Image-Guided Salvage Oligometastasectomy and Radiation Therapy in Recurrent Prostate Cancer (SOAR)

HCI identifier – HCI-17-GU-26/ Lead Trial ID: HCI115811/IRB #115811

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation or Term[1]	Definition/Explanation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
e.g.	Exempli gratia (for example)
EQD2	Equivalent Dose in 2 Gy Fractions
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAC	Novel Oral Anticoagulants
NOAEL	No-observed-adverse-effect level

Abbreviation or Term[1]	Definition/Explanation
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RALP	Robotic-assisted laparoscopic prostatectomy
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TRUS	Transrectal ultrasonography
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	Image-Guided Salvage Oligometastasectomy and Radiation Therapy in Recurrent Prostate Cancer
Short Title	SOAR
Protocol Identifiers (IRB – internal)	IRB #115811 HCI-17-GU-26
IND number	Exempt
Phase	Phase II pilot
Design	This study is establishing baseline data for these patients who have no defined standard of care currently
Study Duration	5 Years total study duration: 2 years for accrual and 3 years for follow up
Study Center(s)	Single-center
Objectives	**Primary objective** • To assess response to treatment of oligometastatic disease. **Secondary objectives:** • To assess additional measurements of response to treatment of oligometastatic disease • To assess PSA progression free-survival following treatment of oligometastatic disease. • To assess time to disease recurrence. • To assess time to initiation of ADT for metastatic prostate cancer following treatment of oligometastatic disease. • To assess the rate of undetectable PSA following treatment of oligometastatic disease in subjects who have been previously undergone prostatectomy. • To assess safety. • To assess the impact of study treatment on change in quality of life over three years.
Number of Subjects	20

Diagnosis and Main Eligibility Criteria	**Diagnosis**
	Histologically proven adenocarcinoma of the prostate
	Inclusion Criteria
	• Recurrent adenocarcinoma of the prostate:
	  • Post-prostatectomy (with/without adjuvant radiotherapy): Patients must have a detectable or rising PSA level that is >0.05 ng/mL, with a second confirmatory level that is >0.05ng/mL after a minimum of 1 week.
	  o Post radiotherapy/ablation: PSA rise ≥ 2ng/mL over nadir.
	• Subjects treated with prior definitive radiotherapy for prostate cancer who have positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)

	suggesting recurrent intraprostatic disease must undergo TRUS biopsy less than or equal to one year before study enrollment: o If the TRUS biopsy is negative, no additional treatment is required to the prostate in addition to that of scan-positive sites. o If the TRUS biopsy is positive, subject must undergo salvage prostatectomy or salvage radiotherapy to the primary site concurrently with the study treatment per the treatment protocol algorithm. o Note: Biopsy is not required for prostate fossa recurrences after radical prostatectomy. • Oligometastatic disease defined as 10 or fewer metastatic lesions to lymph nodes and/or bones only. • For patients with oligometastatic disease involving lymph node, metastasis is confined to the pelvic or para-aortic (below IMA) regions on[1]- molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion), CT, or MRI). • Subjects must be candidates for surgery if indicated per the treatment algorithm. • ECOG Performance Status ≤ 2 **Exclusion Criteria** • Known brain or visceral metastases other than lymph nodes • Patients actively receiving hormone therapy for prostate cancer. Patients may have received hormone therapy previously but must have documented non-castrate levels of testosterone (>50 ng/dL) • Prior or concurrent malignancy whose natural history or treatment, in the opinion of the enrolling investigator, may have the potential to interfere with the safety or efficacy assessment of the investigational treatment protocol of this study. • Use of finasteride within 30 days prior to initiation of therapy. • Use of dutasteride within 90 days prior to initiation of therapy. • Active, uncontrolled, significant intercurrent or recent illness
Study Product, Dose, Route, Regimen	Oligometastasectomy and/or bone radiotherapy and/or nodal radiotherapy and/or prostatectomy
Duration of administration	Surgery: 1 day Radiotherapy: up to 8 weeks
Reference therapy	There is no reference therapy. This is a pilot study to determine a baseline response to the study population.
Statistical Methodology	The planned sample size is N = 20 evaluable subjects. The primary outcome variable of reduction in PSA ≥ 50% at 6 months will be analyzed descriptively via 90% and 95% exact binomial confidence intervals. No hypothesis test will be performed on the primary outcome variables. The sample size is justified by the width of the 95%

	confidence intervals. We anticipate that the PSA 50% response rate at 6 months will be 30% based on the results published by Siriwardana, as their PSA response at 6 weeks and 12 months was 43% and 23% respectively. However, the definition used here is somewhat different than the definition in that clinical study. If the observed PSA 50% response rate is 30% (6/20), the 95% exact binomial confidence interval (Clopper-Pearson) will be 12% to 54 %. With 20 evaluable subjects the maximum width of a 95% exact binomial confidence interval is 46% (27% to 73%) and occurs when the observed response rate is 50% (10/20).

SCHEMA

Figure 1: Overall Treatment Schema (All Arms)

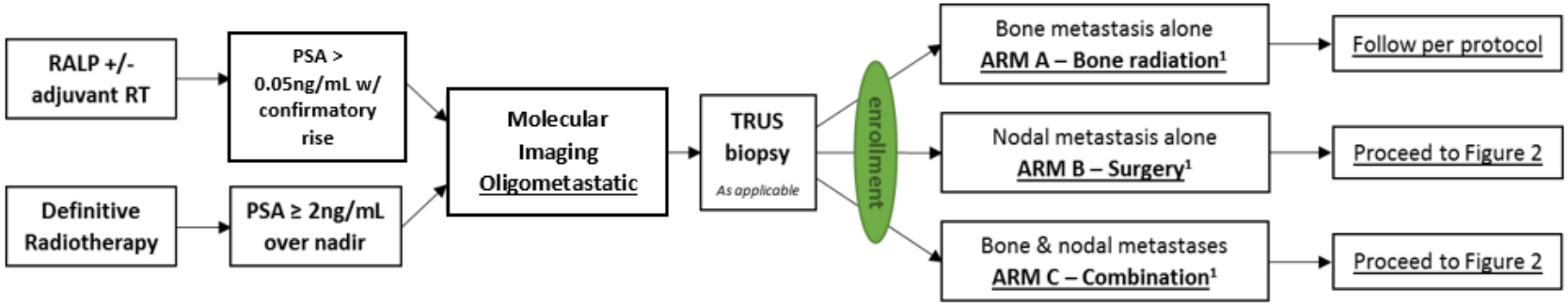
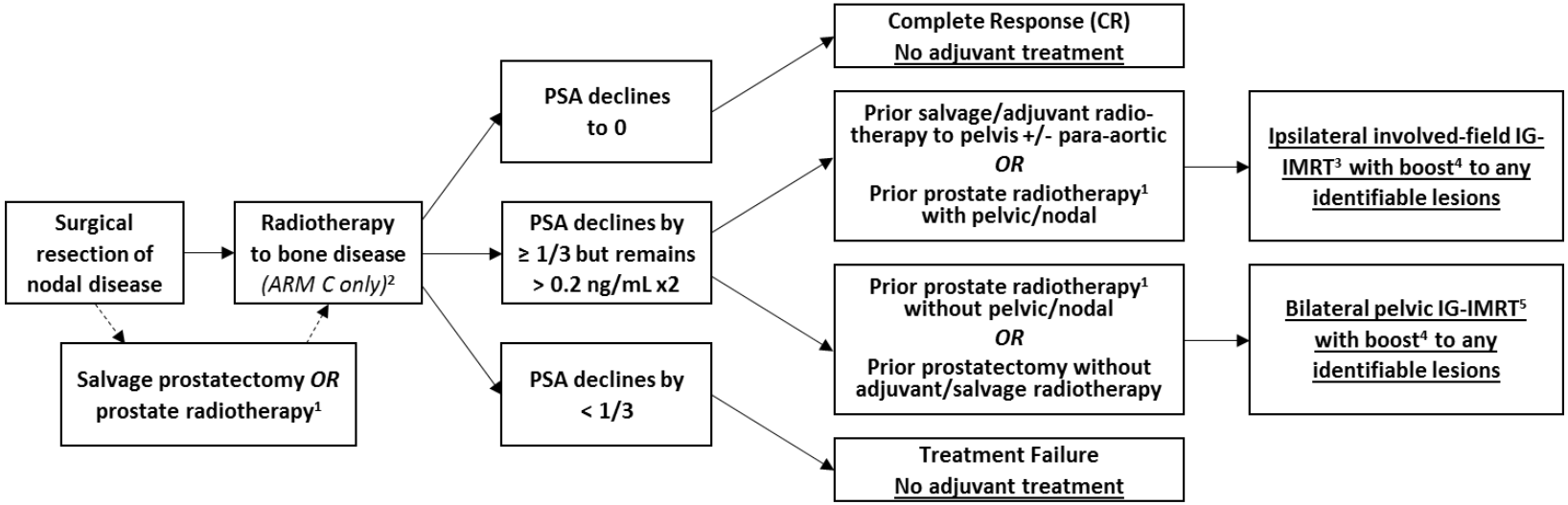


Figure 2: Adjuvant radiotherapy (Arms B and C only)



1. With completion of prostate radiotherapy (for patients who received an incomplete definitive radiation course) OR salvage prostatectomy if positive baseline TRUS biopsy (including subjects enrolled in Arm A)
2. Bone radiotherapy can be completed prior to surgical resection if indicated in the opinion of the investigator.
3. Ipsilateral involved-field radiotherapy to 45 Gy in 25 fractions using image-guided IMRT
4. Simultaneous integrated boost to gross target volumes to be >= 76 Gy EQD2
5. Target volume defined with inferior dosimetric border set immediately above the previously treated area. Nodal volumes will be treated to 50.4 Gy. The prostate fossa will be treated for post-prostatectomy patients who have not had any radiation to the prostate fossa.

1 OBJECTIVES

1.1 Primary Objective

To assess response to treatment of oligometastatic disease.

Primary Endpoints: proportion of subjects with a reduction in PSA ≥ 50% 6 months after completion of all treatment (salvage and adjuvant therapy).

1.2 Secondary Objectives

1.2.1 To assess additional measurements of response to treatment of oligometastatic disease.

Secondary Endpoints: Proportion of subjects with reductions in PSA ≥ 50% 12 months after and ≥ 90% 6 and 12 months after completion of all treatment (salvage and adjuvant therapy).

1.2.2 To assess PSA progression free-survival following treatment of oligometastatic disease.

Secondary Endpoint: Proportion of subjects without PSA progression (defined using Prostate Cancer Working Group 3 Criteria PCWG3), evaluated every 3 months for 3 years after completion of all treatment (salvage and adjuvant therapy).

1.2.3 To assess time to disease recurrence following treatment of oligometastatic disease.

Secondary Endpoint: The time from study enrollment until the date of confirmed radiographic disease progression as defined by RECIST 1.1 and PCWG3.

1.2.4 To assess time to initiation of ADT for metastatic prostate cancer following treatment of oligometastatic disease.

Secondary Endpoint: The time from study enrollment to the initiation of ADT.

1.2.5 To assess the rate of undetectable PSA following treatment of oligometastatic disease in subjects who have previously undergone prostatectomy.

Secondary Endpoint: In subjects who have previously undergone prostatectomy evaluate the proportion of patients with a PSA ≤ 0.2 ng/mL, evaluated 6 and 12 months after completion of all treatment (salvage and adjuvant therapy).

1.2.6 To assess safety.

Secondary Endpoint: Rate of AEs and SAEs as defined by CTCAE version 5.0.

1.2.7 To assess the impact of study treatment on change in quality of life over three years.

Secondary Endpoint: Quality of life (QOL) questionnaires (FACT-P and Expanded Prostate Cancer Index Composite EPIC-26) will be administered at screening, the Response Assessment Visit, and each follow-up visit.

1.3 Exploratory Objective(s)

To assess the correlation of molecular biomarkers with clinical response and resistance to surgery and radiation therapy.

Exploratory Endpoint(s): Evaluation for genomic alterations or abnormal protein expression that correlates with radiation resistance or predilection for early metastasis and worse overall prognosis.

2 BACKGROUND

Most subjects diagnosed with localized prostate cancer are cured with definitive surgery or radiation therapy. However, a significant proportion experience disease progression despite these interventions. Typically subjects will initially have a PSA only relapse, without radiographic evidence of metastatic disease. There is no definitive standard of care for these subjects proven to improve clinical outcomes. Some subjects are treated with immediate androgen deprivation therapy (ADT) either through intermittent or continuous administration. Other subjects are carefully observed until radiographic metastatic disease progression. It is not clear which treatment strategy, if any, is clinically superior. Some studies suggest that immediate therapy may lead to superior clinical outcomes. Duchesne and colleagues[1] reported results from a phase III randomized clinical trial enrolling 293 men total, including de-novo incurable disease and those with a PSA relapse. Subjects were treated with either immediate or delayed ADT. In the PSA relapse population, 137 subjects were treated with delayed ADT while 124 were treated with immediate ADT. The estimated five year survival was 78.2% (95% CI, 67.2% – 85.8%) compared to 84.3% (95% CI, 73.9% – 90.8%) (P = 0.10) for the delayed versus immediate treatment groups respectively, suggesting a possible benefit based on this small study. In contrast, other studies do not support a clinical benefit from immediate therapy. Garcia-Albeniz et al[2] reported on 2096 subject outcomes with immediate compared to deferred ADT. There was no improvement to the 5-year prostate cancer specific survival, 92.8% (95% CI, 86.7% – 98.9%) and 95.8% (95% CI, 92.7% – 98.9%) respectively for immediate and delayed ADT. There is a distinct lack of clear, clinical evidence to guide treatment decisions in this population.

Further complicating the clinical decision making, recently advanced, molecular imaging techniques have been FDA approved or are in the approval process for subjects with PSA only relapse. The ^{18}F-fluciclovine PET scan (also called axumin or [^{18}F] anti-FACBC PET scan) is one example. It is approved specifically in subjects with PSA only relapsed prostate cancer. Unfortunately, there is very limited clinical data to guide any treatment recommendations for these subjects with ^{18}F-fluciclovine PET positive disease. Different approaches appear to be used, such as continued observation, focal radiation therapy, surgical resection or immediate hormonal therapy. There are two reports of institutional experience using radiation or surgery approaches for subjects with a PSA only relapse and oligometastatic disease identified on molecular imaging.

Bouman-Wammes et al[3] reported on stereotactic body radiation therapy (SBRT) in forty-three subjects with oligometastatic (defined as < 5 metastasis) hormone sensitive prostate cancer. This was a single arm, prospective study. Subjects were identified through ^{18}F-fluoromethylcholine positron emission tomography (PET) scans. A PSA response was seen in 67.4% of subjects, and the median ADT-free duration was 15.6 months (95% CI, 11.7 – 19.5 months), but 25.7 months (95% CI, 9.0 – 42.4 months) for subjects with a PSA response. Clinical outcomes were

compared against historic controls. The time until castration resistant prostate cancer was longer for the SBRT-treated subjects with a mean of 66.6 months (95% CI, 53.5 – 79.8 months), compared to 36.41 months (95% CI, 26.0 – 46.8 months) for the historic controls (P = 0.020). There were no significant toxicities associated with this treatment in this study.

Siriwardana[4] and colleagues enrolled 35 subjects with oligometastatic disease identified by ^{68}Ga-PSMA PET scans. Subjects underwent a targeted pelvic dissection (PET positive lesions only), unilateral extended dissection or a bilateral extended dissection. 32 subjects (91%) had pathologically confirmed lymph node metastasis. Subjects with a bilateral extended dissection appeared to benefit from this intervention on univariate analysis, suggesting that many subjects with biochemical recurrence have limited regional disease metastasis and may benefit from aggressive local therapy.

Recently two clinical trials have demonstrated substantial clinical benefit for early, intense treatment for subjects with metastatic hormone sensitive prostate cancer using a combination of ADT plus abiraterone (NCT00268476, NCT01715285). Intensive treatment with combination ADT and chemotherapy (NCT00309985) has similarly been demonstrated to improve clinical outcomes in subjects with metastatic hormone sensitive prostate cancer. Additionally, early treatment in patients with non-metastatic castration-resistant prostate cancer with either enzalutamide[5] or apalutamide[6] compared with placebo both demonstrated a significant improvement to metastasis-free survival and a similar trend for improved overall survival. This body of evidence strongly suggests that early, intense therapy may provide significant clinical benefit in subjects with hormone sensitive oligometastatic prostate cancer.

We hypothesize that local salvage treatment of oligometastatic disease identified on advanced imaging will result in long-term disease control, including optimal PSA responses and prolongation of radiographic progression-free survival. These results might translate into some men obtaining a cure of their prostate cancer, though this will have to be validated in future studies and with longer clinical follow up. Given that there is no standard of care for this setting, this clinical trial is designed to establish a standard reference for this population that can be used as the basis for additional clinical investigations in the future.

3 TREATMENT INFORMATION

3.1 Surgery

3.1.1 Salvage Oligometastasectomy

All subjects with pelvic and/or para-aortic lymph node metastases will undergo surgical dissection covering the bilateral nodal group identified by molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion), and one level above and one level below any identified nodal region.

Nodal groups from distal to proximal include: 1) Obturator fossa, 2) External iliac, 3) Common iliac, 4) Aortic-below IMA, 5) Aortic-above IMA.

Metastases to superficial inguinal nodes will also be considered for surgical dissection in which cases both a superficial inguinal lymph node dissection and pelvic lymph node (obturator fossa and external iliac nodes) dissection will be performed.

3.1.2 Salvage Prostatectomy

Subjects previously treated with definitive radiotherapy whose TRUS biopsy is positive for malignancy when screening for the study (see inclusion criterion 5.1.4) must undergo salvage prostatectomy (or salvage radiotherapy if applicable, see Section 3.2.1). This can be done prior to enrollment on the study or at the same time as the nodal dissection described in Section 3.1.1 above.

3.2 External Beam Radiation Therapy

Radiation therapy will be performed on linear accelerators capable of delivering X-ray or electron therapy in the 4 to 18 MeV range with image guidance systems. One of the fractionation schemes listed in Section 6 will be used.

3.2.1 Salvage Radiotherapy for Subjects with Positive TRUS Biopsy at Baseline

Subjects previously treated with an incomplete course of definitive radiotherapy (as defined according to institutional standards) who have positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion) suggesting recurrent intraprostatic disease and whose TRUS biopsy is positive for malignancy when screening for the study (see inclusion criterion 5.1.4) must undergo completion of their radiation course or salvage prostatectomy as defined in section 3.1.2.

4 STUDY DESIGN

4.1 Description

This is a Phase II non-randomized pilot study meant to establish preliminary reference response rate and duration of response for subjects with recurrent prostate cancer treated with salvage oligometastasectomy and/or radiotherapy. Treatment decisions will be based on molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion): subjects with nodal disease only will be treated with oligometastasectomy, subjects with bone disease only will be treated with SBRT, and subjects with a combination of nodal and bone disease will receive both treatment. Response rates and durations will be based on PSA and imaging.

4.2 Number of Subjects

A total of twenty (20) subjects will be enrolled on this study.

4.3 Number of Study Centers

This study will open at a single center at the Huntsman Cancer Institute.

4.4 Study Duration

The estimated duration of accrual is 2 years, subjects will be followed for up to 3 years for a total study duration of up to 5 years.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine subject eligibility and filed with the enrolling investigator's signature in the subject research chart.

Subject No. _____
Subject's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = subject ineligible)

5.1.1 _____ Male subjects age ≥ 18 years.

5.1.2 _____ Histologically proven adenocarcinoma of the prostate.

5.1.3 _____ Recurrent prostate carcinoma after definitive therapy for primary disease defined as:

- Post-prostatectomy (with/without adjuvant radiotherapy): Patients must have a detectable or rising PSA level that is >0.05 ng/mL, with a second confirmatory level that is >0.05ng/mL after a minimum of 1 week.
- Post radiotherapy/ablation (without radical prostatectomy): PSA rise ≥ 2ng/mL over nadir.

5.1.4 _____ Subjects treated with prior definitive radiotherapy for prostate cancer who have positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion) suggesting recurrent intraprostatic disease must undergo TRUS biopsy less than or equal to one year before study enrollment:

- If the TRUS biopsy is negative, no additional treatment is required to the prostate in addition to that of scan-positive sites.
- If the TRUS biopsy is positive, subject must undergo salvage prostatectomy or salvage radiotherapy to the primary site concurrently with the study treatment per the treatment protocol algorithm.
- Note: Biopsy is not required for prostate fossa recurrences after radical prostatectomy.

5.1.5 _____ Oligometastatic disease defined as 10 or fewer metastatic lesions to lymph nodes and/or bones only.

5.1.6 _____ For patients with oligometastatic disease involving lymph nodes, metastasis is confined to the pelvic or para-aortic (below IMA) regions on molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).

5.1.7 _____ All subjects must be surgical candidates if surgery is indicated per the treatment algorithm.

5.1.8 _____ECOG Performance Status ≤ 2.

5.1.9 _____ Use of condoms for male subjects who have not had surgical removal of their prostate and have a partner of child bearing potential beginning at the time of ICF signature and lasting until at least 6 months after the last radiation treatment. Because of the potential side effect on spermatogenesis associated with radiation, female partners of childbearing potential must agree to use a highly effective contraceptive method during and for 6 months after completing treatment.

5.1.10 _____ Recovery to baseline or ≤ Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy as determined by the treating physician.

5.1.11 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = subject ineligible)

5.2.1 _____ Known brain or visceral metastases other than lymph nodes (defined in section 5.1.6) as defined by CT, MRI, or other molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).

5.2.2 _____ Patients actively receiving hormone therapy for prostate cancer. Patients may have received hormone therapy previously but must have documented non-castrate levels of testosterone (>50 ng/dL).

5.2.3 _____ Prior or concurrent malignancy whose natural history or treatment, in the opinion of the enrolling investigator, may have the potential to interfere with the safety or efficacy assessment of the investigational treatment protocol of this study.

5.2.4 _____ Use of finasteride within 30 days prior to initiation of therapy. Baseline PSA should not be obtained prior to 30 days after stopping finasteride.

5.2.5 _____ Use of dutasteride within 90 days prior to initiation of therapy. Baseline PSA should not be obtained prior to 90 days after stopping dutasteride.

5.2.6 _____ Use of any prohibited therapy noted in 6.3.2.

5.2.7 _____ Active, uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
  - Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
  - Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
  - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose.
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration or within 30 days of registration.
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;

I certify that this subject meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential subjects will be identified by Investigators in the setting of their outpatient clinics.

6 TREATMENT GUIDELINES

6.1 Subjects with Bone Metastases Only

Bone metastases will be treated with stereotactic body or hypofractionated radiation per institutional standard of care guidelines. The investigator will select the type of radiation based on the nature of the disease.

Following completion of radiation treatment subjects will move on to the follow-up phase of the study as described in Section 9.3.

6.1.1 Dose Specification

All subjects will receive stereotactic body or hypofractionated radiation to sites of bone disease seen on imaging studies. Radiation will be administered per institutional standard of care which is commonly 16-44 Gy in 1-6 fractions, using any one of the isoequivalent radiation regimens (based on the linear quadratic model with EQD2≥60 and an alpha/beta ratio for prostate cancer=2) to allow the radiation oncologist flexibility to deliver an ablative dose while sparing normal tissues depending on tumor location. In cases where radiation is administered outside of these parameters, prior approval will be obtained from the PI and medical monitor.

6.1.2 Target Localization

This study requires the use of IGRT, a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the tomotherapy approach.

Simple portal imaging approaches that do not use computer assistance are not considered to be suitable for this study.

When the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam, the recommendations of AAPM Task Group Report 142 for testing the coincidence of the imaging and treatment reference points must be implemented. For example, verification of treatment and imaging isocenter coincidence must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

6.1.3 Target Volume Definition

<u>Non-Spinal Osseous Sites</u>

GTV = gross tumor apparent on CT or MRI, or other molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).
CTV = GTV.
PTV will be uniform expansion of 3-5 mm.

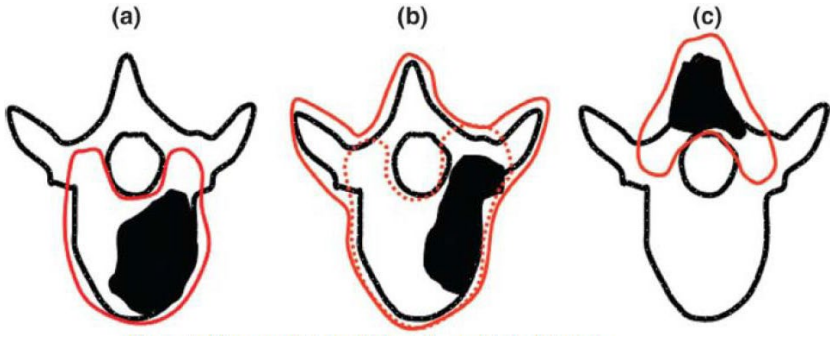
Spinal Osseous Sites

GTV = gross tumor apparent on CT or MRI, or other molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion). The GTV will include 1 of the following (as illustrated in Figure 6.1):

a. The vertebral body only OR
b. The vertebral body and pedicle OR
c. Posterior elements only

CTV = GTV.
PTV will be as per RTOG 0631.

Figure 6.1. Diagram of Spine Metastases and Target Volumes



6.1.4 Planning Techniques

6.1.4.1 General Considerations

A variety of planning techniques can be used to deliver SBRT for each metastasis. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7-13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed treating small metastases.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span at least 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist

within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45Gy/0.6 = 75Gy when 45Gy is prescribed to the 60% isodose).

- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

6.1.4.2 Dose calculations

All dose distributions shall include corrections for tissue heterogeneities.

6.1.4.3 Normalization

The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.

1. **Prescription Isodose Surface Coverage**: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted above.
2. **Target Dose Heterogeneity**: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.
3. **Critical Organ Doses**: Respect all critical organ dose-volume limits as Described by either: The report of AAPM Task Group 101, the NRG BR-001 protocol, or the RTOG 0631 treatment protocol.
4. **High-Dose Spillage:**
    a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.
    b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.
        i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_5000 with the 5000 changing to reflect the prescription dose in cGy.
        ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2 cm (D2cm) from the PTV are given in Table 6.1. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple metastases, this ratio should be evaluated for dose calculated for a single metastasis (i.e., not for composite dose). This is acceptable as long as normal tissue constraints are met.

iii. Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.

iv. These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm results in the inability to meet a conformity ratio of 1.5.

Table 6.1: Guidelines for the Ratio of the 50% Prescription Isodose Volume to the PTV Volume (R50%) and for the Maximum Dose at 2 cm (D2cm) from the PTV

PTV Volume (cc)	Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%	Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	< 57.0
3.8	< 6.5	< 57.0
7.4	< 6.0	< 58.0
13.2	< 5.8	< 58.0
22.0	< 5.5	< 63.0
34.0	< 5.3	< 68.0
50.0	< 5.0	< 77.0
70.0	< 4.8	< 86.0
95.0	< 4.4	< 89.0
126.0	< 4.0	< 91.0
163.0	< 3.7	< 94.0

NOTE: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

NOTE: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be used.

6.2 Subjects with Nodal Metastases (With or Without Bone Metastases)

Subjects with nodal metastases will initially be treated with salvage resection of their nodal disease followed, as needed, by treatment of their bone metastases. In some cases and at the discretion of the investigator (e.g., painful bone lesions), treatment of the bone lesions can take place before nodal resection.

6.2.1 Oligometastasectomy

Subjects with pelvic or para-aortic lymph node metastases will undergo surgical dissection. Treatment will cover the bilateral nodal group identified by molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion), and one level above and one level below any identified nodal region.

Nodal groups from distal to proximal include: 1) Obturator fossa, 2) External iliac, 3) Common iliac, 4) Aortic-below IMA, 5) Aortic-above IMA.

Metastases to superficial inguinal nodes will also be considered for surgical dissection in which cases both a superficial inguinal lymph node dissection and pelvic lymph node (obturator fossa and external iliac nodes) dissection will be performed.

For subjects who were treated with definitive radiotherapy pre-study and have a positive TRUS biopsy at baseline, or less than or equal to a year before study enrollment, salvage prostatectomy will be performed along with the procedure described above (unless salvage radiotherapy is indicated as described in Section 3.2.1).

6.2.2 Radiotherapy to Bone Metastases (As Applicable)

Following recovery from their nodal resection, subjects with bone metastases will be treated with radiotherapy as described above in Section 6.1.

6.2.3 Adjuvant Nodal Radiation Therapy

Within 4 months following completion of salvage therapy (defined as the combination of oligometastasectomy and/or bone radiation) and depending on PSA response as well as previous treatment, patients may receive adjuvant nodal IMRT as highlighted in Figure 2 and as described below.

6.2.3.1 Subjects whose PSA declines to 0 following resection

This will be considered a complete PSA response (PSA CR) and no further treatment will be required. Subjects will move on to the follow-up phase of the study as described in Section 9.3.

6.2.3.2 Subjects whose PSA declines by ≥ 1/3 but remains > 0.2 ng/mL

Following confirmation of the lack of PSA response (2 consecutive PSA values obtained at least 3 weeks apart which have decreased from the pre-resection value by ≥ 1/3 yet remain > 0.2 ng/mL, considered a partial PSA response or PSA PR), subjects will receive IMRT based on their previous treatment history:

Option 1

- Subjects who have undergone prior salvage/adjuvant radiotherapy to the pelvis (with or without treatment of para-aortic lymph nodes)

  OR

- Subjects who have undergone prior prostate radiotherapy with pelvic/nodal irradiation

➢ Ipsilateral involved-field image-guided IMRT with boost to any identifiable lesions.
  - Dose will be 45 Gy in 25 fractions
  - Simultaneous integrated boost to gross target volumes must be ≥ 76 Gy in total equieffective dose (EQD2)

Option 2

- Subjects who have undergone prior prostate radiotherapy without pelvic/nodal irradiation

  OR

- Subjects who have undergone prior prostatectomy without adjuvant/salvage radiotherapy:

➢ Bilateral pelvic image-guided IMRT with boost to any identifiable lesions.
  - Inferior field border functioned immediately above the previously treated field to 50.4 Gy
  - Simultaneous integrated boost to gross target volumes must be ≥ 76 Gy in total equieffective dose (EQD2)

Following adjuvant radiation therapy, subjects will move on to the follow-up phase of the study as described in Section 9.3.

6.2.3.3 Subjects whose PSA declines by < 1/3

This will be considered a treatment failure (PSA response failure), no adjuvant therapy will be given. Subjects will enter the follow-up period until diagnosis of metastatic disease and will not receive any further treatment.

6.3 Concomitant Medications and Therapies

6.3.1 Allowed Therapy

Any medication which is considered necessary for a subject's welfare is permitted and may be given at the discretion of the investigator. Medications for treatment of underlying disease and symptomatic treatment of adverse events are permitted. Exceptions are listed in the section below.

6.3.2 Prohibited Therapy

- Concurrent anti-cancer therapy (chemotherapy, androgen deprivation therapy, immunotherapy, biologic therapy, or tumor embolization) and external beam radiation other than those specified in this protocol.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Major surgery within 30 days prior to enrollment.

6.4 Duration of Therapy

6.4.1 Criteria for the Discontinuation of Treatment ("Off Treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures.

In addition to the drug-specific discontinuation criteria listed in Dose Modification Section, the following will result in treatment discontinuation:

- Adverse events or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment

- The subject or legally authorized representative requests to discontinue the study treatment and/or study procedures
- Salvage treatment failure defined as radiographic progression per PCWG3 criteria OR RECIST 1.1. Patients taken off treatment for treatment failure will continue to be followed for toxicity assessments only every 6 months.
- Failure to initiate adjuvant radiotherapy within 4 months of completion of salvage therapy (oligometastasectomy and/or bone radiotherapy).
- Patient refused further treatment
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the investigator
- Clinical deterioration that, in the opinion of the investigator, increases the risk to the subject

Surgery may be aborted if unforeseen complications arise.

Radiation therapy courses may be shortened in case of RTOG Grade III-IV or persistent (≥ 2 weeks) Grade II toxicities. Continuation of treatment during Grade III toxicities may be allowed if the patient is benefiting as assessed by the treating investigator.

6.4.2 Criteria for the Discontinuation of Study ("Off Study")

Subjects will be taken off study for the following:

- Study terminated by investigator sponsor
- Completed study follow-up period
- Participant or legally authorized representative requests to be fully withdrawn from the study
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Initiation of new anti-cancer therapy
- Subject is lost to follow-up
- Death
- Screen failure

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting. Radiation toxicities will be graded according to the Radiation Therapy Oncology Group (RTOG) toxicity grading system (Appendix A) and surgical complications will graded according to the Clavien-Dindo classification (Appendix B).

7.1 Dose Modifications and Guidelines for Adverse Event Management for Radiotherapy

7.1.1 Dose Modifications

In the event of a clinically significant CTCAE v5 adverse event ≥ grade 3, which is felt to be at least possibly related to radiation therapy, treatment will be discontinued. Treatment related adverse events ≤ grade 2 may result in a reduction in the dose of radiation therapy if the treating physician feels that further radiation would be likely to exacerbate harm to the patient.

Radiation therapy courses may be shortened in case of RTOG Grade III-IV or persistent (≥ 2 weeks) Grade II toxicities. Continuation of treatment during Grade III toxicities may be allowed if the patient is benefiting as assessed by the treating investigator.

7.1.2 Guidelines for Management of Adverse Events

Adverse events related to radiation therapy will be managed at the discretion of the treating radiation oncologist, per institutional standards.

7.2 Supportive Care

All supportive measures consistent with optimal subject care may be given throughout the study.

7.3 Contraception

Subjects who have not had surgical removal of their prostate and have a partner of child bearing potential must agree to use condoms beginning at the signing of the ICF until at least 6 months after the last dose of study treatment. Because of the potential side effect on spermatogenesis associated with radiation, female partners of childbearing potential must agree to use a highly effective contraceptive method during and for 6 months after completing treatment.

8 STUDY CALENDAR

8.1 Arm A

Procedures	Screening[1] (-4 weeks)	On Treatment		Follow-up[2]	
		Salvage Therapy Radiation	Response Assessment[3] (45 days ± 5 days after last day of RT)	Year 1 (Q3M ± 2 weeks)	Year 2-3 (Q3M ± 1 month)
Informed Consent	X				
Medical History[4]	X				
Eligibility Criteria	X				
Clinical Assessments					
Vital Signs, Weight[5]	X		X	X	X
Physical Exam	X		X	X	X
ECOG Performance Status	X		X	X	X
Adverse Event Collection[6]		At each visit			
Concomitant Medication Collection	X	At each visit			
Laboratory Studies					
Hematology[7]	X				
Chemistry[8]	X				
LDH	X				
PSA[9]	X		X	X	X
Disease Assessments					
Molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)[10]	X				
CT Scans				X[11]	X[11]
Nuclear Medicine Bone Scans (if clinically indicated)	X			X[12]	X[12]
TRUS Biopsy[13]	X				
Intervention					
SBRT or Hypofractionated Bone Radiotherapy		X			
Correlative Studies					
Optional Blood[14]	X	X	X[15]		
Optional Archival Tissue[16]	X				
Optional Fresh Tissue[17]	X				
Questionnaires					
PRO and QOL Questionnaires[18]	X		X	X	X
RTOG Toxicity Evaluation[19]			X	X	X

[1] All pre-study/screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment, and imaging assessments which must be completed within 90 days of enrollment.
[2] Follow-up procedures will occur every 3 months for 3 years beginning from the last day of RT unless stated otherwise.
[3] The response assessment visit will take place 45 ± 5 days after completion of salvage therapy (surgery and/or radiation).
[4] To include Charlson Comorbidity Index (See Appendix E)
[5] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature. Height will be captured at screening only.
[6] Adverse events will be assessed after treatment has begun and at each time a patient is seen in clinic or scheduled for correlative sample collections. Adverse events will be collected every three months for one year after treatment discontinuation.
[7] Hematology includes CBC with differential and platelets.
[8] Chemistry includes sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin.
[9] PSA progression must be confirmed according to PCWG3 criteria, after at least 1 week. See Section 10.2.1.
[10] To be performed at screening (within 90 days prior to enrollment).
[11] CT scans of the chest/abdomen/pelvis scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[12] Nuclear medicine bone scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[13] TRUS biopsy must be performed at screening (within 1 year prior to enrollment) only for subjects who have been previously treated with definitive prostate radiotherapy and have disease recurrence in the prostate evidenced by positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).
[14] Optional blood draws may be performed prior to starting salvage therapy, at the next standard of care follow up visit after completion of salvage therapy, and at the time of confirmed PSA progression or radiological progression. See Section 14.3 for details.
[15] After completion of salvage treatment, optional blood will only be collected once at time of confirmed disease progression.
[16] Optional archival tissue may be collected at baseline for all subjects for whom it is available. Archival tissue slides should not be cut until requested from the Central Lab. Lack of archival tissue will not be exclusionary.
[17] Optional fresh tissue may be collected prior to starting salvage therapy during the TRUS biopsy (if performed) and at the time of oligometastasectomy or prostatectomy (if indicated and if available after SOC tissue collection). See Section 14.1 and 14.2 for details.
[18] Quality of life (QOL) questionnaires (FACT-P and Expanded Prostate Cancer Index Composite EPIC-26) will be collected prior to starting salvage therapy, at the Response Assessment Visit, and at each follow-up visits. See Appendices C and D.
[19]To be performed at the Response Assessment Visit and at each follow-up visits See Appendix A.

8.2 Arm B

Procedures	Screening[a] (-4 weeks)	On Treatment			Follow-up[b]	
		Salvage Therapy / Surgery	Response Assessment[c] (45 days ± 5 days after last day of RT)	Adjuvant Radiotherapy[4] (within 4 months after completion of salvage therapy)	Year 1 (Q3M ± 2 weeks)	Year 2-3 (Q3M ± 1 month)
Informed Consent	X					
Medical History[d]	X					
Eligibility Criteria	X					
Clinical Assessments						
Vital Signs, Weight[e]	X		X		X	X
Physical Exam	X		X		X	X
ECOG Performance Status	X		X		X	X
Adverse Event Collection[f]		At each visit				
Concomitant Medication Collection	X	At each visit				
Laboratory Studies						
Hematology[g]	X					
Chemistry[h]	X					
LDH	X					
PSA[i]	X		X		X	X
Disease Assessments						
Molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)[j]	X					
CT Scans					X[k]	X[k]
Nuclear Medicine Bone Scans (if clinically indicated)	X				X[l]	X[l]
TRUS Biopsy[m]	X					
Intervention						
Oligometastasectomy		X				
Salvage Prostatectomy[n]		X				
Nodal IMRT[o]				X		
Correlative Studies						
Optional Blood[p]	X	X	X	X[q]		
Optional Archival Tissue[r]	X					
Optional Fresh Tissue[s]	X					
Questionnaires						
PRO and QOL Questionnaires[t]	X		X		X	X
RTOG Toxicity Evaluation[u]			X		X	X

[a] All pre-study/screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment, and imaging assessments which must be completed within 90 days of enrollment.
[b] Follow-up procedures will occur every 3 months for 3 years beginning from the last day of RT unless stated otherwise.
[c] The response assessment visit will take place 45 ± 5 days after completion of salvage therapy (surgery and/or radiation).
[d] To include Charlson Comorbidity Index (See Appendix E)
[e] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature. Height will be captured at screening only.
[f] Adverse events will be assessed after treatment has begun and at each time a patient is seen in clinic or scheduled for correlative sample collections. Adverse events will be collected every three months for one year after treatment discontinuation.
[g] Hematology includes CBC with differential and platelets.
[h] Chemistry includes sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin.
[i] PSA progression must be confirmed according to PCWG3 criteria, after at least 1 week. See Section 10.2.1.
[j] To be performed at screening (within 90 days prior to enrollment).
[k] CT scans of the chest/abdomen/pelvis scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[l] Nuclear medicine bone scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[m] TRUS biopsy must be performed at screening (within 1 year prior to enrollment) only for subjects who have been previously treated with definitive prostate radiotherapy and have disease recurrence in the prostate evidenced by positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).
[n] Only for subjects who have been previously treated with an incomplete course of definitive prostate radiotherapy and whose baseline TRUS biopsy is positive. Can be replaced with salvage prostatectomy at the discretion of the treating physician.
[o] Only required for subjects with a confirmed lack of PSA response (see section 6.2.3.2) following salvage therapy (see PCWG3 criteria in appendix)
[p] Optional blood draws may be performed prior to starting salvage therapy, at the next standard of care follow up visit after completion of salvage therapy, and at the time of confirmed PSA progression or radiological progression. See Section 14.3 for details.
[q] After completion of salvage treatment, optional blood will only be collected once at time of confirmed disease progression.
[r] Optional archival tissue may be collected at baseline for all subjects for whom it is available. Archival tissue slides should not be cut until requested from the Central Lab. Lack of archival tissue will not be exclusionary.
[s] Optional fresh tissue may be collected prior to starting salvage therapy during the TRUS biopsy (if performed) and at the time of oligometastasectomy or prostatectomy (if indicated and if available after SOC tissue collection). See Section 14.1 and 14.2 for details.
[t] Quality of life (QOL) questionnaires (FACT-P and Expanded Prostate Cancer Index Composite EPIC-26) will be collected prior to starting salvage therapy, at the Response Assessment Visit, and at each follow-up visits. See Appendices C and D.
[u]To be performed at the Response Assessment Visit and at each follow-up visits See Appendix A

8.3 Arm C

Procedures	Screening[i] (-4 weeks)	On Treatment				Follow-up[ii]	
		Salvage Therapy		Response Assessment[iii] (45 days ± 5 days after last day of RT)	Adjuvant Radiotherapy[4] (4 months after completion of salvage therapy)	Year 1 (Q3M ± 2 weeks)	Year 2-3 (Q3M ± 1 month)
		Surgery	Radiation				
Informed Consent	X						
Medical History[iv]	X						
Eligibility Criteria	X						
Clinical Assessments							
Vital Signs, Weight[v]	X			X		X	X
Physical Exam	X			X		X	X
ECOG Performance Status	X			X		X	X
Adverse Event Collection[vi]		At each visit					
Concomitant Medication Collection	X	At each visit					
Laboratory Studies							
Hematology[vii]	X						
Chemistry[viii]	X						
LDH	X						
PSA[ix]	X			X		X	X
Disease Assessments							
Molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)[x]	X						
CT Scans						X[xi]	X[xi]
Nuclear Medicine Bone Scans (if clinically indicated)	X					X[xii]	X[xii]
TRUS Biopsy[xiii]	X						
Intervention							
Oligometastasectomy		X					
Salvage Prostatectomy[xiv]		X					
Salvage Prostate Radiotherapy[xv]			X				

SBRT or Hypofractionated Bone Radiotherapy			**X**				
Nodal IMRT[xvi]					**X**		
Correlative Studies							
Optional Blood[xvii]	**X**	**X**		**X**[xviii]			
Optional Archival Tissue[xix]	**X**						
Optional Fresh Tissue[xx]	**X**	**X**					
Questionnaires							
PRO and QOL Questionnaires[xxi]	**X**			**X**		**X**	**X**
RTOG Toxicity Evaluation[xxii]				**X**		**X**	**X**

[i] All pre-study/screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment, and imaging assessments which must be completed within 90 days of enrollment.
[ii] Follow-up procedures will occur every 3 months for 3 years beginning from the last day of RT unless stated otherwise.
[iii] The response assessment visit will take place 45 ± 5 days after completion of salvage therapy (surgery and/or radiation).
[iv] To include Charlson Comorbidity Index (See Appendix E)
[v] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature. Height will be captured at screening only.
[vi] Adverse events will be assessed after treatment has begun and at each time a patient is seen in clinic or scheduled for correlative sample collections. Adverse events will be collected every three months for one year after treatment discontinuation.
[vii] Hematology includes CBC with differential and platelets.
[viii] Chemistry includes sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, AST, ALT, alkaline phosphatase, total bilirubin.
[ix] PSA progression must be confirmed according to PCWG3 criteria, after at least 1 week. See Section 10.2.1.
[x] To be performed at screening (within 90 days prior to enrollment).
[xi] CT scans of the chest/abdomen/pelvis scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[xii] Nuclear medicine bone scans recommended to be performed 6 months and 1 year after completion of ALL treatments (salvage and adjuvant therapy) (± 2 weeks), and annually for 2 additional years (± 1 month) in patients without evidence of disease progression, otherwise as clinically indicated.
[xiii] TRUS biopsy must be performed at screening (within 1 year prior to enrollment) only for subjects who have been previously treated with definitive prostate radiotherapy and have disease recurrence in the prostate evidenced by positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).
[xiv] Only for subjects who have been previously treated with an incomplete course of definitive prostate radiotherapy and whose baseline TRUS biopsy is positive. Can be replaced with salvage prostatectomy at the discretion of the treating physician.

[xv] Only for subjects who have been previously treated with an incomplete course of definitive prostate radiotherapy and whose baseline TRUS biopsy is positive. Can be replaced with salvage prostatectomy at the discretion of the treating physician.
[xvi] Only required for subjects with a confirmed lack of PSA response (see section 6.2.3.2) following salvage therapy (see PCWG3 criteria in appendix)
[xvii] Optional blood draws may be performed prior to starting salvage therapy, at the next standard of care follow up visit after completion of salvage therapy, and at the time of confirmed PSA progression or radiological progression. See Section 14.3 for details.
[xviii] After completion of salvage treatment, optional blood will only be collected once at time of confirmed disease progression.
[xix] Optional archival tissue may be collected at baseline for all subjects for whom it is available. Archival tissue slides should not be cut until requested from the Central Lab. Lack of archival tissue will not be exclusionary.
[xx] Optional fresh tissue may be collected prior to starting salvage therapy during the TRUS biopsy (if performed) and at the time of oligometastasectomy or prostatectomy (if indicated and if available after SOC tissue collection). See Section 14.1 and 14.2 for details.
[xxi] Quality of life (QOL) questionnaires (FACT-P and Expanded Prostate Cancer Index Composite EPIC-26) will be collected prior to starting salvage therapy, at the Response Assessment Visit, and at each follow-up visits. See Appendices C and D.
[xxii]To be performed at the Response Assessment Visit and at each follow-up visits. See Appendix A

9 STUDY PROCEDURES

9.1 Screening Evaluations

- Informed Consent
- Review of medical history (including Charlson Comorbidity Index), baseline symptoms and medications
- Physical exam with ECOG Performance Status
- Vital signs with weight and height
- Laboratory assessments:
  - CBC with differential
  - CMP to include Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen
  - Lactate Dehydrogenase (LDH)
  - PSA
- Molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)
- TRUS biopsy (and fresh tissue collection for correlative studies) only for patients who have received prior definitive prostate radiotherapy and have disease recurrence in the prostate evidenced by positive molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion).
- Optional Blood and archival tissue for correlative studies. Archival tissue slides should not be cut until requested from the Central Lab (see Section 14 for details)
- Questionnaires (FACT-P and Expanded Prostate Cancer Index Composite (EPIC-26))
- Review of eligibility

- Technetium bone scan (optional)

9.2 On Treatment Evaluations

- Safety (as defined in Section 15.5, using CTCAE v5.0 and the Clavien-Dindo Classification) as well as concomitant medication and treatments must be assessed every time a patient is seen in clinic once treatment has begun. Optional blood and tissue for correlative studies may also be collected.

9.2.1 Salvage Therapy

- Oligometastasectomy for subjects with nodal metastases (Arms B or C, without or with bone metastases).
  - Subjects who have received a full course of definitive prostate radiotherapy and whose TRUS biopsy is positive at screening (or less than or equal to one year before enrollment) can undergo simultaneous salvage prostatectomy, or, if their initial dose of radiation was felt to be insufficient, complete a course of salvage prostate radiotherapy.
  - Some optional tissue resected during the procedures (oligometastasectomy and/or prostatectomy) may be collected for correlative research purposes if available after SOC tissue collection.
- SBRT (or hypofractionated RT) for subjects with bone metastases only (Arm A).
- For subjects with both nodal and bone metastases, surgery will take place on Day 1 and SBRT will follow once the subject has recovered from surgery. (Arm C)

9.2.2 Prior to Response Assessment

- Optional blood collection for correlative studies (see Section 14 for details) may be collected at the first standard of care follow-up visit after completing all salvage therapy. This can be collected any time after completion of salvage therapy but prior to the response assessment visit.

9.2.3 Response Evaluation & Adjuvant Treatment

<u>To be completed 45 days after completion of salvage therapy</u>:

- Physical exam with ECOG
- Vital signs with weight
- Evaluation of PSA response (with confirmation in case of PSA progression)
- Questionnaires (FACT-P and EPIC-26)
- RTOG toxicity evaluation (only required for patients who underwent radiotherapy)
- Optional blood for correlative studies (see Section 14 for details)

9.2.4 Adjuvant Therapy

<u>To be initiated within 4 months in case of confirmed non-complete PSA response</u>:

- Adjuvant radiotherapy course

- The exact treatment modality will be a function of previous treatments received by the subject. See Schema and Section 6.2.3 for details)

9.3 Follow-up Evaluations

The follow-up calendar will be based on the date of completion of all study treatments (salvage and adjuvant therapy as needed)

To be completed every 3 months for 3 years after completion of treatment (salvage ± adjuvant):

- Physical exam with ECOG
- Vital signs with weight
- Evaluation of PSA response (with confirmation in case of PSA progression)
- Safety assessments
- Concomitant medication and treatments
- Questionnaires (FACT-P and EPIC-26)
- RTOG toxicity evaluation (only required for patients who underwent radiotherapy)
- Optional blood for correlative studies
- Adverse event collection for long term safety, mandatory

To be completed every 6 months for 1 year after completion of treatment (salvage ± adjuvant) then yearly for years 2-3:

- CT scans and technetium bone scan (optional)

10 CRITERIA FOR EVALUATION OF ENDPOINTS

10.1 Primary Endpoint: PSA Response Rate

The PSA response rate is defined according to the PCWG3 criteria as the proportion of patients achieving a PSA decline ≥ 50% at 6 months after completion of treatment (salvage ± adjuvant).

10.2 Secondary Endpoints

10.2.1 PSA Progression Free Survival

PSA measurements will take place every 3 months after completion of treatment (salvage ± adjuvant) for a total of 3 years.

The PSA PFS is defined as the time elapsed between completion of treatment (salvage ± adjuvant) and the first occurrence of confirmed PSA progression as assessed according to the PCWG3 criteria: a ≥ 25% relative increase of ≥ 2 ng/mL above the baseline or nadir, which is confirmed by a second consecutive value recorded a minimum of 1 week later.

10.3 Time to Recurrence

CT scans and optional bone scans will take place every 6 months for the first year after completion of per-protocol directed therapy then annually thereafter for a total of 3 years.

The disease-free survival is defined as the time elapsed between study enrollment and first occurrence of confirmed radiographic disease progression as assessed according to the PCWG3 criteria (soft tissue by CT or MRI scans according to RECIST v1.1, bone metastasis by bone scan according to the PCWG3 criteria).

Soft tissue recurrence is defined by RECIST 1.1 as a ≥ 20% increase and absolute ≥ 5 mm increase in the sum of diameters of target lesions (at most 5 lesions and 2 lesions per organ) OR the appearance of one or more new unequivocal lesions OR the unequivocal progression of existing non-target lesions. Soft tissue progression does not require confirmatory scans.

Bone progression is defined PCWG3 criteria as the appearance at any restaging scan of ≥ 2 new lesions which persist or increase at the confirmatory scan (to be performed ≥ 6 weeks later) OR, if ≥ 2 new lesions are observed at the first restaging scan, the appearance of ≥ 2 additional new lesions at the confirmatory scan (to be performed ≥ 6 weeks later).

10.3.1 Time to ADT Therapy

Time to initiation of ADT is defined as the time elapsed between study enrollment and initiation of ADT for metastatic prostate cancer.

10.3.2 Rate of Undetectable PSA

The rate of undetectable PSA is defined as the proportion of patients ever treated with prostatectomy whose PSA remains ≤ 0.2 ng/mL after 6 and 12 months following completion of treatment (salvage ± adjuvant).

10.3.3 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs include blood pressure, respiratory rate, pulse rate and temperature.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

11 STATISTICAL CONSIDERATIONS

11.1 Sample size determination

The planned sample size is N = 20 evaluable subjects. The primary outcome variable of reduction in PSA ≥ 50% at 6 months will be analyzed descriptively via 90% and 95% exact binomial confidence intervals. No hypothesis test will be performed on the primary outcome

variables. The sample size is justified by the width of the 95% confidence intervals. We anticipate that the PSA 50% response rate at 6 months will be 30% based on the results published by Siriwardana, as their PSA response at 6 weeks and 12 months was 43% and 23% respectively. However, the definition used here is somewhat different than the definition in that clinical study. If the observed PSA 50% response rate is 30% (6/20), the 95% exact binomial confidence interval (Clopper-Pearson) will be 12% to 54 %. With 20 evaluable subjects the maximum width of a 95% exact binomial confidence interval is 46% (27% to 73%) and occurs when the observed response rate is 50% (10/20).

11.2 Population for analyses

11.2.1 Evaluable for safety

Patients receiving any amount of treatment or any invasive procedure/surgery will be evaluable for safety.

11.2.2 Evaluable for response

Patients are only evaluable if they complete their designated intervention:

- Patients on Arm A must complete at least 70% of planned radiation treatments;
- Patients on Arm B must complete surgery;
- Patients on Arm C must complete surgery and at least 70% of planned radiation treatments.

Patients that are unevaluable for response will be replaced.

11.3 Statistical Hypotheses and Analyses

This study is establishing baseline data for patients who have no defined standard of care therapy. All study data will use descriptive statistics and will be exploratory only.

Since this study is not using any hormonal therapy, we expect that using PSA analysis will be accurate and provide an early readout regarding the potential efficacy and clinical utility of this approach.

Primary Objective

The primary endpoint is the proportion of subjects with a reduction in PSA ≥ 50% 6 months after completion of all treatment (salvage and adjuvant therapy). The observed proportion and a 95% exact binomial confidence interval with be reported for the entire group of evaluable patients (Arms A, B and C together) as well as for each cohort separately.

Secondary Objectives

1. 95% exact confidence intervals will be reported for the observed proportions with reductions in PSA ≥ 50% 12 months after and ≥ 90% 6 and 12 months after completion of all treatment (salvage and adjuvant therapy). This will be done for the entire group of evaluable patients (Arms A, B and C together) as well as for each Arm separately.
2. The proportion of subjects without PSA progression (defined using Prostate Cancer Working Group 3 Criteria PCWG3), will be evaluated every 3 months for 3 years after completion of all treatment (salvage and adjuvant therapy and analyzed using Kaplan-

Meier methodology. This will be done for the entire group of evaluable patients (Arms A, B and C together) as well as for each Arm separately.

3. The time from study enrollment until the date of confirmed radiographic disease progression as defined by RECIST 1.1 and PCWG3 will be analyzed using Kaplan-Meier methods. This will be done for the entire group of evaluable patients (Arms A, B and C together) as well as for each Arm separately.
4. The time from study enrollment to the initiation of ADT will be analyzed using Kaplan-Meier methods. This will be done for the entire group of evaluable patients (Arms A, B and C together) as well as for each Arm separately.
5. The proportion of patients with a PSA ≤ 0.2 ng/mL will be evaluated 6 and 12 months after completion of all treatment (salvage and adjuvant therapy) in the subset of patients who have previously undergone prostatectomy. This will be done for the entire group of evaluable patients (Arms A, B and C together) as well as for each Arm separately.
6. The number and proportions of subjects with AEs and SAEs as defined by CTCAE version 5.0 will be tabulated both for the entire safety population and also stratified by Arm.
7. 95% confidence intervals will be reported for summary scales of the quality of life (QOL) questionnaires (FACT-P and Expanded Prostate Cancer Index Composite EPIC-26) measured at screening, response assessment visit, and each follow up visit. This will be done for the entire group of evaluable patients (Arms A, B and C combined) and also stratified by Arm. Normal approximations will be used for computation of confidence intervals.

Exploratory Objective

Genomic alterations or abnormal protein expression that correlate with radiation resistance or predilection for early metastasis and worse overall prognosis will be tabulated.

12 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the subject has signed a consent form.

Subjects must meet all of the eligibility requirements listed in Section 5 prior to registration.

Subjects must be registered before receiving any study treatment and must begin treatment as soon as possible after registration.

To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each subject that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be

source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the subject source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant subject information required for planned manuscripts.

14 CORRELATIVE STUDIES

Optional Tissue and blood may be collected at the time points notated in the Study Calendar. Samples will be used to identify biomarkers of response or resistance to the prescribed treatments. For those patients with both archival and fresh tissue, comparison between the pre- and post-treatment tissue will be performed as applicable. All correlative tissue collection is optional and not mandatory.

Testing may include, but is not limited to:

- Genomic alterations such as deletions, mutations or amplifications;
- Transcriptome RNA assessments;
- Immunohistochemistry testing for protein expression.
- Cytokine/chemokines
- Circulating free DNA (cfDNA)
- Circulating tumor cells (CTC) detection, enumeration, and characterization

Specimen collection and processing instructions can be found in the lab manual.

14.1 Screening

Archival tissue may be requested for all subjects. Archival tissue slides should not be cut until requested from the Central Lab. Lack of archival tissue will not be exclusionary.

For subjects previously treated with definitive radiotherapy for prostate cancer with molecular imaging (e.g., fluciclovine PET/CT or PSMA PET/CT scan or other per PI discretion)-positive findings at baseline (or less than or equal to one year before study enrollment), a TRUS biopsy may be performed as per institutional standard. Up to 6 cores from the TRUS biopsy may be obtained for correlative studies.

14.2 Oligometastasectomy and/or Prostatectomy

For subjects undergoing oligometastasectomy and/or salvage prostatectomy, 2 sections of tissue may be collected from the prostate and each of the lymph node dissection if available after SOC tissue collection.

14.3 Blood Correlative Studies

Up to 20 mL of blood may be collected at each time point. Instructions for processing and shipping will be detailed in the lab manual.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version.

15.2 Human Subjects Protections

15.2.1 Participation of Children

Subjects must be at least 18 years of age to participate.

15.2.2 Participation of Subjects Unable To Give Consent

Subjects must be able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

15.3 Institutional Review

This study will be approved by the Institutional Review Board of the University of Utah.

15.4 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of subjects enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This study is classified as moderate risk per the NCI-approved DSM plan.

Each moderate risk study may be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). SAEs occurring in subjects treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for subjects on treatment and within 45 days of their last treatment on a quarterly basis.

Each moderate-risk study will be assigned a dedicated research compliance officer who will monitor the trial. Moderate-risk trials will be monitored by RCO personnel after the first subject is enrolled and every six months thereafter during active enrollment. The RCO

monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. Moderate-risk trials will be formally reviewed by the DSMC after the first subject is enrolled and then semi-annually thereafter.

An initial audit of moderate-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of moderate-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

15.5 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

In addition, the Clavien-Dindo classification will be used to evaluate surgical complications.

15.5.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study treatment even if the event is not considered to be related to study treatment. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study salvage treatment are only considered adverse events if they worsen after starting study salvage treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin with the first study salvage treatment (surgery OR radiotherapy for bone metastases) and end 1 year after the last study treatment (including palliative radiotherapy if applicable) or until a new cancer treatment is initiated.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5 (grade 1-5)
2. Its relationship to the study treatments(s) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study salvage treatment dosage adjusted/temporarily interrupted; study salvage treatment permanently discontinued due to this adverse

event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study salvage treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study salvage treatment, the interventions required to treat it, and the outcome.

All adverse events will be immediately recorded in the subject research chart.

15.5.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires subject hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study salvage treatment
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the subject's general condition

Collection of serious adverse events will begin at the time of salvage treatment and end 1 year after the last dose of study treatment or until a new cancer treatment is initiated, whichever happens the soonest.

Any death from any cause while a subject is receiving treatment on this protocol or up to 365 days after the last dose of protocol treatment will be reported. Any death which occurs up to 3 years after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the subject research chart.

15.6 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, and the IRB according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of event.

DSMC Notifications:

An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.

The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

FDA Notifications:

Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational treatment
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.

All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.

The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.

The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.

The Regulatory Coordinator will submit the report as an amendment to the IND application.

All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

15.7 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 45 days of completing treatment or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

15.8 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

15.9 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.10 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

15.11 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.12 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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Appendix A – Radiation Therapy Oncology Group (RTOG) toxicity grading system

Patient ID: _____ Date: _____ Time point: _____

0	1	2	3	4	5
No symptoms	Minor symptoms requiring no treatment	Symptoms responding to simple out patient management, lifestyle (performance status) not affected	Distressing symptoms altering the patient's lifestyle (performance status) Hospitalization for diagnosis or minor surgical intervention (such as urethral dilation) may be required	Major surgical intervention (such as laparotomy colostomy, cystectomy) or prolonged hospitalization required	Fatal complications

Physician signature: _____ Date: _____

Appendix B – Clavien-Dindo Classification of Surgical Complication

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Appendix C – FACT-P Questionnaire

Patient ID: _____ Date: _____ Time point: _____

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

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P Questionnaire *(page 2/3)*

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

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P Questionnaire *(page 3/3)*

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Subject signature: _____ Date: _____

Appendix D – Expanded Prostate Cancer Index Composite (EPIC-26)

Patient ID: _____ Date: _____ Time point: _____

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers <u>per day</u> did you usually use to control leakage **during the last 4 weeks**?

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number) 27/
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

   (Circle one number on each line)

	No <u>Problem</u>	Very Small <u>Problem</u>	Small <u>Problem</u>	Moderate <u>Problem</u>	Big <u>Problem</u>	
a. Dripping or leaking urine	0	1	2	3	4	28/
b. Pain or burning on urination.....	0	1	2	3	4	29/
c. Bleeding with urination.....	0	1	2	3	4	30/
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4	31/
e. Need to urinate frequently during the day.....	0	1	2	3	4	33/

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number) 34/
   Moderate problem..... 4
   Big problem..... 5

Appendix D – Expanded Prostate Cancer Index Composite (EPIC-26) *(page 2/3)*

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Losing control of your stools.....	0	1	2	3	4	52/
d. Bloody stools	0	1	2	3	4	53/
e. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your ability to have an erection?.....	1	2	3	4	5	57/
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5	58/

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number) 59/
Firm enough for intercourse..... 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

Appendix D – Expanded Prostate Cancer Index Composite (EPIC-26) *(page 3/3)*

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Feeling depressed	0	1	2	3	4	77/
d. Lack of energy	0	1	2	3	4	78/
e. Change in body weight	0	1	2	3	4	79/

Subject signature: _____ Date: _____

Appendix E – Charlson Comorbidity Index

	Yes = 1	**No = 0**
Myocardial infarction *History of definite or probable MI (EKG changes and/or enzyme changes)*		
Congestive Heart Failure *Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents*		
Peripheral vascular disease *Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)*		
Cardiovascular Accident (CVA) or Transient Ischemic Attack (TIA)		
Dementia *Chronic cognitive deficit*		
Chronic Obstructive Pulmonary Disease		
Connective tissue disease		
Peptic ulcer disease *Any history of treatment for ulcer disease or history of ulcer bleeding*		
	Yes = 2	**No = 0**
Hemiplegia		
Moderate to severe CKD *Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)*		
Leukemia		
Lymphoma		
	Yes = 6	**No = 0**
AIDS		
	Score	
Liver disease • 0: None • +1: Mild = chronic hepatitis (or cirrhosis without portal hypertension) • +3: Moderate = cirrhosis and portal hypertension but no variceal bleeding history		

• +3: Severe = cirrhosis and portal hypertension with variceal bleeding history	
Diabetes mellitus • 0: None or diet-controlled • +1: Uncomplicated • +2: End-organ damage	
Solid tumor • 0: None • +2: Localized • +6: Metastatic	
Age • 0: < 50 years • +1: 50-59 years • +2: 60-69 years • +3: 70-79 years • +4: ≥ 80 years	

Total Score _____

Appendix F- Prostate Cancer Clinical Trials Working Group 3 (PCWG3)

The PCWG3 was created to more accurately assess bone lesions and to describe PSA based progression. PCWG3 rules were designed to be used in conjunction with radionuclide (^{90m}Tc) bone scintigraphy and therefore should be used for all bone response assessments. Only bone lesions seen on bone scans will be followed for assessment of response.

Bone Assessments

Baseline Assessment
All bone lesions may be recorded as non-target lesions only and the number of lesions should be noted.

Response Assessment
While on treatment, follow-up scans should be assessed for progressive disease (PD), progressive disease unconfirmed (P Du), no progressive disease (Non-PD), no evidence of disease (NED), or non-evaluable (NE).

Table 1: Bone response assessment categories

Bone Response	Definition
PD	2 new lesions, not flare, persistent
P Du	2 new lesions, but confirmation is required by the second scan. The temporary marker of PD should be updated to PD or non-PD upon subsequent scans. If P Du is determined on the last scan, sponsor should update to PD upon analysis.
Non-PD	At least 1 bone lesion present, but not enough to trigger PD.
NE	Status of bone lesions cannot be determined.
NED	No lesions are seen on bone scan (either none at baseline or all have resolved).

Rules of Progressive Disease

- 2+2 Rule: If 2 new lesions appear on the first scan after the initiation of treatment, the response is classified as P Du and another scan is performed ≥ 6 weeks.
    - If the next scans show at least 2 new bone lesions in addition to those seen in the prior scan, the prior scan is to be considered confirmed PD.
    - If the next scan does not show at least 2 additional new bone lesions the lesions seen on the prior scan are considered pre-existing lesions. The bone response on the prior scan is updated to non-PD and new lesions seen on the first scan are ignored.
- Once outside of the flare window (the first 12 weeks of treatment) the appearance of new lesions must be confirmed with a second scan ≥ 6 weeks after the first scan.
    - If ≥ 2 new lesions appear on a scan the scan will be classified as P Du until a second scan confirms lesion persistence.

        - If lesions are persistent on the second scan, the prior response will be updated to PD.
        - If the lesions disappeared on the second scan, the prior response is updated to non-PD.
    - If 1 new bone lesion is seen on one scan classifying the scan as non-PD, but the following scan shows an additional new lesion (2 new lesions total between subsequent scans) the second scan will be classified as PD.
    - Diffuse skeletal tumor involvement may result in a superscan. In this case, distinguishing between individual new bone lesions may be impossible. If a superscan occurs after baseline, the response will be considered PD and no further confirmation scans are required.

PSA Progression
PSA should be monitored at the beginning of every cycle. Any rise in PSA during the first 12 weeks of treatment should be monitored but should not be deemed evidence of progression. Record the percent change from baseline at 12 weeks. After a decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (i.e., a confirmed rising trend).

Nodal and Soft Tissue Progression
Nodal and soft tissue documentation, tracking, and determination of progression will follow RECIST 1.1.