CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF MEDICAL ONCOLOGY & THERAPEUTICS RESEARCH

TITLE: Phase III Randomized Trial of Standard Systemic Therapy (SST) versus Standard Systemic Therapy Plus Definitive Treatment (Surgery or Radiation) of the Primary Tumor in Metastatic Prostate Cancer

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 18550 PROTOCOL DATE: 01/06/21

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial Approval	Protocol Dated 08/01/18	Version: 00
COH Amendment 01	Protocol Revision 1, dated 11/27/2018	Version: 01
COH Amendment 02	Title page dated 10/22/2019	Version: 02
COH Amendment 03	Protocol Revision 2, dated 09/11/2019	Version: 03
COH Amendment 04	Protocol Revision 3, dated 01/06/2021	Packet: 04

SITE: Prostate

STAGE (If applicable): Metastatic

MODALITY:

TYPE:

PRINCIPAL INVESTIGATOR: Tanya Dorff, M.D.

COLLABORATING INVESTIGATOR(S):

PARTICIPATING CLINICIANS: Sumanta Pal, M.D.
Cy Stein, M.D.
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SWOG CANCER RESEARCH NETWORK

Version Date: January 6, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Veronica Garcia, M.S., Protocol Coordinator II (E-mail: vgarcia@swog.org)

RE: **S1802**, "Phase III Randomized Trial of Standard Systemic Therapy (SST) Versus Standard Systemic Therapy Plus Definitive Treatment (Surgery or Radiation) of the Primary Tumor in Metastatic Prostate Cancer)." Study Chairs: B. Chapin, M.D. (Urology), A. Aparicio, M.D. (Medical Oncology), and R. Valicenti, M.D., M.A., F.A.S.T.R.O. (Radiation Oncology).

REVISION #3

Study Chair: Brian F. Chapin, M. D.
Phone number: 713/794-1466
E-mail: S1802question@swog.org

IRB Review Requirements
(√) Expedited review allowed

Key Updates
(√) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Specimen Submission changes
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

REVISION #3

The primary purpose of this revision is to update inconsistencies throughout the protocol.

The protocol has been updated as follows:

1. The version date of the Protocol has been updated.

2. Formatting, typographical, and grammatical errors not affecting content have been corrected throughout the document.

3. The Table of Contents has been updated.

4. Section 5.1a.3: The explanation of the timing of the scan showing metastases was updated for clarity in Section 5.1a.3.

5. Section 5.1c.4: Section 5.1c.4 criterion was removed as a documented testosterone lab is not required for Step 1 registration. Subsequent sections were renumbered.

6. Section 5.2b.3: The wording of Section 5.2b.3 criterion was updated for clarity. Fatigue, weight gain, and hot flashes were added as exceptions to the requirements for toxicity resolution.

7. Section 7.1a.3: Section 7.1a.3 was added to define the first date of hormonal therapy. Subsequent sections were renumbered.

8. Section 7.1a.4: Section 7.1a.4 was added to note that all treatments intended to be part of SST must be started within 16 weeks of the start of SST and if started after this point, it will be considered a new line of SST, requiring patient to come off protocol treatment. Subsequent sections were renumbered.

9. Section 7.1b.3: The reference for MDT standards was removed from the end of Section 7.1b.3.

10. Section 7.5c: Section 7.5c was added stating that a change in drugs used as part of SST is a criterion for removal from protocol treatment. Subsequent sections were renumbered.

11. Section 8.4: Section 8.4 was updated with the Adverse Event Reporting Requirements previously listed as Section 16.1. This was updated for consistency with the current SWOG protocol template.

12. Section 10.3e.1: Section 10.3e.1 was added stating that an alteration in standard therapy due to changes in any of the listed clinical factors will be considered a progression event.

13. Section 15.1: The number of slides to be submitted at each time point was updated throughout section 15.1 for clarity.

14. Section 15.1b.1: A statement was added to Section 15.1b.1 informing sites that corresponding pathology reports that include diagnosis should be submitted with each FFPE submission.

15. Section 15.2a: This section was updated to clarify that if patients are registered to Steps 1 and 2 at the same time, the sample is sent as the Step 2 time point.

16. Section 15.2a.1: A reference to Section 15.4 was added in Section 15.2a.1.

17. Section 15.3b.2: Yucheng Xu, Ph.D. was removed as a contact for Dr. Goldkorn's lab in Section 15.3b.2.

18. Section 15.4: Section 15.4 was removed as more updated shipping guidelines are available on the SWOG Specimen Submission webpage. Subsequent sections were renumbered.

19. Section 16.1: Adverse event reporting requirements were moved to Section 8.4 from Section 16.1 for consistency with the current SWOG Protocol Template.

The Model Consent Form has been updated as follows:

1. The version date of the Model Consent Form has been updated.

2. Unknown Future Studies: The "Unknown Future Studies" section was updated to inform patients that if they have a second biopsy (or surgery) while on treatment, then a tissue sample from this biopsy (or surgery) will be collected and stored. Additionally, the section was updated to inform patients that some of collected blood samples will be sent to a central lab.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG

PHASE III RANDOMIZED TRIAL OF STANDARD SYSTEMIC THERAPY (SST) VERSUS STANDARD SYSTEMIC THERAPY PLUS DEFINITIVE TREATMENT (SURGERY OR RADIATION) OF THE PRIMARY TUMOR IN METASTATIC PROSTATE CANCER

Study Exempt from IND Requirements per 21 CFR 312.2(b)

NCT#03678025

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NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal:

(Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

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

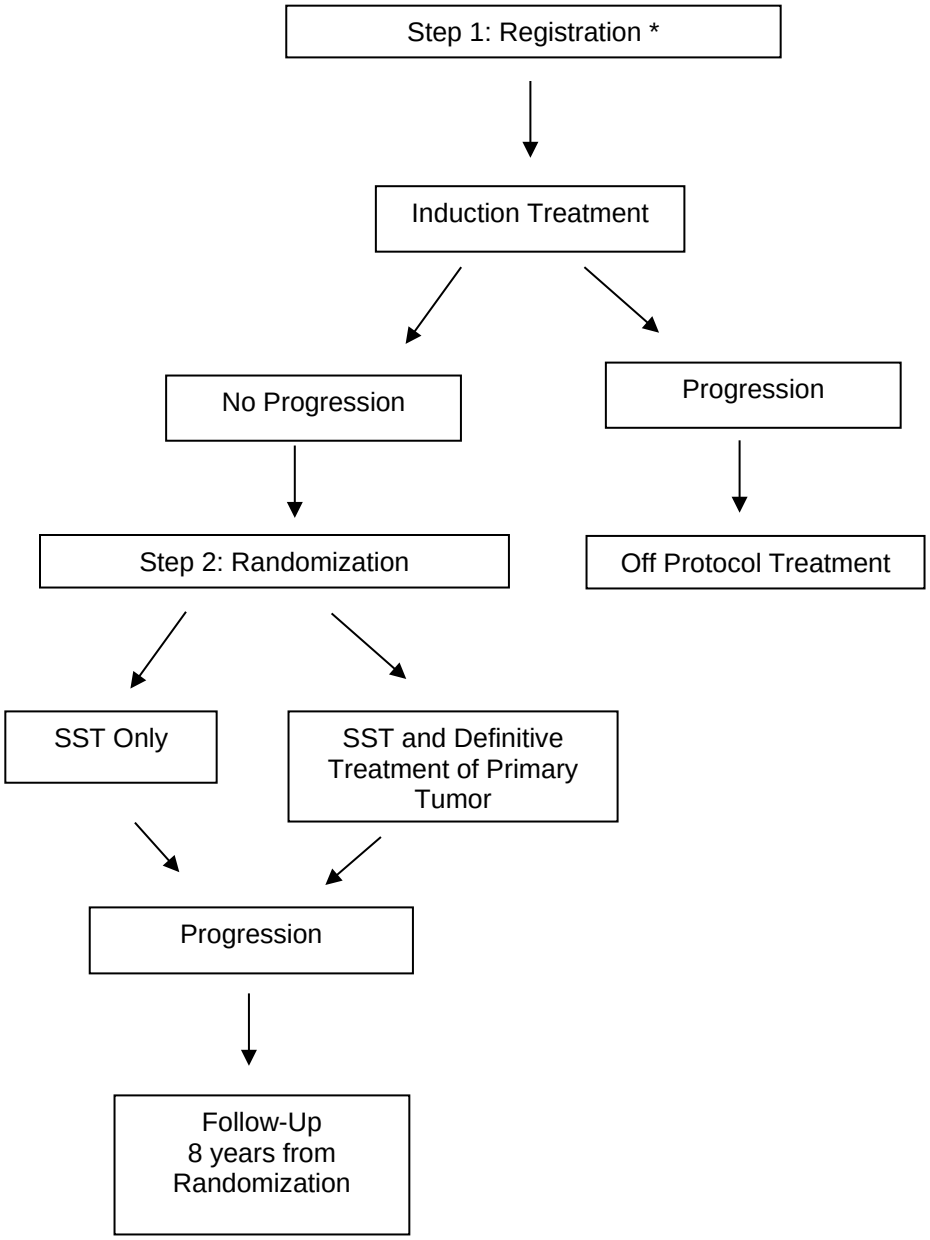
Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com ,</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email:
206/652-2267
guquestion@crab.org

For treatment or toxicity related questions contact S1802question@swog.org.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
</table>

SCHEMA



* Step 1 registration can occur prior to start of SST or up to 28 weeks after start.

1.0 OBJECTIVES

1.1 Primary Objective

To compare overall survival in metastatic prostate cancer patients who are randomized to standard systemic therapy (SST) plus definitive treatment of the primary tumor versus standard systemic therapy alone.

1.2 Secondary Objectives

a. To compare overall survival in metastatic prostate cancer patients who received SST plus surgical excision of the primary tumor versus SST alone in the subset who specify the surgical intent stratification factor.

b. To compare the rate of symptomatic local progression between the treatment arms. (Refer to Section 10.0 for definitions of symptomatic local progression.)

c. To compare progression-free survival (PFS) between the two treatment arms.

d. To compare rates of progression-free survival between arms for the subsets of patients with and without metastasis directed therapy (MDT) to oligometastatic sites (see Section 7.0).

1.3 Quality of Life Objective

To compare between arms patient-reported urinary function and urinary bother over time (after initiation of SST at 6 months, 1, 2, and 3 years) using the Expanded Prostate Cancer Index Composite (EPIC) and patient-reported pain and physical functioning using the EORTC QLQ-C30 between patients receiving standard systemic therapy and those receiving systemic therapy and definitive management of the primary prostate cancer.

1.4 Other Objective

To bank tissue and whole blood specimens for future use.

2.0 BACKGROUND

Definitive treatment of the primary tumor has traditionally been reserved for the treatment of localized prostate cancer (PC) but a growing number of studies suggest that it improves the overall survival (OS) and cancer specific survival (CSS) of men with metastatic (≥M1a) disease. *(1,2,3)* It has been estimated that 24-54% of men treated with non-curative intent will develop symptomatic local progression requiring intervention. (4) Symptomatic progression of local disease is a source of intense suffering as well as health care resource spending, consumed in hospital admissions and unsatisfactory palliative procedures, and is likely to worsen performance status and accelerate death from PC. While salvage cystoprostatectomy and/or pelvic exenteration can offer palliation of symptoms, they carry a high rate of complications and can only be offered to a subset of men in this situation. *(5)*

In addition, definitive treatment of the primary tumor may exert an effect on the biology of the disease that contributes to the improvement in outcomes. For example, persistent viable cancer with features of aggressive disease is known to remain in the prostate tumors of men previously treated with systemic therapies, including docetaxel and abiraterone, and may serve as a continued source for additional metastatic spread and resistant clonal selection. *(6,7,8)* Therefore, definitive treatment of the primary tumor as part of a multimodality approach for metastatic prostate cancer

(M1 PC) may also improve outcomes by removing a major source of continued waves of metastases and thereby increasing freedom from local and distant progression, delaying time to castration resistance and prolonging time to fatal metastatic burden, thus resulting in prolongation of overall survival.

This trial was presented to the Task Force initially as a surgical trial, but after input was provided by the Task Force and members of NRG, radiation was added as an option for the local therapy. In localized disease radiation and surgery have equipoise and it was felt having more than one option for local control would appeal to more patients for study inclusion. Radiation was capped at 1/3 of the total patients to still provide reasonable power to answer the surgical aim as a secondary endpoint.

There is an urgent need to determine if and how treatment of the primary tumor improves outcomes in men with M1 PC. A multimodality approach could provide survival advantages via a biologic mechanism and/or alleviating symptomatic progression. With the stage migration that is occurring due to improved imaging (MRI and newer PET imaging agents) in men with advanced disease, this question needs to be addressed in order to determine appropriate treatment application of local therapies in patients presenting with de novo metastatic disease.

Overall survival in men with metastatic disease has improved over the past 10 years due to the development of multiple systemic therapies. Men presenting with de novo metastatic disease and an intact primary tumor have a median survival of 50 months. Many of these men will develop symptomatic local progression due to an untreated primary, which can be a substantial burden to the patient and provider. Early intervention may provide an opportunity to provide a palliative procedure before the risks of the procedure outweigh the potential benefits and thereby greatly improve upon a patient's quality of life. This question will still be relevant at the completion of this study accrual in 2023 and the current design allows flexibility for standard treatment to change over time.

The central question of this trial is: Does definitive treatment of the primary improve disease control and survival? If so, how does treatment of the primary impact the occurrence of adverse events and quality of life impact? If definitive treatment of the primary tumor improves overall survival or has an impact on local disease progression it would be a practice changing study and alter the approach to men diagnosed with de novo metastatic prostate cancer. If negative, it would provide evidence against the practice of local control in men with metastatic disease, thereby limiting the potential for unnecessary procedures and treatments.

This trial is novel as it incorporates a multimodality approach to the primary tumor in de novo metastatic prostate cancer with the goal of improving survival and alleviating suffering for men with metastatic disease.

Standard Systemic Therapy (SST): Standard of care systemic therapy per the NCCN guidelines includes Androgen Deprivation Therapy (ADT) with or without the use of docetaxel chemotherapy (up to 6 cycles). This is based on the CHAARTED study, which demonstrated a survival advantage with the use of docetaxel in men with hormone naive M1 PC. *(9)* Using SST as defined by NCCN guidelines will allow for flexibility in standards over the time frame of the study. For example, with LATITUDE and STAMPEDE results use of abiraterone in front line therapy has recently become a standard option.

Local Control and Survival: Several population-based data sets have demonstrated an association between treatment of the primary tumor (radiation or surgery) and improved overall survival in men with de novo metastatic prostate cancer. *(10,11,12)*

Safety: Published studies have demonstrated the limited morbidity of surgery in men with metastatic prostate cancer, demonstrating comparable rates of complications to that of surgery for localized prostate cancer. *(13,14)*

Feasibility: NCT01751438: Multicenter, Phase 2, randomized study of Best Systemic Therapy or Best Systemic Therapy plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer, a fully accrued study at MDACC, UCSF, Fox Chase Cancer Center, and University of British Columbia, has demonstrated feasibility of accrual and randomization of patients to a similarly designed study with a progression-free survival endpoint.

Inclusion of Women and Minorities

This study was designed to include minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	2	0	1	3
Asian	0	21	0	2	23
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	0	134	0	3	137
White	0	1033	0	73	1106
More Than One Race	0	3	0	0	3
Total	0	1194	0	79	1273

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

3.0 DRUG INFORMATION

Please refer to the package insert for the drugs that the individual patient will receive for approved language related to information on dosing, toxicities, preparation and administration of these agents.

4.0 STAGING CRITERIA

Distant Metastasis (M) (AJCC 7th Edition)

M1a Nonregional lymph node(s) (common iliac or above)
M1b Bone(s)
M1c Other site(s) with or without bone disease

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the **S1802** Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or guquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1 REGISTRATION

a. Disease-Related Criteria

1. All patients must have a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate. Patients with pure small cell carcinoma* (SCC), sarcomatoid, or squamous cell carcinoma are not eligible. (*morphology must be consistent with SCC; synaptophysin or chromogranin positive by immunohistochemical staining is insufficient to diagnose SCC).

2. Patients must have an intact prostate.

3. Patients must have at least one of the following scans performed, showing evidence of metastatic disease:
   - technetium bone scan OR
   - CT of abdomen & pelvis OR
   - MRI of pelvis.

   The scan showing metastases must be performed in the range of 42 days before and 14 days following the start of first hormonal therapy. Metastatic disease that is detected by PET scan only (NaF, PSMA, FACBC, C11) but not conventional imaging (Tc99 bone scan, CT or MRI) or solitary metastases by conventional imaging, must be confirmed histologically or cytologically.

4. Patients with known brain metastases are not eligible. Brain imaging studies are not required for eligibility if the patient has no neurologic signs or symptoms suggestive of brain metastasis. If brain imaging studies are performed, they must be negative for disease.

b. Prior/Concurrent Therapy Criteria

1. Patients must have received no more than 28 weeks of SST, as measured from the date of first hormonal therapy (LHRH agonist or LHRH antagonist) or surgical castration. SST is defined as current NCCN guidelines for metastatic prostate cancer.

2. No prior local therapy for prostate adenocarcinoma is allowed (e.g., brachytherapy, HIFU, cryotherapy, laser ablative therapies). Any prior therapy for benign conditions, such as obstruction, are acceptable (e.g.,

transurethral resection of the prostate, greenlight laser ablation, microwave ablation).

3. Patients must not have received any prior systemic therapy for prostate cancer, outside of line of SST to be used for duration of study.

4. Patients must not have progressed while on SST (see Section 10.0).

5. Patients with oligometastatic prostate cancer may receive metastasis directed therapy to up to four sites of disease prior to randomization. Acceptable approaches are included in Section 7.0.

c. Clinical/Laboratory Criteria

1. Patients must be ≥ 18 years of age.

2. Patients must have a complete physical examination and medical history within 28 days prior to registration.

3. Patients must have a documented PSA:
   - Prior to initiation of SST
   - Within 28 days prior to registration
   - Any additional PSAs measured while receiving SST should be recorded.

4. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage 0, I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

d. Specimen Submission Criteria

1. Patients must be offered the opportunity to participate in translational medicine studies and specimen banking for future studies as outlined in Section 15.0.

e. Quality of Life Criteria

1. Patients who can complete Patient-Reported Outcome instruments in English, Spanish or French, must participate in the quality of life studies.

f. Regulatory Criteria

1. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

2. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 STEP 2 RANDOMIZATION

a. Disease-Related Criteria

1. Patients must have no evidence of disease progression (see Section 10.0) during the 28 weeks of SST, as shown by:
    - PSA measure
    - imaging (bone scan and one of the following: CT of abdomen & pelvis, MRI of abdomen & pelvis, CT of abdomen & MRI of pelvis) within 42 days prior to randomization.

2. Patients must have no evidence of symptomatic deterioration (as defined by physician discretion) within 28 days prior to randomization.

3. Patients must have consultation with a urologist and have surgically resectable disease regardless of definitive treatment intent or randomization.

b. Prior/Concurrent Therapy Criteria

1. Patients must have received at least 22 and no more than 28 weeks of SST, as measured from the date of first hormonal therapy (LHRH agonist or LHRH antagonist) or surgical castration. SST is defined by current NCCN guidelines for metastatic prostate cancer (see Section 7.0).

2. Patients must not be planning to receive docetaxel after randomization.

3. All SST-related toxicities must have resolved to ≤ Grade 1 (CTCAE Version 5.0) except for fatigue, weight gain, and hot flashes, prior to randomization.

4. Patients may have received elective metastasis directed therapy to oligometastatic sites (≤4 sites). All treatment must be completed prior to randomization. (see Section 7.0).

c. Clinical/Laboratory Criteria

1. Patients must have a PSA performed within 28 days prior to randomization.

2. Patients must have a testosterone < 50 ng/dL within 28 days prior to randomization.

3. Patients must have a Zubrod performance status of 0 – 1 within 28 days prior to randomization (see Section 10.5).

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm with stratification based on:

- Time between initiation of standard systemic therapy (SST) and Step 1 registration (descriptive only): No SST at registration or < 8 weeks vs. ≥ 8 weeks.
- Intended treatment of the primary tumor: radical prostatectomy vs. radiation therapy
- Receipt of docetaxel during induction treatment of SST interval: yes vs. no
- PSA level at randomization timepoint: (≤ 4 ng/mL vs. > 4 ng/mL)
- Disease volume by conventional imaging: polymetastatic (> 4 sites) vs. oligometastatic and no prior treatment vs. oligometastatic and prior treatment.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Brian Chapin at 713/794-1466, Dr. Ana Aparicio at 713/563-6969 or Dr. Richard Valicenti at 916/734-8295. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Induction Treatment

Patients will receive 22-28 weeks of standard systemic therapy (SST) prior to randomization.

a. Standard Systemic Therapy (SST)

1. For this trial, Standard Systemic Therapy (SST) will follow the NCCN Guidelines for Systemic Therapy for Castration-Naïve Disease for M1 Patients, and is subject to change with evolving therapies. Please refer to the most recent NCCN Guidelines for a complete list of acceptable therapies.

2. EBRT to the primary tumor for low-volume disease is NOT permissible.

3. The start date of SST is considered the date of first hormonal therapy (LHRH agonist or LHRH antagonist) or surgical castration.

4. All treatments intended to be part of SST must be started within 16 weeks (i.e. by the 7th day of the 15th week) of the start of SST. Any treatments started after this point will be considered a new line of SST, requiring patients to come off protocol treatment.

5. Acceptable forms of standard systemic therapy include, but are not limited to:

i. Bilateral orchiectomy

ii. LHRH agonist alone

LHRH Agonist	**Dose**
Goserelin	3.6 mg SC q 28 days OR 10.8mg SC q 12 weeks
Histrelin	50 mg SC q 12 months
Leuprolide	7.5 mg SC/IM q 1 month OR 22.5 mg q 3 months OR 30 mg q 4 months OR 45 mg q 6 months
Triptorelin	3.65 mg monthly OR 11.25 q 3 months OR 22.5 mg q 6 months

iii. LHRH agonist (see above) + Andiandrogen

Antiandrogen Therapy	Dose
Nilutamide	300 mg PO daily for 30 days THEN 150 mg PO daily
Flutamide	250 mg PO q 8 hours
Bicalutamide	50 mg PO daily

iv. LHRH antagonist

LHRH Antagonist	Dose
Degarelix	120 mg for 2 doses (i.e. 2 separate injections totaling 240 mg) THEN 80 mg q 28 days

v. Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist as described in Section 7.1a.2i-ix) & Docetaxel +/- prednisone

Treatment	Dose
Docetaxel	75 mg/m^2 over 1 hr. q 3 weeks
Prednisone	5 mg PO q 12 hours

vi. Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist as described in Section 7.1a.2i-ix) & Abiraterone plus prednisone

Treatment	Dose
Abiraterone	1,000 mg PO daily
Prednisone	5 mg PO q 12 hours

vii. Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist as described in Section 7.1a.2i-ix) & Apalutamide

Treatment	Dose
Apalutamide	240 mg PO daily

viii. Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist as described in Section 7.1a.2i-ix) & Enzalutamide

Treatment	Dose
Enzalutamide	160 mg PO daily

ix. Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist

as described in Section 7.1a.2i-ix) & Abiraterone with methylprednisolone

Treatment	Dose
Abiraterone	500 mg PO daily
methylprednisolone	4 mg PO q 12 hours

b. Supportive Care

1. Patients receiving docetaxel as part of SST may be administered dexamethasone per local institutional guidelines.

2. Bisphosphonates and RANK ligand inhibitors can be used at the discretion of the treating physician. Their use must be recorded.

3. Metastasis directed therapy (MDT): Patients with oligometastatic prostate cancer may receive metastasis directed therapy to up to 4 sites of disease. This therapy must be provided prior to the randomization timepoint. Standard approaches include stereotactic body radio therapy (SBRT) or ablative therapies (for example, radio frequency ablation or cryotherapy).

4. Patients suffering from persistent bone pain or impending bone fracture after initiation of systemic therapy but prior to randomization may receive palliative radiation therapy or ablative therapies to the metastatic site as would occur with standard of care therapy.

5. Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

6. Protocol treatment specific pre-medication is not required for routine infusions. If during any infusion, a reaction occurs, pre-medication (e.g., acetaminophen) and/or antihistamine (e.g., diphenhydramine) may be used for subsequent infusions.

7.2 Randomized Treatment

After completion of 22-28 weeks of SST, patients will be randomized to either Standard Systemic Therapy (SST) only or SST and definitive treatment.

a. SST Only

SST will follow the NCCN guidelines for hormone naïve metastatic prostate cancer and is subject to change with evolving therapies. Patients must not be treated with docetaxel +/- prednisone after randomization.

b. SST and Definitive Treatment

Patients randomized to receive SST plus definitive treatment will receive SST as well as physician's choice of radical prostatectomy or radiation therapy to the primary tumor.

SST will follow the NCCN guidelines for hormone naïve metastatic prostate cancer and is subject to change with evolving therapies. Patients must not be treated with docetaxel +/- prednisone after randomization.

The choice between surgery and radiation therapy as definitive treatment of the primary tumor will be left to the discretion of the treating physician and the patient. This decision will be made prior to randomization.

Acceptable surgeries are described in Section 7.3. Radiation treatment details are located in Section 7.4.

If surgery is chosen, it must be completed within 8 weeks after randomization. If radiation therapy is chosen, it must be initiated within 4 weeks after randomization. If surgery is aborted due to complexity and/or safety then radiation can be used as an alternative therapy within 8 weeks of surgery.

c. Supportive Care

After randomization, any new bone pain associated with metastases or presence of two or more new skeletal metastases initiating radiation treatment would be considered progression, as stated in Section 10.0.

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Protocol treatment specific pre-medication is not required for routine infusions. If during any infusion, a reaction occurs, pre-medication (e.g., acetaminophen) and/or antihistamine (e.g., diphenhydramine) may be used for subsequent infusions.

7.3 Arm 2- Surgery Stratum

a. Surgical removal of the prostate. Radical prostatectomy or cystoprostatectomy are acceptable surgical treatments. Extended pelvic lymph node dissection is recommended. Failure to complete does not exclude patients from participating.

b. Acceptable approaches to surgical removal of the prostate will include:
- Robotic Assisted
- Laparoscopic
- Open surgical approaches

c. Post-operative radiation therapy is also allowed and should be based on adverse pathological factors.

7.4 Arm 2- Radiation Therapy Stratum

If radiation therapy is selected as the method of definitive treatment of the primary tumor, it must begin within 4 weeks after randomization. At least two weeks should have elapsed since completion of any radiation therapy to metastatic sites.

a. Prescribed Dose

1. Site directed radiation

Stereotactic Radiotherapy

The goal of SBRT is to deliver appropriate metastasis directed radiotherapy while minimizing exposure of surrounding normal tissues. The dose used to treat a given metastasis should be based on the location of the metastasis, as normal tissue toxicity is likely to arise from the organs at risk surrounding the metastasis.

In the delivery of SBRT there should be the use of stereotactic, fixed gantry angles with 3D conformal fields or Intensity-Modulated Radiation Therapy (IMRT) techniques (VMAT or Tomotherapy allowed). The recommended prescription radiation doses are listed in Table 1.

Table 1. Stereotactic Dose Objectives for Oligometastases

Dose Schedule	Site	BED2	BED3
8-9 Gy x 3	Osseos/Spine	120 – 148.5 Gy	88 – 108 Gy
6-7 Gy x 4	Lymph nodes (without pelvic RT)	120 – 138.1 Gy	90 – 102.9 Gy

The prescription dose should cover 95% of the PTV

- Minimum dose within PTV – 90% of prescribed dose to a 0.03 cc volume
- Maximum dose within the PTV – 130% of prescribed dose to a 0.03 cc volume

2. Treating the whole pelvis is optional and must include any pelvic metastatic lesion.

   Acceptable Treatment Modalities: IMRT or 3DCRT

   Prescribed Dose for pelvic nodes 45 Gy in 1.8 Gy fractions to cover 95% of PTV1

   - Minimum dose within PTV – 95% of prescribed dose to a 0.03 cc volume
   - Maximum dose within the PTV – 107% of prescribed dose to a 0.03 cc volume

3. Prostate or prostatic fossa Boost or primary prostate or prostatic fossa irradiation without pelvic treatment

   Acceptable Treatment Modalities for Prostate Boost after pelvic irradiation: IMRT or 3D CRT

   Prescribed Dose for Prostate boost: 34.2 or 34Gy IMRT in 1.8 or 2.0 Gy fractions

   Prostate irradiation alone: 79.20 or 80 Gy in 1.8 or 2.0 Gy fractions.

   Prostate hypofractionated irradiation alone to 60 Gy in 3.0 Gy fractions is also allowed as well as prostate SBRT to 36.25 Gy in 7.25 Gy

Prostatic fossa boost: 23.4 to 24 Gy IMRT or 3D CRT in 1.8 or 2.0 Gy fractions.

Prostatic fossa irradiation alone: 68.4 or 70 Gy in 1.8 or 2.0 Gy fractions.

Table 2: Dose Constraints for Local Treatment of the Prostate

	PTV dose (encompassing 98% of PTV-P)	Minimum PTV-P Dose to 0.03 cc volume	Maximum PTV-P dose to 0.03 cc volume	CTV-P Dose	PTV V110% of Rx
Per Protocol	100%	≥ 98%	≤ 107%	100%	≤ 10%
Variation Acceptable	96-99.9%	95-97.9%	107.1 – 110%	98-99.9%	
Deviation Unacceptable	<95%	<95%	>110%	<98%	>10%

Dmax must be within PTV

b. Technical Factors

1. For stereotactic treatment, 3D conformal fields at static gantry angles may be used. Noncoplanar beams are permitted. Typically, 8-12 gantry angles are employed for each target volume.

2. For IMRT or 3DCRT, no specific field arrangement is required. Arc therapy is permissible for IMRT components of the treatment. All beams should be coplanar.

3. RT will be delivered with megavoltage equipment at energies ≥ 6 MV. Typically, except for tomotherapy and VMAT techniques, 5 to 9 gantry angles are employed for the boost EBRT treatment.

c. Immobilization, Simulation, and Localization

1. Immobilization

Patients will be positioned supine on a flat tabletop. If patients have bony metastases in the thoracic, or abdominal or pelvic regions, they should optimally be simulated with arms up. If reproducibility or comfort is a concern, then arms down is permissible. Patients will be immobilized with a customized thermoplastic immobilization cast or a molded foam cradle for stabilization and setup reproducibility. Degree of bladder fullness should be made to duplicate the degree of fullness anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such (especially for cases in which image guidance or adaptive treatments are not implemented). The rectum should be kept as empty as possible.

2. CT Simulation

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is not required to help identify the apex of the prostate. Oral contrast may be used for the small bowel. IV contrast is permitted to assist in identifying the pelvic vessels. Rectal contrast is discouraged because it may distend the rectum and artificially displace the prostate in the anterior direction.

CT simulation for all components of treatment will be performed once with virtual treatment planning used for creating a single integrated plan. For any metastatic sites away from the pelvic radiation fields, CT images

should be acquired at a slice thickness of ≤ 2 mm with imaging a minimum of 10 cm above and below the index metastasis.

For pelvic and prostate IMRT, CT images should be acquired at a slice thickness of ≤3 mm from the top of the iliac crests superiorly to mid-femur inferiorly. If there are metastases that will receive a stereotactic boost within the pelvic radiation fields, CT slice thickness should be ≤2 mm. Depending upon equipment capabilities and physician preference, all CT images for the different components of treatment can be acquired in a single CT study.

Target volumes (Section 7.4d.2) and normal critical structures (Section 7.4d.3) will be defined in the slices in which they are visualized. Separate isocenters will be defined for extrapelvic metastases and the pelvis at the time of simulation. All patients will be tattooed for these isocenters. Pelvic metastases being planned for a stereotactic boost may have a separate isocenter defined in treatment planning with shifts designated from the initial pelvic fields.

3. Localization

Stereotactic

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices, an in-room helical CT device, tomotherapy helical CT, cone-beam CT equipment, or standard EPID imaging. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained. For institutions using equipment that does not allow this double-check capability, agreement between the treatment unit isocenter or reference point in space must be carefully checked for agreement with the imaging isocenter. For spinal lesions, couches with six degrees of freedom may be used for roll and pitch corrections.

In multifraction regimens, post-treatment verification CT scans or verification planar images may be taken at the discretion of the participating institution but are not required for protocol. When a single fraction is used, post-treatment verification imaging must be used.

d. Treatment Planning/Target Volumes

1. Patients should have a composite treatment plan generated at the beginning of treatment so that the final EBRT dose to critical structures is evaluated before any dose delivery has begun.

2. The definition of GTV, CTV and PTV will be in accordance with the ICRU Reports #50 and 62:

i. Stereotactic Treatment of extrapelvic nodal and bony metastasis.

The initial treatment will be used only for gross disease where a nodal or bony metastasis is above the aortic bifurcation, away from the planned pelvic fields. The goal is to give an ablative dose

with tolerable risk of side effects that are dependent upon the site of metastasis.

Gross Target Volume (GTV-M1, GTV-M2, GTV-M3, GTV-M4)
Gross target volumes for nodal metastases can be contoured based upon fusion of pre-hormone therapy CT scan to the treatment planning CT scan for localization but treat the involved nodal volume based upon the simulation CT. Bony metastasis GTVs can be defined based upon using pre-hormone diagnostic CT, bone scan and MRI.

Clinical Target Volume (CTV-M1, CTV-M2, CTV-M3, CTV-M4)
The clinical target volume for any isolated metastatic lesions will include any lymph node 1.5-3 cm (pre-hormone therapy) or bony lesion ≤ 5cm or a single vertebral body without epidural/soft tissue extension. CTV = GTV.

If there are technical issues with treatment delivery due to small fields for nodal metastases that have decreased in size to < 1cm with hormone therapy, a CTV expansion of 2-4 mm is acceptable with no overlap with surrounding normal tissue.

Spinal lesions will use International Spine Radiosurgery Consortium Consensus guidelines for target volume delineation [Cox 2012].

Planning Target Volume (PTV-M1, PTV-M2, PTV-M3, PTV-M4)

The PTVs will provide a margin around the CTVs to compensate for the variability of treatment set up and internal organ motion. A range of 3-6 mm around the CTV is required to define each respective PTV.

ii. Pelvic Field +/- Adjacent Metastasis

Dose for pelvic fields (CTV1/PTV1) will be 45.0 Gy at 1.8 Gy per fraction. No specific field arrangement is required for IMRT, although typically 5-9 fields are used for fixed gantry treatment. Arc techniques with RapidArc, Tomotherapy and VMAT are also allowed.

Clinical Target Volumes
Separate CTVs will be defined for the prostate (CTV-P), seminal vesicles (CTV-SV), and the obturator, external iliac, proximal internal iliac and common iliac nodes (CTV-N). Please refer to the pelvic nodal atlas at the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; http://www.rtog.org/atlases/PelvicLymphNodeProstateAtlas/main.html). The presacral nodes from L5-S1 to S3 may be included if desired depending on whether the dose constraints to the rectum are achievable (see Table 1). The CTV1 will include a 0.6 cm margin in 3-dimensions to the contoured iliac vessels, but not extend outside of the true pelvis, into the pelvic musculature nor into adjacent identifiable organs, such as the bladder, rectum or other bowel. Extension of the CTV into adjacent bone may be carved out unless including an identified bony metastasis.

Planning Target Volume (PTV1)
PTV1 will be a composite of mobile (PTV-PSV) and immobile (PTV-N) volumes. Daily alignment for treatment delivery will be based upon pelvic bones, so larger margins are necessary for coverage of the primary tumor.

PTV-PSV will be expansions of the CTV-P and CTV-SV should be larger (e.g. 0.5-0.7 cm posteriorly, 0.5-1.0 cm in other directions) to account for daily variation unless rectal balloon immobilization is used. With rectal balloon immobilization, PTV expansions may be 0.4-0.5 cm posteriorly and 0.5 – 0.7 cm in other directions.

CTV-N will have a 0.5 – 0.7 cm expansion to create PTV-N. PTV1 is then the primary volume for treatment plan optimization. Should coverage require compromise of coverage, see Table 2 in Section 7.4a.3 on evaluating PTV-PSV and PTV-N separately

iii. Full-dose Prostate or Prostate Boost with IMRT or 3DCRT

Combined with the initial pelvic fields, the planned BED2 and BED3 dose to the prostate will be 122 Gy to 145.5 Gy.

No specific field arrangement is required for IMRT, although typically 5-9 fields are used for fixed gantry treatment. Arc techniques with RapidArc, Tomotherapy and VMAT are also allowed. This dose will complete treatment delivery to involved sites with an integrated treatment plan accounting for dose to all CTVs, PTVs and OARs.

Clinical Target Volume (CTV2)
The CTV2 is the CTV-P delineated by the treating physician. Any grossly involved disease in the seminal vesicles on diagnostic pre-treatment CT or MRI may be added as part of CTV2 as the treating physician's discretion, but the uninvolved seminal vesicles may not be included to minimize normal tissue dose.

Planning Target Volume (PTV2)
The PTV2 will provide a margin around the CTV2 to compensate for the variability of treatment set up and internal organ motion. A range of 4-7 mm around the CTV is required to define each respective PTV. Individual selection of a PTV margin should be based on the institution's level of confidence in patient set-up and the availability of image guidance. Superior and inferior margins (capping) should be 5-10 mm cm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 4-7 mm margin in 3 dimensions.

Gross Target Volume (GTV-M1p, GTV-M2p, GTV-M3p)
Gross target volumes for nodal metastases can be contoured based upon fusion of pre-hormone therapy CT scan to the treatment planning CT scan for localization but treat the involved nodal volume based upon the simulation CT. Bony metastasis GTVs can be defined based upon using pre-hormone diagnostic CT, bone scan and MRI.

Clinical Target Volume (CTV-M1p, CTV-M2p, CTV-M3p)
The clinical target volume for any isolated metastatic lesions will include any lymph node 1.5-3 cm or bony lesion ≤ 5cm or a single vertebral body without epidural/soft tissue extension. CTV = GTV.

Planning Target Volume (PTV-M1p, PTV-M2p, PTV-M3p)

The PTVs will provide a margin around the CTVs to compensate for the variability of treatment set up and internal organ motion. A range of 3-5 mm around the CTV is required
to define each respective PTV.

3. Normal Critical Structures

i. Extrapelvic OARs

Normal structures contoured are dependent upon the treatment site of extrapelvic metastasis. All normal tissue constraints will use AAPM Task Group 101 guidelines [Benedict 2010].

ii. Pelvic OARs

Normal critical structures to be defined on the treatment planning CT scan will include the following: bladder, rectum (from its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior to the inferior-most extent of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Any small bowel within the primary beam aperture should be defined as well. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. If IMRT is being used to treat the pelvic nodes, the potential bowel space (not just individual loops of bowel) where the small and large bowel may fall should be outlined. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and inferiorly from the level of the top of CTV1 (outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions). See the NRG web site (https://www.nrgoncology.org/ciro-genitourinary) to view examples of target and normal tissue contours.

The following table summarizes the naming of targets and critical structures for submission
of data.

Table 3. Target Volumes and Organs at Risk

OAR Standard Name	**Description**
Bladder	Bladder
Bowel	Small bowel space (not individual loops)
Femur_L	Left femoral head
Femur_R	Right femoral head

OAR Standard Name	Description
Rectum	Rectum
Sigmoid	Sigmoid colon
PenileBulb	Penile Bulb
Target Volume Standard Name	
PTV1	PTV for pelvic RT, if used
PTV2	PTV for prostate
GTV_M1, GTV_M2, etc	GTV's for extrapelvic metastases
CTV_M1, CTV_M2, etc	CTV's for extrapelvic metastases
PTV_M1, PTV_M2, etc	PTV's for extrapelvic metastases
GTV_M1p, GTV_M2p, etc	GTV's for pelvic metastases
CTV_M1p, CTV_M2p, etc	CTV's for pelvic metastases
PTV_M1p, PTV_M2p, etc	PTV's for pelvic metastases

e. Critical Structures

Critical structure dose constraints shall remain consistent with those represented in prior RTOG 3DCRT/IMRT prostate protocols (see Table 4 below). Of note, the bone marrow constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in compromised coverage of the dose delivery to the target volume.

Table 4. Critical Structure Dose Constraints in 1.8 Gy fractions. For all other fraction schedules a BED constraint must be used for each OAR.

OAR	Parameter	Goal	Variation Acceptable	Deviation Unacceptable
Bladder	V80 Gy	≤ 5%	≤ 15%	
	V75 Gy	≤ 10%	≤ 25%	
	V70 Gy	≤ 25%	≤ 35%	
Bowel	Dmax	≤ 50 Gy	≤ 52 Gy	
Femur (L+R)	Dmax	≤ 50 Gy	≤ 50 Gy to 2 cc	> 50 Gy to 2 cc
	V40 Gy	≤	≤	
Rectum	V75 Gy	≤ 10%	≤ 15%	
	V70 Gy	≤ 20%	≤ 35%	
	V65 Gy	≤ 25%	≤ 40%	
	V60 Gy	≤ 35%	≤ 50%	
Penile Bulb	Mean dose	≤52.5 Gy		

f. Treatment Verification and Delivery

For IMRT the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films/images are not required for IMRT but orthogonal verification films/images are required, just as for 3DCRT. Real-time ultrasound localization and on-line cone beam CT image guidance are important complements to conventional port films or portal imaging; however, there

is some reluctance in a cooperative group setting to rely solely upon these modalities to verify patient positioning.

Daily on-line target localization (kV or MV imaging with fiducials, trans-abdominal ultrasound, or other) or off-line adaptive approaches to account for interfraction organ motion and setup variability are encouraged on this study but not required.

g. Compliance Criteria

Acceptable dose heterogeneity for external beam treatment is summarized in Tables 1 and 2.

The maximum point dose to normal critical structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

Compliance Criteria for SBRT of Oligometastases

	PTV dose (encompassing 95% of PTV)	Minimum PTV Dose to 0.03 cc volume	Maximum PTV dose to 0.03 cc volume
Per Protocol	100%	≥ 90%	≤ 130%
Variation Acceptable	96-99.9%	80-90%	130 – 140%
Deviation Unacceptable	<95%	<80%	>140%

See Table 2 for compliance criteria for the prostate.

7.5 Criteria for Removal from Protocol Treatment

a. Disease progression as defined per Section 10.0.

b. Patient not found to be surgical candidate.

c. Change in drugs used as part of Standard Systemic Therapy

d. Physician discretion.

e. Delay of definitive treatment to primary tumor for any reason beyond the specified window (8 weeks for surgery, 4 weeks for initiation of radiation)

f. The patients may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off-Treatment Notice.

7.7 Follow-Up Period

Patients who are registered but ultimately not randomized will require no additional follow-up.

All randomized patients will be followed for 8 years after randomization or until death, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

Standard of care treatment should be modified based on the treating physician's best judgment and based on NCCN guidelines.

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Radiation Therapy Adverse Events

a. All patients will be seen weekly by their treating radiation oncologist while undergoing EBRT.

Any observations with respect to the following symptoms/side effects will be recorded:

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence
- Radiation dermatitis

b. Clinical discretion may be used in managing radiotherapy-related side effects. Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin.

8.3 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Chapin via phone at 713/794-1466 or email bfchapin@mdanderson.org. For radiation treatment or delay questions, please contact Dr. Valicenti via phone at 916/734-8295 or email rkvalicenti@ucdavis.edu.

8.4 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting per Table 8.1 below, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for commercial agents, radiation therapy, and surgery

Commercial agent, surgery, and radiation therapy reporting requirements are provided in Table 8.1. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 8.1. Expedited reporting requirements for adverse events experienced by patients within 30 days of the last administration of a commercial agent, surgery, or last radiation treatment

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] **This includes all deaths within 30 days of the last dose of treatment with a commercial agent, surgery, or last radiation treatment, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent, surgery, or last radiation treatment and is attributed (possibly, probably, or definitely) to the treatment and is not due to cancer recurrence must be reported according to the instructions above.**

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

f. Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

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

9.0 STUDY CALENDAR

9.1 SST Only

REQUIRED STUDIES	Step 1: Registration	Step 2: Randomization	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 30	M 36	Q6M Until Pro-gression	Q12M Until Pro-gression	Pro-gres-sion	Post-Pro-gression F/U (11)
PHYSICAL																
History and Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Weight and Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Disease Assessment (10)		X				X				X		X		X		
Toxicity Notation (1)			X	X	X	X	X	X	X	X	X	X	X		X	
LABORATORY																
PSA	X	X (3)	X	X	X	X	X	X	X	X	X	X	X		X	
Testosterone		X (3)	X	X	X	X	X	X	X	X	X	X	X		X	
SPECIMEN SAMPLES (2)																
Whole blood	X	X	X												X	
Prostate Biopsy Tissue	X (4)	X													X	
X-RAYS AND SCANS (10)																
Bone Scan	X	X				X				X		X		X	X	
MRI/CT Scan	X	X				X				X		X		X	X	
QUALITY OF LIFE (6)																
EORTC QLQ-C30	X	X				X				X		X				
EPIC-26	X	X				X				X		X				
SURVIVAL UPDATE																
Survival Update																X
Local Symptomatic Progression Notation			X	X	X	X	X	X	X	X	X	X	X			X
TREATMENT																
Standard Systemic Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X			
Docetaxel	X (9)															

Click here for footnotes

9.2 SST & Definitive Treatment

REQUIRED STUDIES	Step 1: Registration	Step 2: Randomization	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 30	M 36	Q6M Until Pro-gression	Q12M Until Pro-gression	Pro-gression	Post-Pro-gression F/U (11)
PHYSICAL																
History and Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Weight and Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Disease Assessment (10)		X				X				X		X		X		
Toxicity Notation (1)			X	X	X	X	X	X	X	X	X	X	X			
LABORATORY																
PSA	X	X (3)	X	X	X	X	X	X	X	X	X	X	X		X	
Testosterone		X (3)	X	X	X	X	X	X	X	X	X	X	X		X	
SPECIMEN SAMPLES (2)																
Whole blood (see Section 15.3)	X	X	X												X	
Prostate Biopsy Tissue	X (4)	X													X	
Seminal Vesicle Tissue (5)			X													
Lymph Node Cores (5)			X													
X-RAYS AND SCANS (10)																
Bone Scan	X	X				X				X		X		X	X	
MRI/CT Scan	X	X				X				X		X		X	X	
QUALITY OF LIFE (6)																
EORTC QLQ-C30	X	X				X				X		X				
EPIC-26	X	X				X				X		X				
SURVIVAL UPDATE																
Survival Update																X
Local Symptomatic Progression Notation			X	X	X	X	X	X	X	X	X	X	X			X
PHYSICAL PROCEDURES																
Definitive Radiation (7) **OR** Prostatectomy (8)		X														
TREATMENT																
Standard Systemic Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X			
Docetaxel	X (9)															

Click here for footnote

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes

(1) Patients will be monitored for toxicity prior to each treatment or at more frequent intervals as determined by the treating physician.
(2) See Section 15.0.
(3) If Step 2 Registration occurs within 28 days after Step 1 Registration, lab values need not be repeated.
(4) Must submit FFPE block or slides from primary tumor (and metastatic FFPE block or slides if available). Archival biopsy tissue acceptable.
(5) Only for patients undergoing prostatectomy. Tissue to be submitted within 30 days after surgical procedure.
(6) See Section 18.3.
(7) Patient to start radiation therapy within 4 weeks after randomization.
(8) Patient to have prostatectomy within 8 weeks after randomization.
(9) Optional; Up to 6 cycles allowed; to be completed prior to Step 2 registration.
(10) A CT/MRI of the abdomen & pelvis AND a bone scan are acceptable for disease assessment. Disease assessments will be done annually until progression (and more frequently if clinically indicated) by the same methods used at baseline.
(11) Post-progression, patients will be followed for a survival update and a notation regarding local symptomatic progression every six months until four years from randomization and then annually until eight years from randomization.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Overall Survival (OS)

From date of randomization to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.2 Measurability of Lesions

a. Measurable disease: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) by ≥ 1.0 cm with CT or MRI scans. All tumor measurements must be recorded in decimal fractions of centimeters.

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm 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 non-measurable as are previously radiated lesions that have not progressed.

   NOTE: **Patients who do not have measurable disease, but are clinically considered to have metastatic prostate cancer based on bone lesions or non-measurable, but pathologically enlarged lymph nodes, are eligible from this perspective.**

c. Notes on measurability

1. For CT and MRIs, 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 by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.3 Progression Criteria (per PCWG2 guidelines)

Progression is defined as any of the following that occur:

For Step 1, baseline is start of Androgen Deprivation Therapy (bilateral orchiectomy, LHRH agonist alone, LHRH agonist + antiandrogen or LHRH antagonist as described in Sections 7.1a.2i-ix)

For Step 2, baseline is randomization.

a. PSA

1. If decline in PSA after baseline: Record time from baseline to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later.

2. If no decline in PSA after baseline: PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks after baseline.

b. Bone

1. The appearance of ≥ 2 new lesions after baseline, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions.

2. The date of progression is the date of the first scan that shows the changes. Initiation of a new systemic agent to treat metastatic prostate cancer will be deemed a progression event.

c. Soft Tissue Progression (per RECIST 1.1)

1. Twenty percent increase in the sum of appropriate diameters of the target measurable lesions over smallest sum observed after baseline (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measureable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/side.

d. Palliative Radiation – Step 2 ONLY

1. Any new bone pain associated with metastases leading to the initiation of palliative radiation treatment after randomization will be considered a progression event.

e. Alteration in Standard Systemic Therapy

1. Changes to systemic therapy due to changes in any of the above clinical factors will be considered a progression event.

10.4 Symptomatic Local Progression

Occurrence of any of the following events post-randomization: CTCAEv5 Grade ≥ 2 hematuria, urinary retention, urinary tract obstruction, urinary tract pain, pelvic pain, renal and urinary disorders-other.

10.5 Progression-Free Survival

From date of randomization to date of first documentation of progression, or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to compare overall survival in metastatic prostate cancer patients who received standard systemic therapy plus definitive treatment of the primary tumor versus standard systemic therapy alone.

11.1 Study Design

A 5-year accrual period and an additional 6 years of follow-up are assumed. We assume the median OS from the time of randomization is 50 months (56 months minus 6 months of lead in SST) for those receiving SST alone. We would be interested in the experimental regimen, SST + definitive treatment, if median survival were improved by 25% (i.e., median of 62.5 months). With 4.3 years of accrual and 6 more years of follow-up, and assuming a one-sided 0.025 and 86% statistical power, we will need 1066 eligible patients randomized to the two arms (translates into 21 patients per month accrual rate).

Using a 1:1 randomization allocation, this equals 533 eligible patients per arm.

We anticipate that 10% of Step 1 enrolled patients will either progress or otherwise not be available for Step 2 randomization. We anticipate that 1173 eligible patients will need to be enrolled in Step 1 in order to obtain 1000 eligible, Step 2 randomized patients. Allowing for an additional 100 patients to be ineligible, total accrual to Step 1 is projected to be 1273 patients. We will limit randomizations so that at least two-thirds of men randomized are from the “planned RP” stratum (i.e., we will close accrual to the RT intent stratum after one-third of total sample size has been randomized).

11.2 Interim Analysis

Evidence suggesting early termination of the trial and a conclusion that the SST + definitive treatment is not better than the standard arm of SST alone would be if the alternative hypothesis of a 25% improvement in OS with the experimental arm is rejected at the one-sided 0.01 level. For the second and third interim analyses, the null and alternative hypotheses with respect to survival will be tested at the one-sided 0.005 and 0.01 level respectively.

If the decision is to continue the study before reporting, the final analysis will be conducted when the required number of deaths have occurred in both arms or at a maximum of 8 years after randomization accrual has been completed, whichever comes first. A one-sided stratified logrank test will be used to test the primary survival null hypothesis at the alpha=0.022 level. All analysis timing will be based on the pooled number of events in both arms. A proportional hazards model will be fit to estimate the hazard ratio adjusting for the stratification factors as covariates in the model.

		# of expected deaths			Interim testing	
Interim analysis	Approximate time since first patient randomized	SST	SST + definitive RT or RP	% of expected death info	Superiority endpoint, Z-score	Futility endpoint, Z-score
1	52 mo.	154	129	39%	Not performed	OS, 2.32

2	72 mo.	246	209	60%	OS, 2.58	OS, 2.32
3	90 mo.	309	268	79%	OS, 2.58	OS, 2.32
Final	10.4 years	393	351	100%	OS, 2.01	

11.3 Secondary Analyses

Radical prostatectomy + SST vs. SST:
We will analyze men from the "planned RP" stratum. There will be approximately 670 eligible patients in this subset (335 per arm). If we make the same assumptions about 4.3 years for accrual and an additional 6 years of follow-up and a one-sided alpha=0.025, then there will be 80% power to detect a hazard ratio of 1.30, equivalent to an increase in the median OS from 50 months in the SST arm to 65 months in the RP + SST arm.

Stratification factors as potential treatment modifiers: Using the ITT population at randomization, we will fit a proportional hazards OS model and adjust for each stratification factor and also include an indicator for treatment arm. We will then assess the residual chi-square test to evaluate whether any of the stratification factor and treatment arm interactions are statistically significant. A two-sided p-value $\leq$ 0.10 will be considered evidence of a statistical interaction.

To compare the rate of symptomatic local progression and progression-free survival between the treatment arms. (Refer to Section 10.0 for definitions), a proportional hazards model will be fit to each of these endpoints where the time interval starts at date of randomization to (i) time of first symptomatic local progression or ii) progression or death due to any cause, where those without the event are censored at their last contact date. Stratification factors will be adjusted for as covariates.

11.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Surgeon Credentialing

a. Completion of accredited urologic residency training (for all participating surgeons).

b. Minimum of 20 major pelvic surgeries (e.g., prostatectomy, cystoprostatectomy) per year. A signed letter to be provided by the chair or chief of urology for each

surgeon at a site. This letter will be maintained on file at the site and may be subject to audit.

12.2 RT Credentialing Requirements

To participate, centers are required to be fully credentialed. The credentialing process includes the completion of a Facility Questionnaire, phantom irradiation (for IMRT only), IGRT credentialing if SBRT is to be used, and the completion of a credentialing status inquiry form (Table 12.1). Instructions for completing these requirements are available on the IROC Houston QA center website. Visit: http://irochouston.mdanderson.org and select "Credentialing".

Table 12.1

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org			
	Treatment Modality			
	3D	IMRT	SBRT	Key Information
Facility Questionnaire	X	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Phantom Irradiation		X	X	An IMRT phantom study provided by the IROC Houston QA Center must be successfully completed. For SBRT credentialing the lung phantom with reciprocating platform must be successfully completed. Instructions for requesting and irradiating the phantoms are found on the IROC Houston website (http://irochouston.mdanderson.org). Note that use of Tomotherapy requires a separate phantom irradiation. A prior successful phantom irradiation need not be repeated for this study.
IGRT Credentialing			X	IGRT credentialing requirements can be found at http://irochouston.mdanderson.org.
Credentialing Status Inquiry Form	X	X	X	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Credentialing Notification Issued to:				
Institution				Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered within 28 weeks after initiation of standard systemic treatment.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

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

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

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

b. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1802** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol #S1802
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For S1802 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- CTSU RT Facilities Inventory Form

- NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

Checking Your Site's Registration Status:

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

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the

OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select):
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White

- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after 28 weeks of SST) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam). and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the RAVE CRA role or CRA Lab Admin role, the user must hold a minimum of a AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. Step 1:

1. WITHIN 15 DAYS AFTER STEP 1 REGISTRATION:

Submit the following:

S1802 Step 1 Onstudy Form

Blood specimens as outlined in Section 15.0

Pathology Report OR Cytology Report

Radiology reports from all scans performed to assess disease & establish eligibility at study registration.

S1802 Cover Sheet for Patient-Completed Questionnaires

EORTC QLQ-C30

EPIC-26

2. WITHIN 8 WEEKS AFTER INITIATION OF SST TREATMENT (IF APPLICABLE):

Submit the following:

Tissue specimens as outlined in Section 15.0

3. WITHIN 15 DAYS AFTER END OF INDUCTION TREATMENT

Vital Status Form

S1802 Induction Treatment Summary Form

S1802 Induction PSA Reporting Form

S1802 Induction Testosterone Reporting Form

S1802 Pre-Randomization Off-Study Form (if patient will not be registered to Step 2)

b. Step 2:

1. WITHIN 15 DAYS AFTER RANDOMIZATION:

Submit the following:

Vital Status Form

S1802 Step 2 Onstudy Form

Baseline Tumor Assessment Form

S1802 PSA Reporting Form

S1802 Testosterone Reporting Form

Radiology reports from all scans performed to assess disease & establish eligibility at randomization.

Specimens as outlined in Section 15.0

S1802 Cover Sheet for Patient-Completed Questionnaires

EORTC QLQ-C30

EPIC-26

2. WITHIN 15 DAYS OF EACH POST-RANDOMIZATION VISIT (EVERY 3 MONTHS POST- RANDOMIZATION FOR 2 YEARS, THEN EVERY 6 MONTHS UNTIL PROGRESSION):

Vital Status Form

S1802 Standard Systemic Therapy Treatment Summary Form (if on protocol treatment)

S1802 Adverse Event Summary Form (if on protocol treatment)

S1802 PSA Reporting Form (if on protocol treatment)

S1802 Testosterone Reporting Form

S1802 Symptomatic Local Progression Form

3. WITHIN 15 DAYS AFTER MONTH 3 POST-RANDOMIZATION VISIT:

   Vital Status Form

   S1802 Surgical Treatment Summary Form (if applicable)

   S1802 RT Summary Form (if applicable)

   OP Report (if applicable)

   Pathology Report (if applicable)

   Radiotherapy Report (if applicable)

   Specimens as outlined in Section 15.0

4. WITHIN 15 DAYS AFTER COMPLETION OF MONTH 9 POST-RANDOMIZATION VISIT:

   Vital Status Form

   S1802 RT Summary Form (if applicable)

   Radiotherapy Report (if applicable)

5. WITHIN 15 DAYS AFTER EVERY DISEASE ASSESSMENT (EVERY 12 MONTHS POST-RANDOMIZATION UNTIL PROGRESSION OR AS CLINICALLY INDICATED):

   Vital Status Form

   Follow-Up Tumor Assessment Form

   Radiology reports from all scans performed

6. WITHIN 15 DAYS AFTER MONTH 12 POST-RANDOMIZATION VISIT, MONTH 24 POST-RANDOMIZATION VISIT & MONTH 36 POST-RANDOMIZATION VISIT:

   Vital Status Form
   S1802 Cover Sheet for Patient-Completed Questionnaires

   EORTC QLQ-C30

EPIC-26

7. WITHIN 15 DAYS OF DISCONTINUATION OF PROTOCOL TREATMENT:

   Submit the following:

   Vital Status Form

   Off-Treatment Notice

   S1802 Standard Systemic Therapy Treatment Form

   S1802 Adverse Event Summary Form

8. WITHIN 15 DAYS AFTER POST-RANDOMIZATION PROGRESSION (as defined in Section 10.0):

   Vital Status Form

   Off-Treatment Notice

   Follow-Up Tumor Assessment Form

   S1802 Standard Systemic Therapy Treatment Form

   S1802 Adverse Event Summary Form

   S1802 PSA Reporting Form

   S1802 Testosterone Reporting Form

   S1802 Symptomatic Local Progression Form

9. WITHIN 30 DAYS AFTER VISIT EVERY 6 MONTHS AFTER PROGRESSION UP TO YEAR 4, THEN ANNUALLY UNTIL 8 YEARS FROM REGISTRATION:

   Submit the following:

   Vital Status Form

   S1802 Follow-Up Form

   S1802 Symptomatic Local Progression Form (if symptomatic local progression event)

   Late Effects Form

10. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

    Submit the following:

    Vital Status Form

    Notice of Death

15.0 SPECIAL INSTRUCTIONS

15.1 Formalin-fixed paraffin-embedded (FFPE) Tissue Specimens for Banking (Optional for ALL patients)

If the patient consents, the following must be submitted to the SWOG Biospecimen Bank, Lab #201:

a. FFPE Tissue Specimen Submission & Timepoints

1. At Step 1 Registration

a. Within 30 days after registration submit 2 FFPE **pre-treatment primary** tissue blocks (strongly preferred) or 1 H&E and 20 unstained, uncharged slides cut from 2 pre-treatment primary tissue blocks (21 slides from each block or 42 slides total). Submission of archival tissue is acceptable.

b. If available, within 30 days after registration submit 1 FFPE tissue block (strongly preferred) or 1 H&E and 10 unstained, uncharged slides from the **archival pre-treatment metastatic** FFPE tumor tissue.

2. Within 30 days after randomization

a. From pre-randomization biopsy, 2 representative blocks (strongly preferred) or 10 unstained, uncharged 4 micron slides cut from 2 tissue blocks (10 slides from each block or 20 slides total).

3. Within 30 days after radical prostatectomy (if done):

2 representative blocks (strongly preferred), or 20 unstained, uncharged slides (6 blocks or 60 slides total) from each of the following tissues:

- Prostate (2 blocks or 20 slides cut from 2 tissue blocks),
- Seminal vesicle (2 blocks or 20 slides cut from 2 tissue blocks) and
- Lymph node cores (2 blocks or 20 slides cut from 2 tissue blocks) from clinically viable nodal disease (positive lymph nodes tissue) from radical prostatectomy and lymph node dissections-within 30 days of procedure

4. At disease progression (as defined in Section 10.0)

a. Within 30 days after biopsy to document progression (if done), submit 2 blocks (strongly preferred) or 20 unstained, uncharged slides (10 unstained slides cut from each block)

b. FFPE Tissue Specimen Submission Collection Instructions

1. Blocks or slides must be shipped at ambient temperature. See Section 15.4 for labeling instructions.

   The corresponding anatomic pathology report that includes the diagnosis is required with FFPE tissue. Label the report with the patient ID# and surgical pathology identification number.

   Refer to the submission instructions on the SWOG Specimen Submission webpage: (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

2. Specimen collection kits are not provided for this submission; sites will use institutional supplies.

15.2 Whole blood for banking (Optional for ALL patients)

If the patient consents, the following must be submitted to the SWOG Biospecimen Bank, Lab #201:

a. At Step 1 Registration

1. Collect 5 mL of whole blood in purple top (EDTA) tube. Invert gently to mix; **do not process**. Ship at ambient temperature on the day of collection. See Section 15.4 for labeling and shipment instructions.

2. Specimen collection kits are not provided for this submission; sites will use institutional supplies.

15.3 Whole Blood Specimens for translational medicine studies (Optional for ALL patients)

If the patient consents, the following must be submitted to Dr. Amir Goldkorn's lab (Lab #181) at the following time points:

a. Collect 7.5 mL of whole blood in each of the following tubes: RareCyte tube, Streck DNA tube, PAXgene RNA tube (3 tubes total) at each of these time points (and ship at room temperature on the day of collection):

1. Registration Step 1 (study enrollment) – only for SST naïve patients

2. Registration Step 2 (randomization to SST + local definitive therapy or SST only) – collect ALL consenting patients, regardless of treatment arm

   Please note that only a single sample is necessary if the patient is registered to Step 1 and Step 2 at the same time, and should be submitted as the Step 2 timepoint.

3. Month 3 visit – collect ALL consenting patients, regardless of treatment arm.

4. Disease Progression – collect ALL consenting patients, regardless of treatment

b. SPECIMEN COLLECTION KITS

Complete blood collection and mailing kits will be mailed in advance to participating centers. **Please email or call the contacts below to receive your kits. Every kit will include a complete collection and mailing instruction sheet.**

1. Peripheral whole blood specimens will be repackaged back into the mailing kits and shipped at room temperature on the day of collection by overnight delivery. A FedEx packing slip will be provided. Specimens should be shipped to:

   Lab#181:
   Goldkorn Lab
   USC Norris Comprehensive Cancer Center
   Harlyne Norris Research Tower, Room 6516
   1450 Biggy Street
   Los Angeles, CA 90033-1006
   Tel: 323/442-7722

2. Specimen collection kits may be ordered by contacting Dr. Amir Goldkorn's laboratory at the University of Southern California (323/442-7722) or by emailing lab members (in order of preference):

   Gareth Morrison, Ph.D.: garethmo@usc.edu
   Tong Xu, Ph.D.: tongxu@usc.edu
   Alex Cunha: alexander.cunha@med.usc.edu
   Amir Goldkorn, M.D.: agoldkor@med.usc.edu

15.4 SWOG Specimen Labeling and Shipment

a. Labeling

1. Liquid specimens must be labeled with the following:
   - SWOG patient number
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Specimen type (e.g. blood, serum, etc.)

2. Solid tissue specimens must be labeled with the following:
   - SWOG patient number
   - Patient initials
   - Collection date, or procedure date
   - Site of collection (e.g., Lymph node, left breast, liver, etc.)
   - Specify whether tissue is from primary (P) or metastatic (M)
   - Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-*1, B, etc.) must be on both the specimen label and the pathology report in order for the Bank to adequately match the specimen with any findings in the pathology report.*

b. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

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

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

17.0 BIBLIOGRAPHY

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18.0 **APPENDIX**

18.1 Translational Medicine Studies

18.2 Instructions for SWOG Biospecimen Bank (BB)

18.3 Quality of Life Studies

18.1 Translational Medicine Studies

TM specimens are to be collected and mailed to the appropriate laboratories per Section 15.0 (SWOG Biospecimen Bank, Lab #201 and Goldkorn Laboratory, Lab#181).

Use of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

18.2 Instructions for SWOG Biospecimen Bank

Formalin-Fixed Paraffin-Embedded (FFPE) Tissue

The SWOG Bank will receive FFPE tissue (blocks or unstained slides) from up to four time points (as described in Section 15.1). Upon receipt, specimens will be accessioned and barcoded. FFPE tissue blocks or slides will be stored at ambient temperature.

Ambient Whole Blood

The SWOG Bank will receive ambient whole blood in EDTA tubes at 1 time point. Upon receipt, the blood will be accessioned, barcoded, and extracted for DNA. DNA is stored in a -80°C freezer until distribution.

18.3 Quality of Life Studies

To compare patient-reported urinary function and urinary bother over time using the Expanded Prostate Cancer Index Composite (EPIC) between patients receiving standard systemic therapy and those receiving systemic therapy and definitive management of the primary prostate cancer. The primary hypothesis is that patients randomized to standard systemic therapy will have significantly worse EPIC urinary bother and urinary function domain scores compared with men randomized to definitive management of the primary tumor in addition to standard systemic therapy.

1. To compare the urinary continence domain scores and urinary bother domain scores between men undergoing radical prostatectomy plus systemic therapy vs. men undergoing external beam radiation therapy plus systemic therapy vs. systemic therapy alone.

2. To compare the prostate cancer-specific quality of life domains of sexual and bowel function with EPIC, comparisons of prostate cancer-specific quality of life adjusting for the extent of worsening of urinary function or bother since initial presentation, and comparisons of generic quality of life domains of pain and physical function using the EORTC QLQC-30 over time by treatment arm.

    a. Background

        Clinical trials in the setting of metastatic disease often focus on clinical rather than patient-reported outcomes. Yet, men with metastatic prostate cancer have extended expected survival time compared with other patients with metastatic solid organ cancers. As such, men with *de novo* metastatic prostate cancer may experience progression of the primary tumor over the years it takes to progress from hormone sensitive prostate cancer to castrate-resistant prostate cancer. The incidence of a requirement for palliative procedures for local progression is unknown, but the magnitude of these palliative procedures can be substantial: some men require total pelvic exenteration for progressive disease involving the bladder and rectum. Thus, there is a critical need to incorporate patient-reported outcomes into studies that investigate new therapeutic strategies in the management of metastatic prostate cancer and clarify the impact of these strategies on local symptoms.

        The impact of definitive treatment to the primary prostate cancer on patient-reported generic and prostate cancer-specific quality of life has been most robustly characterized among men with localized prostate cancer. Across prospective observational registries, men undergoing radical prostatectomy tend to have worse urinary continence outcomes but improved urinary storage and voiding symptoms compared with men undergoing radiation therapy to the prostate. *(1,2,3)* The degree to which these symptoms impact the bother, or distress that men experience as a result of their urinary dysfunction does not appear to vary by treatment modality.[4] Composite measures of mental and physical health vary little after definitive treatment of localized prostate cancer. *(4,5,6)*

        Among men with metastatic prostate cancer, these patient-reported outcomes have been incompletely characterized. Most clinical trials of new investigational agents or therapeutic strategies assessed generic quality of life instruments. Understanding the impact of new treatment strategies on prostate cancer-specific quality of life would facilitate comparison of patient-centered outcomes such as urinary function and

bother, in addition to generic quality of life outcomes such as physical functioning. Ascertainment of the severity of patient-reported prostate cancer-specific quality of life (based on pre-specified measures of clinically meaningful change) between the time of presentation with metastatic prostate cancer and randomization will be used for covariate adjustment when examining the primary randomized treatment questions. For example, men with clinically meaningful worsening in EPIC urinary function between baseline and randomization may be more likely to benefit from surgery or radiation to the prostate in addition to systemic therapy. *(7)*

b. Quality of Life Instruments

1. EPIC is an instrument that measures urinary, sexual, and bowel symptoms in function and bother domains. *(8)* The 26-question EPIC short form was selected by the International Consortium for Health Outcomes Measurement (ICHOM) as the preferred prostate cancer-specific health-related quality of life instrument for the assessment of men with localized and advanced prostate cancer. *(9)* The function domains represent objective measures of treatment-specific dysfunctions, such as the magnitude of urinary leakage that patients experience. The bother domains represent subjective measures of the distress that patients experience. EPIC is the most commonly used PCa-specific QOL instrument. EPIC survey results are transformed into summary scores scaled from 0-100 (one each for function and bother in the urinary, sexual, and bowel categories), with a higher score indicating better QOL. EPIC demonstrates high test-retest reliability ($r \geq 0.80$ for all domains) and internal consistency (Cronbach's-$\alpha \geq 0.82$ for all domains) [6]

2. The EORTC QLQ-C30 is a generic health-related quality of life instrument that has been extensively validated in diverse cancer populations including men with advanced prostate cancer. *(10)* The EORTC QLQ-C30 measures domains of physical functioning, emotional functioning, social functioning, cognitive functioning, pain, fatigue, nausea, and includes single items that assess symptoms such as insomnia and appetite loss. The EORTC QLQ-C30 was selected by ICHOM as the preferred generic health-related quality of life instrument for the assessment of men with advanced prostate cancer. *(11)* The EORTC QLQC-30 is reliable (Chronbach's alpha > 0.70) and has discriminatory association with clinical status, disease stage, and symptom severity.[8]

3. Dr. Gore has extensive experience with the assessment and interpretation of quality of life among men with prostate cancer and leads a global effort to implement a web-based tool for the assessment and presentation of quality of life data to men at all stages of prostate cancer.

c. Timepoints

The quality of life assessments are scheduled to occur at initial registration, at randomization (i.e., 6 months after initial registration), and at 1, 2, and 3 years after randomization.

If a patient is planned to be randomized within one week of the initial study registration, quality of life assessments do not need to be performed separately at randomization.

d. Experimental research techniques/tests employed and expertise of PI:

Research staff members will be trained to administer quality of life forms by viewing a training module available on the SWOG website [www.swog.org]; the program can be found at the CRA WorkBench/Tools of the Trade. For example, this training program indicates that research staff should not influence the patient's responses to the questionnaires. Research staff will need to enter the reported data into the online Medidata RAVE system. Efforts to minimize missing data are critical to obtaining interpretable results. The training module addresses methods for reducing missing data.

e. Recall period:

Recall periods for all EPIC domains are 1 month. *(12)* Respondents are asked to answer questions regarding their symptoms and/or quality of life with a 1-month recall reference period. Recall for the EORTC QLQ-30 is 1 week. *(13)* Respondents are asked to answer questions regarding their symptoms over the past week.

f. Statistical Plan:

Quality of life assessments will occur in conjunction with the clinical follow-up schedule in order to minimize missing data and to link the clinical assessments with patients' self-reported symptom burden. This design should also minimize patient and staff burden. The assessment times are scheduled to occur at initial registration, at randomization (i.e., 6 months after initial registration), and at 1, 2, and 3 years after randomization. The primary endpoint assessment time will occur at 1 year after randomization given that the largest changes in urinary function occur within 12 months of treatment of curative intent with surgery or radiation.2

The primary quality of life endpoints are the EPIC urinary function and bother domain scores. A minimally important difference has been suggested derived from distribution and anchor-based approaches of 5-7 points for the EPIC urinary storage domain score.13 The anticipated standard deviation at 1 year has been identified by about 15 points.13 The minimally important difference of the EPIC urinary incontinence domain was estimated to be 6-9 points, with an anticipated standard deviation at 1 year of 21 points.13 For both domains, the lower MID will be chosen to enable identification of potentially small effect sizes.

The primary objectives are to test whether EPIC 26 urinary function and bother symptoms differ by arm. Given two testable hypotheses, multiplicity will be accounted for by setting alpha=.025 (by Bonferonni) for each test. Assuming median OS from time of randomization of 44 months for those receiving SST alone, under exponential survival, about 18% of patients

would be expected to die by Year 1. Further, patients may drop out for other reasons (an additional 8% is assumed), including illness, travel constraints, or other reasons. Therefore we assume that 25% of patients will drop out at 1 year, and a further 10% are estimated (conservatively) to be non-adherent at the 1 year timepoint.

In the examination of EPIC 26 urinary function scores, we note that in power calculations, the 10% non-adherence rate reduces the nominal effect size of a 5.0 point target difference to 4.5 points, while the 25% dropout rate inflates the estimated sample size by a factor of 1/(1-0.25) or 33%. Under these parameters, 1000 total patients (500 per arm) will give 97% power to detect the target difference using a two-arm normal design.

In the examination of EPIC 26 urinary bother scores, the 10% non-adherence rate reduces the nominal effects size of a 6.0 point target difference to 5.4 points, and as before the 25% dropout rate inflates the estimated sample size by about 33%. Under these parameters, 1000 total patients will give 90% power to detect the target difference using a two-arm normal design.

Consistent with the design, the analyses of the 12-month EPIC urinary function domain summary score will be conducted using multiple linear regression analysis, adjusting for stratification factors and baseline EPIC urinary function or bother domain scores (as appropriate) as covariates. We will also conduct longitudinal modeling of the patient-reported outcome measures over time. Power for the longitudinal analysis will be greater since the addition of all available EPIC urinary function and bother domain scores over time will provide more information. For longitudinal modeling, linear mixed models will be used. The potential for differential dropout by arm will be mitigated by reminder notifications to site investigators to encourage proper assessment and submission of forms at every required time point for all patients. Dropout patterns will be monitored on an ongoing basis. Nonetheless the potential for non-random dropout exists. Cohort plots will be prepared to examine the extent to which missing data are informative (i.e., scores are higher (worse) for patients just before their data are missing for the subsequent assessment). If there is evidence of non-random dropout, pattern-mixture models will be utilized as a sensitivity analysis. Covariates for longitudinal modeling will include intervention assignment, assessment time, their interaction, the baseline score, and the stratification factors as covariates.

18.3 REFERENCES

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