Weill Cornell Medicine | NewYork-Presbyterian

COVER PAGE

Official Title: PRE-ProstAtectomy MRI-GuidEd Stereotactic Body RadioTherapy for High-Risk Prostate Cancer Trial (PREPARE SBRT)

IRB Protocol #: 19-07020533

NCT03663218

Document date: 09OCT2024

Weill Cornell Medicine | NewYork-Presbyterian

TITLE:
PRE-ProstAtectomy MRI-GuidEd Stereotactic Body RadioTherapy for High-Risk Prostate Cancer Trial (PREPARE SBRT)

IRB Protocol #: 1712018849
Version number: 7.0
Version Date: 09OCT2024

Principal Investigators: **Silvia Formenti, MD**
[redacted]

Christopher Barbieri, MD PhD
[redacted]

Co-Investigators: **Sandra Demaria, MD**
[redacted]

Olivier Elemento, PhD
[redacted]

Bishoy M.Faltas, MD
[redacted]

Jim Hu, MD MPH
[redacted]

[redacted]

Josephine Kang, MD PhD

[redacted]

Francesca Khani, MD

[redacted]

Daniel Margolis, MD

[redacted]

Ana M. Molina, MD

[redacted]

Juan Miguel Mosquera, MD MSc

[redacted]

David Nanus, MD

[redacted]

Brian D. Robinson, MD

[redacted]

[redacted]

Douglas S. Scherr, MD
[redacted]

Peter Schlegel, MD
[redacted]

Scott Tagawa, MD MS
[redacted]

Statisticians:
Karla Ballman, PhD
[redacted]

Xi Kathy Zhou
[redacted]

Study Contact, Radiation Oncology:
Fabiana Gregucci, MD
[redacted]

Responsible Study/Data Manager- Radiation Oncology:
Dakota Trick
[redacted]

Maahi Patel
[redacted]

[redacted]

Responsible Study contact-Urology:
Thomas Flynn
[redacted]

Responsible Study contact-Urology:
Miko Yu
[redacted]

Participating Sites: *Weill Cornell Medicine – NewYork-Presbyterian Hospital*

For Protocol enrollments and Study related matters, please email our list serv:

rocto@med.cornell.edu

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

All abbreviations used throughout the protocol must be defined.

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
RP	Radical Prostatectomy
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

Protocol Summary

Full Title:	PRE-ProstAtectomy MRI-GuidEd Stereotactic Body RadioTherapy for High-Risk Prostate Cancer Trial
Short Title:	PREPARE SBRT
Clinical Phase:	I
Principal Investigators:	Himanshu Nagar and Christopher Barbieri
Sample Size:	N = 20-40 (3 patients per dose escalation arm with 7 additional patients in maximum tolerated dose arm)
Accrual Ceiling:	This study will enroll up to 45 subjects.
Study Population:	Men with prostate cancer with Gleason Score of 8 or greater or clinical/radiographic evidence of T3 disease
Accrual Period:	3 years
Study Design:	Single arm, feasibility and safety dose escalation study
Study Duration:	Patients will remain on study for 5 years.
Study Agent/ Intervention Description:	Stereotactic Body Radiotherapy (SBRT)
Primary Objective:	The primary outcome is that a patient can undergo a radical prostatectomy after SBRT without a post-operative dose limiting toxicity (DLT) within 30 days after prostatectomy. DLT will be considered as Grade 3 or higher adverse events according to the Clavien-Dindo Classification
Secondary Objectives:	Secondary objectives include assessment of acute toxicity and quality of life scores.
Exploratory Objectives:	Exploratory objectives will include analysis of tumor and normal biopsied and resected tissue and serum markers and interpretation of interfraction and intrafraction MRIs.
Endpoints:	The primary endpoint is the ability of a patient to undergo a radical prostatectomy without a post-operative Grade 3 or higher adverse events within 30 days according to the Clavien-Dindo Classification

Document History

Document Name	Version number	Version Date
Amendment 7	**7.0**	**09OCT2024**
Amendment 6	6.0	10SEP2020
Amendment 5	5.0	26JUN2020
Amendment 4	4.1	18MAR2020
Amendment 3	4.0	10.03.2019
Amendment 2	3.0	06.18.2019
Amendment 1	2.0	10.25.2018
Initial Protocol	1.0	04.24.2018

Summary of changes: Protocol 09OCT2024 version 7.0

1. Removing Dr. Himanshu Nagar as PI from the protocol, as he has left WCM.
2. Updating Dr. Formenti's role to be the new PI for the protocol.
3. Removing Pragya Yadav, Ariel Marciscano, Sharanya Chandrasekhar and Jessica Richman, as they have left WCM.
4. Adding Fabiana Gregucci as Study Contact.
5. Adding Dakota Trick and Maahi Patel as Responsible Study/Data Manager.
6. Removing personnel will not affect the integrity of the research.

Summary of changes: Protocol 10SEP2020 version 6.0

1. Removing Stool sample collection from the protocol.
2. Updating schema to reflect changes in the study design.

Summary of changes: Protocol 26JUN2020 version 5.0

1. Reducing the dose escalation to include only 3 doses, 5 Gy, 6Gy and 6.5 Gy.
2. Removing Viji Nagaraj from the study as she is no longer with our department.

Summary of changes: Protocol 18MAR2020 version 4.1

1. Adding Dr. Ariel Marciscano as a Co-investigator on the study.

Summary of changes: Protocol 10.03.2019 version 4.0

1. Change study title to PREPARE SBRT: PRE-ProstAtectomy MRI-GuidEd Stereotactic Body RadioTherapy for High-Risk Prostate Cancer Trial

2. Modify primary objective and primary end point-- The primary outcome is that a patient can undergo a radical prostatectomy after SBRT without a post-operative Dose limiting toxicity (DLT). DLT will be defined as Grade 3 or higher adverse events within 30 days of prostatectomy according to the Clavien-Dindo Classification.

3. In Secondary end points: added International Prostate Symptom Score (IPSS) instead of EQ5D.

4. Revised stats section 8 and stopping rule section 10.2
5. Removed from Exclusion criteria: Prior chemotherapy and ADT
6. Remove pre-surgery research samples from the Table 1 Study procedures
7. Updated- serum to PBMCs in Section 6 to make it consistent with the initial e IRB application
8. Added Xi Cathy Zhou as a statistician
9. Remove Michael Smith as a co-investigator.

Summary of changes: Protocol 06.18.2019 version 3.0

1. Removing SPACEOAR™ from the protocol as Augmenix is no longer the sponsor of the study.
2. Adding Viji Nagaraj as an additional data manager for the study
3. Revising phone numbers for Sharanya and Pragya
4. Revising study calendar section 5.1. Removing SPACEOAR™ from the calendar and indicating that certain procedures are required only at the first follow up visit.

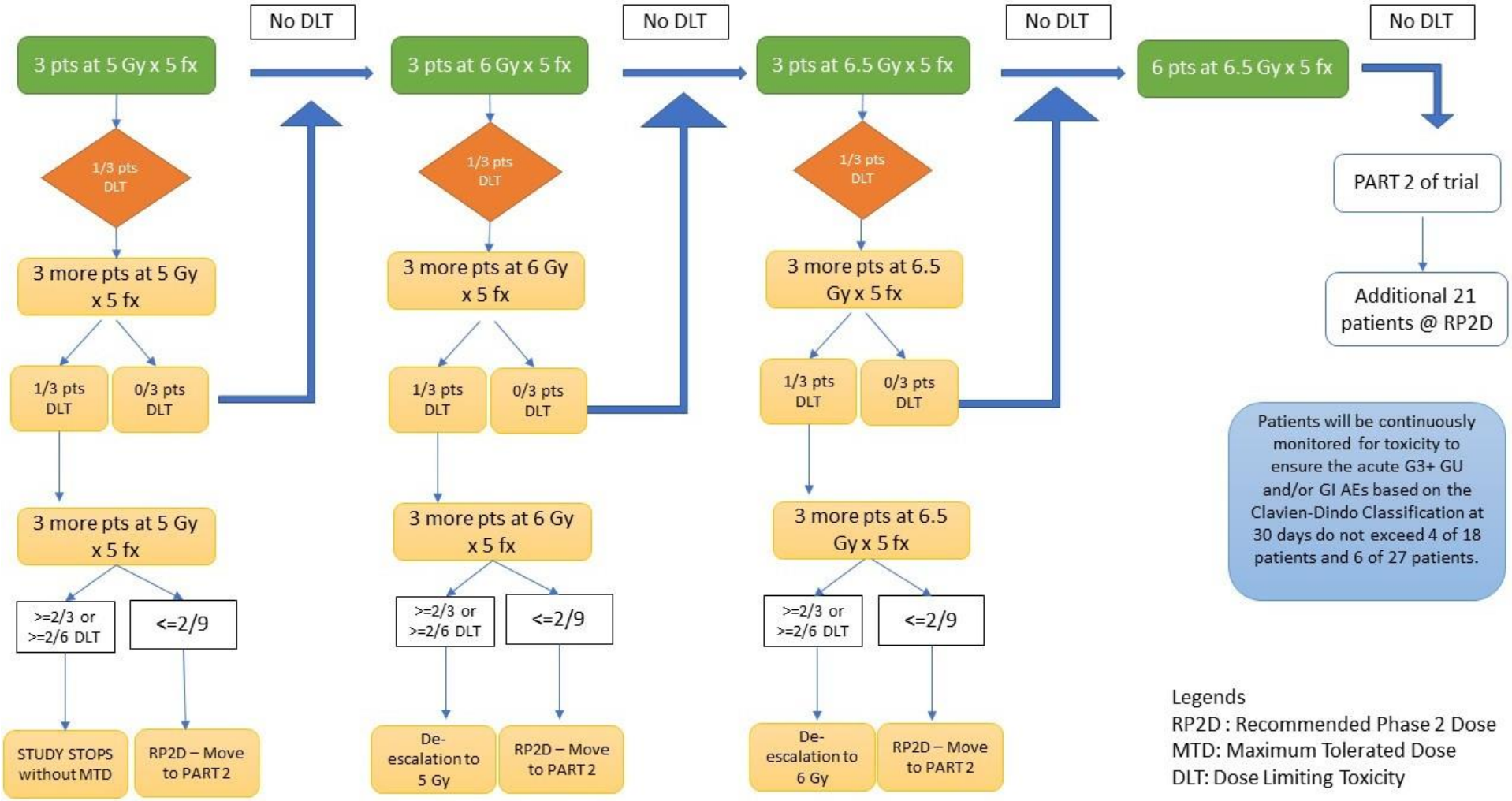
Summary of changes: Protocol 10/25/2018 version 2.0

1. Revised the time between radiation therapy and surgery from 3-6 weeks to less than 4 weeks.
2. Removed pre-surgery Radiation Oncology follow up visit
3. Adding Miko Yu and Thomas Flynn as study coordinators

Informed consent version date 10/25/2018.

1. ICF has been updated to be consistent with the protocol.

SCHEMA



Legends
RP2D : Recommended Phase 2 Dose
MTD: Maximum Tolerated Dose
DLT: Dose Limiting Toxicity

Table of Contents

SCHEMA ..... ERROR! BOOKMARK NOT DEFINED.

1 STUDY OBJECTIVES **13**

1.1 Primary Objectives **13**

1.2 Secondary Objectives **13**

1.3 Exploratory Objectives **13**

2 BACKGROUND **13**

2.1 Disease **13**

2.2 Rationale **14**

2.3 Risk/Benefit Assessment **14**

3 SUBJECT SELECTION **15**

3.1 Study Population **15**

3.2 Inclusion Criteria **15**

3.3 Exclusion Criteria **15**

4 REGISTRATION PROCEDURES **16**

4.1 Patient Registration **16**

5 STUDY CALENDAR **17**

5.1 Table 1. Schedule of trial events **17**

5.2 Screening Visit **17**

5.3 Imaging Studies **17**

5.4 Radiation Treatment Planning **18**

5.5 Trial Procedures **19**

5.6 General Concomitant Medication and Supportive Care Guidelines **19**

5.7 Duration of Therapy and Criteria for Removal from Study **19**

5.8 Duration of Follow Up 20

6 CORRELATIVE/SPECIAL STUDIES 20

7 DATA REPORTING / REGULATORY CONSIDERATIONS 20

7.1 Data Collection 20

7.2 REDCap 20

7.3 Data Management 21

7.4 Regulatory Considerations 21

8 STATISTICAL CONSIDERATIONS 21

8.1 Study Design/Endpoints 21

8.2 Sample Size/Accrual Rate 22

8.3 Stratification Factors 23

8.4 Analysis of Endpoints 23

8.5 Analysis of Primary Endpoints 23

8.6 Analysis of Secondary Endpoints 23

8.7 Interim Analysis 23

9 ADVERSE EVENT REPORTING REQUIREMENTS 23

9.1 Assessing and Recording Adverse events 24

9.2 Definition of SAE 25

10 DATA AND SAFETY MONITORING PLAN (DSMP) 25

10.1 DSMB safety Review 26

10.2 Stopping Rules 26

11 REFERENCES 27

1 Study Objectives

1.1 Primary Objectives

Assess the feasibility of stereotactic body radiotherapy (SBRT) before radical prostatectomy (RP) in patients with high risk prostate cancer. The primary outcome is that a patient can undergo a radical prostatectomy after SBRT without a post-operative dose limiting toxicity (DLT). DLT will be defined as Grade 3 or higher adverse events within 30 days after prostatectomy according to the Clavien-Dindo Classification.

1.2 Secondary Objectives

Assess the acute toxicity and quality of life scores in subjects after SBRT and RP. Assess negative margin rate and neurovascular bundle preservation rate.

1.3 Exploratory Objectives

Analyze tumor and normal biopsied and resected tissue and serum markers. Interpret interfraction and intrafraction MRI of prostate and seminal vesicles.

2 Background

2.1 *Disease*

Prostate cancer is the most common non-cutaneous cancer in men and the second leading cause of cancer death in men [1]. It is predicted that the number of cases will almost double by 2030 (GLOBOCAN 2012). The standard of care for patients with high-risk prostate include radiotherapy with androgen deprivation therapy (ADT) or prostatectomy which may be followed by adjuvant therapy [2]. Radical prostatectomy is the most common treatment for prostate cancer according to the National Cancer Institute's Pattern of Care study from 14 regional cancer registries with the proportion of men undergoing prostatectomy was 70% for age <60 years, 51% for 60-64 years, and 39% for 65-75 years [3]. An increasing number of patients with high-risk prostate cancer are undergoing primary radical prostatectomy with a 20% increase from 2004 to 2012 [4].

High-risk features for recurrence include extra-capsular extension and/or seminal vesicle invasion (pT3 disease) and positive surgical margins, which occur in an estimated 20% and 16% of patients, respectively [5]. Post-prostatectomy radiotherapy to the prostate bed for pT3 disease or positive surgical margins has been shown to reduce the risk of recurrence in three

randomized trials: Southwest Oncology Group, European Organization for Research and Treatment of Cancer and Auckland Radiation Oncology [6-8]. As such, adjuvant radiotherapy after prostatectomy is the standard for care for patients with pT3 disease, positive margins or Gleason Grade 8-10 [2].

2.2 Rationale

Patients at high risk of recurrence are recommended to undergo post-operative radiotherapy as a surrogate to eradicate subclinical disease. The clinical target volume (CTV) is the prostate bed which is difficult to delineate once the prostate has been surgically removed and can be overestimated by the utilizing location of surgical clips [9]. As such, controversy exists in the field as to the optimal target volume. National and international guidelines suggest including a significant portion of the posterior and inferior aspects of the bladder, and anterior aspect of the rectum, exposing a significant amount of normal tissue to high dose radiation [10-12]. Additionally, post-operative radiotherapy is delivered in 37-39 fractions over the course of 7 weeks, representing a high burden of therapy, which may be related to lower utilization of post-operative radiotherapy [13].

Modern radiotherapy for untreated prostate cancer has been afforded many advantages including improved target delineation with multiparametric MRI and image-guided radiotherapy allowing for larger dose delivery in fewer fractions and tighter margins with stereotactic body radiotherapy (SBRT) [14]. Moreover, newer technologies with MRI based image guided radiotherapy with the ViewRay® and MRIdian linear accelerator now available at NewYork-Presbyterian/Weill Cornell Medicine will allow for significantly improved daily adaptive target delineation.

In patients that are likely to need radiotherapy after RP, the potential advantages of SBRT delivered over 5 fractions *prior* to surgery (preoperative) are: 1) reduced radiation dose to normal tissues, 2) increased convenience to patients because of fewer treatment days, 3) reduced costs to patients because of reduced travel expenses and copays, 4) improved resource utilization for physicians because of the fewer number of treatments per patient and overall and consequently 5) reduced cost to society. In prostate cancer specifically, SBRT has the added potential of not increasing toxicity while delivering a higher biological dose and therefore increased efficacy [16].

2.3 Risk/Benefit Assessment

Two prior phase I trials have explored preoperative radiotherapy prior to prostatectomy for patients with high risk prostate cancer. A trial at Duke University treated the patients' prostate and seminal vesicles in a dose escalation fashion in 1.8 Gy daily fractions to total doses of 39.6 Gy, 45 Gy, 50.4 Gy and 54 Gy. **Acute GU and GI toxicities were limited to Grade 1 and no observed intraoperative complications occurred.** Late urinary toxicity was within the range expected for adjuvant radiotherapy [17]. A trial at Princess Margaret Hospital utilized a preoperative dose of 25 Gy delivered in 5 fractions without image guidance. Similar to the trial at Duke University, **there were no observed intraoperative complications and urinary toxicity was within the range expected for adjuvant radiotherapy [18]**. The current trial has the potential benefit of limiting radiation dose received by normal tissues that would be exposed in the postoperative setting, namely the bladder and rectum, with advanced image guided and dose delivery techniques. Additionally, as the prior phase I preoperative study using a hypofractionated dose of 25 Gy in 5 fractions did not demonstrate significantly different toxicities or any observed intraoperative complications, this study will begin at that dose level of 5 Gy x 5.

3 Subject Selection

3.1 Study Population

Subjects with a diagnosis of high-risk prostate cancer who meet the inclusion and exclusion criteria will be eligible for participation in this study.

3.2 Inclusion Criteria

1. Men aged $\geq$ 18 with histologically confirmed primary prostate cancer.
2. KPS $\geq$ 70
3. Patient with a negative staging bone scan.
4. Patient can undergo an MRI.
5. Patient with negative staging CT or MRI of pelvis. Suspicious evidence of nodal involvement on staging CT or MRI of pelvis is defined as greater than 1 cm on short axis. Documented negative biopsy of suspicious node required.
6. Patient is medically fit to undergo prostatectomy.
7. Patient has either Gleason Score $\geq$ 8 on biopsy and/or clinical/radiographic evidence of T3 disease.

3.3 Exclusion Criteria

1. Prior history of receiving pelvic radiotherapy.
2. Patient is unwilling to undergo prostatectomy.
3. Patient with active inflammatory bowel disease defined as currently receiving therapy for IBD.

4 Registration Procedures

4.1 Patient Registration

Once patient signs consent, please notify via email to rocto@med.cornell.edu. ROCTO will begin registration process as soon as the signed consent and the eligibility documents are obtained either as hard or soft copies.

Patients will be centrally registered in onCORE by ROCTO. To register a patient, upload the following documents to onCORE:

- Signed Informed consent
- Email the completed eligibility document to CancerCTRegistrar.

Registration must be completed within 24 hours of the signing of informed consent.

5 Study Calendar

5.1 Table 1. Schedule of trial events

	Screening	Before Radiation	Day 1 – Day 5 Radiation therapy					Tumor assessment (pre-surgery)	Surgery (less than 4 weeks post RT)	Follow up 1month post-surgery and q3months for 5 years
Radiotherapy			X	X	X	X	X			
Surgery									X	
EPIC SCORE		X							X	X*
IPSS		X							X	X*
Informed consent	X									
Demographics/Medical history	X									
Physical exam	X						X		X	X
PSA serum	X								X	X*
CT or MRI pelvis (with and without contrast)	X							X		
Adverse Events	X						X		X	X
Immune monitoring samples		X					X			X*

* - These procedures are required per protocol at the 1st follow up visit (post-surgery) only.

5.2 Screening Visit

- Informed Consent
- MRI pelvis
- Medical History, demographics and any baseline adverse events
- Routine Physical exam
- Serum PSA

5.3 Imaging Studies

Patients enrolling on the protocol will be treated as follows. Patients will be instructed to undergo a Fleet enema prior to planning CT/MRI and prior to each SBRT treatment.

Treatment planning CT/MRI will be performed with vac loc immobilization. Patients will be advised to drink 1-2 cups of water 1 hour prior to the CT/MRI simulation to allow for a comfortably full bladder, if tolerated. A rectal catheter will be utilized to dispel any excess

bowel gas, if necessary. A urethral catheter to delineate the urethra at time of simulation can be considered if it is difficult to visualize the urethra on initial MRI.

5.4 Radiation Treatment Planning

After consent and eligibility verification, patients will be undergo CT/MRI simulation/radiation therapy planning. This is a dose escalation study and the trial accrues 3 patients at each dose level. The dose levels that are being tested are 5 Gy x 5 fractions, 6 Gy x 5 fractions and 6.5 Gy x 5 fractions.

Three (3) patients will initially receive 5 Gy for 5 fractions. If patients tolerate the dose and undergo surgery without a post-operative Grade 3 or higher DLT 30 days, another set of 3 patients are selected for the next dose level. If the patients are to develop a post-operative Grade 3 or higher DLT, the trial will accrue additional 6 patients to the previous dose level.

Contours

The treatment planning CT will be fused to the T2 sequence of the MRI. The prostate + seminal vesicles (SV) will be contoured as the clinical target volume (CTV). The PTV expansion for the CTV will be 3-5 mm depending on physician discretion.

The rectum will be drawn from the bottom of the ischial tuberosities to the sigmoid flexure. The urethra will be delineated on MRI from the prostatic apex, to entry of urethra into the penile bulb, using a 5 mm brush. The physician will have the option of placing a urethral catheter at time of sim as per standard care.

The bladder, femoral heads, penile bulb will also be contoured as normal structures.

Dose/Treatment Planning Parameters

The CTV (prostate + SV) will be treated to the prescribed dose (5, 6, or 6.5) Gy in 5 fractions.

PTV = CTV + 3-5 mm (treating physician's discretion)

VPrescription Dose (5, 6, or 6.5) Gy (volume of the PTV receiving Prescription Dose (5, 6, or 6.5) Gy should be ≥ 95%

Critical organ limits:

1. Rectum: Maximum dose to 1 cc 38.5 Gy, Max dose to 3 cc 34.4 Gy, D53% 24 Gy, Max point dose 40 Gy

2. Bladder: Maximum dose to 1 cc 38.5 Gy, Max point dose 40 Gy

3. Penile Bulb: No more than 105% of prescription dose; D3cc 25 Gy. This is a soft constraint.

4. Femoral heads: Maximum point dose 30 Gy

5. Small bowel: Maximum point dose 25 Gy

6. Urethra: Max dose 38.78 Gy

5.5 Trial Procedures

The Study Procedures Section 5.1 summarizes the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

5.6 General Concomitant Medication and Supportive Care Guidelines

a. Urinary: A proportion of patients undergoing prostate SBRT can expect increase in urinary frequency or urgency. If this becomes bothersome to the patient, medication to alleviate symptoms can be prescribed at the discretion of the treating radiation oncologist and documented in patient chart.

b. Bowel: Bowel symptoms during time of prostate SBRT are rare. If patients develop rectal urgency, tenesmus or diarrhea, medication to alleviate symptoms can be prescribed at the discretion of the treating radiation oncologist and documented in patient chart.

5.7 Duration of Therapy and Criteria for Removal from Study

Radiotherapy will be delivered in a total of 5 fractions. Treatments extending over a weekend period are allowed.

In the absence of treatment delays due to adverse event(s), treatment may continue or until one of the following criteria applies:

- Patients unable to tolerate radiation therapy
- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Duration of Follow Up

Patients will be followed up 30 days post-surgery. There will be a follow up every 3 months for 5 years post-surgery or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6 Correlative/Special Studies

Paraffin-embedded tissue block, PBMCs, plasma will be collected for future translational research analyses for predictors of toxicity and response following radiotherapy. Note: Testing of banked specimens will not occur until an amendment to this treatment protocol is reviewed and approved in accordance with IRB policies.

7 Data Reporting / Regulatory Considerations

7.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

7.2 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

7.3 Data Management

All patient data will be entered and maintained in REDCap. These data include clinical data and all patient safety data. The REDCap provides audit trails that track creation and modification of records that include user ID and timestamp. Once entered, the data is subjected to validation procedures that are executed either immediately or upon saving the eCRF page or during the batch validation process. Validation failures that are identified before the page is saved can be corrected immediately. Validation failures during saving of the eCRF page and during batch validation processes will generate a discrepancy. Depending on the database account privileges, the data managers may be able to correct a discrepancy or if not, route it to the project data manager at WCMC who can take appropriate action to correct the problem. Once the discrepancy is closed, by marking "resolved" or "irresolvable", the data is marked clean and an audit trail is generated by the system.

All key end points will be source verified by a second person at each site and errors will be corrected. Once the data is verified and all discrepancies are closed, the data can be locked/frozen. Locking and freezing can be done at different granular levels and will follow institutional SOPs and any specific requirements for the project.

Security measures that will be taken in order to protect patient data will include firewall technology and database level security which will be achieved by assigning roles and privileges to different levels of users and by requiring that the users authenticate themselves using user id and password. Additional security for data transfer between remote clients and servers will be achieved by using digital certificates/SSL. All data will be backed-up to tape periodically according to the Institutional SOPs. All data will be stored for at least 5 years following the termination of this study.

7.4 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator.

8 Statistical Considerations

The primary endpoint for this trial will be successful completion of radical prostatectomy after SBRT without a post-operative DLT of grade 3 or higher within 30 days after prostatectomy.

8.1 Study Design/Endpoints

This is a single-arm study including two parts. Part 1 will be a modified dose

escalation and de-escalation study to determine maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) based on acute toxicity measures. Part 2 will be a cohort expansion study to further evaluate the safety and tolerability of the RP2D based on toxicities measured at 1 year.

In part 1 of the study, a modified dose escalation and de-escalation design with an expansion of 3 or 6 patients to allow the recommended phase II dose (RP2D) be examined in a total of 9 patients will be used. The dose limiting toxicity (DLT) is defined as Grade 3 or higher (G3+) gastrointestinal (GI) and/or urinary (GU) AEs related to preoperative radiotherapy according to the Clavien-Dindo Classification at 30 days. Three radiation dose levels, 5 Gy, 6 Gy and 6.5Gy are considered. A 3+3 dose escalation plan will be used. At the start of each dose level k (k=1, 2, or 3), 3 patients will be enrolled and treated for five days. If none of the 3 patients develop the DLT, the testing dose will escalate to the next level, k+1. If 1 of the 3 patients develops the DLT, the current dose will be tested in an additional 3 patients. If no additional patients develop the DLT, the dose will escalate. If 1 of the additional 3 patients develops DLT, i.e. a total of 2 of 6 patients with DLT, the previous dose will be deemed the maximum tolerated dose (MTD) and tested in a total of 9 patients. If <=2 among the 9 patients experience the DLT, this dose will be considered as the RP2D. If >=2 of 3 patients or >=2 of 6 patients develop DLT, the study will stop without MTD if k=1 or consider dose level k-1 to be the MTD and tested in an additional 3 or 6 patients so that a total of 9 patients are evaluated. If >=3 of 9 patients experience the DLT, the de-escalation will continue. This design ensures that the DLT rate to be <=2/9 for the RP2D.

In part 2 of the study, additional 21 patients will be enrolled to further examine the safety of the R2PD in a total of 30 patients. The primary safety endpoint will be G2+ GI and/or GU AEs related to preoperative radiotherapy according to the CTCAE v5.0 measured at 1 year. Patients will be continuously monitored to ensure the acute G3+ GU and/or GI AEs based on the Clavien-Dindo Classification at 30 days do not exceed 4 of 18 patients, and 6 of 27 patients.

8.2 Sample Size/Accrual Rate

The sample size for part 1 portion of the study will vary depending on the number of patients that develop the DLT. If no DLTs are seen, we will recruit 3+3+3+6=15= patients at 5, 6, and 6.5 Gy, respectively. Following the schema above, the maximum number recruited would be 27, which would only occur if 0 of 3 or 1 of 6 patients develop the DLT in dose escalation phase but >2 of 6 or >1 of 3 patients in the expansion cohort develop the DLT, triggering an expanded cohort at a lower dose.

Sample size for part 2 portion of the study will be 30 including the 9 patients from part 1. Having a total of 30 patients in the expansion cohort will allow us to estimate the 1-year G2+ toxicity rate based on CTCAE v5.0 within a 95% CI width of 0.37 and help with the decision making at the end of the trial. For example, an observation of >=8 of the 30 patients having G2+ toxicity at 1-year based on CTCAE v5.0 would suggest that the probability of the toxicity rate being > 0.20 is greater than 80%, which will allow us to make an informative decision on whether the R2PD is worth to be examined at a larger trial.

8.3 Stratification Factors

No stratification factors are planned for the primary endpoint.

8.4 Analysis of Endpoints

8.5 Analysis of Primary Endpoints

Primary endpoints for this study are G3+ GU and/or GI toxicities at 30 days based on Clavien-Dindo Classification (Part 1) and G2+ GU and GI toxicities at 1 year based on CTCAE v5.0 (Part 2). Adverse events based on the two classification systems will be recorded. Descriptive statistics including the number, proportion of patients experience AEs, and 95% confidence interval of the proportion estimate calculated using the Clopper-Pearson method will be summarized. The analysis set will include patients who receive any dose of the preoperative radiation therapy.

8.6 Analysis of Secondary Endpoints

Assessment and analysis of secondary endpoints including toxicity and quality of life scores will be descriptive.

8.7 Interim Analysis

This study will have interim analyses after every dose in the sense that if any unacceptable dose limiting toxicities are seen, future patients will be recruited at a lower dose.

9 Adverse Event Reporting Requirements

Adverse events (AEs) will be recorded REDCAP for the duration of the trial, regardless of whether or not the event(s) are considered related to the trial. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment

modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the case report form and source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.

The investigator must determine the toxicity of adverse events according to the CTCAE version 5.0 and their causal relationship.

9.1 Assessing and Recording Adverse events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

9.1.1 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

9.1.2 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart. The AEs are documented in REDCAP database.

9.1.3 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

9.2 Definition of SAE

SAE's include death, life threatening adverse experiences, prolonged hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

10 Data and Safety Monitoring Plan (DSMP)

The study will be monitored internally by the study teams in Radiation Oncology and Urology. Adverse events will be reviewed at every dose level.

The WCMC Data and Safety Monitoring Board (DSMB) is the central monitoring board for this study. The WCMC Cancer Institute DSMB is the local monitoring board for WCMC patients. This study will be conducted in accordance with the guidelines in the 2001 NCI approved data Safety and Monitoring plan for the WCMC Cancer Institute and with the WCMC approved data Safety and Monitoring plan for the WCMC Cancer Institute. Reports to the DSMB will include the following information: accruals, targets, responses, adverse events and evidence of reporting to appropriate review committees. The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, the data and safety monitoring plan and any stopping guidelines during protocol initiation. During the course of the study, the DSMB will

review cumulative study data twice a year to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address.

10.1 DSMB safety Review

Safety reports will be submitted to the DSMB every six months.

10.2 Stopping Rules

For Part1, after completion of a dose level, if >=2 of 3, >=2 of 6 or >=3 of 9 patients develop develop a post-operative gastrointestinal or urinary grade 3 or higher toxicity at 30 days related to preoperative radiotherapy, the trial will accrue patients to the previous lower dose level. If >=2 of 3, >=2 of 6 or >=3 of 9 patients develop a post-operative gastrointestinal or urinary grade 3 or higher toxicity at 30 days related to preoperative radiotherapy at 5 Gy x 5 fractions, the trial will stop. During Part 2, the study will stop if >=5 of 18, or 7 of 27 patients develop a post-operative gastrointestinal or urinary grade 3 or higher toxicity at 30 days related to preoperative radiotherapy at the R2PD. Adverse events at 30 days will be recorded based on according to the Clavien-Dindo Classification.

If safety concerns arise, the DSMB will identify these concerns and recommend modification or termination of the clinical trial. There is no formal interim analysis for this trial.

11 References

1. Haas, G.P., Delongchamps, N., Brawley, O.W., Wang, C.Y. & de la Roza, G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* 15, 3866-3871 (2008).
2. NCCN Clinical Practice Guidelines in Oncology - Prostate Cancer (Version 2.2017). (2017).
3. Hamilton, A.S.*, et al.* Trends in the treatment of localized prostate cancer using supplemented cancer registry data. *BJU Int* 107, 576-584 (2011).
4. Weiner, A.B.*, et al.* Contemporary management of men with high-risk localized prostate cancer in the United States. *Prostate Cancer Prostatic Dis* 20, 442 (2017).
5. Tewari, A.*, et al.* Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. *Eur Urol* 62, 1-15 (2012).
6. Thompson, I.M., Jr.*, et al.* Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 296, 2329-2335 (2006).
7. Bolla, M.*, et al.* Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 380, 2018-2027 (2012).
8. Wiegel, T.*, et al.* Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 27, 2924-2930 (2009).
9. Fortin, I.*, et al.* Using fiducial markers in the prostate bed in postprostatectomy external beam radiation therapy improves accuracy over surgical clips. *Strahlenther Onkol* 190, 467-471 (2014).
10. Poortmans, P.*, et al.* Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol* 84, 121-127 (2007).
11. Sidhom, M.A.*, et al.* Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol* 88, 10-19 (2008).
12. Wiltshire, K.L.*, et al.* Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. *Int J Radiat Oncol Biol Phys* 69, 1090-1099 (2007).
13. Kalbasi, A.*, et al.* Low rates of adjuvant radiation in patients with nonmetastatic prostate cancer with high-risk pathologic features. *Cancer* 120, 3089-3096 (2014).
14. Kang, J.K.*, et al.* Image-guided stereotactic body radiation therapy for localized prostate cancer. *Tumori* 97, 43-48 (2011).
15. Hamstra, D.A.*, et al.* Continued Benefit to Rectal Separation for Prostate Radiation

Therapy: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys* 97, 976-985 (2017).

16. Abdel-Wahab, M. & Pollack, A. Radiotherapy: encouraging early data for SBRT in prostate cancer. *Nat Rev Urol* 6, 478-479 (2009).
17. Koontz, B.F.*, et al.* Phase 1 trial of neoadjuvant radiation therapy before prostatectomy for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 87, 88-93 (2013).
18. Supiot, S.*, et al.* A phase I trial of pre-operative radiotherapy for prostate cancer: clinical and translational studies. *Radiother Oncol* 88, 53-60 (2008).