ID: UMCC 2017.163

FOcal Radiation for Oligometastatic Castration-rEsistant Prostate Cancer (FORCE)

NCT03556904

UMCC 2017.163

FOcal Radiation for oligometastatic Castration-rEsistant prostate cancer (FORCE): A phase II randomized trial

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Initial version: 06/07/2018, Version 4.0
Amended: 07/25/2018, Version 5.0
01/16/2019, Version 6.0
05/15/2020, Version 7.0
11/11/2020, Version 8.0
02/05/2021, Version 9.0

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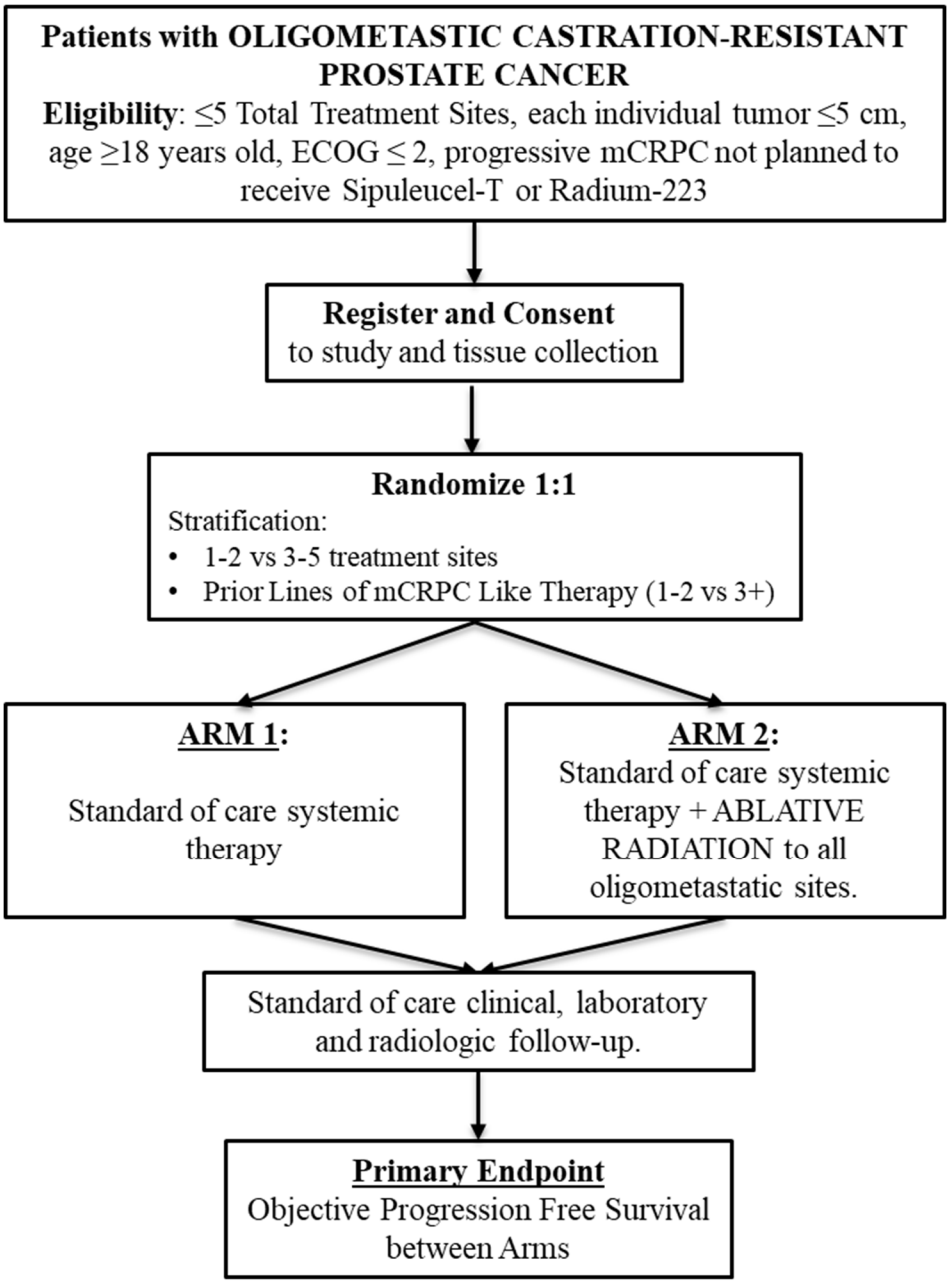
ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AR	Androgen Receptor
AR-V7	Androgen Receptor Splice Variant 7
AST	Aspartate Aminotransferase
ASTRO	American Society for Radiation Oncology
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRPC	Castration Castration-Resistant Prostate Cancer
CT	Computed Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTSU	Clinical Trials Support Unit
CTV	Clinical Target Volume
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ERG	ETS-Related Gene
FU	Follow-up
GTV	Gross Tumor Volume
Gy	Gray
HER2	Human Epidermal Growth Factor Receptor 2
HRPP	Human Research Protections Program
IRB	Institutional Review Board
IV (or iv)	Intravenously
LDH	Lactate Dehydrogenase
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PTV	Planning Target Volume

PR	Partial Response
PRC	Protocol Review Committee
PSMA	Prostate Specific Membrane Antigen
RP	Radical Prostatectomy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Severe Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	FOcal Radiation for oligometastatic Castration-rEsistant prostate cancer (FORCE): A phase II randomized trial
Phase	Phase II
Methodology	Randomized, non-blinded
Study Duration	6 years
Study Center(s)	University of Michigan, Ann Arbor Veterans Healthcare System
Objectives	To determine whether the addition of radiotherapy to standard of care systemic therapy improves objective progression-free survival, compared to systemic therapy alone.
Number of Subjects	36
Inclusion Criteria	1. Biopsy-proven adenocarcinoma of the prostate 2. Discontinue any prior systemic therapies (excluding GnRH agonist/antagonists) without PSA withdrawal effects if using first generation anti-androgens - Patients who recently started systemic therapy for mCRPC are eligible to enroll if new therapy was started ≤ 14 days prior to consent (see section 3.1.2 for discussion) 3. Progressive metastatic CRPC (progressive disease by PSA or radiographic progression defined in the same modality with testosterone <50 ng/dL) 4. Oligometastatic prostate cancer defined as at least 1 and ≤5 treatment sites measured by conventional imaging with CT, bone scan or ^{68}GA-PSMA PET/CT scans. Each metastatic tumor must be ≤5 cm in maximum cross section. If the patient's prostate itself has not been treated (radiation or surgery), it will be treated and count as 1 treatment site. Any site treated with radiation in the preceding 4 weeks from registration are counted as a trial relevant treatment site toward the 5 or less criteria. The patient must have at least 1 non-irradiated site remaining though. 5. Medically fit for radiation and medical therapy 6. Age ≥18 years old 7. ECOG ≤2 8. No prior invasive malignancy in the past 3 years. Exceptions include non- melanomatous skin cancer or in situ cancers of bladder or head and neck which are permissible. 9. Subjects must freely sign informed consent to enroll in the study. 10. Subjects must use contraception up to 90 days after last drug dose.
Exclusion Criteria	1. Planned systemic therapy with Radium-223 dichloride or sipuleucel-T 2. Tumor requiring emergent radiation in view of provider 3. Life expectancy <3 months 4. Presence of known parenchymal brain metastasis 5. Uncontrolled intercurrent illness 6. Inability to undergo radiotherapy, systemic therapy, CTs or bone scans. 7. Biopsy proven pure small cell or neuroendocrine prostate cancer

Study Product(s), Dose, Route, Regimen	External beam radiotherapy. Dose will depend on lesion location and size, but eqd2(2) ranges of dose fractionation typically is between 30 Gy in 10 fractions and 50 Gy in 5 fractions.
Duration of Administration	Radiotherapy will be delivered based on lesion location. Radiation will start within 8 weeks of randomization and complete by day 84.
Reference Therapy	Both study arms will receive a systemic therapy for mCRPC.
Statistical Methodology	Using prior studies, the disease control rate at 6 months for systemic therapy alone is approximately 50% when averaged over the various lines of therapy for prostate cancer. Assuming the experimental arm increases the median duration of disease control to 15 months, 16 patients per arm provides 80% power assuming a 1-sided alpha of 0.1. This results in 32 total patients for randomization. To accommodate a 10% loss to follow-up rate, accrual will continue to a total study sample of 36.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Cancer is the second leading cause of death in the United States, chiefly from an inability to control metastatic disease. Similarly, prostate cancer is the second leading cause of death in men with cancer, accounting for nearly 30,000 deaths per year. Hormonal based therapies are the mainstay of treatment for men with recurrent and metastatic prostate cancer. Systemic therapy alone is not curative for these patients, and treatment resistance develops, termed castration-resistant prostate cancer (CRPC). One primary theory of progression is the development of resistance within a metastatic site that then seeds other sites to form new metastases. The uncontrolled progression of disease to a castration-resistant state is uniformly fatal for men with prostate cancer with a limited number of durable systemic treatment options.

Metastatic CRPC (mCRPC) is a disease spectrum that ranges from a limited burden of disease, termed oligometastatic mCRPC, to diffuse mCRPC. The presence of an oligometastatic state was originally proposed by Hellman who suggested oligometastatic patients would benefit from effective local therapy in addition to systemic therapy [1]. In agreement with this hypothesis, focal treatments for metastatic patients with renal cell carcinoma, non-small cell lung cancer, and small cell lung cancer have shown benefit in select circumstances [2-5]. The most prevalent example though is colorectal cancer, where chemotherapy combined with surgery (or other ablative therapies) is the standard of care for isolated hepatic or pulmonary metastases with 5-year survival rates of ~45% [6, 7].

Given the success of treating oligometastatic cancer with a combination of local and systemic therapy in other diseases, this approach may prove beneficial in prostate cancer for multiple reasons. First, patients with mCRPC often receive radiotherapy for the palliation of pain, or systemic radiotherapy with Radium-223 dichloride, which has demonstrated both pain palliation and also improved overall survival in a randomized phase III trial [8, 9]. Hence, the use of radiotherapy in these patients is routine and toxicities well-known. Secondly, resistance to common treatments suppressing the androgen pathway (e.g. enzalutamide or abiraterone) is inevitable and patients with a higher volume of metastatic disease have shorter responses [10]. By depleting the viable mCRPC tumor volume, the stochastic nature of resistance may be exploited and sensitivity to therapy prolonged.

1.2 Study Agent(s) Background and Associated Known Toxicities

The study agent in this trial is the use of external beam radiotherapy. External beam radiotherapy is a standard treatment approach for the palliation of symptomatic metastatic sites in most cancers, and is commonly used in metastatic prostate cancer. National guidelines from both NCCN and ASTRO support the use of palliative radiotherapy for bone metastasis in prostate cancer. Over a dozen trials have been conducted and numerous meta-analyses have demonstrated the safety and tolerability of palliative radiotherapy. Most of these trials included a 30 Gy in 10 fractions arm.

Radiotherapy can be delivered in many ways and the dose, fractionation, and location of the tumor all dictate the potential side effects. On this trial, radiotherapy can be delivered

in either moderate hypofractionation (examples could be 30 Gy in 10 fractions or 50 Gy in 20 fractions) or stereotactic body radiotherapy (SBRT). Ablative doses should be used, but as radiotherapy is a rapidly evolving field, flexibility in dose/schedule is offered to the delivering radiation oncologist. SBRT reduces the overall time of radiation treatment and offers a greater potential for cell kill compared to standard fractionation schemas of 1.8-3.0 Gy/Day. This technique allows for rapid delivery of tumoricidal doses of radiotherapy and provides ablative treatment to metastases not amenable to surgical intervention. Single studies have demonstrated that SBRT for ablative treatment of non-symptomatic, solitary metastases is technically feasible, with acceptable toxicity and high rates of in-field cancer control [11]. SBRT or ablative RT approaches have been studied in four Radiation Therapy Oncology Group (RTOG) clinical trials: RTOG 0236, 0813/0915, 0438 and 0613 for solitary lesions in lung, liver and spinal metastases respectively. These trials have provided a framework for successful delivery and quality assurance of complex radiotherapy in the cooperative group setting. Regardless of the dose/fraction implemented, well established international dose constraints will be followed to ensure predictable and low rates of side effects from external beam radiotherapy.

Table 1: A partial list from QUANTEC as to the dose constraints for well-established toxicity metrics and estimated rates of toxicity and toxicity endpoint.

Critical Structure	Volume	Dose/Volume	Max Dose	Toxicity Rate	Toxicity Endpoint
Spinal cord			50 Gy	0.2%	Myelopathy
Larynx	Mean	<44 Gy		<20%	Edema
Lung	Mean	7 Gy		5%	Symptomatic pneumonitis
Esophagus	V35	<50%		<30%	Grade 2+ esophagitis
Liver	Mean	<30-32 Gy		<5%	RILD (in normal liver function)
Liver	Mean	<28 Gy		<5%	RILD (in Child-Pugh A or HCC)
Kidney, bilateral	Mean	<15-18 Gy		<5%	Clinical dysfunction
Stomach	D100	<45 Gy		<7%	Ulceration
Small bowel (individual loops)	V15	<120 cc		<10%	Grade 3+ toxicity
Rectum	V75	<15%		<10%	Grade 3+ toxicity
Bladder			<65	<6%	Grade 3+ toxicity

1.3 Other Agents

All patients will be treated with standard of care systemic therapy, most commonly with a second generation androgen pathway inhibitor (e.g. enzalutamide or abiraterone), although other standard agents (e.g. docetaxel, cabazitaxel) are allowed. These have known safety profiles from large phase III and IV trials. Radium-223 dichloride is not allowed due to overlapping radiotoxicity. Concurrent sipuleucel-T is not allowed as there is no safety data with concurrent radiation. The use of palliative radiotherapy (for pain or urinary obstructive symptoms) is commonly delivered concurrently with some of these systemic agents (e.g. abiraterone or enzalutamide). Radiotherapy, in combination with

many forms of hormonal based treatments, have been studied in over 15 randomized clinical trials and have not shown any enhanced toxicity from the combination, and delivery together is part of the standard of care for localized, recurrent, and node positive prostate cancer. If other agents (e.g. docetaxel, cabazitaxel) are used, the dose of drug may be adjusted or held during radiation (or radiation adjusted) at the discretion of the medical and radiation oncologists. This is done occasionally in standard practice for patient's receiving docetaxel in mCRPC and requiring emergent radiation.

1.4 Rationale

There are several studies supporting the use of ablative therapy in the setting of oligometastatic disease. Salama et al. performed a prospective study examining the results of radiation dose escalation in patients with one to five sites of metastatic disease with any histology, all with a life expectancy of >3 months [11]. The starting dose was 8 Gy x 3 fractions, and the protocol-specified maximum dose was 20 Gy x 3 fractions. In an interim analysis of 29 patients with 56 metastatic lesions, the authors found a response rate of 59%, and 21% of patients did not have progression following treatment [12]. In those patients that did progress, this progression was amenable to further local treatment in 48% of patients. In the final analysis, the authors confirmed that patients with 1 to 5 metastases could be safely treated to multiple body sites and could thus benefit from hypofractionated, "ablative" radiation doses in this setting.

Recently, a trial in non-small cell lung cancer randomized patients who responded to initial systemic chemotherapy and had ≤ 3 lesions to continue chemotherapy or have oligometastatic radiation, then resume chemotherapy (although only 1 of 20 patients continued non-molecularly targeted systemic treatment). They found a dramatic improvement in PFS; the median progression-free survival in the local consolidative therapy group was 11.9 months (90% CI 5.7–20.9) versus 3.9 months (2.3–6.6) in the maintenance chemotherapy group (hazard ratio 0.35 [90% CI 0.18–0.66], log-rank p=0.0054) [4].

Given that the systemic treatment in these patients is not curable, and that a greater burden of disease correlates to a more rapid development of treatment resistance, it is rational to provide radiotherapy to destroy macroscopic clonogens to decrease the probability of resistance formation and reduce the capacity for existing metastases to seed to form new metastasis. If these theories hold true, this would manifest in a prolongation in progression-free survival on first/early line systemic therapy. Oligometastatic treatment for prostate cancer in the earlier hormone-sensitive clinical space was just published [13]. This trial showed that oligometastatic radiation (3 or fewer sites as determined by choline PET), delayed the start of ADT (dictated by symptomatic progression, new radiographic sites or local progression of treated sites) from 13 months (80% CI, 12-17 months) to 21 months (80% CI, 14-29 months) with a hazard ratio of 0.6 (80% CI, 0.4-0.9, log-rank P = 0.11). Effects on survival or subsequent treatment response are unknown.

1.5 Correlative Studies

1.5.1 Circulating Analytes (CTC and ctDNA)

Extensive work has been done on circulating analytes in mCRPC. They have explored both molecular insights into disease and have the potential to inform treatment decisions (although none are in routine practice). CTC's

were shown to recapitulate ERG rearrangements seen in metastatic biopsies, simulate tumor heterogeneity by maintaining variable AR copy number gains, and also imply a role for HER2 and EGFR in bone metastases [14, 15]. The predictive capacity for ctDNA or CTC is reflected by tumor AR-V7 transcript presence (enzalutamide resistance), and CTC expression of EGFR or CTC count (docetaxel resistance) [16-19]. This work has never been explored uniquely in the oligometastatic state (which may have different molecular features then widely metastatic patients), nor with radiation in mCRPC.

As discussed above, the hypothesis that ablating the bulk of disease may eliminate resistant clones which can be queried through circulating analytes. If radiation (while we know oral therapy does not) converts a patient with positive circulating signatures for androgen pathway resistance (AR-V7 positive or AR copy number/mRNA amplification) into a negative one, and the trial's outcome is positive, that theory would be reinforced. Also, if the number of CTCs are eliminated, and development of new metastatic sites prolonged, this would support the hypothesis that metastases may seed other metastases, and radioablation delays it.

1.5.2 Radiographic Correlative Study

If any patients have undergone previous nuclear imaging prior to enrolment those images will be collected and may be used for enrolment (if obtained within mCRPC state) and therapy designation. As there is no data supporting the superiority of these newer radiologic techniques in regards to treatment decision designation, patients without molecular imaging will not undergo them for treatment designation. Patients in Arm 2 who have not undergone prior molecular imaging will be offered (patients may accept or refuse this extra study) nuclear imaging towards prostate specific membrane antigen (PSMA). This ^{68}Ga-PSMA PET/CT analysis will be done before starting radiation therapy as a research scan. The results will be sequestered and not disclosed to provider until after that patient has completed the therapeutic study (so does not play a role in eligibility or treatment planning). This will allow the evaluation of whether patients who received radiation progress in lesions that were undetectable by standard imaging, but present on ^{68}Ga-PSMA PET/CT. It will create a knowledge foundation to support or refute whether a ^{68}Ga-PSMA PET/CT guided study oligometastatic mCRPC should be pursued exclusively.

2.0 STUDY OBJECTIVES

The purpose of this study is to assess if the addition of radiotherapy to systemic treatment for men with oligometastatic CRPC improves outcomes over systemic therapy alone.

2.1 Primary Objectives

To determine whether the addition of radiotherapy to standard of care early systemic therapy improves objective progression-free survival, compared to systemic therapy alone.

2.2 Secondary Objectives

2.2.1 To compare PSA PFS between arms.

2.2.2 To compare radiographic PFS between arms.

2.2.3 To compare PSA response rates (≥90% and ≥50% decline from baseline) and rate of undetectable PSA (≤ 0.2 ng/mL) between arms.

2.2.4 To compare measurable disease response rate between arms.

2.2.5 To compare non-irradiated distant metastasis free survival between arms.

2.2.6 To compare patient-reported outcomes based on NCCN-FACT FPSI-17.

2.2.7 To compare overall survival between arms

2.2.8 To compare prostate cancer specific survival between arms

2.2.9 To describe the adverse events associated with radiotherapy when administered in combination with systemic therapy.

2.3 Exploratory Objectives

2.3.1 Circulating analytes (circulating tumor DNA (ctDNA) and circulating tumor cells (CTC)) will be evaluated alone and in combination with standard laboratory measures for biologic insights and predictive/prognostic capacities.

2.3.2 If patients were on continuous treatment with second generation androgen inhibitors (e.g. abiraterone or enzalutamide) in the metastatic hormone-sensitive phase, the ctDNA and CTC cells will be investigated before and after radiation and at ~3 months post-radiotherapy to measure eradication and/or relapse of resistance signatures (AR-V7 presence, androgen receptor mRNA copy number).

2.3.3 ^{68}Ga-PSMA PET/CT will be offered to patients in ARM 2 (unless already done in routine care) to evaluate if areas of subsequent relapse were present on the molecular study compared to standard imaging.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Subjects must have biopsy-confirmed adenocarcinoma of the prostate (pure small cell or pure neuroendocrine prostate cancer are not allowed).

3.1.2 Subjects must discontinue any prior systemic therapies (excluding GnRH agonist/antagonists) without PSA withdrawal effects if using first generation anti-androgens. LHRH analogues (agonist or antagonist) must be continued if they have not undergone orchiectomy.

- Patients who recently started systemic therapy for mCRPC are eligible to enroll if new therapy was started ≤ 14 days to consent date. No washout or new PSA rise is required. Labs and/or imaging prior to starting the new therapy are used for disease progression criteria (see 3.1.3). Scans may be obtained after consent if PSA progression was deemed cause of mCRPC designation (within 28 days).

3.1.3 Subjects must have progressive metastatic castration-resistant prostate cancer based on <u>at least one</u> of the following criteria while having castrate levels (<50 ng/dL) of testosterone:

A) PSA progression defined as a 25% increase over baseline value with an increase in the absolute value of at least 2.0 ng/mL that is confirmed by another PSA level with a minimum of a 1-week interval.
B) Progression of bidimensionally measurable soft tissue or nodal metastasis by CT scan or MRI based on RECIST v1.1 criteria (see section 7.0 for definitions). Note, new lesions diagnosed by ^{68}Ga-PSMA PET/CT alone are insufficient for enrolment in absence of PSA progression.
C) Progression of bone disease on bone scan as defined by two new lesions arising

3.1.4 Subjects must have oligometastatic prostate cancer, defined as between 1 and ≤5 treatment sites that can be treated within a radiotherapy treatment field. All sites must be ≤5 cm in maximum cross section. If the patient's prostate itself has not been treated (radiation or surgery), it will be treated and count as 1 treatment site.

Any site treated within 4 weeks of registration counts as a trial relevant treatment site toward the 5 or less criteria. The patient must have at least 1 non-irradiated site remaining though. Treatment sites are designated by ^{68}Ga-PSMA PET/CT or CT/MRI/NM bone imaging, whatever is available.

The radiation oncologist should designate the number or treatment sites.

-Examples: 2 adjacent vertebral bodies would count as 1 treatment site, multiple contiguous external iliac LNs would count as 1 treatment site, and

untreated/intact prostate would count as 1 site. Also, a single symptomatic lesion that required treatment before enrollment would count as 1 site.

3.1.5 Subjects must be medically fit to undergo radiotherapy and systemic therapy as determined by the treating physician.

3.1.6 Age ≥ 18

3.1.7 ECOG ≤ 2.

3.1.8 No prior invasive malignancy in the past 3-years. Exceptions include non-melanomatous skin cancer and in situ cancers of the bladder or head and neck are permissible.

3.1.9 Subjects must freely sign informed consent to enroll in the study.

3.1.10 Subjects must use contraception up to 90 days after last drug dose.

3.2 Exclusion Criteria

3.2.1 Planned systemic therapy with Radium-223 dichloride or sipuleucel-T

3.2.2 Tumor requiring emergent radiation in view of provider

3.2.3 Life expectancy estimate of <3 months

3.2.4 Presence of known parenchymal brain metastasis

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements. This will be determined by one of the study PIs if in question.

3.2.6 Inability to undergo radiotherapy, systemic treatment, CTs or bone scans

3.2.7 Biopsy proven pure small cell or neuroendocrine prostate cancer

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

4.1 Screening, Enrollment and Randomization

- Patients who are identified by medical oncology and are candidates for a systemic therapy will be discussed with radiation oncology. Radiation oncology will review the imaging and confirm radiographic candidacy.
- If a patient is identified by radiation oncology as a candidate, they will refer to medical oncology. Medical oncology will meet (virtual or in person) and evaluate the patient for systemic candidacy.
- Only when both radiation oncology (at minimum by radiography assessment) and medical oncology (in person or virtual visit) have deemed the patient a candidate for their respective therapies, will the patient be registered.

Patient registration and randomization for this trial will be centrally managed by the Coordinating Center of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent redacted source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator (MSC) of the Coordinating Center will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the MSC to the requesting site registrar to confirm patient registration and randomization and to provide the study identification number and randomization number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the MSC, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in a Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

All patients who are treatment candidates will be stratified by the number of metastatic sites (1-2 or 3-5 treatment sites) and prior lines of mCRPC like therapy (1-2 or 3+ lines of therapy). Note, a patient who receives a second-generation anti-androgen (e.g. enzalutamide, apalutamide, darolutamide) or abiraterone or docetaxel in mHSPC or non-metastatic CRPC and progresses while ON the treatment, it counts as one line of mCRPC therapy. Next generation mCRPC directed therapies also count as lines of therapy. They will be enrolled 1:1 between Arms 1 and 2. Randomization will be performed at the University of Michigan.

5.0 TREATMENT PLAN

5.1 Radiotherapy Treatment Dosage and Administration

Arm 1 patients should begin systemic treatment within 3 weeks of randomization. Arm 2 patients should start systemic therapy within 3 weeks of randomization and receive radiotherapy within 8 weeks of randomization. For Arm 2, systemic therapy (if not safe to do concurrently with radiation) may be held at provider's discretion until after radiation completes if radiation begins within 3 weeks of randomization. Sites of disease are designated by prior ^{68}Ga-PSMA PET/CT and CT/MRI/NM bone scan- whatever are available.

Radiotherapy will typically be delivered to a total EQD2 (alpha/beta 2) that ranges between conventional 30 Gy in 10 fractions, to SBRT with 50 Gy in 5 fractions. Use of 3D conformal radiotherapy (3DCRT), Intensity-Modulated Radiation Therapy (IMRT), or SBRT will be used as needed to meet dose constraints for tumor coverage and organs

at risk. Some flexibility is given to radiation oncology to allow newer techniques to be accounted for as long as goal remains ablative radiation dosing.

Simulation, Treatment planning, Set-up and Localization

Computed Tomography (CT) Simulation and Treatment Planning
CT will be the primary image platform for simulation and treatment planning. The simulation should be performed in the supine treatment position if possible. Axial cuts of ≤3 mm will be acquired to encompass the relevant tumor sites and organs at risk. Oral and IV contrast are allowed but not required.

Patient Set-up
Patients will be positioned usually supine depending on the target sites in a comfortable posture. The minimum immobilization apparatus will be a pillow or knee fix under the knees and the feet taped or rubber-banded together. More complex immobilization devices are allowed, as per the discretion of the treating physician.

Localization
Daily MV, KV or cone-beam CT can be used as required for appropriate localization.

Treatment Planning/Target Volumes

1. The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.
2. Gross tumor volume (GTV) delineation will be performed based on the CT simulation and any relevant additional diagnostic imaging.
3. The Clinical Target Volume (CTV) is defined by the physician as the GTV plus any necessary margin to account for microscopic disease. This margin will typically be between 0-5 mm depending on the location of the tumor. If lymph nodes are involved, the entire nodal chain should be included in the CTV.
4. The planning target volume (PTV) will be defined as the CTV plus a 3-5 mm margin based on immobilization and image guidance utilized.

Dosimetry

1. Axial or non-axial beam arrangements may be utilized.
2. The prescription isodose line must encompass at least 95% of the PTV with a maximal differential between the prescription isodose line and the maximum dose to the PTV of 20%. Thus, PTV coverage will be within the range of +19% to -1%. Maximal dose to the PTV is defined as to a single point or voxel within the PTV. In addition, <15% of the PTV or < 10 cc (whichever is smaller) should be treated to >115% of the prescription dose.

Critical Structures

Critical Organ Dose-Volume Limits
1. The normal tissue volume to be contoured will include any organ at risk that is within 2 cm superior or inferior to each PTV. Structures that have mean volume constraints must be contoured in their entirety.
2. The normal tissues will be contoured and considered as solid organs.

Dose limits should be followed by either SBRT criteria or 3DCRT/IMRT criteria as listed below:

DVH Criteria

Table 2: SBRT dose constraints in 1, 3, or 5 fractions:

Normal Structures & Goals:	**Measure**	**Limit (5 Fx)**	**Limit (3 Fx)**	**Limit (1 Fx)***
SpinalCord	D0.1cc	<28 Gy	<22 Gy	<14 Gy
Brainstem	D0.1cc	<20 Gy	<18 Gy	<14 Gy
BrachialPlex	D0.1cc	<30 Gy	<24 Gy	<17.5 Gy
Esophagus	D0.1cc D5cc	<35 Gy <19 Gy	<27 Gy <16.5Gy	<16 Gy <12 Gy
Heart	D0.1cc	<38 Gy	<30 Gy	<22 Gy
Great Ves	D0.1cc V47Gy	<52.5Gy <10 cc	<30 Gy N/A	<18 Gy
Trachea	D0.1cc V32Gy	<52.5Gy <5 cc	<30 Gy N/A	<20 Gy
Chestwall / Rib	V30Gy	<70 cc	<30 cc	N/A
Liver	NTCP >700 cc	<15% N/A	N/A <15 Gy	N/A <9.6 Gy
Stomach	D0.5cc	<30 Gy	<22.5Gy	<16 Gy
Kidneys	D35.0%	<15 Gy	<12 Gy	<8 Gy
Kidney_R	D67.0%	<15 Gy	<12 Gy	<8 Gy
Kidney_L	D67.0%	<15 Gy	<12 Gy	<8 Gy
Duodenum	D0.1cc	<30 Gy	<24 Gy	<10 Gy
Bowel_Small	D0.1cc	<30 Gy	<24 Gy	<11 Gy
Colon	D0.5cc	<32 Gy	<24 Gy	<16 Gy
Rectum	D0.1cc D2cc	<39.3Gy <37 Gy	<28 Gy N/A	<18 Gy N/A
CaudaEquina	D0.1cc	<32 Gy	<24 Gy	<16 Gy
SacralPlex	D0.1cc	<32 Gy	<24 Gy	<18 Gy

*Other organs at risk that investigators identify not provider should contact the study PI to determine the appropriate dose constraint based on the most recent national clinical trials.

3DCRT and IMRT constraints:
Should follow QUANTEC for estimated risks of grade 3 toxicity of ≤10%.

5.3 Systemic Therapy

Current systemic therapies include second generation androgen pathway agents (enzalutamide or abiraterone) and chemotherapies (docetaxel, cabazitaxel), all which are FDA approved in mCRPC. Radium-223 dichloride and sipuleucel-T are not allowed (see section 1.3 for discussion). The choice of agent will be up to the treating medical oncologist and is not the study intervention. Treatment holds or adjustments to accommodate radiation are up to the treating oncologist (see section 5.1 for timing). Otherwise, normal use, dose reductions and discontinuation of therapy for toxicity will be executed as described in the package inserts and provider discretion. If there is any

question on appropriate holds or discontinuation, please contact the Principal Investigator(s).

5.4 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.5). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 3. Non-Hematological Toxicity Dose Reductions for Radiation

Event	**Action**
Name of Toxicity	
Grade 1-2	No action.
Grade 3	Grade 3 toxicity during radiotherapy, consider holding radiotherapy until reduced to grade 2 toxicity, or reduce dose of radiotherapy as deemed appropriate by the PI.
Grade 4	If any grade 4 event attributed during radiotherapy then radiotherapy should be discontinued.

5.5 Concomitant Medications/Treatments

Only systemic therapy with radiation is allowed concurrently at discretion of providers in arm 2.

5.6 Duration of Radiotherapy

In the absence of treatment delays due to adverse events, radiotherapy treatment may continue unless one of the following criteria apply:

- Intercurrent illness that prevents further administration of radiotherapy
- Unacceptable adverse event(s); grade 4.
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.7 Off Radiotherapy Treatment Criteria

Patients will be removed from radiotherapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending radiotherapy and the date the patient was removed from radiotherapy. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.8 Duration of Systemic Therapy

In the absence of treatment toxicities, systemic therapy may continue unless one of the following criteria apply:

- Disease progression as defined in Section 7
- Intercurrent illness that prevents further administration of systemic treatment
- Unacceptable adverse event(s); grade 4.
- Patient voluntarily withdraws from treatment **OR**

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Note, patient whose therapy is held for toxicity and no new therapy is started, will remain on study if they have not clinically or radiographically progressed. If a new therapy is started, they will be defined as having progressed.

5.9 Off Systemic Therapy Criteria

Patients will be removed from systemic therapy treatment when any of the criteria listed in Section 5.8 apply. Document in the source the reason for ending systemic therapy treatment and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.10 Duration of Follow-Up

After treatment discontinuation, patients should return for an End of Treatment Visit 30 days (±14 days) after last treatment dose.

If off treatment for reasons other than progression, patient should be followed for disease status every 6 months (± 31 days) via telephone, virtual visit or office visit documentation for up to 2.5 years from treatment discontinuation or until death, objective progression, or initiation of another prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors), whichever comes first.

If off treatment for progression, patients should be followed for survival and initiation of any other prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors) every 6 months (± 31 days) via telephone or office visit documentation for up to 2.5 years from treatment discontinuation or until death, whichever comes first.

5.11 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be removed at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.11.1 Patient withdraws consent (termination of treatment and/or follow-up);

5.11.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.11.3 Patient is unable to comply with protocol requirements;

5.11.4 Treating physician judges continuation on the study would not be in the patients best interest;

5.11.5 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.11.6 Lost to Follow-up. If a research subject cannot be located to document survival after a period of 2.5 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the 2.5 years must be documented.

5.11.7 Termination of the study by The University of Michigan;

5.11.8 Patient completes protocol treatment and follow-up criteria.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

- All screening procedures must be performed within 28 days prior to registration unless otherwise stated

6.2 Study Calendar:

Note: a cycle is **42** days.

	Screening (Day -28 to registration)	Day 1 of Cycle 1 and 2	Day 1 of Cycle 3[l] and 4	Day 1s of Cycle 5+[a]	End of Treatment[m]	Follow-up[g]
Informed Consent, HIPAA Form	X					
Medical/Surgical History[h], Demographics, Histologic Confirmation	X					
Randomization	X					
PE[i], Vitals[i], Weight, Height[i]	X	X	X	X	X	
Performance Status (Appendix A)	X	X	X	X	X	
Adverse Event, Toxicity Evaluations		X	X	X	X	
Medication Review including Systemic Therapy	X	X	X	X	X	
Radiotherapy Administration		X[d]				
Systemic Therapy		X	X	X		
Radiologic evaluations and measurements[b]	X	Radiologic tests are performed every 12 weeks (± 7 days) for the first 2 years. Radiologic tests then are performed every 6 months (± 2 weeks) while in the treatment phase of the study.			X[e]	
Serum Chemistry, LDH[c]	X	X	X	X	X	
CBC with Differential	X	X	X	X	X	
PSA	X	X	X	X	X	
Testosterone	X					
PRO[j]	X	Within 30 days (±7 days) after radiation completion and every 3 months (± 4 weeks) from randomization for the first 24 months.			X	
Circulating Correlatives[f]		X	X		X	
Radiologic Correlatives[k]	X					
Follow-up						X

a. Patients will have a clinical and laboratory evaluation every 42 days (±14 days) for 24 weeks. At the discretion of the oncologist, it can be extended to a maximum of 12 weeks (±14 days) at week 25. All patients remaining on study at 18 months (±14 days), should be evaluated at that time. Starting at

Cycle 3 of treatment, remote monitoring virtual clinic visits will be allowed at the discretion of the provider, but will not be allowed for the End of Treatment visit.

b. Radiographic evaluation will include radionuclide bone scan, CT or MRI of abdomen and pelvis, and CT, CXR or MRI of the chest as appropriate. All disease sites must be assessed using the same methodology as performed at baseline. At the discretion of the investigator, additional radiological evaluations may be performed at an unscheduled time point. A patient must have a valid standard radiographic evaluation within screening window, even if disease is visible only on ^{68}Ga-PSMA PET/CT scan.
c. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT (AST), SGPT (ALT), sodium
d. Radiotherapy must be delivered during Cycles 1 and 2.
e. If radiographic evaluations were completed within 30 days of End of Treatment, they do not need to be repeated.
f. Circulating correlatives are collected if available at the local lab at Cycle 1 Day 1 (-14 days), Cycle 3 Day 1 (±14 days), Cycle 4 Day 1 (±14 days) and EOT (±14 days). Any missed time points due to lab closure will be recorded as protocol deviations.
g. Follow-up: If off treatment <u>for reasons other than progression</u>, patient should be followed for disease status every 6 months (± 31 days) via telephone or office visit documentation for up to 2.5 years from treatment discontinuation or until death, objective progression, or initiation of another prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors), whichever comes first. If off treatment <u>for progression</u>, patients should be followed for survival and initiation of any other prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors) every 6 months (± 31 days) via telephone or office visit documentation for up to 2.5 years from treatment discontinuation or until death, whichever comes first.
h. Complete medical and surgical history (especially in regards to prior treatments for prostate cancer), history of infections, history of bowel/bladder problems, history of seizures
i. Vitals: should include temperature, pulse, respirations, blood pressure, height (baseline only), and weight. Vitals. PE, Weight will NOT be required when a remote monitoring virtual clinic visit is determined at the discretion of the provider.
j. PRO: Patient reported outcome measure: NCCN-FACT FPSI-17 (Appendix B)
k. For patients in Arm 2 and undergoing the correlative ^{68}Ga-PSMA PET/CT scan, this needs to be completed before the start of radiation. It may be done after systemic therapy begins though, but within 4 weeks of treatment start date.
l. Starting at Cycle 3 of treatment, remote monitoring virtual clinic visits are allowed at the discretion of the provider.
m. Virtual remote monitoring clinic visit will not be allowed for the End of Treatment visit. This must be completed in-person.

7.0 MEASUREMENT OF EFFECT

7.1 Response Definitions and Evaluations

Response and progression definitions contain various parts of the criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee and the Prostate Cancer Working Group 3 [20, 21]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity: all patients will be evaluable for toxicity from the time of their first treatment with radiation or oral drug.

Evaluable for progression-free survival: only patients who begin treatment will be evaluable for progression-free survival

Evaluable for measurable disease response: Only those patients with measurable disease present at entry (as defined below), have received at least 7 weeks of therapy from randomization, and have had their disease radiographically re-evaluated at 7 weeks or beyond will be considered evaluable for measurable disease response. Patients who are removed from study prior to 7 weeks or prior to any follow-up imaging (regardless of response) are censored.

Non-measurable, non-target disease response: Patients who have non-measurable/non-target disease will be evaluated for non-measurable/non-target disease resolution, stability or unequivocal progression.

7.1.2 Disease Parameters

All disease parameters noted below are based on CT, MRI or bone scan. Patients that enter the trial with a negative CT, MRI and bone scan, but positive ^{68}Ga-PSMA PET/CT, will be deemed as having no "radiographic disease" at baseline. If a patient has a combination of ^{68}Ga-PSMA PET/CT and CT/MRI/bone scan disease, only the lesions noted in CT/MRI/bone scan are utilized per below.

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). A previously untreated, intact prostate primary is NOT considered measurable.

Note: Measurable tumor lesions on the baseline scan that are irradiated should be measured for measurable disease response/progression. In Arm 2, all target lesions on the baseline scan should be irradiated.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

For existing pathologic adenopathy (≥15 mm), progression is defined per RECIST v1.1.

Note: All measurable malignant lymph nodes on the baseline scan should be irradiated in Arm 2 and followed for response/progression. Whether indeterminate lymph nodes (between 10 and <15 mm in short axis) on the baseline scan represent prostate cancer is up to the radiation oncologist's discretion and may be discussed with medical oncology. Any irradiated site, should be documented and followed.

Previously normal (<10 mm) lymph nodes must have grown to ≥ 10 mm in the short axis to be considered to have progressed. Nodes that have progressed between 10 and <15 mm are pathologic, subject to clinical discretion, and non-measurable.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions should be identified as target lesions and recorded and measured at baseline. All target lesions should receive radiation in Arm 2. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All non-measurable lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurement of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up. In Arm 2, all non-target lesions at baseline should receive ablative therapy.

7.1.3 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

^{68}Ga-PSMA PET/CT. This modality does NOT define lesions as target, non-target or measurable. See section 7.1.2. A patient with disease ONLY visible by ^{68}Ga-PSMA PET/CT is designated as having no target or measurable lesions at baseline for measurement purposes. Sites of disease presence are noted in the record, but visualization on CT, MRI, bone scan (when previously negative) are deemed new lesions- thus potential progression.

7.1.4 Methods of Evaluation of Bone disease

Bone disease will be evaluated using radionuclide bone scan.

7.2 Response Criteria

7.2.1 Response Evaluation of Target/Measurable Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduced in short axis to <10 mm. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions. The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new target lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.2.2 Response Evaluation of Non-Measurable/Non-Target Lesions

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

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

Progressive Disease (PD): Appearance of one or more new non-measurable lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed with a Principal Investigator.

If there are no non-target lesion, it is described as none.

7.2.3 Response Evaluation of Radionuclide Bone Scans for Bone Metastases

The subjectivity in interpreting serial changes in a radionuclide bone scan is well recognized. Thus, the primary outcome will be whether the scan is stable or improved, vs. progression. Changes in intensity will not be used as an outcome measure. Bone scans can be altered from non-oncologic changes as well. If there is evidence of trauma or infection by history of exam to explain a bone scan finding, that site shall not be counted as a new lesion at the provider's discretion and documented appropriately. Bone metastases without accompanying measurable soft tissue component should only use radionuclide bone scans to classify lesion.

Stable Bone Disease: A stable classification requires that no more than 1 new lesion appears compared to the screening bone scan.

Progression (Non-Response): Appearance of **two or more** new skeletal lesions compared to the screening bone scan. *An increase in the size or intensity of known skeletal lesions will not be considered progression.*

7.2.4 Response Evaluation Based on Post-Therapy PSA Changes

These definitions are intended to characterize the PSA changes on study for the purpose of reporting of results.

Complete Response (CR): Undetectable PSA (≤0.2 ng/ml) that is confirmed by another PSA level at no less than 4 weeks interval.

Partial Response 50 (PR^{50}): Decrease in PSA value by ≥ 50% that is confirmed by another PSA level at no less than 4 weeks interval.

Partial Response 90 (PR^{90}): Decrease in PSA value by ≥ 90% that is confirmed by another PSA level at no less than 4 weeks interval.

Stabilization (SD): Patients who do not meet the criteria for PR^{50} or PD for at least 90 days on study will be considered stable.

Progression (PD): 25% increase over baseline or nadir whichever is lower and an increase in the absolute value of PSA level by 2 ng/ml that is confirmed by another PSA level at no less than 4 weeks interval.

7.2.5 Response Evaluation Based on Disease Symptoms (Including Pain)

Stable/Improved: Absence of progression of symptoms.

Progression: Progression by disease symptoms is based on the interpretation of the provider that a patient is having progressive disease-related symptoms (e.g. urinary obstruction, pain). Death is considered a progressive symptom.

Progression by pain due to prostate cancer requires evidence of disease at the site of pain and one or more of the following palliative interventions:

- Opioid Therapy: Intravenous, intramuscular or subcutaneous opioid therapy administered as a single dose; oral or transdermal opioid analgesic use administered for 10 out of 14 consecutive days
- Radionuclide Therapy
- Radiation Therapy

7.2.6 Outcomes Based on Response Evaluations

A patient's designated response at any one time is a combination of the assessment of target lesions, non-target lesions, bone lesions and disease symptoms.

Table 4: For Patient's with Measurable Disease (i.e. Target Disease)

Target Lesions	Non-Target Lesions	New Non-Bone Lesion(s) or Bone Metastases Progression*	Disease Symptom Progression**	Overall Response
CR	CR	No	No	CR
CR	Non-CR/ Non-PD	No	No	PR
CR	None	No	No	PR
PR	Any	No	No	PR
SD	Non-CR/ Non-PD, None	No	No	SD
PD	Any	Yes or No	Yes or No	PD
Any	PD***	Yes or No	Yes or No	PD
Any	Any	Yes	Yes or No	PD
Any	Any	Yes or No	Yes	PD

* See RECIST 1.1 manuscript for details on what is evidence of a new non-bone lesion and see section 7.1.5.3 for definition of bone metastases progression.
** See section 7.1.5.5 for definition of disease symptom progression.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Table 5: For Patients with Non-Measurable Disease/Non-Target Disease, Bone Metastases Only or exclusive ^{68}Ga-PSMA PET/CT disease at baseline.

Non-Target Lesions	New Non-Bone Lesion(s) or Bone Metastases Progression*	Disease Symptom Progression**	Overall Response
CR	No	No	CR
Non-CR, Non-PD	No	No	Non-CR, Non-PD***
None	No	No	Stable Bone Disease
Unequivocal PD	Yes or No	No	PD
Any	Yes	No	PD
Any	Yes or No	Yes	PD

* See RECIST 1.1 manuscript for details on what is evidence of a new non-bone lesion and see section 7.1.5.3 for definition of bone metastases progression.
** See section 7.1.5.5 for definition of disease symptom progression.
*** Non-CR/Non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is misleading.

7.2.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. Patients with initiation of a different prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors) are deemed to have progressed. Patients lost-to-follow-up before progression will be censored at the date of last scan respectively.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Patients with initiation of a different prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors) are deemed to have progressed. Patients lost-to-follow-up before progression will be censored at the date of last scan respectively.
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7.2.8 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to date of progression or death (whichever is first). Patients with initiation of other prostate directed therapies (excluding bisphosphonates or RANKL inhibitors) are progressors. Those lost-to-follow-up before progression will be censored at the last scan date respectively.

7.2.9 Prostate Cancer Specific Survival

Prostate Cancer Specific Survival is defined as the duration of time from start of treatment to death from prostate cancer. Patients who have not died will be censored at the last known alive date and patients who died of other causes will be censored at the date of death.

7.2.10 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to death. Patients who have not died will be censored at the last known alive date.

7.2.11 Non-irradiated Distant Metastases Free Survival

Non-irradiated metastases free survival is defined as the duration of time from start of treatment to the date of progressive disease of a new target lesion (as defined in section 7.2.1, progressive disease description), a new non-measurable/non-target lesion (as defined in section 7.2.2) or emergence of 2 or more new skeletal lesions on a bone scan (as defined in section 7.2.3). Patients lost-to-follow-up before progression will be censored at last known scan date respectively.

7.3 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE EVENTS

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment through 30 days after the last dose of study treatment or study intervention. Any serious adverse event that occurs more than 30 days after the last study treatment or intervention and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment or intervention for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration or intervention is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.2, occurring from the initial study treatment administration or intervention through 30 days following the last dose of the study treatment or study intervention must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment or intervention is also considered an adverse event.

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.2.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- It relates to a common side effect associated with radiotherapy to the region of interest. All grade 3 or higher expected side effects should be discussed with the study PI and Dr. Daniel Spratt to determine if it is an expected radiotherapy associated AE.
- It is described in the approved Package Insert for the systemic therapy being given.

8.2.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it occurs outside of the radiotherapy treatment field and both is not reported in the published medical literature to be associated with radiotherapy and is not in the patient's systemic therapy Package Insert.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment/intervention.
Probable – The AE *is likely related* to the study treatment/intervention.
Possible – The AE *may be related* to the study treatment/intervention.
Unlikely – The AE *is doubtfully related* to the study treatment/intervention.
Unrelated – The AE *is clearly NOT related* to the study treatment/intervention.

8.4 Serious Adverse Event Reporting Guidelines

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study treatment, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 48 hours of first awareness of the event. Events should be reported using the Coordinating Center's SAE form as available in the study database. A copy of the SAE form should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 48 hours of the site's knowledge of the event.

Follow-up information should also be reported within 48 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current local institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study intervention.

8.5 Routine Reporting of Non-Serious AE

All other adverse events (e.g. not meeting criteria for SAE), such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.6 Reporting of Unanticipated Problems

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB per local institutional standards.

9.0 CORRELATIVE PROTOCOLS

For the biologic rationale of all correlative studies, see section 1.5.

9.1 Laboratory Correlative Studies

Refer to Section 6.2 for correlative study collection time points and the Lab Manual for collection and processing details.

9.1.1 Laboratory Protocol for CTC Analysis

For the CTC-based evaluation, blood collected will be processed using an immunomagnetic bead enrichment approach. Briefly, whole blood is incubated with anti-EpCAM microbeads (Dynabeads, Life Technologies) and washed multiple times. Lysis buffer is then added and the supernatant containing pooled cell lysateis collected for expression analysis. Oligo(dT)25 mRNA Dynabeads (Life Technologies) are used for mRNA capture, and cDNA prepared using the Superscript III One-Step RT-PCR system (Life Technologies). Following pre-amplification and library establishment, multiplex qPCR will be performed for a total of 48 prostate cancer-related genes, including AR, AR-V7, Schlap1, PSMA, PSA, cytokerratins (8, 18, 19), and CD45 as well as actin and tubulin as internal controls. Quantitative RT-PCR will be performed using SYBR Green Mastermix (Life Technologies) on the ABI 7900 real time PCR machine. Gene expression signatures associated with response/resistance to therapy will be identified.

9.1.2 Laboratory Protocol for CTC Analysis

Circulating tumor DNA (ctDNA) will be isolated from plasma using the QIAamp Circulating Nucleic Acid Kit. Low quantities of genomic ctDNA from each sample will be subjected to whole genome amplification using the ThruPlex-FD Prep Kit for Ion Torrent, and all samples will be sequenced on an Ion Proton sequencer with 10-20 samples loaded per chip (to at least 0.05x depth). Whole-genome copy number profiles will be generated using a read-binning, circular binary segmentation method optimized for low-input DNA to yield genome wide copy number profiles. Additionally, we will profile ctDNA using the DNA component of the Oncomine Comprehensive Assay (OCP), to assess for prioritized mutations, insertions/deletions and copy number alterations in ~135 recurrently altered oncogenes and tumor suppressors. Sequencing to >1000x will be performed.

9.1.3 Excess Sample Banking

With optional patient permission, excess blood specimens may be stored long-term for potential use not outlined in the protocol. This is to answer questions not identified *a priori* or future hypothesis. These are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

9.2 Radiographic Correlative Study

Any patient who is undergoing ^{68}Ga-PSMA PET/CT (see section 1.5.2), will have the scan done at the University of Michigan Rogel Cancer Center. The data will be labeled with the subject's coded study number and study date. The results will not be made available to any of the providers until that patient has completed the study.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a phase II randomized clinical trial in men with oligometastatic castration-resistant prostate cancer to determine if the addition of radiotherapy to standard of care systemic therapy improves duration of response compared to systemic therapy alone within any line of mCRPC. Patients will be stratified and then randomized 1:1 to

systemic treatment (Arm 1) versus systemic treatment plus radiotherapy (Arm 2). The primary endpoint is objective duration of response.

10.2 Statistical Analysis

10.2.1 Analysis of the Primary Endpoint

The primary endpoint of the study is duration of response to therapy. As this study includes all lines of systemic therapy within mCRPC, progression on therapy is related to prior lines which is stratified for. Progression is defined a worsened pain or new sites of disease on imaging. The time to changing therapy will be collected for use in survival analysis. The primary analysis will use Kaplan-Meier methods to estimate the median duration of response and associated 90% confidence intervals and compare groups using a stratified log-rank test. We will also include 12 months and 18 months proportions with 90% confidence intervals by treatment arm. Patients who are lost to follow-up prior to changing therapies will be censored at the time they are lost-to-follow-up.

10.2.2 Analysis of Secondary Endpoints

See section 7 for endpoint descriptions

- *Objective PFS, PSA PFS, Radiographic PFS, OS, PCSS, Non-irradiated DMFS*
  Each time-to-event endpoint will be presented with a Kaplan-Meier figure and corresponding estimates, including median, 12 months', and 24 months' proportions with 95% confidence intervals will be reported by treatment arm. Stratified log-rank tests will be used for testing.

- *PSA Response Rate*
  The PSA response rate (CR, PR^{50}, PR^{90}) will be calculated and proportion of responders by arm reported with the corresponding 95% exact binomial confidence intervals. A Cochran-Mantel-Haenszel statistic will be used for testing treatment differences.

- *Measurable Disease Response Rate*
  The measurable disease response rate (CR + PR) will be calculated for patients evaluable for measurable disease response. The proportion of responders by arm will be reported with corresponding 95% exact binomial confidence intervals. A Cochran-Mantel-Haenszel statistic will be used for testing treatment differences.

- *Patient-reported outcomes*
  Patient-reported outcomes (PROs) will be described using means or medians with associated measures of variability by treatment arm at each time collected. A cumulative logistic model or general linear model with repeated measures throughout treatment with a primary test of the treatment arm fixed effect will be used to assess PROs.

- *Adverse events*
  AE summaries will be reported by treatment arm and organized by body system, frequency of occurrence, intensity (e.g. severity, grade), and causality or attribution. Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modification or delays, and duration of therapy.

10.2.3 Analysis of Correlative Objectives

Many correlative biomarkers are described in the correlative objectives. A general statistical analysis plan is described here to provide a skeleton for the known correlatives planned:

Continuous correlative biomarkers will be described using means and standard deviations or medians with percentiles. Categorical covariates will be described with counts and frequencies. These descriptors will be provided by classifications by arm and/or by outcome. Change from baseline and percent change will be described for biomarkers collected at post-baseline time points. Prognostic or predictive associations of correlative biomarkers with response will be assessed using logistic models with response as the outcome and the correlative covariates and the independent predictors. Cox models will be used when the outcome is time-to-event (PFS/OS). Correlations of liquid assays to each other and/or clinical data will be reported using Pearson or Spearman correlation coefficients as is appropriate.

^{68}Ga-PSMA PET/CT comparisons to standard imaging will be descriptive only.

10.3 Sample Size and Accrual

Sample Size

This is a two-arm randomized, open-label phase II study in men with oligometastatic mCRPC. 36 patients with oligometastatic disease who are candidates for systemic and local therapy will be randomized 1:1 to each arm.

Arm 1: standard of care
Arm 2: standard of care with ablation of all metastatic sites

Using prior studies, the median duration of response for systemic therapy alone is approximately 6 months (e.g. AFFIRM with enzalutamide, COU-AA-301 with abiraterone). There is no clear data for oligometastatic patients. Assuming the experimental arm increases this median duration of response to 15 months and exponential distribution of duration of response for both groups, with a 1 sided alpha of 0.1 and power of 0.8 allows for 16 patients per arm. This results in 32 total patients for randomization. To accommodate a 10% loss to follow-up rate, the total study sample is 36.

Accrual

Accrual of 36 subjects with 1 subject per month (as now allowing multiple lines of prior therapy) results in complete accrual in 28 months. 3 years of follow-up will result in a total trial time of approximately ~6 years.

10.4 Stratification Factors

There will be two stratification factors: 1-2 vs 3-5 treatment sites and line of therapy (1/2 or 3+). Block randomization will be completed by stratification group.

10.5 Derived Variables

- Change from baseline will be calculated as the rating after baseline minus the rating at baseline

- Percent change from baseline will be calculated as the rating after baseline minus the rating at baseline quantity divided by the baseline.
- Duration of treatment will be defined as the number of days from the first day of protocol assigned intervention to the last day of protocol treatment. If the last day of protocol treatment is missing, the date of the last visit will be substituted for the missing value.

10.6 Analysis Datasets

10.6.1 Survival Populations

All patients who meet eligibility criteria and receive at least 1 dose of radiation or study medication will be included in the analysis of duration of response even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Primary conclusions are to be based on the population of all eligible treated patients with an intent-to-treat analysis. Sub-analyses will be performed on various subsets of patients, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely by patient choice) as these sub-analyses will be important for designing future trials. However, sub-analyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.6.2 Response Rates

All patients who meet eligibility criteria and receive at least one dose of study medication or radiation and undergo one response evaluation will be included in the main analysis of the response rate, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Each patient will be assigned to one of the following categories for each response outcome:

Table 6: Categories for Response to Treatment

Category	Response
1	Complete Response
2	Partial Response
3	Stable Disease
4	Progressive Disease
5	Early Death from Malignant Disease
6	Early Death from Toxicity
7	Early Death from Other Causes
8	Unknown (not assessable/insufficient data)
Note: By arbitrary convention, category 8 designates unknown status in a clinical database. Patients in response categories 4-8 will be considered to have treatment failure (disease progression).	

Conclusions are to be based on the population of all eligible patients. Sub-analyses will be performed on various subsets of patients, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Sub-analyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.6.3 Patient-Reported Outcome

All patients enrolled in the study who receive at least one dose of standard of care or radiation will be included in patient-reported outcome assessments.

10.6.4 Safety Population

All patients enrolled in the study who receive at least one dose of study or radiation treatment will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Analysis will be completed by treatment received rather than treatment assigned. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (e.g., race/ethnicity) and by descriptive statistics for continuous data (e.g., weight, vital signs, EKG readings, disease status).

11.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

12.0 DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into EDC
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

13.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

14.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate University of Michigan Rogel Cancer Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes first treatment cycle.

The study site will send the redacted source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent redacted source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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16.0 APPENDICES

Appendix A: PERFORMANCE STATUS CRITERIA
Appendix B: NCCN-FACT FPSI-17 (Version 2)

Appendix A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix B: NCCN-FACT FPSI-17 (Version 2)

NCCN-FACT FPSI-17 (Version 2)

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.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	P7	I have difficulty urinating	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	W17	I feel fatigued	0	1	2	3	4
	NCCN2	I have weakness in my legs	0	1	2	3	4
	P3	My pain keeps me from doing things I want to do	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
DRS-E	GP5	I am sleeping well	0	1	2	3	4
	GE4	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	P6	I have trouble moving my bowels	0	1	2	3	4
TSE	GS7	I am satisfied with my sex life	0	1	2	3	4
	GP6	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GP3	I am able to enjoy life	0	1	2	3	4
	GP7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

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