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DEPARTMENT OF UROLOGY/UROLOGIC ONCOLOGY

TITLE: SIMCAP (Surgery in Metastatic Carcinoma of Prostate): Phase 2.5 multi-institution randomized prospective clinical trial evaluating the impact of cytoreductive radical prostatectomy combined with best systemic therapy on oncologic and quality of life outcomes in men with newly diagnosed metastatic prostate cancer

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***SIMCAP** (**S**urgery **i**n **M**etastatic **Ca**rcinoma of **P**rostate): Phase 2.5 multi-institution randomized prospective clinical trial evaluating the impact of cytoreductive radical prostatectomy combined with best systemic therapy on oncologic and quality of life outcomes in men with newly diagnosed metastatic prostate cancer*

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Not Applicable

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LIST OF ABBREVIATIONS

(examples of some commonly used abbreviations, include any used in protocol)

AE	Adverse Event
ANC	Absolute neutrophil count
BST	Best systemic therapy
BUN	Blood urea nitrogen
CBC	Complete blood count
CRP	Cytoreductive radical prostatectomy
CT	computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EPIC	Expanded Prostate Cancer Index Composite.
FDA	Food and Drug Administration
FFS	Failure-Free Survival
HADS	Hospital Anxiety and Depression Scale
HFRDIS	Hot Flash Related Daily Interference Scale
HHS	Department of Health and Human Services
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
mcg/μg	Micrograms
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PET	Positron Emission Tomography
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate specific antigen
PSQI	Pittsburgh Sleep Quality Index
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SD	Stable disease
sCr	Serum creatinine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ULN	Upper limit of normal

1. Purpose/Specific Objectives

To assess the role of radical surgery in men who present with newly diagnosed M1a, M1b, or M1c metastatic prostate cancer (mPCa).

1.1 Primary Objective(s)

To assess the clinical benefit of combining radical surgery – cytoreductive radical prostatectomy (CRP) - with the best systemic therapy (BST) in men with newly diagnosed clinical mPCa.

1.2 Secondary Objective(s)

There are two secondary objectives: clinical and tissue correlates.

The clinical secondary objective is to determine the impact of CRP+BST on time to biochemical progression, cancer-specific survival, complication rates, and quality of life (QOL) in patients with mPCa.

The tissue correlate secondary objective is to determine the transcription levels of bone morphogenetic protein -6 (BMP-6) and transforming growth factor-β (TGF-β).

1.3 Primary Hypothesis/hypotheses

The primary hypothesis is that CRP in men with mPCa will increase survival by rendering the systemic therapy more effective.

1.4 Secondary Hypothesis/Hypotheses

There are four secondary hypotheses.

- CRP will delay biochemical progression and cancer-specific survival in men with mPCa.
- CRP is safe in men with clinical mPCa.
- CRP will improve the quality of life by mitigating local urinary symptoms.
- Cytoreductive radical prostatectomy (CRP) in men with mPCa will increase survival by releasing the systemic immune suppression driven by the primary tumor via BMP-6 and TGF-β.

1.5 Primary Endpoint(s)

This is a hybrid phase 2.5 study. As such, there are two primary endpoints.

- The primary endpoint for the Phase 2 portion of this study is the failure-free survival (FFS) rate at two years after randomization. Failure is defined as: biochemical recurrence, clinical progression, or death from prostate cancer (1).

- During or at the end of the phase 2 study, if the FFS rate at 2 yrs shows a minimum of 30% improvement with the pre-specified statistical power as described in section 15 in the CRP+BST group, the trial will convert to a Phase 3 study and the primary endpoint will switch to overall survival. If the expansion to phase 3 study is triggered, a protocol modification that specifies the sample size and power calculation will be submitted.

  Although the BST in men with mPCa is androgen deprivation therapy (ADT) based on the 2016 National Comprehensive Cancer Network (NCCN) guideline (2), the most aggressive form of systemic therapy shown to be effective is the combination of ADT+docetaxel. Specifically, CHAARTED trial, PSA < 0.2 ng/ml at six months after randomization in the ADT+docetaxel group was 32% (3). Previously, it has been reported that PSA nadir less than 0.2 ng/ml following ADT is an independent predictor of survival in men with mPCa (4). In our recently closed phase 1 study, the proportion of men with PSA < 0.2 ng/ml at six months after CRP and systemic therapy (ADT +/- docetaxel) was more than twice that of the CHAARTED at 64.7%. Therefore, in this trial, we have conservatively estimated that the anticipated improvement in outcome is 30%.

1.6 Secondary Endpoints

There are three secondary endpoints: 1) time to biochemical progression, 2) cancer-specific survival, and 3) overall complication rate.

2. Background and Significance

In this application, we have proposed a phase 2.5 international multi-institution randomized clinical trial to evaluate the potential therapeutic effect of CRP combined with the BST in men with mPCa prospectively. Such hybrid design permits the inclusion of the patients who have accrued to the phase 2 investigation to phase 3 trial, thereby decreasing the number of patients needed overall (5-7). In the initial phase 2 study, we plan to accrue 190 patients.

Prostate cancer is the most common non-skin cancer diagnosed and the second leading cause of cancer deaths among men in the United States (8). Although radiation and surgery are quite effective for localized disease, there is no effective cure for men with metastatic disease. In these patients with mPCa, the 2016 NCCN Prostate Cancer Guideline states that ADT is the standard of care (2). Notwithstanding, the combination of ADT and docetaxel has also been shown to be effective by multiple investigators (1, 3).

Most recently, a series of retrospective studies have reported that local tumor control may be beneficial in men with mPCa (9-12). Indeed, a review of the SEER-Medicare database reported

that approximately 2.99% of the patients who present with metastatic disease undergo surgery (9). When compared to men who received no local treatment, those who had surgery experienced the most benefit (5-year overall survival of 22.5% vs 67.4%, $p < 0.001$). Notwithstanding, due to the retrospective design of these studies, the reported benefit of surgery in men with newly diagnosed mPCa may be due to a selection bias. Therefore, to determine the therapeutic role of CRP in patients with mPCa, a well-designed randomized prospective clinical trial that satisfies the level 1 evidence criteria is necessary.

To formally investigate the role of CRP prospectively in men with newly diagnosed mPCa, we launched a phase 1 study to first investigate the safety and feasibility in 2015 (RCINJ protocol # 081403, NCT 02458716). Because this study confirmed CRP to be safe and feasible, we now wish to take the next step and propose a randomized prospective clinical trial to investigate the role of CRP in men with mPCa.

2.1 Supporting Data and Rationale

Combining cytoreduction with systemic therapies has been shown to improve survival in renal cell carcinoma, colon cancer, and ovarian cancer (13-15). However, surgery is not part of the standard treatment armamentarium in men with mPCa. Nevertheless, in 2006, Swanson et al have proposed that CRP may be beneficial in men with mPCa due to tumor debulking, enhanced anti-tumor immunity, removing the primary site of tumor shedding, blocking paraneoplastic effects, and disrupting tumor production of hormones (16). Since then, a body of evidence has accumulated supporting the hypothesis that treating the primary tumor improves outcome in prostate cancer patients with clinical evidence of metastasis. First, analysis of the SEER database demonstrated that local tumor control, especially surgery, resulted in a significantly better overall survival and cancer-specific mortality in men with stage IV prostate cancer (M1a-c) (9, 11). However, only 2.99% of eligible patients underwent CRP (245 out of 8185). Within the local therapy group, patients who received CRP had a lower mortality rate when compared to radiotherapy (17). Although the benefit of cytoreductive surgery was detected for all three stages of metastasis (M1a, b, and c), the most dramatic survival benefit was seen in men with the most advanced M1c disease (adjusted hazard ratio 1.88) (29). Second, in patients found to have lymph node metastasis at the time of surgery, completing radical prostatectomy is associated with improved cancer-specific and overall survival (18, 19). Third, primary prostate cancer debulking has been shown to improve the effectiveness of ADT (20). Fourth, we have observed that the overall survival after recurrence is better in men who had radical prostatectomy than primary radiation therapy (21). Since these studies collectively constitute a level 3 evidence, well-designed and executed randomized clinical trials are necessary to determine whether CRP should be incorporated into the armamentarium against mPCa.

As the initial step in investigating the effect of CRP in men with newly diagnosed mPCa, we launched a phase 1 study at Rutgers Cancer Institute and City of Hope National Medical Center focused on assessing the safety and feasibility of surgery in 2015 (open to accrual in June 2015). This ground breaking study enrolled 26 patients and the following conclusions were made: 1) CRP is safe and feasible as the overall major complication rate was 7.7% (2/26); 2) without pharmacologic prophylaxis, post-operative venous thrombotic event following surgery is relatively high at 15.4% (4/26); 3) pre-operative docetaxel treatment is associated with a

longer operative time and higher estimated blood loss; 4) PSA kinetics demonstrated three groups – PSA nadir < 0.2 ng/ml within six months after surgery (64.7%), PSA declined but nadir ≥ 0.2 ng/ml (29.4%), and rapid rise (5.9%). Although the precise clinical implication of PSA kinetics is still debated, these three disparate responses in our phase 1 study suggest that there is a group of patients who likely will not benefit from surgery. We hope to characterize these patients in this trial using deep sequencing and bioinformatics analysis. In designing the current phase 2.5 trial, we have incorporated the lessons learned from the phase 1 study to ensure the optimal risk/benefit ratio for study participants.

As the threshold for converting the study from phase 2 to 3, we have benchmarked the CHAARTED trial (3). In this study, 32% of men reached PSA < 0.2 ng/ml at six months after randomization in the ADT+docetaxel group (3). Previously, it has been reported that PSA nadir less than 0.2 ng/ml following ADT is a strong predictor of survival in men with mPCa (4). In our recently closed phase 1 study, the % of men with PSA < 0.2 ng/ml at six months after CRP combined with ADT +/- docetaxel was more than twice the historical result at 64.7%. Therefore, in the current protocol, we have conservatively estimated that the anticipated improvement in outcome in the CRP+BST group is 30%.

There are two important correlative studies that will leverage this clinical trial. First, based on the PSA kinetics from our aforementioned Phase 1 study on CRP, there likely is a group of patients with mPCa who will not benefit significantly from surgery. Therefore, using whole exome and RNAseq, we wish to establish the molecular profile of these men and eventually develop a personalized approach in determining whether CRP should be carried out.

Second correlative study is focused on quality of life (QOL). Specifically, local urinary symptoms inevitably deteriorate in men with mPCa. Indeed, some clinicians have argued that a local urinary symptom control is a major benefit of surgery in men with locally advanced prostate cancer (22, 23). Therefore, it is possible that removing the prostate in men with newly diagnosed mPCa may improve the quality of life. In this application, we propose to use eight validated instruments to assess the impact on QOL.

3. Experimental Design and Methods

This is a prospective 1:1 randomized hybrid phase 2.5 study (phase 2-3 design). This innovative study design decreases the overall number of patients needed by establishing the criteria prior to the initiation of the investigation for converting a phase 2 into phase 3 trial (5-7).

Control group: BST (ADT +/- docetaxel at the discretion of the treating physician). ADT is defined surgical castration (orchiectomy) or LHRH agonist/antagonist +/- abiraterone (24).

Experimental group: CRP+BST.

To demonstrate at least 30% improvement in FFS at 2 years after randomization with the power of 90% and α-error of 5% on a one-sided exponential MLE test, 190 patients are needed (170 plus 10% dropout rate). Following consent, men will be randomized via a dynamic

minimization approach based on stage, geography, planned/current docetaxel use, planned/current abiraterone use, and duration of ADT prior to consent. If the primary endpoint demonstrates at least a 30% increase in %FFS in the experimental arm, the trial will convert automatically into a phase 3 study with the primary endpoint of overall survival and will accrue additional patients based on the results from the phase 2 study.

Phase 2

The initial phase 2 part of the study will enroll 190 men (170 needed with 10% dropout rate assumed) who have newly diagnosed clinical N1, M1a, M1b, or M1c mPCa using standard imaging modalities (bone scan and CT or MRI abd/pelvis) or tissue diagnosis (biopsy) and have received ADT for no longer than six months. Solitary metastatic lesion must be demonstrated by biopsy or two different imaging modalities confirmed by two radiologists independently (each radiologist must issue a report) to be eligible for this study. The accrual period is two years and follow-up duration is a minimum of two years.

Potentially eligible patients will undergo a thorough work-up by a surgeon to determine resectability of the prostate. Patients deemed to have resectable disease will be offered participation in this clinical trial. After eligibility is verified, men will be stratified based on stage (M1a vs M1b/M1c), geography (US vs non-US), planned/current docetaxel use (yes vs no), planned/current abiraterone use (yes vs. no), and duration of ADT prior to consent (ADT $\leq$ 3 months vs ADT > 3 months). In the control group, BST will be initiated. At the present time, BST for men with newly diagnosed mPCa based on the NCCN guideline and recent clinical trials is ADT +/- docetaxel (1-3). Based on a recent study, ADT includes surgical castration (orchiectomy) or LHRH agonist/antagonist with or without abiraterone (24). If the provider chooses to use docetaxel, it is suggested that ADT be given for at least one month prior to the initiation of docetaxel chemotherapy. In patients who were on ADT for more than one month prior to randomization, docetaxel will be started at any time as determined by the treating physician.

Patients randomized to the experimental group will undergo CRP. It is suggested that patients receive at least one month of ADT prior to surgery. Docetaxel can be given at the discretion of the treating physician prior to surgery. The preferred surgical approach is Robot-Assisted Radical Prostatectomy (RARP). However, the surgeon will ultimately choose the optimal technique.

Patients randomized to the experimental group will undergo extended pelvic lymph node dissection (ePLND), if feasible, at the time of CRP. The template for ePLND as defined by NCCN and European Association of Urology (EAU) is as follows: external iliac, obturator, and internal iliac nodes (24, 25). In patients where the lymph node dissection may cause significant morbidity (i.e. lymphadenopathy surrounding the obturator nerve), the surgeon may choose to carry out a limited or even forego lymphadenectomy. Prior to the induction of anesthesia, DVT prophylaxis is suggested with 5000 U of subcutaneous heparin and repeated every 12 hrs for the remaining hospital stay.

While on-study, subjects will be followed with serial PSAs at least every three months until progression. Imaging modalities including bone scan and CT/MRI will be used at the discretion

of the provider to determine progression of disease. At minimum, bone scan and CT/MRI pelvis will be obtained at year 1 and 2 after randomization for patients enrolled on-study with M1a or M1b disease because these patients have non-measurable disease. For patients enrolled on-study with M1c disease (with measureable disease), radiographic assessments will be obtained every 3 to 6 months per standard of care.

Phase 3

If the Phase 2 portion demonstrates greater than 30% improvement in the %FFS at two year after randomization in the CRP+BST group, this study will convert automatically to a phase 3 trial. Upon the conversion, the **primary endpoint** will change to overall survival and the study will recruit additional patients as determined based on the results of the phase 2 study.
The precise sample size and power calculation as well as secondary endpoints will be provided via a protocol modification.

At the end of the study, all biopsy and surgical specimens will undergo a central pathology review by the lead GU pathologist of this study. To this end, all representative pathologic specimens will be shipped to Rutgers Cancer Institute of New Jersey. In the awarded grant, this cost has been budgeted (See section #10.1).

3.1 Duration of Study

For the phase 2 portion, the duration of the study is four years (two years for accrual and two years for follow-up). If the study converts to phase 3 trial, the additional time will be dictated by the results of the phase 2 study.

Therefore, the expected duration of the study is a minimum of 4 years.

4. Patient Selection Criteria

4.1 Inclusion Criteria

4.1.1 Histologically proven adenocarcinoma of the prostate.
4.1.2 Evidence of metastasis by MRI/CT scan, bone scan, or histologic confirmation.
4.1.3 Clinical stage M1a (distant lymph node positive), M1b (bone metastasis), or M1c (solid organ metastasis).
4.1.4 If solitary lesion, metastasis confirmed with either biopsy or two independent imaging modalities (i.e. CT and PET, bone scan and MRI, modality at the discretion of the treating physician).
4.1.5 No previous local therapy for prostate cancer (i.e. prostate radiation, cryotherapy, etc.).
4.1.6 Give informed consent.
4.1.7 Prostate deemed resectable by surgeon.
4.1.8 Must be male and 18 years or older
4.1.9 Plans to start or has already started ADT no longer than 6 months prior to consent.
4.1.10 ECOG Performance Status of 0 or 1.
4.1.11 Organ functions compatible for surgery.
HgB $\geq$ 9 g/dL
Platelets >80,000/mcL

AST ≤ 2x ULN
ALT ≤ 2x ULN

4.2 Exclusion Criteria

4.2.1 Males under the age of 18.
4.2.2 Refuses to give informed consent.
4.2.3 Deemed to have unresectable disease by surgeon.
4.2.4 Received ADT for more than 6 months prior to consent.
4.2.5 Life expectancy of less than 6 months prior to consent.
4.2.6 Known spinal cord compression.
4.2.7 DVT/PE in the past 6 months prior to consent.
4.2.8 Previous local therapy for prostate cancer.
4.2.9 Patients who have chemotherapy or radiotherapy for non-prostate cancer related treatment within 3 weeks prior to consent.

4.3 Inclusion of Women and Minorities

Men of all ethnic groups are eligible for this trial. Women are excluded as they do not have a prostate.

4.4 Participation of Children

Children are not eligible for the study because adenocarcinoma of the prostate is extremely rare in pediatric population.

4.5 Sources or Methods of Recruitment

Subjects will be recruited from all participating institutions.

4.6 Study Enrollment Procedures

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol will be on file at the Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institutions may enroll patients.

Sites will register and enroll patients through OnCore, the Clinical Trials Management System for this study. Please refer to the study OnCore instructions and Data Capture Plan for additional information. Contact the Rutgers Cancer Institute of New Jersey's SIMCAP study team at rbhs_cinj_simcap@email.rutgers.edu if you have any questions about the Registration/Enrollment process.

- **Registration:** Any patient who has signed consent will be entered into OnCore. A sequence number will be assigned at time of registration. Site staff will assign each patient a unique ID number.

  This number will be made up of two parts: pre-fix and suffix. The pre-fix will be the site's 2-digit ID number which is assigned during the time of Site Initiation. The suffix will be a 3-digit number (i.e. 001, 002, 003) representing the order the patient is consented/entered into OnCore at each site. For example, if you are site #03, your first

patient to sign consent would be patient ID# 03-001. Please note that if a patient does not meet eligibility their ID number will **not** be re-issued to another patient.

A copy of the signed consent form will be uploaded into OnCore.

- **Eligibility:** A study-specific eligibility checklist (ECL) will be used to determine each patient's eligibility. This checklist is provided to the sites by the SIMCAP study team during study start-up. The ECL contains two parts. Part 1 of the ECL lists the inclusion and exclusion criteria found on pages 10-11 of this protocol. Part 2 of the ECL lists the protocol specific pre-treatment parameters required prior to randomization as well as stratification questions. The ECL must be completed in its entirety. Submission of an incomplete ECL will delay patient randomization.

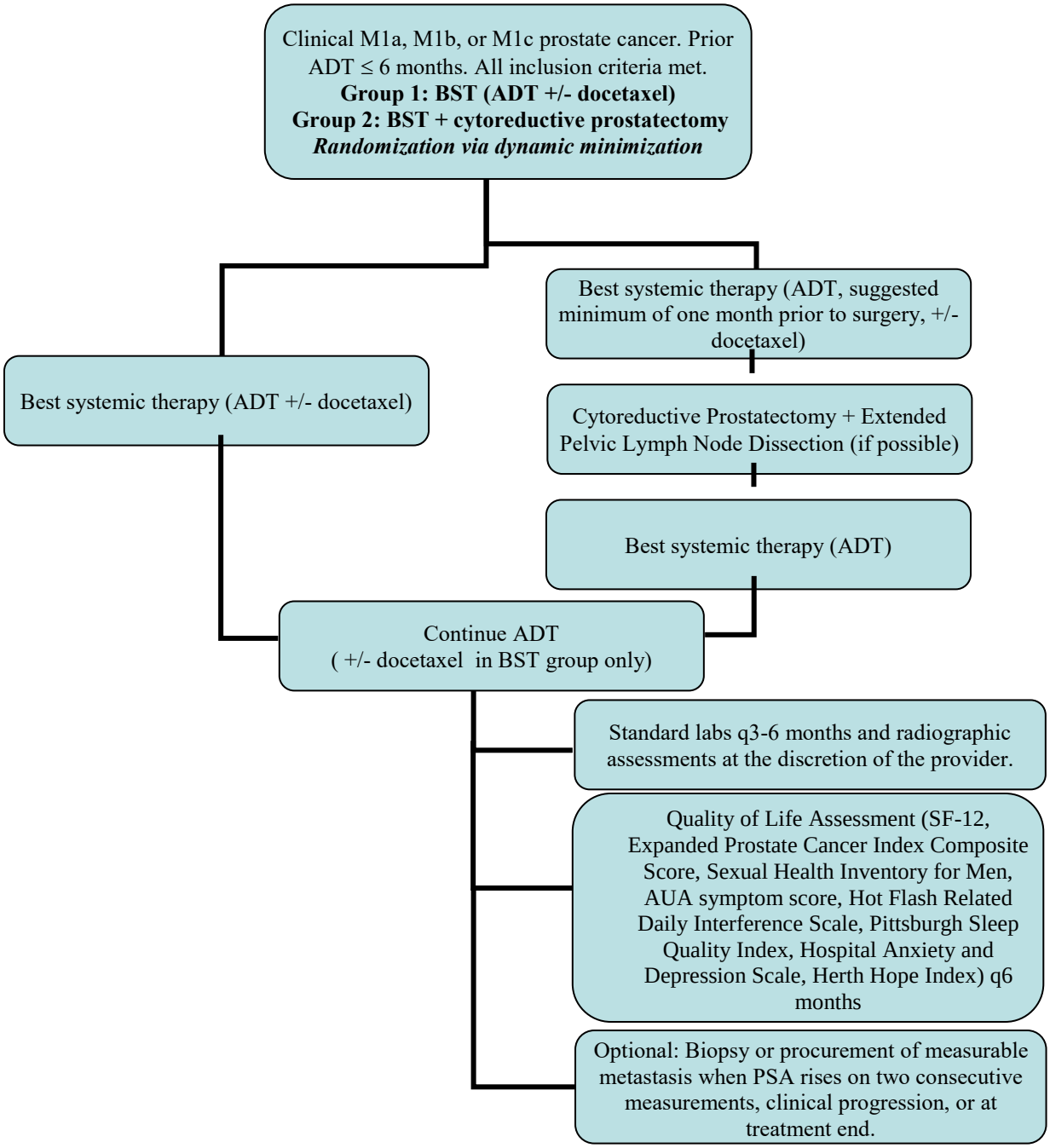
- **Enrollment:** Once the patient's eligibility has been confirmed, the completed, signed, and dated ECL must be uploaded into OnCore. Site staff will update OnCore to reflect the patient's On-Study date as the date the patient was deemed eligible by the investigator (date investigator signed the ECL). The SIMCAP study team will be notified that a patient is ready for randomization once the site staff update OnCore and send the "Subject Registration Notice" (please see the SIMCAP OnCore instructions for additional details). The Biostatistician will randomize the patient. Sites will receive notification that the patient's treatment assignment is listed in OnCore within 24-48 hours.

- **On-Treatment:** The "On-Treatment" date for all patients, is the **date of randomization.**

5. Study Schema / Parameters

Evaluations	Pre-Study within 4 months prior to randomization	Day of Surgery (CRP+BST group only)	Post-operative visit (CRP+BST group only; catheter removal, 1-3 wks post-surgery)	Every 3 months +/- 30 days[7]	Every 6 months +/- 30 days[7]	End of Tx visit	Follow-up
History & Physical	X[11]		X	X	X	X	
ECOG Performance Status[1]	X		X	X	X	X	
Adverse events/ Concomitant Medications	X		X	X	X	X	X[8]
Complications[2]			X	X	X		
DatStat Post-op visit survey			X[10]				
Quality of Life questionnaires[3]	X				X		X[8]
Radiographic Assessments & RECIST	X[4]			X[9]	X[9]	X	
Serum PSA	X			X	X	X	
Blood Studies[5]	X				X	X	
Correlative tissue harvest or Biopsy		X				X[6]	
Survival[8]							X

1. See Appendix A
2. Clavien-Dindo classification for surgery. Assessed at the Post-op visit and the first 3-month visit. See Appendix B.
3. Quality of life questionnaires consist of the following Patient-reported outcome surveys: Sexual Health Inventory for Men (SHIM), AUA Symptom Score, SF-12, Expanded Prostate Cancer Index Composite (EPIC), Hot Flash Related Daily Interference Scale (HFRDIS), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), and Herth Hope Index (HHI).
4. Radiographic assessments will be selected by the attending physician as clinically indicated and in accordance with the criteria for tumor measurement assessments and/or assessment of progression of disease. Pre-study radiographic assessments and RECIST must be within 4 months of initiating ADT therapy.
5. Includes: Complete Blood Count with Differential and Complete Metabolic Panel. Optional labs include: Testosterone, Free Testosterone, Chromagranin A and Prostate Acid Phosphatase. Please note: if Testosterone and Free Testosterone were collected prior to initiating ADT, there is no need to redraw these optional labs at screening. Lab values from the earlier collection can be used for these optional labs at screening.
6. Optional.
7. For CRP+BST group, the study visits will be from the first post-op visit. For the BST group, study visits will be from the date of randomization. A month is defined as 30 days. The date of randomization (BST group) and the date of the first post-op visit (CRP+BST group) will be considered Day 0.
8. Patients will be contacted every six months from time of progression for survival status and cancer related treatments since progression. Contact can be via phone, email, or documented MD visit. PRO questionnaires are to be completed annually (optional).
9. At minimum, bone scan and CT/MRI pelvis will be obtained at year 1 and 2 after randomization for patients enrolled on-study with M1a or M1b disease because these patients have non-measurable disease. For patients enrolled on-study with M1c disease (with measureable disease), radiographic assessments will be obtained every 3 to 6 months per standard of care.
10. Post-op visit survey within Datstat needs to be completed by site staff once a patient in the CRP+BST group has completed his surgical post-op visit.
11. Physical exam, including digital rectal exam



Complete List of Parameters Below:

Patient demographics (age, race)
Preoperative pathology results of prostate biopsy
Preoperative imaging studies (CT, MRI, Bone Scan, X-RAY)
Preoperative laboratory results (PSA, CBC, CMP; optional labs: Chromogranin A, Testosterone, Free Testosterone, PAP)

Clinical staging (T/N/M)
Patient height
Patient weight
Body mass index
Preoperative hemoglobin
Preoperative creatinine
Pathologic stage (T/N/M)
Surgical margin status
Prostate specimen mass (in grams)
ECOG Performance Status
Total Procedure time (in min)
Estimated blood loss (in ml)
Gleason score (biopsy and surgical pathology)
Post-operative complications
Routine serial post-operative PSA (every 3 months)
Imaging during follow-up if done at any point (CT/MRI/Bone Scan)
Androgen Deprivation Regimen
Docetaxel Regimen
Overall Response
Overall Survival
Cancer Specific Survival
Failure Free Survival
Prostate Cancer Specific Mortality
SF-12
Expanded Prostate Cancer Index Composite Score
SHIM scores
AUA symptom score
Hot Flash Related Daily Interference Scale
Pittsburgh Sleep Quality Index
Hospital Anxiety and Depression Scale
Herth Hope Index
Correlative tissues

6. Treatment Plan

On the initial visit, eligibility for study participation will be assessed. If the patient is deemed eligible, he will be randomized based on geography (US vs. non-US), stage (M1a vs. M1b/M1c), number of bone metastasis (≤3 vs. > 3), docetaxel planned or use (yes vs. no), abiraterone planned or use (yes vs. no), and duration of ADT prior to consent (≤ 3 months vs. > 3 months).

Control group: BST. Currently, BST is permanent ADT +/- docetaxel (1-3). In patients who were treated with ADT ≥ 1 month prior to randomization, docetaxel, if chosen by the provided, will be given as soon as feasible. In men not treated with ADT or for a duration less than or

equal to one month prior to randomization, ADT will be given for a minimum of one month prior to docetaxel therapy.

ADT is defined as surgical castration (orchiectomy), LHRH antagonist or a short course of anti-androgen combined with LHRH agonist. The regimen will be at the discretion of the treating physician.

Docetaxel regimen will be at the discretion of the provider.

At the time of disease progression, the patient will come off-treatment. The next line of therapy will be at the discretion of the provider.

Experimental group: CRP+BST. Patients will undergo surgery as soon as feasible if the duration of ADT is greater than one month prior to surgery. In men who have not been treated with ADT or received ADT less than or equal to one month prior to entering the study, ADT will be initiated or continued to ensure that the patients have been treated with ADT for at least one month prior to CRP. Docetaxel must be administered, if selected, prior to surgery. Following surgery, ADT will be continued. Although the surgical approach is at the discretion of the surgeon, robot assistance is the preferred primary approach.

Upon disease progression, the patient will come off-treatment. The next line of therapy will be at the discretion of the provider.

7. Toxicity Monitoring and Adverse Event Reporting

7.1 Adverse Event Reporting Requirements

An adverse event is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy. The study therapy for this trial is defined as the CRP; therefore, there is no study therapy for patients on the BST arm as the ADT (+/- docetaxel) is standard of care treatment.

For reporting purposes, all non-laboratory Grade 2 and greater adverse events and only Grade 2 and greater clinically significant lab abnormalities <u>related or possibly related</u> to investigational treatment (i.e. surgery**)** will be reported in OnCore as an adverse event from the time of surgery until completion of the subject's last study-related procedure. AEs for subjects on Arm 1 (BST) do <u>not</u> need to be reported. All AEs will be graded based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Serious adverse events will be reported for **<u>ALL</u>** patients.

All **"unexpected"** adverse events (UAEs; defined below) and/or **"serious"** adverse events (SAEs; defined below), regardless of causality/attribution, occurring from when the patient is considered "On-treatment" (pg. 12) through 30 days from progression/recurrence will be reported to the Rutgers CINJ Office of Human Research Services via OnCore within 24 hours of site notification. The completed SAE report (signed by the Investigator) must be sent to the

Rutgers CINJ OHRS QA department by email at: qaohrs@cinj.rutgers.edu with the email subject: **081707 SAE report**. Events will be promptly reported, in writing, in accordance with the local and Rutgers CINJ IRB policy.

If a death occurs, while On-treatment or within 30 days of progression/recurrence or start of new therapy, the local IRB and WIRB will be notified within 24-hours of initial receipt of information. All other SAEs will be reported to the local IRB and WIRB as per institutional policy. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the local IRB and WIRB will be kept in the study regulatory file.

7.2 Definition of Unexpected Adverse Events and Serious Adverse Events

An adverse event is considered "unexpected" if it is not listed in the Investigator Brochure or it is not listed at the specificity or severity that has been observed. UAEs may or may not be serious.

An adverse event is considered "serious" if the event or experience results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires unexpected inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

The definition of serious adverse event (experience) also includes important medical events. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious.

8. Treatment Evaluation/Criteria for Response

Response and progression will be evaluated in this study using the serum tumor marker PSA and imaging (either CT, MRI, or bone scan). When PSA rises on two consecutive measurements or radiologic studies demonstrate disease progression, the patient will be considered to have castration resistance. In addition, we will use the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3): 205-216, 2000]. Changes in only the sum of diameters (uni-dimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria (26). Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1 Measurable Disease

Measurable non-nodal lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional technique (X-ray) or as ≥10 mm with CT scan and MRI. Nodal lesions must be ≥15 mm in the short axis to be considered measureable. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.2 Non-Measurable/Evaluable Disease

Non-measurable lesions are defined as evaluable disease that meets the following criteria:

- non-nodal lesions: longest diameter measuring < 20 mm with conventional technique or < 10mm with CT scan and MRI
- nodal lesions: short axis measuring < 15mm with CT scan and MRI
- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions.

Bone-only disease is allowed and will be evaluated based on the number of bone lesions at each restaging assessment. Two or more new bone lesions would be indicative of progressive disease.

8.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. During screening, target lesions will be selected on the basis of their size (lesions with the longest diameter for non-nodal lesions) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD; for non-nodal lesions) and the shortest diameter (SD; for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize the objective tumor response at each restaging time point.

8.4 Non-Target Lesions

All other lesions (or sites of disease) will be identified as non-target lesions and will be recorded at baseline. Non-target lesions may include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each will be noted at each restaging time point.

8.5 Guidelines for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of ADT treatment. Baseline radiographic assessments must be within 4 months of initiating ADT therapy.

The same method of assessment and the same technique will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-

based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

8.5.1 Clinical lesions- Clinical lesions will only be considered measurable if they are palpable on digital rectal exam.

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

8.5.3 Conventional CT and MRI- These techniques will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

8.5.4 Ultrasound (US)- Because one of the endpoints of the study is objective response evaluation, US will not be used to measure tumor lesions. US may be used at the discretion of the investigator for disease management.

8.5.6 Tumor markers/Biochemical Progression- The tumor marker, PSA, will be used as one of the endpoints. Biochemical disease progression is defined using the Prostate Cancer Clinical Trials Working Group 2 (PCTWG2) definition. That is, a rising PSA that is > 2 ng/mL higher than the nadir and the rise must be at least 25% over nadir, and the rise must be confirmed by a second PSA at least three weeks later (28).

8.5.7 Cytology, histology- These techniques may be used to differentiate between partial responses (PR) and complete responses (CR) if necessary and determined by the investigator. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.6 Response Criteria

8.6.1 Evaluation of Target Lesions

Response	Description
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters (nadir) recorded since the treatment started or the appearance of one or more new lesions.

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

8.6.2 Evaluation of Non-Target Lesions

Response	**Description**
Complete Response (CR):	Disappearance of all non-target lesions and *normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. **Bone-only disease:** appearance of **two** or more new bone lesions.
Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the investigator will prevail.	
*Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.	

8.6.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort will be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, the residual lesion will be investigated (fine needle aspirate/biopsy if possible) before confirming the complete response status.

8.7 Confirmatory Measurement/Duration of Response

8.7.1 Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks.

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

9. Removal of Patients from Study

9.1. Off-Treatment Parameters
Patients will be considered "Off-Treatment" at the time of progression.

In the absence of progressive disease, study "treatment" may continue until one of the following criteria applies:

a) Patient is unable to undergo CRP (due to patient decision change or technical reasons).
b) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

c) Intercurrent illness that prevents further administration of treatment.
d) Patient decides to withdraw from the study.
e) Noncompliance with treatment plan.
f) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.

9.2. Off-Study Parameters

Patients will be considered "Off-Study" if they withdraw consent and no longer wish to be followed for survival, if they are lost to follow-up (after two consecutive survival follow-up "visits" with exhausted failed attempts to contact the patient for survival status), or in the event of death.

10. Laboratory Evaluations and Procedures/Correlative and Pharmacokinetic Studies

This protocol has two correlative studies.

10.1. Genomics

Based on the phase 1 study, there is a subgroup of patients who do not benefit from CRP. To further define this group, we propose to carry out whole exome seq and RNAseq from the primary prostate cancer tissues removed during surgery in the experimental group. The genomic and transcriptomic data will be combined with the clinical outcomes result to identify potential hallmarks of patients who do not respond to surgery. This portion of the proposal will be spearheaded by Dr. Neil Sarkar, Professor and Chair, Department of Bioinformatics, Brown University in collaboration with Macrogen, Inc (Seoul, Korea). Brown University in collaboration with Macrogen, Inc (Seoul, Korea) will get in touch with the sites to provide the information about slide collections and shipment; these slides will be shipped to them and not CINJ. Data analysis will be carried out as follows.

Whole exome sequence data will be complemented with the RNAseq data to increase the overall quality of molecular data available for analysis. Genomic analysis will be done primarily using the Genome Analysis Toolkit (GATK). GATK Best Practices workflows will be used to identify somatic Single Nucleotide Variants (SNVs). To identify known functional variants, SNVs will be respectively linked to data from database of Single Nucleotide Polymorphisms (dbSNP), Online Mendelian Inheritance in Man (OMIM), Human Gene Mutation Database (HGMD), and Catalogue of Somatic Mutations in Cancer (COSMIC). Prostate cancer data from The Cancer Genome Atlas (TCGA) will be compared to the data generated from this study to identify previously identified SNVs of interest. Attention will be given to those SNVs that have not been previously characterized and are found to be associated strongly with patients who do not benefit from CRP, with the goal to identify molecular signatures that can be used to better predict treatment success. Clinical data will be correlated with SNVs and clustering techniques will be used to identify potential patterns associated with patients who were responsive to CRP versus those who were not. In addition to statistical clustering methodologies, such as those that are incorporated into commonly used tools (e.g., genoPlotR), phylogenetic techniques will be used to analyze how SNVs characterize the CRP-responsive versus non-CRP-responsive populations. Lastly, the Cytoscape tool will be used for enabling additional exploration of the molecular data in the context of pathways (e.g., as

catalogued in the Kyoto Encyclopedia of Genes and Genomes [KEGG]) and interacting proteins (e.g., as catalogued in the Search Tool for Recurring Instances of Neighbouring Genes [STRING]).

Tumor specimen for the above research will be collected at the time of surgery. If a patient has a biopsy of the tumor or surgery involving the tumor for any reason while on study, the patient will be asked for permission to collect left over tissue samples from this biopsy or surgery for the above evaluation.

Central pathology review: All tumor specimen will be shipped at the end of the study. Shipping material will be provided by CINJ to each site at the end of the study, to ship out the samples for central review. Slides should be sent according to the outside institutional policy. Slides have to represent the key diagnosis and have to be accompanied by the pathology report. No specific storage medium or temperature is required for the shipment. CINJ will be performing the central review. Slides will be stored at CINJ and will not be returned.

For surgical resection: H&E slides which represent tumor grade (with AND without treatment effect), extra prostatic extension, seminal vesicle(s) involvement, positive margin, positive lymph nodes, and metastatic sites (1-30 Slides).

10.2. Quality of life

Dr. Brian Gonzalez (Moffitt Cancer Center, Tampa, FL), an expert in patient-reported outcomes among prostate cancer patients, will oversee this project. One benefit of surgical control of local tumor in men with advanced and metastatic prostate cancer has been improved quality of life (QOL) (22, 23). Thus, we propose to assess QOL between the two groups. We plan to collect the data electronically via the CINJ Population Science Research Support Core.

Collection of Patient-Reported Outcome (PRO) Data.

Study related questionnaires will be completed by subjects online using DatStat, a survey data system maintained by the CINJ Population Science Research Support Core using HIPAA-compliant DatStat software. Approval for use of this software in research studies has been provided by the Rutgers Biomedical and Health Sciences Institutional Review Board (IRB). (The approval process included: obtaining a Technology Professional Service Agreement and a Business Associate Agreement from DatStat; the approval of a Security Questionnaire from the Rutgers Office of Information Technology; and the completion of a Security Risk and Assessment Tool by the Rutgers CINJ Office of Information Technology.) The software allows for research study personnel to be assigned data access and privileges specific to their role on the study. Online surveys will be completed by participants using a secure website (hosted on DatStat servers) developed and maintained by the CINJ Population Science Research Support Core.

DatStat secure servers are registered with site certificates provided by AddTrust that provide for advanced encryption over the wire. As each user moves through the survey form, his/her responses are encrypted while in-transit between the browser and DatStat's server using SSL (Secure Sockets Layer) and 40, 56, or 128-bit Public Key Encryption. All servers used for data collection are highly fault-tolerant and equipped with redundant, hot-pluggable power

supplies, redundant network interfaces, and RAID 5 hot-swappable disk storage. All primary servers are plugged into a monitored, uninterruptible power supply (UPS). DatStat servers are stored in a locked server cabinet/rack, which are housed in a state-of-the-art, wellventilated data center. Physical access to servers and data backup is restricted to a minimal number of information technology professionals. The servers are secured with physical and firewall security.

In the event that the online questionnaires are not available, completion of the paper copy of the approved questionnaires by the patient is allowed. Once the questionnaires become available in DatStat, site staff will need to enter the data into DatStat using the patient's completed paper questionnaires. Any questionnaires completed on paper must be kept in the patient's chart and made available for auditing purposes. If a patient is unable to complete the questionnaire in person, a paper copy of the questionnaire may be mailed to the patient. Site staff will need to enter the data into DatStat using the patient's completed paper questionnaires. Questionnaires cannot be completed by phone.

Measures: The measures below will be administered at each assessment. Thus, participants will complete each measure in their native language. Questionnaires are available in English, Spanish, Japanese, Korean, and Chinese.

Health-Related Quality of Life. The 12-Item Short Form Survey (SF-12) is a valid and reliable 12-item measure of health-related quality of life. This scale will be used to assess general health function. This scale provides a Physical Health Composite as well as a Mental Health Composite. Both range from 0 - 100 with higher scores indicating better health-related quality of life.

Prostate-Related Quality of Life. The Expanded Prostate Cancer Index Composite (EPIC) is a validated and reliable 32-item measure of quality of life among prostate cancer patients. This measure will be used to assess the domains of function and bother from urinary, bowel, sexual, and hormonal symptoms.

Urinary Symptoms. The American Urological Association Symptom Score (AUASS) is a valid and reliable 8-item measure that will be used to assess urinary symptomatology. Scores range from 0 to 35, with higher scores reflecting greater severity of urinary symptoms.

Sexual Health. The Sexual Health Inventory for Men (SHIM) is a valid reliable 5-item measure that will be used to assess sexual health. Questions assess severity of symptoms of erectile dysfunction. Scores range from 0 to 25 with lower scores reflecting worse erectile dysfunction symptomatology.

Hot Flash Interference. The 10-item Hot Flash Related Daily Interference Scale (HFRDIS) will be used to measure interference, the degree to which hot flashes disrupt patients' daily activities and quality of life. This scale yields a total score ranging from 0 - 100 with higher scores indicating greater hot flash interference.

Sleep Quality. The Pittsburgh Sleep Quality Index (PSQI) is a valid and reliable 18-item measure of sleep quality. This measure will be used to assess several components of sleep quality, including perceived quality, the time taken to fall asleep, the duration of sleep, time spent awake after initially falling asleep, and use of sleep medications. A total score combines these domains and ranges from 0 - 21 with higher scores indicating worse sleep quality.

Psychological Distress. The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable 14-item measure of psychological distress. This scale assesses severity of anxiety and depression. It yields a total score ranging from 0 - 42, with higher scores indicating greater psychological distress.

Hope for the Future. The Herth Hope Index (HHI) is a 12-item measure of patients' sense of hope. It yields three subscales assessing one's sense of temporality and future (e.g., "I have short and/or long range goals"), positive readiness and expectancy (e.g., "I can see possibilities in the midst of difficulties"). And interconnectedness with others (e.g., "I am able to give and receive caring/love"). The overall scale provides a total score between 12 – 48, with higher scores indicating greater hope.

Data Management: All patient-reported outcomes will be collected via tablet computer at each clinic visit in each participant's native language. Online data collection ensures that data are in valid format (e.g., numeric, date, string) and that all questions are answered before proceeding. Dr. Gonzalez will oversee implementation of the patient-reported outcome data collection system. As a founding member of the Scientific Advisory Board prior to his move to the Moffitt Cancer Center, he is intimately familiar with the Population Science Research Support Core at Rutgers Cancer Institute of New Jersey. He will monitor accrual weekly and address any issues that arise at study sites over time.

Analysis Plan

A. To compare men treated with BST to men treated with BST + CRP on quality of life outcomes, including health-related quality of life, sleep disturbance, hot flash interference, and psychological distress.

Approach. To test the hypothesis that men treated with BST + CRP will report improvements in these outcomes over time relative to men treated with BST only we will compare groups on change over time in quality of life outcomes. Specifically, we will compare slopes of change in quality of life outcomes between groups using mixed model analyses with SAS PROC MIXED. This will enable us to determine whether the BST + CRP group shows improvement over time relative to the BST group. In addition, we will test our hypothesis that men treated with BST + CRP will report significantly better quality of life outcomes at two years post-randomization relative to men treated with BST. This will also be conducted with mixed models by comparing group values at the 24-month follow-up assessment. A major benefit of this methodology is that, unlike repeated measures ANOVA, mixed models allow for the use of all available data at each assessment without imputing any missing data. Dr. Gonzalez will oversee analysis of patient-reported outcome data, having personally conducted and overseen mixed model analyses in several studies with prostate cancer patients.

B. To identify genomic predictors of improvements in quality of life outcomes, including health-related quality of life, sleep disturbance, hot flash interference, and psychological distress.

Approach. To identify genomic predictors of improvement in quality of life we will examine residualized change in quality of life outcomes as a function of genomic predictors. These analyses will be conducted for the overall sample as well as in analyses examining a genomic marker X group X time interaction using JMP Genomics with a positive false discovery rate of $q<0.05$. This methodology has been previously conducted by members of this study team for quality of life outcomes in prostate cancer samples with similar sample sizes.

11. Pharmaceutical Information

In the current application, the BST is defined as ADT +/- docetaxel (1-3).

ADT is defined as surgical castration (orchiectomy), or LHRH agonist/antagonist +/- abiraterone.

11.1 Concomitant Medications

Given that the medications patients enrolled on this trial will be taking are approved, standard of care drugs, there are no protocol specified requirements for concomitant medication review. However, it is suggested that each treating physician reviews the patient's concomitant medications against the BST he/she prescribes for possible drug interaction risks. The Flockhart Table @ http://medicine.iupui.edu/clinpharm/ddis/main-table/ can be used to cross reference the potential for interactions.

12. Data Collection and Records to be Kept

12.1 Case Report Forms

A subset of the National Cancer Institute (NCI) CRFs, in electronic format, will be utilized. Completion of the electronic CRFs (eCRFs) will be done in accordance with the instructions in a study specific data capture plan. All eCRFs will be completed by research staff at each study site. The data reporting requirements for each eCRF are detailed in the SIMCAP Data Capture Plan provided to each site. The eCRFs will be maintained in a confidential format in a secure database.

12.2 Data Submission Timeline and Forms

Completion of eCRFs will occur in accordance with NCI guidelines. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, disease assessment, etc.) will be completed no later than 14 days after the start of treatment. Treatment eCRFs (e.g., surgery, adjuvant therapies etc.) will be completed no later than 14 days following each treatment event. Off-treatment information (e.g., follow-up, best response, etc.) will be completed no later than 14 days after the end of protocol treatment.

12.3 Research Charts

For Rutgers CINJ patients, a research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the Cancer Institute of New Jersey, OHRS.

For non-Rutgers CINJ sites, research charts should be maintained according to each site's standard operating procedure. At the end of the study, a complete copy of each patient's chart will be made available to HROC of Rutgers-CINJ for auditing.

12.4 Reports

Publications and annual reports for submission to the IRB will be written by the Cancer Institute of New Jersey PI using the data captured on the e-CRFs.

13. Data and Safety Monitoring

We will utilize an external Data Safety Monitoring Committee (DSMC). This committee will be composed of four urologists and one statistician from institutions not affiliated with this study. In addition, Data Safety Monitoring Board at each institution will have the oversight authority at the respective institution. The DSMC will review the data every six months during the entire duration of the trial.

In addition, the Rutgers Cancer Institute of New Jersey Human Research Oversight Committee (HROC) as the Data Safety and Monitoring Board for this trial. The HROC is the institutional body at Rutgers-CINJ charged with data and safety monitoring. Members of the HROC are selected for their broad range of operational expertise and possess specific expertise in clinical trials, biostatistics, regulatory affairs, data management, nursing, and pharmacy. The Associate Director for Clinical Sciences appoints the Chairman and Co-Chair of the HROC. The HROC reviews each of the following areas at their bi-weekly meeting: quarterly review of clinical trial portfolio including data completeness, response data (particularly for planned and/or interim analyses), and adverse events, all serious adverse event (SAE) reports occurring on Rutgers-CINJ coordinated trials, all protocol deviation reports, and audit reports.

In the event of high complication rates, or audit findings suggestive of non-compliance with the protocol, the HROC may recommend suspension of enrollment onto a trial for safety concerns. These recommendations will be communicated to the PI for response and the recommendations and any response will be reviewed by the study sponsor and made available to all participating site's IRB and other appropriate regulatory bodies.

Minutes are generated from each HROC meeting, and these minutes and reports (e.g., audit reports, etc.) are provided in electronic format on a quarterly basis. Members of the HROC Executive Committee are appointed by the Caner Center Director and include the Chairman of the HROC and leadership representing the clinical research enterprise.

14. Multi-Institutional Guidelines

There are multiple US and non-US institutions participating in this trial. The regulatory approval will be coordinated by each institution's research coordinator and OHRS of Rutgers-CINJ. Quarterly, a conference call will be made to discuss the progress of the trial among the site PIs. At the end of the study, a complete copy of the patient's chart will be made available to HROC of Rutgers-CINJ for auditing.

At the end of the study, all pathology specimens will undergo a central pathology review at Rutgers Cancer Institute of New Jersey. The entire cost of this process will be paid by the anticipated grant support for this study.

15. Statistical Considerations

15.1 Primary and Secondary Hypotheses and Endpoints

Refer to Section 1.5 and Section 1.6.

15.2 Sample Size Justification

The primary outcome of phase 2 portion of the study is %FFS at 2 years after randomization. STAMPEDE study (1) reported %FFS at 2 years was 60% for patients in BST group. We expect the %FFS in the experimental group (CRT+BST) to be at least 78%, which is 30% improvement from BST group.

We assume the followings for sample size calculation: (i) exponential survival time; (ii) uniform accrual over 2 years; and (iii) 2 years of follow-up after the last accrual of patient. With 170 patients (85 per group), we can achieve 90% of power to detect at least 30% improvement in %FFS at 2 years in CRP+BST group from BST group using an one-sided exponential MLE test at a significance level 5%. Total expected number of failures (as defined in Section 1.5) is 71 (45 from BST and 26 from CRP+BST) under the alternative hypothesis and 74 (37 per group under the null hypothesis). With the anticipated drop-out rate of 10% , we will need 190 patients in total.

Extension to Phase 3

This is a Phase 2.5 design, which integrates Phase 2 and Phase 3. Therefore, Phase 2 portion of the design will play a role of 'internal pilot' study for Phase 3. When Phase 2 study's primary endpoint meets the pre-specified statistical requirement of 30% improvement in %FFS at 2 yrs after randomization, we will extend the study to Phase 3 with the overall survival as its primary endpoint. Results obtained in Phase 2 portion will be used to decide expected CRP+BST treatment effect on overall survival in order to calculate the additional sample size needed for Phase 3. When approved by the independent external DSMC, protocol modification requesting the expansion to Phase 3 study will be submitted along with the specifics of the sample size and power calculation.

15.3 Methods for Masking, Randomization and Stratification

All patients who sign consent for this study will be registered. The following information will be needed to register a patient:

- Institution Name
- Patient Initials
- Clinical Stage
  - M1a, M1b, or M1c
  - If M1b, how many bone metastases?
- Docetaxel planned or use
- Abiraterone planned or use
- Prior duration of ADT use
- Demographic information
- Gender
- Birth date

- Race
- Ethnicity
- Zip Code (if applicable)
- Country

After confirming that all eligibility criteria are met, patients will be stratified by geography (US vs non-US), stage (M1a, and M1b/M1c), number of bone metastasis (≤ 3 vs > 3), planned/current docetaxel use (yes vs no), planned/current abiraterone use (yes vs no), and duration of ADT prior to consent (ADT > 3 months vs ADT ≤ 3 months). Randomization will be done through OnCore, with the ratio of 1:1.

15.4 Statistical Analysis

Summary of descriptive statistics of all clinical variables measured will be provided. We will estimate time-to-event distributions (i.e. FFS and time to biochemical recurrence) using Kaplan-Meier methods. FFS will be compared using a one-sided log-rank test with the stratification by treatment arm Hazard ratio (HR) and corresponding two-sided 95% confidence intervals will be estimated using Cox proportional hazard models.

15.5 Compliance and Missing Data

Compliance will be defined as patients who continue to follow up as scheduled after randomization and undergo assigned treatment modalities and have routine imaging and blood work as dictated by the protocol and/or prescribed by their physician. If the dropout rate is greater than 10%, new accruals will be permitted to satisfy the total sample size requirement.

15.6 Interim Analysis

Review of the progress of the trial will be performed by the Data Safety Monitoring Board (DSMB) at Rutgers-CINJ as well as the external independent Data Safely Monitoring Committee (DSMC). Rutgers- CINJ DSMB will assess the results at least every six months during the entire duration of the study. The first analysis will take place when 30% of the failures have occurred but no later than six months. Rutgers-CINJ DSMB will continuously monitor excessive rate of adverse events including death especially in the CRP+BST arm, and accumulated information will be analyzed by the trial team. All meeting minutes of the Rutgers-CINJ DSMB will be shared with the external DSMC within 1 month.

Formal interim analysis of the results by the independent external DSMC will occur after 30% and 60% of the information is obtained using a one-sided log-rank test for FFS. Therefore, the first and second futility test will take place when 22 and 43 failures have occurred respectively.

The independent external DSMC has the authority to close the study throughout the duration of the study based on patient safety or futility. In the event that DSMC determines an early efficacy, the study will convert to phase 3 design immediately.

Early stopping will be determined using the Hwang-Shih-DeCani spending function, controlling for type I error and Type II error (29). Type II error and type I error are controlled at 10% and 5 %, respectively.

At 30% of the total failures (about 22), stop early due to efficacy if estimated HR < 0.267 and stop early due to futility if estimated HR > 1.188.

At 60% of the total failures (about 44), stop early due to efficacy if estimated HR < 0.446 and stop early due to futility if estimated HR > 0.809.

16. Human Subjects

16.1 Subject Population

The population is men of any ethnicity diagnosed with clinical M1a, M1b, or M1c prostate cancer.

16.2 Potential Risks

Risk of Harm, includes that which normally is associated with any patient undergoing Radical Prostatectomy (injury to bowels including the rectum, bleeding, impotence, incontinence, recto-urinary fistula, DVT and death).

There is minimal risk of loss of subjects' privacy and confidentiality of data collected or produced. Data will be maintained in a secure database accessible to the investigators only. There is no direct risk to the patient.

16.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI, or designee, shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

16.4 Potential Benefits

Removal of the prostate may enhance the effectiveness of the current standard-of-care: docetaxel+ADT. In addition, by controlling local tumor, quality of life may be improved.

16.5 Risk-Benefit Ratio

The risks involved with this study in the carefully selected patients who meet all inclusion criteria will be the risk of surgery. Based on the phase 1 study, the risk is no different than patients with only a localized disease who undergo radical prostatectomy.

16.6 Gender and Minorities

Male over the age of 18 are eligible. Females are excluded because they do not have prostate cancer and children (<18years of age) do not develop prostate cancer.

17. Economic/Financial Considerations

ADT +/- docetaxel is already one of the accepted standard of care option in men with mPCa. Surgery cost will be covered by the insurers. In the pilot phase 1 study, no insurers in the US

denied coverage for surgery to eligible patients. In addition, since this protocol is now funded and qualifies as a clinical trial, waiver from Medicare will be obtained.

In patients with no health insurance in the US, charity care will be obtained. In the countries outside the US and involved in this study, surgery in men with mPCa is covered by the national health insurance.

If the treating physician deems tissue biopsy to be necessary on progression, a portion of the samples will be requested at the clinical assessment has been completed.

18. Publication of Research Findings

The policies and procedures of Rutgers University's legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The Cancer Institute of New Jersey PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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Appendix A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B

Clavien-Dindo Classification of Peri-operative Complications.

Grades	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
III-a	Intervention not under general anesthesia
III-b	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
IV-a	Single organ dysfunction (including dialysis)
IV-b	Multi-organ dysfunction
V	Death of a patient