most directly been verified in breast and ovarian tumors that are BRCA deficient, and which manifest particular sensitivity to PARP inhibition (O'Connor 2015; Yap 2011). Following clinical trials that confirmed efficacy, the PARP inhibitor olaparib was FDA-approved in 2014 for women with BRCA-deficient ovarian cancer. Niraparib was approved in 2017 for maintenance treatment of ovarian cancer following response to platinum-based chemotherapy. Several other potent PARP inhibitors are in late stages of clinical development, including talazoparib (BMN-673; Medivation, San Francisco, CA, USA), veliparib (ABT-888; Abbvie, North Chicago, IL, USA), and rucaparib (AGO14699; Clovis, Boulder, CO, USA), in a variety of malignancies.

The potential role of PARP inhibition in prostate cancer was introduced in a landmark study in 50 patients with advanced metastatic prostate cancer (Mateo 2015). In total, approximately one third of men responded to therapy with olaparib, but much more striking was the finding that among 16 men with deficiencies in DNA repair pathways (including deletions and/or deleterious mutations in BRCA1, BRCA2, ATM, Fanconi's anemia genes, and/or CHEK2), 88% responded to therapy. Two important conclusions from this study were that: 1) a substantial percentage of men with advanced prostate cancer, perhaps up to 25%-30%, may have either germline or sporadic mutations in DNA repair pathway genes within the tumors; and 2) these patients have a remarkably favorable response rate to PARP inhibition. The great excitement generated by this study has led to rapid development of late stage clinical trials of various PARP inhibitors in advanced prostate cancer.

The role of PARP inhibition has not been investigated in the treatment of localized prostate cancer. There is a particularly compelling rationale for combining PARP inhibition with radiation therapy and ADT in prostate cancer. In preclinical models, PARP inhibitors improve efficacy of radiation therapy by blocking DNA repair mechanisms (Brock 2004; Chalmers 2004). Various animal models have confirmed these results, such as the HCT-116 colon cancer xenograft model, in which the addition of veliparib to radiation, compared with radiation alone, nearly doubled median survival while veliparib alone had no demonstrable activity (Donawho 2007). Whereas efficacy of PARP inhibitors alone may require innate DNA repair deficiencies within tumors, the efficacy of PARP inhibitors when combined with radiation may not, but this has yet to be explored comprehensively. The best data to suggest that biomarkers of response to radiation and PARP1 inhibition will differ from biomarkers of response to PARP1 inhibition alone is from preclinical studies in breast cancer (Chalmers 2004). Across a large panel of cell lines, members of our team demonstrated that treatment with a PARP1 inhibitor radiosensitized the majority of breast cancer cell lines independent of BRCA mutation status, suggesting that determinants of synthetic lethality to monotherapy with PARP1 inhibitor were not effective predictors of response to combination therapy with radiation plus a PARP1 inhibitor. Finally, ADT may induce a conditional synthetic lethal phenotype with PARP inhibition in hormone naïve prostate cancers where DNA damage could then further be augmented by radiation therapy.

In this trial, we propose to study the combination of niraparib with standard radiation and ADT in men with high risk prostate cancer. A phase I component will be utilized to establish the preferred dose of niraparib in combination with radiation and ADT. Given that the purpose of the phase I component is to establish safety and the maximum tolerated dose of niraparib in combination with radiation and ADT, the phase I component will enroll only patients with Gleason 9-10 disease, the subgroup with the highest risk of recurrence and cancer-specific mortality in RTOG 0521 (unpublished NRG Oncology data). After safety and a maximum tolerated dose have been established, a randomized phase II will then compare clinical outcomes with standard radiation and ADT with and without niraparib in a broader group of high-risk prostate cancer patients. Additionally, we will profile tumor and blood samples from these patients, and determine predictors of treatment response. Specifically, somatic DNA damage repair status will be determined at the initiation of therapy. We hypothesize that PARP inhibition added to radiation and ADT for high risk prostate cancer will improve outcomes relative to standard therapy with radiation and ADT.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Submission of tumor tissue is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See Section 10 for details.)

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Histologically confirmed (within 180 days prior to registration) adenocarcinoma of the prostate at high risk for recurrence as determined by the following criteria, according to AJCC 8th edition:

Phase I enrollment

- Gleason ≥ 9, PSA ≤ 150 ng/mL, any T-stage

Phase II enrollment

- Gleason ≥ 9, PSA ≤ 150 ng/mL, any T-stage
- Gleason 8, PSA < 20 ng/mL, and ≥ T2
- Gleason 8, PSA ≥ 20-150 ng/mL, any T-stage
- Gleason 7, PSA ≥ 20-150 ng/mL, any T-stage

3.2.2 No distant metastases as evaluated by:

- Bone scan 90 days prior to registration;
- Lymph node assessment by CT or MR of pelvis or nodal sampling within 90 days prior to registration (Please note: Lymph nodes will be considered negative (N0) if they are < 1.5 cm short axis).

3.2.3 History/physical examination within 90 days prior to registration

3.2.4 Age ≥ 18;

3.2.5 ECOG performance status of 0 or 1 within 180 days prior to registration;

3.2.6 Pretreatment serum PSA, obtained prior to any androgen suppression therapy and within 180 days of registration.

3.2.7 Phase I patients: Prior androgen suppression for prostate cancer is not allowed prior to registration.

Phase II patients: Prior androgen suppression for prostate cancer is allowed ≤ 45 days prior to registration.

3.2.8 Adequate hematologic, renal, and hepatic function within 90 days prior to registration defined as follows:

- Hemoglobin ≥ 9.0 g/dL
- Platelets ≥ 100, 000 cells/mm^3

- ANC ≥ 1.5 X 10^9/L
- Serum creatinine ≤1.5 x upper limit of normal (ULN) OR a calculated creatinine clearance ≥60 mL/min estimated using the following Cockcroft-Gault equation:

$$\textit{Creatinine Clearance (mL/min)} = \frac{\textit{[140-Age (years)] x Weight (kg)}}{\textit{72 x serum creatinine (mg/dL)}}$$

- AST and ALT ≤3.0 x ULN
- Serum albumin ≥3 g/dL
- Serum potassium ≥3.5 mg/dL
- Serum total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 x ULN (Note: in subjects with Gilberts syndrome, if total bilirubin is >1.5 x ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5 x ULN, subject may be eligible)

3.2.9 Men of child-producing potential must be willing to consent to use effective contraception while on treatment and for at least 3 months afterwards.

3.2.10 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 PSA > 150 ng/mL

3.3.2 Definitive clinical or radiologic evidence of metastatic disease

3.3.3 Pathologically positive lymph nodes or nodes > 1.5 cm short axis on CT or MR imaging.

3.3.4 Prior radical prostatectomy, cryosurgery for prostate cancer, or bilateral orchiectomy for any reason.

3.3.5 Any active malignancy within 2 years of study registration that may alter the course of prostate cancer treatment

3.3.6 Prior systemic therapy for prostate cancer; note that prior therapy for a different cancer is allowable

3.3.7 Prior radiotherapy, including brachytherapy, to the region of the prostate that would result in overlap of radiation therapy fields.

3.3.8 Current treatment with first generation anti-androgens (bicalutamide, nilutamide, flutamide). For patients enrolled to phase II, if prior anti-androgens were administered, a washout period of ≥ 30 days is required prior to enrollment.

3.3.9 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Uncontrolled Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition
- Presence of uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of

hypertension are allowed, provided that BP is controlled to within these limits by anti-hypertensive treatment.

3.3.10 Prior allergic reaction to the drugs involved in this protocol.

3.3.11 HIV positive with CD4 count < 200 cells/microliter.

- Note that patients who are HIV positive are eligible, provided they have a CD4 count ≥ 200 cells/microliter within 90 days prior to registration. Patients receiving treatment with highly active antiretroviral therapy (HAART) will not be eligible due to concern for radiosensitization.
- Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be affected by these drugs.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP
(18-JUN-2019)

PRE-TREATMENT ASSESSMENTS

Assessment	Prior to registration	Prior to treatment
Biopsy with Gleason score	≤ 180 days	
Nodal staging per pelvic CT or MR or nodal sampling/dissection	≤ 90 days	
H&P, vital signs (heart rate, blood pressure)	≤ 90 days	
Bone scan	≤ 90 days	
ECOG performance status	≤ 180 days	
Serum PSA (prior to GnRH agonist therapy)	≤ 180 days	
CBC with diff (to include ANC, plt, Hgb)	≤ 90 days	
CMP (to include AST, ALT, total bilirubin, albumin, creatinine, potassium)	≤ 90 days	
Concomitant Medications	At baseline any time prior to registration	
For DDR sub-study • H&E stained slide from primary tumor • FFPE block from primary tumor		Obtained pre-treatment and submitted per Section 10.1
For WGS-SNPs sub-study • Whole blood for DNA		Obtained pre-treatment and submitted per Section 10.1
For banking for future research (for pts who consent to biobanking) • Serum • Plasma • Urine		Ph I pts and Ph II pts randomized to niraparib: Prior to niraparib start Ph II pts not randomized to niraparib: 8 weeks prior RT start

ASSESSMENTS DURING TREATMENT-Phase I

Assessment	Prior to RT Start	Months 1, 2, 3, 4, 5, 6, 9, 12	Months 15, 18, 21, 24	At Month 24
History/physical/vital signs/performance status (heart rate, blood pressure) Vital signs should be documented in patient chart and reported as AEs if appropriate.		X	X	
Disease Assessment		X*	X	
PSA		X*	X	
CMP (to include AST, ALT, total bilirubin, albumin, creatinine, potassium)		X	As clinically indicated	
CBC (to include ANC, plt, Hgb)		X**	As clinically indicated	
AE evaluation		X	X	
Prostate MRI	X			
Prostate Biopsy				Recommended

*Disease assessments and PSA required at months 3, 6, 9, and 12 only

**Obtain weekly during month 1 and then every two weeks for months 2 and 3 then monthly starting with month 4

ASSESSMENTS DURING TREATMENT-Phase II

		Both ARMS	ARM 2	
Assessment	**Prior to RT Start**	**Months 3, 6, 9, 12, 15, 18, 21, 24 from start of GnRH Agonist Androgen Suppression Therapy**	**During Niraparib: Months 1, 2, 3, 4, 5, 6, 9, 12 of Niraparib treatment***	**At Month 24**
History/physical/vital signs/performance status (heart rate, blood pressure) Vital signs should be documented in patient chart and reported as AEs if appropriate.		X	X	
Disease Assessment		X		
PSA		X		
CMP (to include AST, ALT, total bilirubin, albumin, creatinine, potassium)		As clinically indicated	X	
CBC (to include ANC, Plt, Hgb)		As clinically indicated	X**	
AE evaluation		X	X	
Prostate MRI	X			
Prostate Biopsy				Recommended

*These times are relative to the start of niraparib

**Obtain weekly during month 1 and then every two weeks for months 2 and 3 then monthly starting with month 4

ASSESSMENT IN FOLLOW UP

Assessments	**Beginning month 30: Q 6 months x 3 years, then annually for 3 years**
History/physical/PS	X
Disease assessment	X
PSA	X
AE evaluation	X
For banking for future research (for pts who consent to biobanking) • Serum • Plasma	Within 7 days after completing niraparib (Phase I pts and Phase II, Arm 2 pts) or 12 months of ADT (Phase II, Arm 1 pts) and, if applicable, at recurrence. See Section 10.

Definition of Disease Assessments

PSA examinations during and following treatment will be the primary method for assessing response to treatment. Radiographic imaging, including bone scan and CT or MRI of the abdomen/pelvis, will be done at baseline and thereafter as clinically indicated. A prostate biopsy at 24 months following the initiation of ADT is strongly recommended for assessment of complete response.

Treatment failure is the presence of one of the following:

- Biochemical failure – defined by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA, the presence of local, regional, or distant recurrence
- Local failure – defined as biopsy proven recurrence within the prostate gland
- Regional or distant metastasis – defined as imaging or biopsy demonstrated evidence for regional or distant metastatic disease. Biopsy is not required to define metastasis; however, in the absence of rising PSA, biopsy is strongly encouraged.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (07APR2020)

All study subjects will be treated with GnRH agonist androgen suppression therapy. GnRH agonist androgen suppression therapy will continue for 24 months.

Phase I: GnRH agonist androgen suppression therapy cannot begin prior to registration, and niraparib will begin at the same time as GnRH agonist androgen suppression therapy. Niraparib and GnRH agonist androgen suppression therapy must begin 8 weeks (+/-7 days) prior to RT. Niraparib will be administered for 12 months.

Phase I Dose Levels

Dosing will begin at Level 1 and proceed according to the dose escalation algorithm described in Section 14.1.1.

Dose Level	GnRH Agonist Suppression Therapy	Dose Escalated IMRT*	Niraparib
1	24 months	70 Gy in 28 fractions or 79.2 Gy in 44 fractions	100 mg PO once daily for 12 months beginning with GnRH agonist androgen suppression therapy (including during IMRT)
2	24 months	70 Gy in 28 fractions or 79.2 Gy in 44 fractions	200 mg PO once daily beginning with GnRH agonist androgen suppression therapy. During the weeks of IMRT, niraparib will be dosed at 100 mg PO once daily. Following IMRT, niraparib will resume at 200 mg PO once daily, until a total of 12 months of niraparib is completed
3	24 months	70 Gy in 28 fractions or 79.2 Gy in 44 fractions	200 mg PO once daily for 12 months beginning with GnRH agonist androgen suppression therapy (including during radiation)
0**	24 months	70 Gy in 28 fractions or 79.2 Gy in 44 fractions	100 mg PO once daily for 12 months beginning with beginning with GnRH agonist androgen suppression therapy (EXCEPT during IMRT, when niraparib will NOT be administered)

*Dose escalated radiation to prostate and pelvic lymph nodes delivered with IMRT with a boost to be provided with EBRT.

**Dose Level 0 will be utilized if 2 or more DLTs are observed at Dose Level 1 and Dose Level 1 is closed; or provisionally if 1 DLT is observed at Dose Level 1, although Dose Level 1 may be re-opened pending further data.

Phase II

GnRH agonist androgen suppression therapy may be started prior to enrollment. Dose-escalated IMRT can begin anywhere from 56-115 days (-7 days) after initiation of GnRH agonist therapy androgen suppression therapy.

Patients randomized to niraparib should receive niraparib for 8 weeks (+/- 7 days) prior to IMRT, and will continue niraparib for a total of 12 months.

If, for example, a patient has not yet begun GnRH agonist androgen suppression therapy prior to enrollment, the patient may begin GnRH agonist androgen suppression therapy and niraparib together, and then start IMRT 8 weeks (+/- 7 days) later. On the other hand, if a patient has already received GnRH agonist androgen suppression therapy and is then enrolled and randomized to begin niraparib 4 weeks after starting GnRH agonist androgen suppression therapy (for example), IMRT must begin 8 weeks (+/- 7 days) after starting niraparib and 12 weeks into GnRH agonist androgen suppression therapy.

Summary of Treatment Start Times

Treatment	**Start Time**
GnRH Agonist Androgen Suppression Therapy	Ph I: Same time as niraparib Ph II: Within 45 days of registration/randomization
Niraparib	Ph I: Same time as GnRH agonist androgen suppression therapy; both GnRH agonist and niraparib must begin within 7 days after registration and must start 56 (+/- 7) days prior to start of radiation Ph II, arm 2: Must begin within 7 (+/- 7) days after registration/randomization AND 56 (+/- 7) days prior to start of radiation
Dose Escalated IMRT	Ph I: Must begin 56 (+/- 7 days) after initiation of GnRH and niraparib Ph II, arm 1: Must begin within 56-115 days (- 7 days) after GnRH agonist androgen suppression therapy initiation Ph II, arm 2: Must begin within 56-115 days (- 7 days) after GnRH agonist androgen suppression therapy initiation AND 56 (+/- 7 days) after initiation of niraparib

5.1 Systemic Therapy

5.1.1 Niraparib

For the phase I regimen, niraparib will be administered per the table above. For the phase II regimen in Arm 2, the niraparib dose will be administered per the phase I results.

5.1.2 GnRH Agonist Androgen Suppression Therapy

GnRH agonist androgen suppression therapy (leuprolide, goserelin, buserelin, or triptorelin) will be administered for the phase I and II regimens. Agent selection is per treating physician discretion and will be administered per institutional standard and FDA-approved labeling.

5.2 **Radiation Therapy** (07-APR-2020)

All patients will begin radiation 56-115 days (- 7 days) after the initiation of GnRH agonist therapy. Patients receiving niraparib will begin radiation therapy 56 days (+/- 7 days) after initiation of niraparib.

All patients will be treated with intensity modulated radiation therapy (IMRT) to the prostate, seminal vesicles, and pelvic lymph nodes using daily image guidance. Treatment with a full bladder is strongly recommended in all patients. Physicians may elect to treat the prostate with either standard fractionation or hypofractionation.

Patients receiving standard fraction will receive radiation delivering 45 Gy to the prostate, seminal vesicles, and pelvic lymph nodes in 25 fractions, followed by a sequential prostate boost (+/- seminal vesicle treatment) to a total dose of 79.2 Gy in 44 total fractions (1.8 Gy/fraction). Patients receiving hypofractionation will receive radiation delivering 45 Gy pelvic lymph nodes (1.8 Gy/fraction) as above with a simultaneous integrated boost delivering 62.5 Gy to the prostate (+/- seminal vesicle treatment) in 25 fractions (2.5 Gy/fraction), followed by a 3 fraction sequential prostate boost (+/- seminal vesicle treatment) to a total dose of 70 Gy in 28 total fractions.

A composite EBRT plan that includes both Phases 1 and 2 treatment plans must be generated and summed at the beginning of the patient's treatment.

For credentialing requirements, please refer to Section 8 of the protocol.

5.2.1 Treatment Technology

All patients are required to be treated with intensity modulated radiotherapy (IMRT) techniques, including volume modulated arc therapy (VMAT) and tomotherapy. RT should be delivered with megavoltage equipment at energies ≥6 MV and ≤15 MV. MRI-based linear accelerators that fulfill these criteria are allowed. For the fixed gantry angle IMRT technique, a minimum of five gantry angles and a maximum of nine gantry angles are recommended for each phase of treatment. For the VMAT technique, a minimum of two arcs and a maximum of three arcs are recommended for each phase of treatment..

Daily image guidance with cone beam CT (CBCT), CT-on-rails, 2D-kV, 2D-MV, or MRI imaging is required. Fiducial markers placed in the prostate prior to simulation are preferred for all patients, and required for patient's monitored with 2D-kV and 2D-MV image guidance. Intra-fraction motion tracking, such as Calypso beacons, are not allowed given lack of compatibility for post-treatment MRI.

5.2.2 Immobilization and Simulation

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is

allowed but not required. Rectal contrast is discouraged because it may distend the rectum and artificially displace the prostate in the anterior direction. IV contrast is permitted to assist in identifying the pelvic vessels. Patients will be positioned supine on a flat tabletop with a customized thermoplastic immobilization cast or a molded foam cradle for stabilization and setup reproducibility. **Simulation with a comfortably full bladder is strongly recommended** for all patients able to maintain this state in order to minimize dose to the bowel and improve bladder dosimetry. The degree of bladder fullness should be made to duplicate the degree of fullness anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such. Typically this will require drinking 2-3 cups of water at least 30-45 minutes prior to simulation and all treatments. The rectum should be kept as empty as possible. An enema 1-2 hours prior to simulation is strongly recommended. CT images should be acquired at a slice thickness of ≤3 mm from the top of the iliac crests superiorly to the perineum inferiorly. Target volumes (Section 5.2.4) and normal critical structures (Section 5.2.4) will be defined in the slices in which they are visualized.

In cases where fiducial markers are used, markers should be placed at least 5 days prior to simulation.

If a rectal spacer will be used for treatment, it must be placed prior to simulation. If a patient will be treated with an endorectal balloon, the balloon should be present at simulation.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

Fusion with prostate or pelvis MRI is highly encouraged to aid in target delineation, particularly with respect to the prostate apex. If a rectal spacer is used, an MRI with the spacer in place is strongly recommended for fusion with the CT simulation in order to ensure adequate delineation of the spacer and rectum during treatment planning.

5.2.4 Definition of Target Volumes and Margins

Clinical and Planning Target Volumes

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Fractionation		
Standard Name	**Description**	**Validation** **Required/Required when applicable/Optional**
CTV_4500	CTV to receive 45 Gy	**Required**
CTV_7920	CTV to receive 79.2 Gy	**Required**
PTV_4500	PTV to receive 45 Gy	**Required**
PTV_7920	PTV to receive 79.2 Gy	**Required**
PTV_4500PRV10	Volume defined to control intermediate dose spillage, ring from 0.1cm to 1.0 cm from PTV_4500	**Required**
PTV_7920PRV10	Volume defined to control intermediate dose spillage, ring from 0.1cm to 1.0 cm from PTV_7920	**Required**

Hypofractionation		
Standard Name	**Description**	**Validation** **Required/Required when applicable/Optional**
CTV_4500	CTV to receive 45 Gy	**Required**
CTV_7000	CTV to receive 70 Gy	**Required**
PTV_4500	PTV to receive 45 Gy	**Required**
PTV_7000	PTV to receive 70 Gy	**Required**
PTV_4500PRV10	Volume defined to control intermediate dose spillage, ring from 0.1cm to 1.0 cm from PTV_4500	**Required**
PTV_7000PRV10	Volume defined to control intermediate dose spillage, ring from 0.1cm to 1.0 cm from	**Required**

	PTV_7000	

Detailed Specifications
Target volumes: The definitions of volumes will be in accordance with the 1999 ICRUReport#62.

CTV_4500: The CTV_4500 will include any portion of the seminal vesicle not included in a higher dose CTV, and the obturator, external iliac, proximal internal iliac and common iliac nodes, using the vascular structures, up to a level corresponding to the top of L4-L5. Please refer to the Pelvic Lymph Node Volumes for Prostate Cancer Atlas on the NRG Oncology Web site (https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/Prostate%20Pelvic%20Lymph%20Nodes.ppt). The presacral nodes from L5-S1 to S3 may be included if desired depending on whether the dose constraints to the rectum are achievable (see Normal Structure Constraints and Compliance Criteria Table). The inferior extent of the external iliac lymph nodes is at the top of the femoral heads. The inferior extent of the obturator lymph nodes is at the top of the symphysis pubis. The CTV_4500 will include a 7 mm margin in 3-dimensions to the contoured iliac vessels, but not extend outside of the true pelvis, into adjacent bone, into the pelvic musculature, nor into adjacent identifiable organs, such as the bladder, rectum or other bowel.

PTV_4500: The PTV_4500 margins should be a minimum of 5 mm and a maximum of 8 mm margin around CTV_4500 in all dimensions. Margins can either be uniform in all directions, or asymmetric within the 5-8 mm range. Using different margins for the part of CTV_4500 that covers the pelvic lymph nodes and the part of CTV_4500 that covers the prostate and seminal vesicles is allowed, as long as all margins are within a 5-8 mm range. Additionally, a margin as small as 3 mm can be used posteriorly near the rectum.

CTV_7000: The CTV_7000 includes the entire prostate and proximal 1 cm of the seminal vesicles in all cases. In patients with known seminal vesicle invasion or at very high risk of seminal vesicle invasion, the CTV_7000 can include the entire prostate and seminal vesicles as long as rectal and bowel dose constraints can be met. **This structure should be used for patients undergoing hypofractionation only.**

PTV_7000: The PTV_7000 will provide a margin around the CTV_7000 to compensate for the variability of treatment set up and internal organ motion. A range of 4-6 mm around the CTV_7000 can be utilized. Margins can either be uniform in all directions, or asymmetric. Individual selection of a PTV margin should be based on the institution's level of confidence in patient set-up and the type of image guidance. A smaller margin of 3 mm is permitted posteriorly near the rectum. Careful consideration should be made when defining the margin in 3 dimensions. **This structure should be used for patients undergoing hypofractionation only.**

CTV_7920: The CTV_7920 includes the entire prostate and proximal 1 cm of the seminal vesicles in all cases. In patients with known seminal vesicle invasion or at very high risk of

seminal vesicle invasion, the CTV_7920 can include the entire prostate and seminal vesicles as long as rectal and bowel dose constraints can be met. **This structure should be used for patients undergoing standard fractionation only.**

PTV_7920: The PTV_7920 will provide a margin around the CTV_7920 to compensate for the variability of treatment set up and internal organ motion. A range of 4-6 mm around the CTV_7920 can be utilized. Margins can either be uniform in all directions, or asymmetric. Individual selection of a PTV margin should be based on the institution's level of confidence in patient set-up and the type of image guidance. A smaller margin of 3 mm is permitted posteriorly near the rectum. Careful consideration should be made when defining the margin in 3 dimensions. **This structure should be used for patients undergoing standard fractionation only.**

PTV_4500PRV10: This volume is ring structure including only the area in between a symmetric 0.1cm expansion around PTV_4500 and a 1cm expansions around PTV_4500.

PTV7000PRV10: This volume is ring structure including only the area in between a symmetric 0.1cm expansion around PTV_7000 and a 1cm expansions around PTV_7000. **This structure should be used for patients undergoing hypofractionation only.**

PTV7920PRV10: This volume is ring structure including only the area in between a symmetric 0.1cm expansion around PTV_7920 and a 1cm expansions around PTV_7920. **This structure should be used for patients undergoing standard fractionation only.**

Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Normal Critical Structures

The normal tissues will be contoured and considered as solid organs. See the ITC web site (http://atc.wustl.edu) to view examples of target and normal tissue contours. Normal critical structures to be defined on the treatment planning CT scan will include the following:

Standard Name	Description	Validation **Required/Required when applicable/Optional**
Bladder	Bladder	**Required**
Rectum	Rectum	**Required**

Sigmoid	S-shaped loop of bowel connecting the rectum to the descending colon in the left pelvis	**Required**
Spc_Bowel	Potential space of both small and large bowel, excluding the rectum and sigmoid	**Required**
Femur_L	Left femur	**Required**
Femur_R	Right femur	**Required**
Femurs	Femur_L + Femur_R	**Required**
PenileBulb	Entire penile bulb	**Required**
SeminalVes	Seminal Vesicles	**Required**
SemVes_Prox	1 cm Proximal Seminal Vesicles	**Required**
External	External Patient Contour	**Required**

Detailed Specifications
-**Bladder:** Contoured from the base to the dome
-**Rectu**m: From its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior, to the anus at the inferior-most extent of the ischial tuberosities. The length is usually about 10-15 cm.
-**Sigmoid:** The loop of large bowel, typically S-shaped, connecting the rectum distally to the descending colon in the left pelvis proximally.
-**Spc_Bowel:** The potential bowel space including all large and small bowel loops in a bowel bag excluding the rectum and sigmoid. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions).
-**Bilateral femora:** The proximal femur from the lowest level of the ischial tuberosities (right or left) and superiorly to the top of the ball of the femur, including the trochanters.
-**PenileBulb:** The entire penile bulb, consisting of the proximal corpus spongiosum.
-**SeminalVes:** The entire length of the seminal vesicles.
-**SemVes_Prox:** Proximal 1 cm of the seminal vesicles.
-**External:** External patient contour encompassing all patient anatomy with a single contour on each slice.

5.2.5 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here.

Cases will be scored using the Compliance Criteria table.

STANDARD FRACTIONATION

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_4500	45	1.8	25	Daily	Covering 95% of PTV
PTV_7920	79.2	1.8	44	Daily	Covering 95% of PTV

HYPOFRACTIONATION

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_4500	45	1.8	25	Daily	Covering 95% of PTV
PTV_7000	70	2.5	28	Daily	Covering 95% of PTV

Dose Specifications

Standard fractionation

Dose for Phase 1 will be 45.0 Gy at 1.8 Gy per fraction in both arms. Once Phase 1 is completed, a cone down boost to the prostate and proximal seminal vesicles will be delivered in Phase 2 to 34.2 Gy at 1.8 Gy per fraction, for a total prostate dose of 79.2 Gy.

- ***Phase 1: Treat pelvic lymph nodes, prostate, and seminal vesicles***
  - 45 Gy in 25 fractions to cover 95% of PTV_4500 and PTV_7920
  - Minimum PTV dose for a volume of 0.03cc is 95% of prescription (42.8 Gy)
  - Maximum dose for a volume of 0.03cc within the PTV should be ≤107% of prescription (48.2 Gy). The maximum dose should not overlap with organs at risk such as the bowel, bladder or rectum.

- ***Phase 2: Prostate or prostate/seminal vesicle boost***
  - 34.2 Gy in 19 fractions to PTV_7920 such that prescriptions dose on the plan sum covers 95% of the PTV_7920
  - Minimum PTV_7920 dose on the plan sum for a volume of 0.03cc is 95% of prescription (75.2 Gy)
  - Maximum dose for a volume of 0.03cc within PTV_7920 on the plan sum should be ≤107% of prescription (84.7 Gy). The maximum dose should not overlap with organs at risk such as the bowel, bladder or rectum.

Hypofractionation

Dose for Phase 1 will be a simultaneous integrated boost treatment delivering 45.0 Gy at 1.8 Gy per fraction to the pelvic lymph nodes and 62.5 Gy at 2.5 Gy per fraction to the prostate and

proximal seminal vesicles in both arms. Once Phase 1 is completed, a cone down boost to the prostate will be delivered in Phase 2 to 7.5 Gy at 2.5 Gy per fraction, for a total prostate dose of 70 Gy.

- ***Phase 1: Treat pelvic lymph nodes, prostate, and seminal vesicles***
  - 45 Gy in 25 fractions to cover 95% of PTV_4500
  - Minimum PTV dose for a volume of 0.03cc is 95% of prescription (42.8 Gy for PTV_4500)
  - Maximum dose for a volume of 0.03cc within the PTV should be ≤107% of prescription (48.2 Gy). The maximum dose should not overlap with organs at risk such as the bowel, bladder or rectum.

- ***Phase 2: Prostate or prostate/seminal vesicle boost***
  - 7.5 Gy in 3 fractions such that 70 Gy covers 95% of the PTV_7000 in the plan sum
  - Minimum PTV_7000 dose for a volume of 0.03cc is 95% of prescription (66.5 Gy) on the plan sum
  - Maximum dose for a volume of 0.03cc within the PTV_7000 should be ≤107% of prescription (74.9 Gy) on the plan sum. The maximum dose should not overlap with organs at risk such as the bowel, bladder or rectum.

5.2.6 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. Goal constraints are given, and meeting these should be attempted. Plans meeting the goal constraints can be viewed as ideal plans. However, even if achieving the goal constraints is not possible, the Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as near ideal plans not meeting goal constraints, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Normalization of Dose: The plan is normalized such that 95% of the PTV_4500 volume receives prescription dose of 45 Gy and 95% of the PTV_7000/PTV_7920 volume receives prescription dose of 70 Gy/79.2 Gy. Please note the PTV_4500 and PTV_7000/PTV_7920 will overlap. Therefore, the target volume constraints for PTV_4500 should be evaluated based on Phase 1, the first 25 fractions. PTV_7000/PTV_7920 and all normal organ structures should be evaluated based on the plan sum of Phase 1 and Phase 2.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_4500	D95%[Gy]	>=45	>=42.8
	D99%[Gy]	>=42.8	>=41.9
	D0.03cc[Gy]	<=48.2	<=48.6
PTV_7000	D95%[Gy]	>=70	>=66.5
	D99%[Gy]	>=66.5	>=65.1
	D0.03cc[Gy]	<=74.9	<=75.6
PTV_7920	D95%[Gy]	>=79.2	>=75.2
	D99%[Gy]	>=75.2	>=73.7
	D0.03cc[Gy]	<=84.7	<=85.5

Per Protocol range is excluded from Variation Acceptable range.

Normal Structure Constraints and Compliance Criteria

Standard Fractionation

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
Rectum	D0.03cc[%]	<=104	<=106
	V80Gy[cc]	<=3	<=7
	V75Gy[%]	<=8	<=15
	V70Gy[%]	<=10	<=20
	V60Gy[%]	<=20	<=35
	V50Gy[%]	<=30	<=40
Bladder	D0.03cc[%]	<=105	<=107
	V80Gy[%]	<=2	<=10
	V75Gy[%]	<=5	<=20
	V70Gy[%]	<=10	<=25
	V60Gy[%]	<=20	<=40
	V50Gy[%]	<=30	<=50
Sigmoid	D0.03cc[Gy]	<=54	<=60
	V50Gy[cc]	<=45	<=60
Spc_Bowel	D0.03cc[Gy]	<=48.2	<=53
	V45Gy[cc]	<=50	<=90
Femurs	D0.03cc[Gy]	<=45	<=55

Hypofractionation

Name of	Dosimetric parameter	Per Protocol	Variation

Structure			Acceptable
Rectum	D0.03cc[%]	<=104	<=106
	V70Gy[cc]	<=5	<=12
	V65Gy[%]	<=8	<=15
	V60Gy[%]	<=10	<=20
	V50Gy[%]	<=20	<=35
	V40Gy[%]	<=30	<=40
Bladder	D0.03cc[%]	<=105	<=107
	V71Gy[%]	<=2	<=10
	V65Gy[%]	<=5	<=20
	V60Gy[%]	<=10	<=25
	V50Gy[%]	<=25	<=50
Sigmoid	D0.03cc[Gy]	<=50	<=56
	V50Gy[cc]	<=45	<=60
Spc_Bowel	D0.03cc[Gy]	<=48.2	<=53
	V45Gy[cc]	<=50	<=90
Femurs	D0.03cc[Gy]	<=40	<=50

Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PenileBulb	Mean[Gy]	<=50	<=60

Delivery Compliance criteria

	Per Protocol	Variation Acceptable
Start date	56-115 days after GnRH antagonist/agonist initiation AND 56 days after niraparib	56-115 days (- 7 days)after GnRH antagonist/agonist initiation AND 56 days after niraparib (+/- 7 days)
Overall Radiation Treatment time	60-65 days	66-70 days
Interruptions	0-2 unplanned treatment days missed (not including holidays)	3-5 unplanned treatment days missed (not including holidays)

5.2.7 Treatment Planning Priorities and Instructions

- Critical Structure and Target priorities must be listed in order of decreasing importance

The following list is given as an example
1. Rectum
2. Spc_Bowel
3. Sigmoid
4. PTV_7920/PTV_7000
5. Bladder
6. PTV_4500
7. Femur_L and Femur_R
8. PenileBulb

Acceptable choices of algorithm are listed at
http://rpc.mdanderson.org/RPC/Services/Anthropomorphic_%20Phantoms/Phantoms.htm
Review TPS (Treatment Planning Systems) approved for calculation of dose with heterogeneities

-Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

5.2.8 Patient specific QA
For IMRT/VMAT delivery, although an automated MU verification calculation may be permitted subject to protocol credentialing and approval, a direct measurement of the dose distribution from the designated treatment system shall be performed prior to delivery of the first fraction. All components of the inverse-plan verification technique, including the planning system, treatment machine, and detector hardware and analysis procedure, shall be credentialed according to guidelines established by IROC-Houston for protocols utilizing inverse planning.

For IMRT/VMAT delivery, patient specific QA is highly recommended. Any patient-specific QA performed should follow your institutional guidelines. The recommended minimum patient specific QA criterion is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis.

5.2.9 Treatment Localization/IGRT

All patients are required to have daily image guidance prior to each fraction with 3D CBCT or 2D kV imaging. Intrafraction tracking, such as with Calypso beacons is not allowed since this will preclude post-treatment MRI. 3D CBCT is strongly preferred, as this allows assessment of both rectal and bladder filling. Matching should either focus on the prostate-rectum interface or on fiducials in patients that have them. Fiducials are strongly recommended for 3D CBCT patients. If 2D KV imaging is used, then fiducial markers are required. If Calypso beacons are utilized, then 3D CBCT to evaluate for bladder and rectal filling is recommended but not required.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

5.3.2 Prohibited Therapies

- Investigational agents other than the study drugs
- Other anticancer therapies
- Other agents that target the androgen axis (eg, antiandrogens such as enzalutamide and apalutamide, or CYP17 inhibitors such as ketoconazole)
- Testosterone
- Administration of radiation therapy other than the radiation therapy specified in this protocol. (Radiation protocol therapy is outlined in Section 5.2.)
- Chemotherapy
- Immunotherapy
- Diethylstilbestrol (DES) or similar estrogen receptor agonists
- Pomegranates and pomegranate juice
- Spironolactone
- Radiopharmaceuticals such as radium-223 (223Ra), strontium (89Sr), or samarium (153Sm)
- Strong inducers of CYP3A4 (eg, rifampin)

5.3.3 Participation in Other Trials

Patients are not to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, etc).

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Dose Modifications for GnRH Agonists (Leuprolide, Goserelin, Buserelin, Triptorelin)

There are no modification guidelines for GnRH agonist therapy. All patients should be dosed with standard dosing for the full 24 months of treatment. Please refer to the FDA-approved package inserts for each GnRH agonist.

6.2 Dose Modifications for Niraparib

The dosing schedule for the phase I portion of the study is provided in Section 5 above.

Dose modifications will occur according to the following schedule:

Dose Level	Niraparib Starting Dose	Reduced Niraparib Dose
0	100 mg daily, except during the weeks of radiation when drug will be held	Off study treatment
1	100 mg daily	100 mg daily, except during the weeks of radiation when drug will be held
2	200 mg daily, except during weeks of radiation therapy, when it will 100 mg daily	100 mg daily
3	200 mg daily, including during weeks of radiation therapy	200 mg daily, except during weeks of radiation therapy, when it will 100 mg daily

Dosing of niraparib will continue until 12 months after initiation.

Hematologic Toxicities

The site should consider discontinuation of niraparib if:

- Hematologic toxicity has not recovered to Grade 1 or baseline after prolonged (greater than 1 week) period of dose interruption.
- A diagnosis of MDS/AML is confirmed by a hematologist.

Niraparib Dose Modifications for Anemia

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 sponsor should be notified. For Grade ≥3 anemia, niraparib should be interrupted until resolution to Grade <3.

- Weekly monitoring and/or interruption are not required if at baseline grade, eg, subject with baseline Hgb 9.1 (Grade 2 anemia) does not need to be monitored weekly for Grade 1 or 2 anemia.

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	Interrupt until ≤Grade 1 or baseline, then: • Resume at 200 mg or 1 dose-level reduction (at the discretion of the investigator). • If subject was already reduced dose at 100 mg, discuss with PI prior to resuming treatment. Weekly monitoring is required until resolution to Grade 1 or baseline. Weekly monitoring is recommended for 28 days after restarting dose.
Second occurrence Grade ≥3	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. If subject was on 100 mg, discuss with PI prior to resuming treatment.
Third occurrence Grade ≥3	Permanently discontinue

Notes:

- For subjects with a platelet count ≤10,000 cells/μL, prophylactic platelet transfusion 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 ≤20,000 cells/μL.
- 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.
- If standard of care treatment with radiation and/or GnRH agonist therapy is stopped for any reason, then niraparib should be discontinued as well.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

Adverse Event reporting begins at the time a patient signs consent; please report all AEs that start after consent is signed. Report serious adverse events that meet expedited reporting criteria via CTEP-AERS.

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GU007, niraparib, is exempt and distributed by a third party distributor. For niraparib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5 of the protocol.

Commercial Agents
The commercial agents in NRG-GU007 are FDA-approved GnRH agonists.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk that niraparib may have an effect on sperm, the impregnation of a study participant's partner must be reported via CTEP-AERS in an expedited manner.

7.3 Adverse Events for Investigational Study Agent Provided by Janssen (07-APR-2020)

Please refer to the niraparib Investigator Brochure for comprehensive information.

Very Common (>10%)	Common (1-10%)	Very Rare (< 1%)
Decrease in red blood cells; may cause anemia	Tachycardia	MDS
Decrease in blood cells; may increase risk of bleeding	Leukopenia	AML
Neutropenia, Neutropenic infection, Neutropenic Sepsis	Hypokalemia	
Constipation	Dry mouth	
Nausea	Anxiety	
Vomiting	Depression	
Decreased appetite	Nose bleeds	
Abdominal pain	Rash	
Diarrhea	Muscle pain	
Dyspepsia	Peripheral edema	
Insomnia	Swelling or irritation of lining of throat or intestinal tract	
Headache	Increases in AST, ALT, GGT, ALP – may indicate damage to liver cells	
Fatigue	Increase in kidney test called blood creatinine	
Urinary tract infection	Decrease in weight	
Bronchitis		
	Conjunctivitis	
Back pain		
Arthralgia		
Dyspnea		
Nasopharyngitis		
Hypertension		
Dizziness		
Cough		
Asthenia		
Heart Palpitations		
Dysgeusia		

The following situations should be reported as adverse events on the case report form and if any of these events meet the criteria for seriousness, they should be reported expeditiously via CTEP-AERS:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure of the medicinal product

- Medication error, with or without patient exposure (e.g. name confusion)
- Suspected transmission of any infectious agent via administration of the medicinal product
- Drug exposure during pregnancy (paternal)

7.3.1 Adverse Events of Special Interest

Adverse events of special interest are events that Janssen is actively monitoring as a result of a previously identified signal (even if non-serious). Janssen identified the following as AESI specific for prostate trials (*this may* ***not*** *be reflected in the current IB version****):***

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

Any adverse event of special interest should be reported to Janssen within 24 hours of becoming aware of the event.

7.4 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information

7.5 Expedited Reporting of Adverse Events

Adverse Event reporting begins at the time a patient signs consent; please report all AEs that start after consent is signed. Report serious adverse events that meet expedited reporting criteria via CTEP-AERS.

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.

- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events

Phase 1: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Niraparib [1, 2]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

Additional Protocol-Specific Instructions to Expedited Reporting Requirements

Please see Section 7.3.1

Phase II, Arm 2: Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of Niraparib[1,2]

Starting 30 days after last dose of niraparib expeditiously report AEs reasonably related to niraparib per footnote 1 in the table below.

For AEs unrelated to niraparib during the period of GnRH only therapy starting 30 days after last dose of niraparib should be reported per the Ph II, Arm 1 table.

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

Additional Protocol-Specific Instructions to Expedited Reporting Requirements

Please see Section 7.3.1

Phase II, Arm 1: Any Phase Study Utilizing a Commercial Agent[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

Second Malignancy:

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

7.6 Routine Reporting Requirements for Adverse Events

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

7.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be

completed and submitted to NRG Oncology. Any pregnancy occurring in a patient's partner from the time of consent to 90 days after the last dose of study drug must be reported within 24 hours of awareness and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (18-JUN-2019)

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and

NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

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

8.1 Cancer Trials Support Unit Registration Procedures (07APR2020)

This study is supported by the NCI CTSU.

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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

- Holds an Active CTEP status;

- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GU007 Site Registration
Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- Compliance with all protocol-specific requirements (PSRs).

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) credentialed provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

  To complete protocol-specific credentialing the RT/I provider or enrolling site should follow instructions in protocol section 8.2 to submit documentation or other materials to the designated IROC Quality Control (QC) center. Upon the IROC QA center approving the RTI provider for the study modality, the credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

Additional Requirements for sites in Canada
Prior to clinical trial commencement, sites in Canada must also complete and submit via the Regulatory Submission portal on the CTSU website:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure Signature Page
- Delegation of Tasks (DTL) Log
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions)*.

*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

Requirements for the Initial Shipment of Niraparib for ALL sites
Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the protocol web site Institutions must submit the SASF via the Regulatory Submission Portal on the CTSU website as soon as the individual responsible for the study agent has been identified.

Downloading Site Registration Documents:

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

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-GU007*;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:

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

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

Checking Your Site's Registration Status:

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go.

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

8.2 RT-Specific Pre-Registration Requirements (18-JUN-2019)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is

RT credentialed to enter patients onto this study. This document must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Credentialing Status Inquiry Form	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	**X**	An IMRT Head & Neck phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).
Credentialing Notification Issued to:		
Institution	**X**	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.2.1 Digital RT Data Submission to NRG Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:
Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment (18-JUN-2019)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of

registration and treatment information. Please print this confirmation for your records.

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

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9. DRUG INFORMATION

9.1 Commercial Agents: GnRH Agonists (leuprolide, goserelin, buserelin, triptorelin)

Sites must refer to the package insert for detailed dosing, pharmacologic and safety information.

9.2 Investigational Study Agent: Niraparib (IND exempt) (07APR2020)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety information. The Investigator Brochure can be obtained from the CTSU by completing the Request for Clinical Brochure form. This form can be found on the CTSU website under documents > site registration.

9.2.1 Adverse Events

See Section 7.3 and consult the investigator brochure for comprehensive information.

9.2.2 Dosage Selected, Preparation, and Schedule of Administration

Niraparib is administered orally on a once daily dosing schedule as outlined in Section 5.1. Niraparib can be taken with or without food.

Preparation and Safe Handling

Niraparib may have adverse effects on a fetus in utero. Caregivers should handle niraparib with protection (eg, gloves).

9.2.3 Agent Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F).

9.2.4 Supply, Packaging, Accountability, and Drug Ordering

Niraparib will be distributed by a vendor, Clinical Research Services, a division of RxCrossroads by McKesson. Niraparib will be packaged as 100 mg capsules in 93 count bottles. Niraparib must be stored in a secure area and administered only to subjects enrolled in the clinical study in accordance with the conditions specified in this protocol.

Patients will be asked to bring their medication bottle and a pill diary at the 1, 2, 3, 4, 5, 6, 9, and 12 month visits, regardless of whether the bottle is empty. A pill count and evaluation of the pill diary will be completed to assess compliance. The pill diary is located in Appendix I and on the CTSU website.

Janssen will supply niraparib free of charge to subjects on study in the U.S. and Canada. The investigator, or responsible party designated by the investigator, must maintain a careful record of the receipt, distribution, and return of all drugs received from Clinical Research Services according to good clinical practices. Sites are encouraged to use the NCI Investigational Agent Accountability Record available on the CTEP website or their institutional drug accountability log.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction. Sites should complete the drug destruction form located on the CTSU website under protocol-specific page and send the form to Clinical Research Services (see below for contact information).

The Study Agent Shipment Form (SASF), available on the CTSU website, under the NRG-GU007 study page must be completed and submitted to the CTSU Regulatory Office via the Regulatory Submission Portal as soon as the individual responsible for the study agent has been identified.

The drug supply will not be shipped by Clinical Research Services until the subject has been registered. NRG Oncology will notify Clinical Research Services to initiate each of these shipments after registration of the subject. Clinical Research Services will ship drug for subjects registered to phase I and to subjects randomized to Arm II in the phase II portion.

Each shipment includes a sufficient supply of niraparib for 180 days of treatment. Each patient can receive up to 2 shipments. At approximately 6 months, McKesson will contact the study site to confirm their requirement for additional study drug for the patient and arrange a day and time of delivery.

Upon notification of a new subject enrollment, Clinical Research Services will call the site contact to confirm that the site's shipment is being processed. Clinical Research Services' distribution team will monitor packages throughout the duration of transit via the FedEx website and FedEx One Call Solution (live support). Real-time monitoring enables McKesson to mitigate potential delivery delays.

Clinical Research Services will ship drug to sites in the U.S. and Canada, according to the following schedule:

NRG-GU007 Shipment Schedule				
Subject Registered	Initial e-order sent by NRG	Initial e-order received by CRS (before 2 p.m. ET)	Initial order shipped by CRS	Initial order received at site
Monday	Monday	Monday	Monday	Tuesday

Tuesday	Tuesday	Tuesday	Tuesday	Wednesday
Wednesday	Wednesday	Wednesday	Wednesday	Thursday
Thursday	Thursday	Thursday	Thursday	Friday
Friday	Friday	Friday	Monday	Tuesday

For orders intended for sites in the U.S., Clinical Research Services will ship the order "same day" for all orders received before 2 p.m. ET, Monday through Thursday, via FedEx Priority Overnight/FedEx International Priority. Orders received after 2 p.m. ET, Monday through Wednesday, will be processed and shipped the next business morning.

Drug deliveries are restricted during weekends and holidays. Clinical Research Services observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate subjects being treated during restricted times.

Please contact the Clinical Research Services program manager listed below directly for shipment tracking information and for anticipated delivery dates or if a shipment has not been received by the expected date.

Questions about supply and delivery should be directed to:

Clinical Research Services, a division of RxCrossroads by McKesson
845 Regent Blvd.
Suite 100B
Irving, TX 75063
Email: clinicalresearchservices@mckesson.com
Phone: Toll Free 800-693-4906

10. PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables (07-APR-2020)

10.1.1 Mandatory Specimen Submissions

See detailed specimen collection/processing/shipping on the protocol-specific page of the CTSU website, www.ctsu.org.

Required Study #1: Analysis of DDR mutations associated with PARPi therapy response
1) The synthetic lethality shown in breast, ovarian and prostate cancer that are deficient in homologous recombination (HR) repair and which manifest as exquisite sensitivity to PARP monotherapy is the impetus for us to perform integrated HR and DDR biomarker analysis in this trial. We propose to identify genomic biomarkers of response to combination therapy with radiation, ADT and PARP inhibition from tumor.

Biomarker Assay Description
Next generation sequencing (NGS) using the FoundationOne® platform will be used to determine patient's mutation status. FoundationOne® is a comprehensive genomic profile that applies next-generation sequencing in a unique manner to identify all four types of genomic alterations across

genes known to be unambiguous drivers of solid tumors with high accuracy. The test simultaneously sequences the coding region of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer to a typical median depth of coverage of greater than 500x. Each covered read represents a unique DNA fragment to enable the highly sensitive and specific detection of genomic alterations that occur at low frequencies due to tumor heterogeneity, low tumor purity and small tissue samples. FoundationOne detects all classes of genomic alterations, including base substitutions, insertions and deletions (indels), copy number alterations (CNAs) and rearrangements using a small, routine FFPE sample (including core or fine needle biopsies).

A. Specimens and Processing:
Formalin Fixed Paraffin Embedded (FFPE) tumor specimens will be collected and prepared following standard pathology practices and sent to the NRGBB. The NRGBB will provide the FFPE tissue to FoundationOne at the end of the study.
Prior to starting the assay, a Hematoxylin and Eosin (H&E) stained slide is prepared, and then reviewed by a board certified pathologist to confirm disease ontology and to ensure that adequate tissue (0.6 mm3), tumor content (≥20% tumor) and sufficient nucleated cells are present to proceed with the assay.

Data on the Clinical Utility of the Integrated Assay

A. Background information*:*
FoundationOne is a validated comprehensive genomic profile (CGP) for solid tumors. The test is designed to provide physicians with clinically actionable information to guide treatment decisions for patients based on the genomic profile of their disease. Since the genomic profile will not be prepared and results will not be available until the end of the study, the profile will not guide treatment decisions for patients enrolled on this trial.

B. Biomarker Distribution:
FoundationOne® provides a genetic profile for each specimen submitted.

C. Assay Cutpoints:
Not applicable (no cutpoints are to be used by Foundation Medicine to identify patients for study).

2) **Forms**: ST Form and copy of pathology report with accession number and date of procedure visible. All other PHI information should be redacted.

3) **Shipping:** Sites are responsible for all FFPE shipping costs. Sites can ship FFPE samples Monday-Friday. Instructions for packing and shipping FFPE material is included with the protocol documents included on the CTSU website, www.ctsu.org.

Ship FFPE samples to:
Attn: NRG Oncology Biospecimen Bank – San Francisco
UCSF box 1800
2340 Sutter Street- Room S341
San Francisco, CA 94115
415-476-7864/Fax 415-476-5271
Email: NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements/	Shipping

		Instructions for Site	
H&E Stained Slide from primary tumor	Pre-treatment	H&E stained slides Slides can be duplicate cut H&Es, they do not have to be the diagnostic slides. H&E slides cannot be returned to sites.	Ship to NRGBB-San Francisco (use cold packs during warm weather)
FFPE Block from primary tumor	Pre-treatment	Paraffin-embedded block. Must be same block as H&E being submitted. Unstained slides are NOT an acceptable alternative for this study.	Ship to NRGBB-San Francisco (use cold packs during warm weather)

10.1.2 Optional Specimen Submissions

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

See detailed specimen collection/processing/shipping on the protocol-specific page of the CTSU website, www.ctsu.org.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Specimen Collection for Biobanking for Potential Future Research
Forms: ST Form
Kits: Frozen Specimen kits can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.
Shipping: One prepaid return label provided for each case for batch shipping all frozen biospecimens only. Batch shipments can be made once sites have collected the post treatment samples or with other cases.
Shipping Days: Frozen specimens should be shipped on dry ice by priority overnight Monday-Wednesday for US Sites, or Monday-Tuesday for Canadian sites.

Processing: Instructions for processing and shipping are included with the protocol documents included on the CTSU website, www.ctsu.org.

Ship all specimens to:
Attn: NRG Oncology Biospecimen Bank Staff– San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/Instructions for Site**	**Shipping**
WHOLE BLOOD: 5-10 mL of anticoagulated whole blood in EDTA tube (purple/ lavender top) and freeze	Pre-Treatment prior to radiation therapy	Mix whole blood and aliquot a minimum of 1.5ml of whole blood into three (3) 2 ml cryovials. Storage: Freeze at -80°C and ship frozen with serum and plasma	Batch ship on Dry Ice by Priority Overnight Courier to NRGBB - SF
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-Treatment Ph I pts and Ph II pts randomized to niraparib: Prior to niraparib start Ph II pts not randomized to niraparib: 8 weeks prior RT start Post-Treatment Within 7 days after completing niraparib or 12 months of ADT administration At recurrence, if applicable.	Process serum and aliquot a minimum of **0.5 mL** per aliquot into five (5) 1 mL cryovials. Storage: Freeze at -80°C and ship frozen with whole blood and plasma.	Batch ship on Dry Ice by Priority Overnight Courier to NRGBB - SF
PLASMA: 5-10 mL of anticoagulated whole blood in THREE (3) EDTA tubes (purple/ lavender top) and centrifuge	Pre-Treatment Ph I pts and Ph II pts randomized to niraparib: Prior to niraparib start Ph II pts not randomized to niraparib: 8 weeks prior RT start	Process plasma as per special instructions in Appendix II and aliquot a minimum of 4.0 ml per aliquot into two 5 ml Cryovials and the remaining plasma into five 2 ml cryovials (**See Appendix II**). Storage: Freeze and store at -80°C until ready to batch ship frozen with blood and serum.	Batch ship on Dry Ice by Priority Overnight Courier to NRGBB - SF

	Post-Treatment Within 7 days after completing niraparib or 12 months of ADT administration At recurrence, if applicable.		
Urine	Pre-Treatment Ph I pts and Ph II pts randomized to niraparib: Prior to niraparib start Ph II pts not randomized to niraparib: 8 weeks prior RT start	One **10 mL** urine aliquot in one sterile 15 ml polypropylene centrifuge tube. Store frozen at -80°C. (-20° C is allowed for short term storage).	Batch ship on Dry Ice by Priority Overnight Courier to NRGBB - SF

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable to this study.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chair, Dr. Zach Zumsteg, or NRG Oncology Headquarters approved designee will perform an RT Quality Assurance Review after IROC Philadelphia-RT has received complete data in TRIAD. The RT reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Variation Acceptable, and Unacceptable Deviation**.

12.2 Medical Oncology Modality Quality Assurance Reviews

The Study Chair, Dr. Dror Michaelson, or NRG Oncology Headquarters approved designee will perform a Systemic Therapy Assurance Review for niraparib for all patients who receive or are to receive systemic therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of niraparib treatment data as specified in Section 12.1. The scoring mechanism is: **1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable**.

Dr. Michaelson/designee will perform a Quality Assurance Review after NRG Headquarters has received complete data for cases enrolled. The reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (07-APR-2020)

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

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

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

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

13.2 Summary of Data Submission (07-APR-2020)

Adverse event data collection and reporting, which are required as part of every clinical

trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.
Summary of Data Submission: Refer to the CTSU website.
Summary of Dosimetry Digital Data Submission

DICOM DIGITAL DATA	DICOM CT Data Set DICOM RT Structure DICOM RT Dose (2) DICOM RT Plan	Due within 1 week of the start of RT TRIAD submission time point = RT DIGITAL PLAN
All required structures MUST be labeled per the tables in Section Sections 5.2.4		
Digital Data Submission Information Form (DDSI) Upon submission of the digital data via TRIAD, complete an online Digital Data Submission form https://www.irocqa.org/Resources/TRIAD		
DVH Analysis Worksheet Available on the CTSU website and submitted via TRIAD with the RT Digital Data listed.		

Submit Digital RT Data via TRIAD; see Section 8 for TRIAD account access and installation instructions.

13.3 Data Quality Portal (18-JUN-2019)

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

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available

on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (18-JUN-2019)

14.1.1 Phase I Design

To evaluate the safety and tolerability of the combined regimen, a phase I trial will be conducted. Dose limiting toxicities (DLTs) will be defined by NCI CTCAE version 5. Any treatment-related gastrointestinal or genitourinary Grade 3 or higher adverse events (AE) lasting > 1 week, despite maximal medical interventions, will be considered a DLT. Additionally, any treatment-related Grade 4 AEs lasting > 1 week will be considered a DLT. Relationship to treatment will be determined by the responsible clinician, and specifics of each putative DLT will be reviewed by the study chairs prior to formal declaration of DLT. The evaluation window for DLTs will be from inception of combined ADT and niraparib therapy through 6 months of treatment. Three dose tiers will be considered as described in Section 5.1. The dose-identification scheme will proceed as follows:

Background

- The basic treatment schedule is 8 weeks daily niraparib (PO) + ADT (GnRH agonist), then 6-8 weeks niraparib + ADT + RT, then niraparib + ADT for total duration of 12 months
- The proposed DLT window is the first 6 months of therapy
- Safety has already been established for 200 mg of niraparib given concurrently with ADT
- Given the myelosuppression of niraparib as a single agent, although in platinum treated patients, when given with pelvic RT, myelosuppression can be expected to dictate the MTD
- Thus, the part of the regimen for which safety must be more clearly established begins **after the first 8 weeks of therapy**, when patients start to receive concurrent niraparib and RT

Note: For the remainder of this summary, we break the treatment schedule into three parts:
Part 1: the first 8 weeks of niraparib + ADT
Part 2: the 6-8 weeks following part 1 when patients receive niraparib + ADT + RT
Part 3: the period following part 2 when patients receive niraparib + ADT until 12 months of therapy have been completed

The following is a summary of the four dose levels. Though we don't include it in the table, note

that patients will also receive concurrent ADT throughout parts 1-3.

	Part 1	Part 2	Part 3
Level 0	100 mg niraparib	0 mg niraparib + RT	100 mg niraparib
Level 1 (**starting dose)**	100 mg niraparib	100 mg niraparib + RT	100 mg niraparib
Level 2	200 mg niraparib	100 mg niraparib + RT	200 mg niraparib
Level 3	200 mg niraparib	200 mg niraparib + RT	200 mg niraparib

Dose escalation scheme

1. Enroll 3 patients at dose level 1 and observe for 2 months (i.e. until the completion of part 1). Once all 3 of these patients have completed part 1, enroll up to 3 additional patients at dose level 1.

- If none of the first 3 patients experience a DLT by the time the second cohort of patients reaches part 2, the second cohort may continue with part 2 of dose level 1.
- If 1 of the first 3 patients experiences a DLT before the second cohort reaches part 2, the second cohort should proceed to part 2 of **dose level 0**. Note that these patients will become "level 0" patients, since the regimen they receive will be identical to that of dose level 0. No additional patients should be enrolled at dose level 1 until the first 3 have been observed for the full 6-month DLT window.
- If 2 or more of the first 3 patients experience a DLT before the second cohort of patients have reached part 2, the second cohort should proceed to part 2 of **dose level 0**, and dose level 1 (and levels 2 and 3) should be permanently closed.
- Escalation to dose level 2 should follow the safety guidelines outlined below.

2a. If dose level 1 is closed, either permanently or temporarily (i.e. until the first 3 patients complete the "full" evaluation period) for reasons outlined above, up to 6 patients may be enrolled at dose level 0 (including those who were moved to dose level 0 due to toxicity in the first cohort at dose level 1). Escalation should follow the safety guidelines outlined below.

2b. If initial evidence suggests dose level 1 is safe (i.e. the criteria for escalation have been met), enroll up to 6 patients at dose level 2 (since part 2 of dose level 2 is the same as that for dose level 1) and observe. Escalation/de-escalation should follow the safety guidelines outlined below.

3. If appropriate, enroll 3 patients at dose level 3 and observe until the completion of part 1. Once all 3 of these patients have completed part 1 of dose level 3, enroll up to 3 additional patients at dose level 3.

- If none of the first 3 patients experience a DLT by the time the second cohort of patients reaches part 2, the second cohort may continue with part 2 of dose level 3.
- If 1 of the first 3 patients experiences a DLT before the second cohort reaches part 2, the second cohort should proceed to part 2 of **dose level 2**. Note that these patients will become "level 2" patients, since the regimen they receive will be identical to that of dose

level 2. No additional patients should be enrolled at dose level 3 until the first 3 have been observed for the full 6-month DLT window.

- If 2 or more of the first 3 patients experience a DLT before the second cohort of patients have reached part 2, the second cohort should proceed to part 2 of **dose level 2**, and dose level 3 should be permanently closed.
- De-escalation should follow the safety guidelines outlined below.

4. Once all dose levels are permanently closed and all patients have been observed for the full 6-month DLT window, identify the recommended phase II dose (RP2D). **The RP2D will be the highest dose at which at least 6 patients have been enrolled and < 33% of patients have experienced a DLT.**

Additional safety guidelines

- Dose levels at which 6 or more patients have been treated should be permanently closed to **new** patients.
- A maximum of 12 patients may be enrolled at a dose level; however, this number may only exceed 6 in situations where a second cohort of patients has been enrolled to a dose level and at least 1 of the first 3 patients at that dose level subsequently experiences a DLT before the second cohort of patients has reached part 2 of the treatment (in which case the second cohort of patients would be moved to the previous dose level).
- If 1 DLT is observed on a dose level, no more patients may be added to this dose level until the full DLT evaluation period has been completed on the first 3 patients.
- After the first 3 patients have been fully evaluated for DLT, if 1 out of 3 DLTs have been observed, then up to 3 additional patients may be accrued to the dose level (not to exceed a maximum of 6 total patients at this dose level).
- New patients should not be assigned to a dose level **at which** 4 or more patients have been fully evaluated and ≥ 33% of the patients have experienced a DLT.
- New patients should not be assigned to a dose level **above** a dose level where ≥ 33% of the fully evaluated patients have experienced a DLT.
- After the first 3 patients have been fully evaluated for DLT, if 1 out of 3 DLTs have been observed, then at least 1 additional patient must complete the full evaluation period before an escalation decision can be made.
- The dose can be escalated if 0/3 DLTs are observed among a fully evaluated cohort or 1/4 among a fully evaluated cohort.

NOTES:

- If any patients experience protocol-defined DLTs during the pre-radiation portion of the study treatment, they will be considered unevaluable for safety and tolerability of the combined regimen. Such patients will be discontinued from study treatment, and should be replaced with another patient.
- The duration of the phase I trial is projected to last between 2.3 to 3.3 years.
- After the start of the accrual, NRG Headquarters will provide current toxicity data to the study chairs every two weeks. The study chairs will follow up any report of an SAE or DLT with the site investigators. The study team, including the study chairs, study statisticians, data managers and protocol administrator, as well as a representative from any site with a patient currently within the DLT window, will

hold monthly conference calls to review the overall conduct of the study. Data on treatment dose delivery, adverse events reported, patient demographics and eligibility will be assembled and reviewed. At each meeting, consideration will also be given to the rate of accrual. When a decision on dose de-escalation/escalation must be made, the study team will hold a special conference call to review information including the categorization and grading of reported adverse events, determination of the dose-limiting toxicities, etc. The decision to de-escalate or escalate will be made by consensus of the study team in accordance with the decision rules outlined in the protocol. Brief minutes of each meeting will be written to document the review of information and any decision made. The meeting minutes will be submitted to the NRG Early Phase Protocol Monitoring Oversight Committee for review.

- Any patient who has not experienced a DLT and withdraws from the trial before completion of the 6-month DLT evaluation window will be considered unevaluable for safety and tolerability. Such patients will be discontinued from study treatment, and should be replaced with another patient.

14.1.2 Phase II Design

The objective of the phase II trial is to determine whether the combination of niraparib with radiation and ADT is sufficiently promising to warrant phase III testing. The dose of niraparib will be the MTD established in phase I. The triple combination will be compared to a concurrent, randomized control arm consisting of RT and ADT without niraparib. Randomization will be stratified according to the eight strata defined in the study schema (4 risk groups x 2 types of RT). The primary endpoint, considered a good surrogate for disease-specific survival, is maintenance of PSA <0.1 for 2 years from the start of ADT.

From observations in RTOG 0521 (conducted among the same patient population as this trial), at the end of ADT, 32% of patients maintained a PSA < 0.1. These patients exhibited a lower frequency of distant metastasis, consistent with other studies evaluating functions of PSA as surrogate endpoints for later clinical disease endpoints (Denham 2008; D'Amico 2012; Royce 2017). Specifically, among patients who maintained the low PSA state, subsequent incidence of distant metastatic disease is currently about 5%. Among men with PSA exceeding 0.1 during or at completion of ADT, about 20% subsequently have experienced distant metastatic disease. Overall survival rates through 6 years post-trial entry are 88% among those who maintained low PSA through 2 years post-RT, compared to 81% among those who had PSA exceeding 0.1 by 2 years.

More mature data from a trial in the same class of patients (but for which the proposed endpoint is not available and thus conventional 'PSA failure' status by the Phoenix definition was used) also indicates that early avoidance of PSA progression is indicative of longer term prognosis. Among patients from the long-term ADT arm of RTOG 9202 who were free of conventional PSA failure at 2 years, subsequent 5-year *overall* survival (i.e., 7 years from diagnosis) was 76%, compared to 54% among those who had PSA failure during the 2-year treatment interval. As expected, this difference was almost wholly due to avoidance of prostate cancer death, as the

difference in cumulative incidence of prostate cancer death was over 20% (4% vs. 28%), while the difference in other cause-death was negligible (20% vs. 18%) (unpublished, submitted manuscript). Thus it is anticipated that this endpoint will provide an informative evaluation of whether the experimental regimen will lead to material gains in clinical endpoints, and thus whether a larger scale trial is warranted.

14.2 Study Endpoints

14.2.1 Primary Endpoint: Maintenance of a disease-free state characterized by PSA values sustained below 0.1 ng/ml for 2 years following initiation of ADT.

14.2.2 Secondary Endpoints

- Overall survival, i.e., time from randomization until death from any cause.
- Prostate cancer-specific survival, defined as time from randomization until death from prostate cancer. Patients who die from other causes will be censored as of the time of death.
- Pathologic complete response among patients undergoing 12-core biopsy at 24 months.
- Time to local/regional or distant progression. Patients who die prior to development of local/regional or distant progression will be censored at the time of death.
- Time to distant metastases, defined as time from randomization until detection of distant metastatic disease. Patients who die prior to development of distant metastases will be censored at the time of death.
- Biochemical progression-free survival (bPFS), defined as PSA $\geq$ 2 ng/ml over the nadir PSA, the presence of local, regional, or distant recurrence, or death from prostate cancer. Patients who receive salvage androgen deprivation therapy prior to the occurrence of a bPFS event will be censored at the time of salvage treatment. Patients who die from causes other than prostate cancer will be censored as of the time of death.
- Adverse event**s**, which will be categorized as early (within 90 days of completion of radiotherapy) or late (more than 90 days after the completion of radiotherapy).

14.2.3 Exploratory Endpoints

- Targeted exome sequencing of the genes most commonly altered in prostate cancer, including DNA repair genes (BRCA2, BRCA1, ATM, PALB2, RAD51B, and RAD51C) and more commonly detected alterations (p53 mutation, ETS gene fusions, and PTEN loss).
- Transcriptome-wide analysis of gene expression using a high-density Affymetrix oligonucleotide array to profile the transcriptome of tumor samples
- Whole blood samples will be analyzed for single nucleotide polymorphisms previously associated with prostate cancer risk. Plasma samples will be assessed for baseline and post-therapy alterations in a targeted gene panel and for reversion mutations in DNA repair genes as early biomarkers of treatment resistance.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

The primary endpoint is maintenance of a disease-free state characterized by PSA values sustained below 0.1 ng/ml until the completion of treatment; specifically, for two years

following the start of ADT. PSA levels will be assessed prior to the start of RT, at the end of RT, and every three months for 24 months. Based on data from RTOG 0521, it is hypothesized that treatment with ADT and RT alone achieves a 30% disease-free rate at 24 months and that the addition of niraparib will increase this percentage to 50%, i.e., a 20% absolute improvement.

14.3.2 How Primary Endpoints Will Be Analyzed

A modified intent-to-treat (mITT) analysis will be conducted that includes all randomized patients except those deemed to have been inappropriately randomized due to ineligibility and those lost to follow-up prior to 2 years. In order to be considered a responder, all PSA values obtained up to and including the two-year landmark must be < 0.1 ng/ml. Patients who die prior to two years from prostate cancer will be counted as failures. Patients who die from causes other than prostate cancer will be considered non-evaluable for the primary endpoint. It is not anticipated that early deaths will diminish the cohort in any meaningful way, but cumulative incidence of deaths and other events that render patients unevaluable for the primary endpoint will be estimated to assess any impact on statistical power and whether adjustments to the sample size are required.

Patients still under follow-up but who have a missing PSA value at two years or more than two missing values prior to two years will also be counted as failures. The proportion of patients disease-free at 24 months will be compared in the two treatment arms using a non continuity-corrected chi-square test. As a secondary analysis, a logistic regression model will be fit to adjust for the stratification factors (risk group and type of RT).

14.3.3 Sample Size and Power Calculations

Assuming that high-risk patients targeted for enrollment in this trial have a true response rate to ADT+RT of 30% for this endpoint, then for 85% power at a one-sided type I error rate of 5%, 85 patients per arm (**170** total) are required to detect a 20% absolute improvement (to 50%) in the 2-year rate of maintained low PSA with the addition of niraparib. **With an assumed ineligibility rate of 5%, a *maximum* of 90 patients per arm will be accrued, for a total *maximum* of 180 patients**.

14.4 Study Monitoring of Primary Objectives

14.4.1 Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis. A formal futility rule will be employed. If at 50% of trial endpoint information, the response rate in the experimental regimen is equal to or less than that in the standard treatment, then discontinuation of accrual (if relevant) and further experimental agent treatment will be considered. This futility rule is associated with a minimal power loss of typically less than 2% (Wierand 1987). At this juncture an O'Brien-Fleming (O'Brien 1979) efficacy bound will also be employed. If the z-statistic exceeds 2.37 in favor of niraparib (one-sided $p<0.0089$), then early termination of the trial for efficacy will be considered. This boundary will maintain the overall type I error rate at 5% (one-sided) with a slight adjustment of the final critical p-value to 0.047.

14.4.2 Safety

Because this is a novel combination in this setting, two additional comprehensive safety

evaluations will be conducted during the Phase II portion. After **50 randomized patients** (25 per arm) reach **6 months** on study, we will summarize and compare the frequency of specific adverse events of concern. Grade 3 and grade 4 estimated frequencies in the experimental arm will be compared to threshold values, with particular regard to CBC values, gastrointestinal and genitourinary adverse events. The overall adverse event frequency distributions will also be compared between the standard and experimental arms to assess tolerability of the regimen, as well as any likely impact on compliance, using chi-square and Fisher exact tests. Note that accrual to the trial will not be suspended during these evaluations unless a major concern is identified. If no major concerns arise and the study continues, another comprehensive safety evaluation will then be performed after **100 randomized patients** (50 per arm) reach **6 months** on study.

Second primary malignancies will be recorded throughout the trial, with observed incidence compared between arms and to expected incidence based on age-standardized national rates.

14.5 Accrual/Study Duration Considerations (18-JUN-2019)

The phase I portion will enroll cohorts of 3-6 patients at an expected rate of 3 patients every 2 months. Given the requirement for suspensions of accrual, the duration of the phase I trial is projected to last between 2.3 to 3.3 years, and phase II enrollment will then proceed seamlessly. Based on recent history with high-risk prostate cancer, accrual of 10-15 patients per month is readily achievable during phase II. It is projected that the phase II study will complete accrual in 18 months. The last patient enrolled will be followed for two years, giving a total study duration for the phase II trial of 3.5 years.

14.6 Dose Level Guidelines

These are specified in Sections 5.1, 6.1, and 6.2 above.

14.7 Secondary Analyses

Analysis of secondary time-to-event endpoints will consist of comparison of Kaplan-Meier (Kaplan 1958) curves using a logrank test for overall survival, prostate-cancer specific survival, and biochemical progression-free survival (bPFS). Cumulative incidence curves for time to local/regional or distant progression, time to distant metastases, and death from prostate cancer and their associated competing risk will be compared using the Fine-Gray test (Dignam 2008). Cox (1972) regression models will also be fit to assess and adjust for the effects of the stratification variables and other covariates. The proportional hazards assumption will be tested using graphical methods (Kay 1997) and Schoenfeld residuals (Grambsch 1994), and if violated an alternative metric, such as comparison of restricted means at 3 years, will be performed (Karrison 1997). The restricted means will be compared both unadjusted and adjusted for the stratification factors (Karrison 2018).

The proportion of patients with complete pathologic response (pCR) at 24 months will be compared using a chi-square test. Assuming that in this high risk population the expected positive biopsy rate is 25%, then for 80% power at one-sided type I error rate of 5%, 45 patients per arm (90 total) will be required to detect an absolute reduction of 20% (to 5%) in the 2-year pCR rate. If a biopsy participation rate of at least 60% can be achieved

among trial enrollees, then this sample size will be obtained. It is anticipated that greater participation may be achieved, which will allow for adequate power over a range of control group biopsy positivity rates and reductions due to the addition of niraparib.

Adverse event (AE) rates in the two treatment arms will be summarized by time of occurrence (early vs. late), type, grade, and attribution to treatment. For each type of AE, the worst grade occurring during the early treatment period, late treatment period, or entire treatment period will be determined. For each time period, treatment group comparisons will be conducted using chi-square or Fisher exact tests**..**

14.8 Exploratory Hypothesis and Endpoints

Exploratory endpoints/objectives are:

- Targeted exome sequencing of the genes most commonly altered in prostate cancer, including DNA repair genes (BRCA2, BRCA1, ATM, PALB2, RAD51B, and RAD51C) and more commonly detected alterations (p53 mutation, ETS gene fusions, and PTEN loss).
- Transcriptome-wide analysis of gene expression using a high-density Affymetrix oligonucleotide array to profile the transcriptome of tumor samples.
- Whole blood samples will be analyzed for single nucleotide polymorphisms previously associated with prostate cancer risk. Plasma samples will be assessed for baseline and post-therapy alterations in a targeted gene panel and we will assess for reversion mutations in DNA repair genes as early biomarkers of treatment resistance.

Descriptive statistics will be generated summarizing the frequency of gene alterations, mutations, and gene expression levels. The percentage of patients with baseline or post-therapy alterations in targeted genes will be reported and the association between the occurrence of reversion mutations in DNA repair genes and clinical outcomes will be assessed using logistic regression models for dichotomous endpoints (disease-free state, pCR), and Cox regression or competing risk regression modeling for time-to-event data.

14.9 Gender/Ethnicity/Race Distribution

Phase I (assumes maximum 36 patients enrolled)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	N/A	0	N/A	0	0
Asian	N/A	1	N/A	0	1
Native Hawaiian or Other Pacific Islander	N/A	0	N/A	0	0
Black or African American	N/A	4	N/A	0	4
White	N/A	23	N/A	4	27
More Than One Race	N/A	0	N/A	0	0
Total	N/A	28	N/A	4	32

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	N/A	0	N/A	0	0
Asian	N/A	1	N/A	0	1
Native Hawaiian or Other Pacific Islander	N/A	0	N/A	0	0
Black or African American	N/A	1	N/A	0	1
White	N/A	2	N/A	0	2
More Than One Race	N/A	0	N/A	0	0
Total	N/A	4	N/A	0	4

Phase II

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	N/A	1	N/A	0	1
Asian	N/A	2	N/A	0	2
Native Hawaiian or Other Pacific Islander	N/A	1	N/A	0	1
Black or African American	N/A	21	N/A	0	21
White	N/A	122	N/A	13	135
More Than One Race	N/A	2	N/A	0	2
Total	N/A	149	N/A	13	162

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	N/A	1	N/A	0	1
Asian	N/A	3	N/A	0	3
Native Hawaiian or Other Pacific Islander	N/A	0	N/A	0	0
Black or African American	N/A	2	N/A	0	2
White	N/A	10	N/A	1	11
More Than One Race	N/A	1	N/A	0	1
Total	N/A	17	N/A	1	18

REFERENCES

Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. 2005;293(17):2095-101.

Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med. 1997;337(5):295-300.

Bratan F, Melodelima C, Souchon R, et al. How accurate is multiparametric MR iamging in evaluation of prostate cancer volume? Radiology. 2015;275(1):144-54.

Brock WA, Milas L, Bergh S, Lo R, Szabo C, Mason KA. Radiosensitization of human and rodent cell lines by INO-1001, a novel inhibitor of poly(ADP-ribose) polymerase. Cancer Lett. 2004;205(2):155-60.

Chalmers A, Johnston P, Woodcock M, Joiner M, Marples B. PARP-1, PARP-2, and the cellular response to low doses of ionizing radiation. Int J Radiat Oncol Biol Phys. 2004;58(2):410-9.

Chism DB, Hanlon AL, Horwitz EM, Feigenberg SJ, Pollack A. A comparison of the single and double factor high-risk models for risk assignment of prostate cancer treated with 3D conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2004;59(2):380-5.

Cox DR. Regression models and life tables (with discussion). J R Stat Soc B. 1972;34:187-220.

D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol. 2002;20(23):4567-73.

D'Amico AV, Chen MH, de Castro M, et al. Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localised or locally advanced prostate cancer: an analysis of two randomised trials. Lancet Oncol. 2012;13(2):189-95.

Denham JW, Steigler A, Wilcox C, et al. Trans-Tasman Radiation Oncology Group 96.01 Trialists: Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. Lancet Oncol. 2008;9:1058-68.

Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. J Clin Oncol. 2008;26:4027-34.

Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res. 2007;13(9):2728-37.

Fair WR, Cookson MS, Stroumbakis N, et al. The indications, rationale, and results of

neoadjuvant androgen deprivation in the treatment of prostatic cancer: Memorial Sloan-Kettering Cancer Center results. Urology. 1997;49(3A Suppl):46-55.

Goodwin JF, Schiewer MJ, Dean JL, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. Cancer Discov. 2013;3(11):1254-71.

Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-26.

Jordan EJ, Fiske C, Zagoria RJ, et al. Evaluating the performance of PI-RADS v2 in the non-academic setting. Abdom Radiol. 2017;42(11):2725-31.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-481.

Karrison TG. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups--interpretation and power considerations. Control Clin Trials. 1997;18:151-67.

Karrison T, Kocherginsky M. Restricted mean survival time: Does covariate adjustment improve precision in randomized clinical trials? Clinical Trials. 2018;15:178-88.

Kay R. Proportional hazards regression models and the analysis of censored survival data. Appl Statist. 1977;26:227-37.

Klotz LH, Goldenberg SL, Jewett M, et al. CUOG randomized trial of neoadjuvant androgen ablation before radical prostatectomy: 36-month post-treatment PSA results. Canadian Urologic Oncology Group. Urology. 1999;53(4):757-63.

Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med. 2015;373(18):1697-708.

Meyer F, Moore L, Bairati I, Lacombe L, Tetu B, Fradet Y. Neoadjuvant hormonal therapy before radical prostatectomy and risk of prostate specific antigen failure. J Urol. 1999;162(6):2024-8.

Mostaghel EA, Nelson PS, Lange P, et al. Targeted androgen pathway suppression in localized prostate cancer: a pilot study. J Clin Oncol. 2014;32(3):229-37.

Nougaret S, Robertson N, Golia Pernicka J, et al. The performance of PI-RADSv2 and quantitative apparent diffusion coefficient for predicting confirmatory prostate biopsy findings in patients considered for active surveillance of prostate cancer. Abdom Radiol. 2017;42(7):1968-74.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56.

O'Connor MJ. Targeting the DNA damage response in cancer. Mol Cell. 2015;60(4):547-60.

Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol. 1997;15(3):1013-21.

Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys. 2005;61(5):1285-90.

Pisansky TM, Kahn MJ, Bostwick DG. An enhanced prognostic system for clinically localized carcinoma of the prostate. Cancer. 1997;79(11):2154-61.

Polkinghorn WR, Parker JS, Lee MX, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov. 2013;3(11):1245-53.

Royce TJ, Chen MH, Wu J, et al. Surrogate endpoints for all-cause mortality in men with localized unfavorable risk prostate cancer treatment with radiation therapy vs radiation therapy plus androgen deprivation. A secondary analysis of a randomized clinical trial. JAMA Oncology. 2017;3:652-8.

Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 2005;23(28):7199-206.

Symon Z, Griffith KA, McLaughlin PW, Sullivan M, Sandler HM. Dose escalation for localized prostate cancer: substantial benefit observed with 3D conformal therapy. Int J Radiat Oncol Biol Phys. 2003;57(2):384-90.

Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol. 2014;32(33):3705-15.

Vargas HA, Hötker, AM, Goldman DA, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur Radiol. 2016;26(6):1606-12.

Wieand S, Therneau T. A two-stage design for randomized trials with binary outcomes. Controlled Clin Trials 1987;8:20-8.

Weinreb JC, Barentszb JO, Choykec PL, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2. Eur Urol. 2016;69(1):16-40.

Yap TA, Sandhu SK, Carden CP, de Bono JS. Poly(ADP-ribose) polymerase (PARP) inhibitors:

Exploiting a synthetic lethal strategy in the clinic. CA Cancer J Clin. 2011;61(1):31-49.

Zelefsky MJ, Gomez DR, Polkinghorn WR, Pei X, Kollmeier M. Biochemical response to androgen deprivation therapy before external beam radiation therapy predicts long-term prostate cancer survival outcomes. Int J Radiat Oncol Biol Phys. 2013;86(3):529-33.

Zhao C, Gao G, Gang D, et al. The efficiency of multiparametric magnetic resonance imaging (mpMRI) using PI-RADS Version 2 in the diagnosis of clinically significant prostate cancer. Clin Imaging. 2016;40(5):885-8.

APPENDIX I
PATIENT'S PILL DIARY: NIRAPARIB

NRG-GU007: Randomized Phase II Trial of Niraparib With Standard Combination Radiotherapy and Androgen Deprivation Therapy (ADT) in High Risk Prostate Cancer (With Initial Phase I)

Today's date: **Patient Initials:** **Patient Study ID: CASE #**

Instructions to patient: Place the date and number of pills taken in the appropriate column. Complete one page for each 30 days of treatment for a total of 365 days. Be sure to bring the pill diary to your appointments as instructed.

Take (___) pills each day and at the same time each day with or without food unless you have been instructed by your physician to take less or to stop taking the drug for a period of time. If you forget to take pills on one day do NOT take a double dose the next day just chart that no pills were taken on that date (0). Feel free to make any comments during treatment.

Month #

DATE	DAY	NUMBER OF PILLS TAKEN DAILY	COMMENTS
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
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	28		
	29		
	30		

SITE USE ONLY: NUMBER OF PILLS TAKEN:
_____TOTAL DOSE TAKEN (# PILLS X 100mg):

APPENDIX II (07-APR-2020)
PLASMA PROCESSING GUIDELINES

Collect THREE 10mL EDTA tubes. Fill tubes completely.
Mix gently by inverting the tubes ten (10) times.

SPIN #1

Centrifuge at room temperature for 10 min at 1600 (±150) g. If centrifuge uses rpm (revolutions per minute), see centrifuge instructions for the conversion to g. Centrifugation at 4°C is acceptable.

To ensure stability of the sample, time between draw and preservation should not exceed 4 hours.

After centrifugation, transfer supernatant of the EDTA tubes to two fresh 15mL centrifuge tubes without disturbing the cellular layer using a disposable pipette. Be sure to pre-label the transfer tubes.

Discard EDTA tubes.

SPIN #2 CRITICAL STEP

Centrifugation separates plasma from leukocytes and erythrocytes. Leaving sufficient residual plasma in the tubes after the centrifugation and not disturbing the leukocyte layer when pipetting is a critical step in the sample preparation process. Be careful not to disturb leukocyte layer in the tubes when transferring the plasma

Centrifuge the plasma in the 15mL centrifuge tubes at room temperature for 10 min at 3000 (±150) g.

CRITICAL STEP

The 2nd centrifugation is intended to remove any residual intact blood cells carried over from the 1st centrifugation step.

After centrifugation, transfer supernatant to a fresh 15mL centrifuge tube without disturbing the cellular layer using a disposable pipette. Be sure to pre-label the transfer tubes.

CRITICAL STEP

Expect ~4 mL plasma per 10 mL of whole blood. Leave a residual volume of about 0.3mL (~7 mm) on the bottom of the 15mL tube to avoid contaminating the plasma with cells.

After transferring the plasma to a new 15mL centrifuge tube as described, gently mix plasma.

Transfer plasma into each of the two 5 mL cryovials and the remainder into five 2 mL cryovials. All plasma should be retained.

Immediately after processing, place cryovials into a storage box and freeze upright. Store

samples at -80°C or lower in a non-self-defrosting freezer until shipment.