

COVER PAGE

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Phase II Randomized, Placebo-Controlled Trial of PROSTVAC® (PSA-TRICOM) in Patients with Clinically Localized Prostate Cancer Undergoing Active Surveillance

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SCHEMA

Phase II Randomized, Placebo-Controlled Trial of PROSTVAC® (PSA-TRICOM) in Patients with Clinically Localized Prostate Cancer Undergoing Active Surveillance

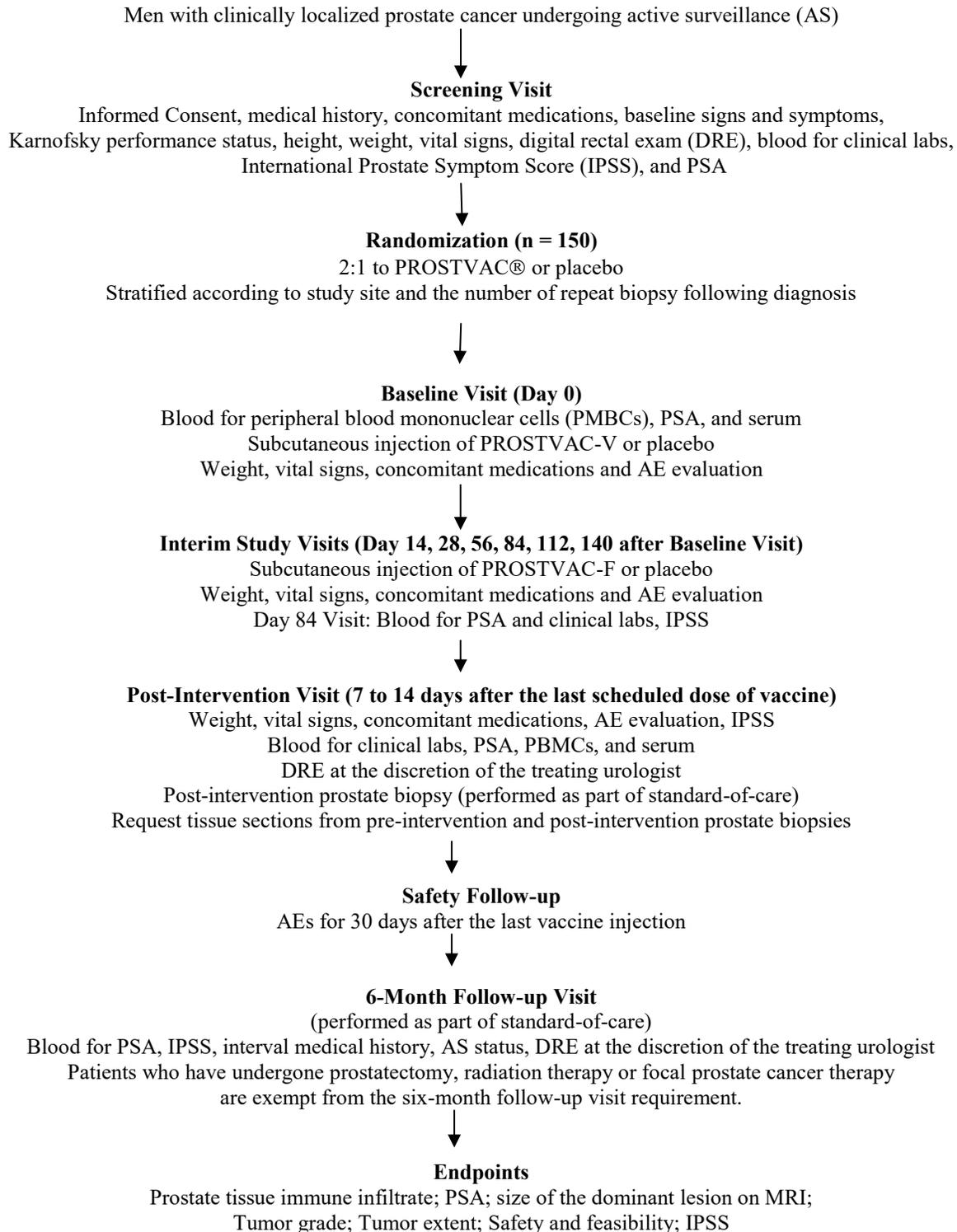


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1. OBJECTIVES

The overall objective is to conduct a randomized, placebo-controlled, double-blind trial of PROSTVAC® in patients with clinically localized prostate cancer undergoing active surveillance to determine the immunologic response to PROSTVAC® and the clinical indicators of disease progression.

1.1 Primary Objectives

- 1.1.1 To determine the effect of PROSTVAC® on the change (from pre to post-intervention) in CD8⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies.
- 1.1.2 To determine the effect of PROSTVAC® on the change in CD4⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies.

1.2 Secondary Objectives (prioritized list)

- 1.2.1 To assess the effect of PROSTVAC® on PD-L1 positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies.
- 1.2.2 To assess the correlation between the change in CD8⁺ and the change in PSA.
- 1.2.3 To assess the effect of PROSTVAC® on CD8⁺, CD4⁺, and PD-L1 positive cells in the benign portion of the prostate biopsies.
- 1.2.4 To assess the effect of PROSTVAC® on the change in PSA.
- 1.2.5 To assess the effect of PROSTVAC® on tumor grade (Gleason score).
- 1.2.6 To assess the effect of PROSTVAC on tumor extent (percent of positive random biopsy cores).
- 1.2.7 To compare the proportion of men on the two study arms with no cancer on post-intervention biopsy.
- 1.2.8 To assess the effect of PROSTVAC on the size of the dominant lesion on MRI (largest histopathologically confirmed lesion) in the subgroup of patients with MRIs pre and post-intervention.
- 1.2.9 To assess the effect of PROSTVAC® on circulating 15-Mer PSA-specific, MUC-1 and Brachyury-specific T cells.
- 1.2.10 To assess the effect of PROSTVAC® on soluble antibodies to tumor-associated antigens.
- 1.2.11 To assess the immunologic effects of PROSTVAC® in prostate tissue using multiplex immunofluorescence.
- 1.2.12 To assess the safety and feasibility of PROSTVAC® in the active surveillance population.
- 1.2.13 To assess the effect of PROSTVAC® on lower urinary tract symptoms (LUTS) in the active surveillance population.

2. BACKGROUND

2.1 Prostate Cancer

Due to widespread screening with the prostate-specific antigen (PSA) assay, prostate cancer is the most frequently diagnosed non-cutaneous cancer among U.S. men. While prostate cancer mortality has declined during the screening era, this has occurred at the cost of substantial over diagnosis and overtreatment, unnecessarily exposing many patients to side effects of therapy, such as erectile dysfunction, urinary incontinence, and proctitis [1, 2].

Population studies suggest that a substantial proportion of men diagnosed with localized prostate cancer in the US are over-treated [3-5]. This public health problem—unnecessarily aggressive treatment of tens of thousands of men each year who subsequently suffer chronic side effects—challenges us to develop innovative therapeutic models to refine treatment paradigms within this patient population.

In recent years, active surveillance has increasingly garnered attention as an alternative, and less morbid, approach to surgery or radiation in men with clinically localized, low-risk prostate cancer. Follow-up

assessments in patients on active surveillance include serial PSA measures, repeat prostate biopsy and, increasingly, prostate MRI. Most men on active surveillance followed for up to 15 years will not require treatment. However, up to one-third of active surveillance patients will undergo treatment within 2 to 5 years of initiating surveillance [6].

Development of intervention strategies to prevent disease progression in patients on active surveillance thus represents an important area of prostate cancer chemoprevention. Prior studies have yielded promising early results. The Prostate Cancer Lifestyle Trial compared intensive dietary and lifestyle modifications for men on active surveillance to usual care and reported a significantly lower rate of secondary treatment for the intervention arm after 2 years of follow-up [7]. The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial assessed the efficacy of dutasteride in preventing disease progression in active surveillance patients. After 3 years, 38% and 48% of the dutasteride and control participants, respectively, had progressed by pathologic or therapeutic criteria, a relative risk reduction of 21% for dutasteride [8]. An ongoing multicenter study is evaluating whether a dietary intervention could delay disease progression in men on active surveillance [9].

However, definitive interventions for preventing clinical progression in active surveillance patients are lacking.

2.2 PROSTVAC®

An alternative and novel approach for delaying disease progression in men on active surveillance is immunotherapy. Prostate cancer presents an attractive model for immunotherapy based on several characteristics. It is a relatively slow-growing tumor, thus allowing time for elicitation of effective immune response. In addition, prostate cells express many tissue-specific proteins that could act as therapeutic targets. In the past decade, a variety of vaccines against prostate cancer have been developed and tested in clinical trials in metastatic castration-resistance prostate cancer patients [10]. Sipuleucel-T became the first prostate cancer vaccine approved by the FDA based on results of two randomized placebo controlled Phase III clinical trials that demonstrated an overall survival advantage with the use of Sipuleucel-T [11, 12]. Sipuleucel-T is a cell-based vaccine that employs the patient's own antigen-presenting cells that have been treated (*ex vivo*) with a recombinant fusion protein. Due to the complex preparation processes, the clinical adaption of this vaccine in the long-term prevention setting is likely to be limited.

Another therapeutic vaccine that has recently reported an overall survival advantage in prostate cancer is PSA-TRICOM (PROSTVAC®). PROSTVAC® is a poxviral vaccine using a vaccinia vector for priming and fowlpox vector for boosting. It contains PSA and three T-cell co-stimulatory molecules (B7.1, ICAM-1, and LFA-3). PROSTVAC® can be manufactured in large quantities, stored frozen for many years, and then thawed and injected into patients. Based on the RFP summary provided by the NCI, DCP, PROSTVAC® has been evaluated in 13 completed clinical trials with six additional trials in progress.

A Phase I study determined the safety and feasibility of PROSTVAC® in men with locally recurrent or progressive prostate cancer. PROSTVAC® was administered with initial subcutaneous injection of recombinant vaccinia (rV)-PSA-TRICOM and intraprostatic booster vaccinations with recombinant fowlpox (rF)-PSA-TRICOM. There were no dose-limiting toxicities. Common adverse events were fever and subcutaneous injection site reactions. The study also showed improved serum PSA kinetics and increased tumor infiltrates of CD4⁺ and CD8⁺ cells [13].

A double-blind, randomized, placebo controlled Phase II multicenter trial evaluated PROSTVAC® in 125 patients with minimally symptomatic castration-resistant metastatic prostate cancer. The priming and boosting vaccinations were given subcutaneously. PROSTVAC® was found to be well tolerated. Common adverse events included injection site reactions and fatigue. Although the progression free survival was similar between the two groups, PROSTVAC®-treated patients had an overall survival advantage. At 3

years post study, PROSTVAC®-treated patients had a 44% reduction in the death rate and an 8.5 months improvement in median overall survival compared to the placebo [14]. A smaller study evaluated PROSTVAC® in 32 patients with metastatic castration-resistant prostate cancer and reported an overall survival of 26.6 months with a median improvement in survival of 9.2 months compared with a Halabi-predicted survival (HPS) [15].

The consistent survival advantage observed in these studies has led to the design and initiation of a Phase III trial of PROSTVAC® in 1200 subjects with asymptomatic or minimally symptomatic castration-resistant prostate cancer.

In addition, evaluation of emerging data supports the use of immunotherapy earlier in the disease course and in patients with less aggressive disease and lower tumor burden [16, 17]. In one of the PROSTVAC® studies described above [15], patients with more aggressive or more advanced disease (HPS < 18 months) had a 2.3- month improvement over predicted overall survival, whereas those with less advanced or less aggressive disease (HPS ≥ 18 months) had an improvement in overall survival of 16.5 months or more. This supports the evaluation of PROSTVAC® in the active surveillance setting.

2.3 Rationale

In recent years, active surveillance has increasingly garnered acceptance as an alternative, and less morbid, approach to surgery or radiation in men with favorable-risk prostate cancer. However, definitive interventions for preventing clinical progression in active surveillance patients are lacking. Available data suggest that PROSTVAC® improved the overall survival in patients with castration-resistant prostate cancer and the survival benefit increased with less advanced or less aggressive disease. We, therefore, hypothesize that PROSTVAC® will prevent or delay disease progression in patients on active surveillance. We propose to conduct a randomized, placebo-controlled, double-blind trial of PROSTVAC® in patients with clinically localized prostate cancer undergoing active surveillance to assess the immunologic response to PROSTVAC® and its effect on clinical indicators of disease progression.

3. SUMMARY OF STUDY PLAN

This is a Phase II randomized, placebo-controlled, double-blind trial of PROSTVAC® in patients with clinically localized prostate cancer undergoing active surveillance. We plan to recruit men with a diagnosis of localized prostate cancer who are being monitored by active surveillance. Detailed inclusion and exclusion criteria are listed in sections 4.1 and 4.2.

Participants will undergo a screening evaluation in which the informed consent form and medical records and tissue release form will be signed in order to obtain information from urologic assessment, biopsy pathology reports, PSA test results, and biopsy tissues. Participants will undergo a brief physical exam and be evaluated for concomitant medications, medical history and baseline symptoms and signs. International Prostate Symptom Score (IPSS) will be obtained. Blood will be collected for complete blood count with differentiation (CBC-diff), comprehensive metabolic panel (CMP), and PSA. Screening visit procedures, including PSA, performed within 90 days prior to the Baseline Visit (first vaccine injection), may be applied toward eligibility.

Participants will also undergo a digital rectal exam (DRE) to confirm clinical stage at screening, if a DRE has not been performed within 180 days before the Baseline Visit.

Following the screening evaluation, eligible participants will be randomized 2:1 to receive PROSTVAC® or placebo. Randomization will be stratified according to the study site and the number of repeat biopsies following diagnosis (≤ 2, or >2). We plan to randomize 150 eligible men (i.e., 100 receiving PROSTVAC® and 50 receiving placebo).

Following randomization, participants will return for the Baseline Visit and be evaluated for weight, vital signs, AEs and concomitant medications. Blood will be collected for isolation of peripheral blood mononuclear cells (PBMC). Blood will also be collected for PSA and for serum soluble antibodies to tumor-specific antigens. Blood will be collected prior to administration of the vaccine injection. Participants will receive a priming vaccination with subcutaneous injection of PROSTVAC-V or placebo, injected into the upper outer thigh or upper arm. Participants will be provided with instructions for caring for injection site. Participants will be instructed to record adverse events and concomitant medications throughout the intervention. Participants will be reminded to avoid close contact or household contact with the following high-risk individuals for three weeks after the Day 1 vaccination or until the vaccination site heals completely: (a) children ≤ 3 years of age, (b) pregnant or nursing women, (c) individuals with prior or concurrent extensive eczema or other eczematoid skin disorders, (d) individuals with other acute, chronic, or exfoliative skin condition, or (e) immunocompromised or immunosuppressed persons (by disease or therapy).

On Day 14, 28, 56, 84, 112, 140 following the baseline visit, participants will return for booster vaccinations with subcutaneous injection of PROSTVAC-F or placebo injected into the upper outer thigh or upper arm. It is recommended to alternate the injection sites. Other evaluations at each visit include weight, vital signs, AEs and concomitant medications. At the Day 84 visit International Prostate Symptom Score will be obtained, blood will be collected for PSA and for CBC-diff and CMP. CMP and CBC test results will be evaluated prior to administering the scheduled vaccine to determine whether the injection should be given or omitted. If needed, the labs can be done on a different day prior to the day of the scheduled vaccine injection, but the labs and the vaccine injection should fall within the window specified on the schedule of events.

Participants will return for the post-intervention visit 7-14 days after the last scheduled dose of vaccine. Blood will be collected prior to the biopsy procedure for CBC-diff, CMP, PSA, PBMCs, and serum. Participants will be evaluated for weight, vital signs, AEs and concomitant medications. International Prostate Symptom Score will be obtained. DRE will be performed at the discretion of the individual urologist. TRUS-guided prostate biopsy or targeted prostate biopsy using MR-US fusion will be performed as part of the routine care of patients on active surveillance. The results of all PSA tests performed during the intervention will be collected. Pre- and post-intervention biopsy pathology reports will be collected and submitted to the University of Arizona Early Phase Chemoprevention Consortium Office. Unstained slides from the pre- and post-intervention prostate biopsies will be requested from the institutional pathology lab for analysis of the change in immune infiltrates in the target tissue.

If available, reports from the prostate MRI scans performed (and companion pathology reports) from 3 years prior to and 6 months after the study intervention will be collected and submitted to the University of Arizona Early Phase Chemoprevention Consortium Office to capture the lesion size information.

Study subjects will be followed for 30 days after the last study dose is given. Participants will continue to record adverse events during the follow-up period. The diary will be mailed back to the study staff in a pre-addressed, stamped envelope. Study staff will contact the subject by phone, if necessary, to clarify any of the diary entries.

Participants will return for a follow-up visit 6 months after the post-intervention biopsy or 6 months after the last study dose is given, if no post-intervention biopsy was performed, as part of the standard-of-care. Blood will be collected for PSA. International Prostate Symptom Score, interval medical history, and documentation on whether participant is still on active surveillance will be obtained. DRE will be performed at the discretion of the individual urologist. Patients who have undergone prostatectomy, radiation therapy or focal prostate cancer therapy are exempt from the six-month follow-up visit requirement.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

- 4.1.1 Biopsy-proven (consisting of ≥ 10 tissue cores) adenocarcinoma of the prostate with cancer present in at least one biopsy core, either random or targeted, in the most recent biopsy.
- 4.1.2 All prior biopsies must meet the following: $\leq 50\%$ of the total number of random biopsy cores positive for cancer
 - Gleason score $\leq (3+4)$
- 4.1.3 Clinical stage $\leq T2a$ by DRE
- 4.1.4 Biopsies performed at outside institutions should have Gleason score confirmed at the study site by a GU pathologist to ensure eligibility.
- 4.1.5 Pre-intervention biopsy tissue (most proximal to enrollment) containing sufficient tumor tissue to cut 5-10 unstained slides confirmed to be available upon request.
- 4.1.6 Screening serum PSA < 20 ng/mL. For men treated with 5-alpha-reductase inhibitors (e.g., finasteride, dutasteride), PSA needs to be < 10 ng/mL.
- 4.1.7 Hematological eligibility parameters:
Neutrophil count $\geq 1,200/\text{mm}^3$ (≥ 1.2 k/ μL)
Stable platelet count $\geq 75,000/\text{mm}^3$ (≥ 75 k/ μL)
- 4.1.8 Hepatic and renal function eligibility parameters:
Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL for patients with Gilbert's syndrome)
ALT and AST ≤ 2.5 x ULN
Serum creatinine ≤ 1.5 x ULN
- 4.1.9 Karnofsky $\geq 70\%$; see Appendix A.
- 4.1.10 Must agree to use medically acceptable barrier and/or chemical method of contraception while on study and for at least one month following the last vaccine injection because the effects of PROSTVAC® on the developing human fetus at the recommended therapeutic dose are unknown. Should a participant's partner become pregnant or suspect she is pregnant while the participant is participating in this study, the study physician should be informed immediately. In the event a participant's partner becomes pregnant, the study sponsor may request additional information regarding the course of the pregnancy and if the pregnancy is carried to term, the birth of the child (i.e., the outcome of the pregnancy).
- 4.1.11 Ability to understand and the willingness to sign a written informed consent document.
- 4.1.12 No planned prostate biopsies during the intervention until after the post-intervention biopsy.
- 4.1.13 Men on stable doses of 5-alpha reductase inhibitors are eligible as long as there is no planned dose change while on study.

4.2 Exclusion Criteria

- 4.2.1 Have had prior treatment for prostate cancer by surgery, irradiation, local ablative (i.e., cryosurgery or high-intensity focused ultrasound), or androgen-deprivation therapy.
- 4.2.2 Patients who have prostate cancer with distant metastases.
- 4.2.3 Have undergone treatment of hormone therapy, immunotherapy, chemotherapy and/or radiation for any malignancies within the past 2 years.
- 4.2.4 Uncontrolled intermittent illnesses or medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. Such illnesses/conditions may include, but are not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or unstable cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 4.2.5 Positive for HIV or active infections for hepatitis B, and /or hepatitis C, based on medical history.
- 4.2.6 Prior solid organ or bone marrow transplant.
- 4.2.7 Immunodeficiency or splenectomy.
- 4.2.8 Chronic immunosuppressive therapy within 30 days of screening.
- 4.2.9 Inflammatory eye disease requiring steroid treatment within 28 days of screening.
- 4.2.10 Chronic administration (defined as daily or every other day for continued use > 14 days) of systemic corticosteroids within 28 days of the first planned dose of PROSTVAC-V/F. Use of inhaled steroids, nasal sprays, and topical creams for small body areas is allowed.
- 4.2.11 History of or active autoimmune disease including but not limited to autoimmune neutropenia, thrombocytopenia, or hemolytic anemia, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, myasthenia gravis, Goodpasture's syndrome. Persons with vitiligo are not excluded. Persons with well-controlled autoimmune endocrinopathies, e.g., diabetes mellitus, Graves' disease, Hashimoto's thyroiditis, Addison's disease are not excluded. Persons with well-controlled rheumatoid arthritis, psoriatic arthritis and polymyalgia rheumatica are not excluded.
- 4.2.12 Known allergy to eggs, egg products.
- 4.2.13 Prior or concurrent eczema or other eczematoid skin disorders or active skin condition (acute, chronic, or exfoliative) that disrupts the epidermis. Persons with psoriasis are not excluded except in cases of:
 - any active lesion
 - any active lesion in the previous 6 months that required treatment, either systemic or topical
 - any prior episode, at any time, extensive enough or severe enough as to require systemic treatment.
- 4.2.14 Previous adverse reactions to smallpox vaccination.
- 4.2.15 Unable to avoid close contact or household contact with the following high-risk individuals for three weeks after the Day 1 vaccination or until the vaccination site heals completely: (a) children \leq 3 years of age, (b) pregnant or nursing women, (c) individuals with prior or concurrent extensive eczema or other eczematoid skin disorders, (d) individuals with other acute, chronic, or

exfoliative skin condition, or (e) immunocompromised or immunosuppressed persons (by disease or therapy).

4.2.16 Participants may not be receiving any other investigational agents.

4.2.17 History of allergic reactions attributed to compounds of similar chemical or biologic composition of PROSTVAC®.

4.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Since women and children are not subject to prostate cancer, they will be excluded from this study.

4.4 Recruitment and Retention Plan

Study participants will be mainly recruited from patients seen at the institution urology clinics.

Additional recruitment methods include community physician referral, posting the study information on the institution websites, community outreach activities, and advertisement in print and web media.

The study team will provide a friendly and comfortable study setting for participants from initial contact through the completion of their study activities. Demands upon the subjects will be minimized to foster comfort while preserving the research goals. Wherever possible, flexibility will be built into the study schedule to promote compliance.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

- The study agent is PROSTVAC®.
- Participants will be randomly assigned (2:1) to PROSTVAC® or placebo.
- One injection of PROSTVAC-V (or placebo) at baseline.
- Six injections of PROSTVAC-F (or placebo) over 140 days.

5.2 PROSTVAC® Administration

- Participants will receive subcutaneous injection of PROSTVAC® or placebo in the study clinic injected into the upper outer thigh or upper arm. It is recommended to alternate the injection sites.
- The treatment regimen will include a priming vaccination with subcutaneous injection of 2×10^8 pfu (in 0.5 mL) of PROSTVAC-V or placebo (empty vector) at baseline, followed by booster vaccinations with subcutaneous injection of 1×10^9 pfu (in 0.5 mL) of PROSTVAC-F or placebo (empty vector) on Day 14, 28, 56, 84, 112, and 140 following the priming injection.
- Participants should remain in the clinic for at least 30 minutes following administration of PROSTVAC-V/F or placebo for observation for signs of adverse reactions.

5.3 Run-in Procedures

Not applicable.

5.4 Contraindications

Participants will be reminded to avoid close contact or household contact with the following high-risk individuals for three weeks after the Day 1 vaccination or until the vaccination site heals completely: (a) children \leq 3 years of age, (b) pregnant or nursing women, (c) individuals with prior or concurrent extensive eczema or other eczematoid skin disorders, (d) individuals with other acute, chronic, or exfoliative skin condition, or (e) immunocompromised or immunosuppressed persons (by disease or therapy).

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (e.g., biopsy) should also be included. Participants may receive other vaccines (e.g., flu, shingles, pneumonia) while on study. However, the non-study vaccines should not be given within a week of the PROSTVAC vaccine to avoid the confusion of potential AE symptoms of one vaccine versus the other. All non-study vaccines should be documented on the concomitant medication CRF.

5.6 Dose Modification

No dose modification will be made for Grade 1 adverse events.

For Grade 2 adverse events not considered related to study agent persisting until the next scheduled injection of vaccine, the scheduled injection may be given or omitted at the discretion of the study physician.

For Grade 2 or 3 adverse events definitely, probably or possibly related to study agent persisting until the next scheduled injection of vaccine, the scheduled injection will be omitted. Participants will receive subsequent doses of study agent when toxicity is resolved to Grade 1 or less.

For Grade 3 adverse events unrelated or unlikely related to study agent persisting until the next scheduled injection of vaccine, the scheduled injection will be omitted. Participants will receive subsequent doses of study agent when toxicity is resolved to Grade 2 or less.

For Grade 4 events unrelated or unlikely related to study agent persisting until the next scheduled injection of vaccine, the scheduled injection will be omitted. Participants may receive subsequent doses of study agent when toxicity has resolved to Grade 2 or less, at the discretion of the study physician. Participants with Grade 4 events that are definitely, probably or possibly related to the study agent will receive no further doses of vaccine/placebo and be followed for resolution of adverse events. If appropriate, they should remain on-study and undergo the post-intervention biopsy.

Vaccine injections may be held at the discretion of the patient and/or investigator for any concerns related to drug toxicity.

5.7 Adherence/Compliance

5.7.1 Participants will be considered compliant for statistical analysis if they have received 2 or more doses of the PROSTVAC-F (boost).

5.7.2 The compliance will be measured by the number of vaccine administered.

6. PHARMACEUTICAL INFORMATION

6.1 PROSTVAC[®] (IND#16,220, Sponsor NCI, DCP)

PROSTVAC[®] is a vaccinia vector-based vaccine developed by the National Cancer Institute (NCI) and licensed to BN Immunotherapeutics (Bavarian Nordic, Mountain View, CA). It is designed to enhance T-cell co-stimulation through enhanced expression of the transgenes of PSA as the encoded antigen and three T-cell co-stimulatory molecules (CD58/LFA-3, CD80, and ICAM-1/CD54). CD80 (B7.1) is known to react with CD28 on T cells for positive co-stimulation and CTLA4 for negative immune checkpoint inhibition. Initial clinical studies with PSA recombinant vaccinia vectors (rV-PSA) demonstrated safety and immunogenicity [18-20], but neutralizing antibody responses limited the ability for continued rV-PSA treatment; a heterologous prime boost strategy was used with rFowlpox-PSA (rF-PSA) as a boosting agent. This configuration constitutes PROSTVAC-VF, vaccinia-PSA-TRICOM (PROSTVAC-V), and fowlpox-PSA TRICOM (PROSTVAC-F). NCI, DCP (Division of Cancer Prevention) will sponsor an initial Investigational New Drug application (IND) to undertake this study.

Vaccinia virus is considered a Biosafety Level 2 agent with specific precautions for healthcare or laboratory workers. Fowlpox virus is considered Biosafety Level 1 agent and no specific precautions for healthcare or laboratory workers are currently recommended by the Center for Disease Control.

6.2 Reported Adverse Events and Potential Risks

PROSTVAC[®] has been evaluated in 13 completed clinical trials with six additional trials in progress. Notably, the vaccine showed an 8.5-month improvement in overall survival relative to placebo (p=0.006) in men with prostate adenocarcinoma with metastasis and refractory to androgen deprivation therapy in a multicenter randomized Phase 2 trial [14]. In a similar but smaller NCI trial, PSA-Tricom was shown to generate an antigen-specific immune response, which was associated with favorable survival outcomes [15]. A multicenter Phase 3 trial of PSA-Tricom in metastatic castrate-resistant prostate cancer (mCRPC) is underway (PROSPECT, NCT01322490). PROSTVAC[®] has been tested clinically in two Phase 1 studies [21, 22] and one single-arm Phase 2 study [14]. Both Phase 1 studies demonstrated safety of the vectors, with the second study also evaluating biodistribution kinetics [22]. NCI has also performed a smaller Phase 2 study in 32 patients to evaluate immune and regulatory T-cell responses as well as the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) as an additional vaccine adjuvant [15]. Additionally, a Phase 1 trial to assess the safety and tolerability of escalating doses of the CTLA-4 checkpoint antagonist monoclonal ipilimumab in combination with a fixed dose of PROSTVAC[®] was recently completed [23]. Thus, clinical safety data are available from trials with PROSTVAC[®] alone and in combination with other immunomodulatory modalities.

In a Phase 1 study, 10 patients with androgen-independent prostate cancer with or without metastatic disease were enrolled [21]. Patients were treated with 2×10^8 pfu of PROSTVAC-V followed by 1×10^9 pfu of PROSTVAC-F. No patients experienced dose-limiting toxicity (DLT) and there were no deaths on study. Nine patients reported 37 adverse events (AEs), and none were above grade 2. The most commonly reported AEs, regardless of causality, were injection site reactions and fatigue. Grade 2 AEs experienced by at least two patients that were assessed as being at least remotely related to study drug were diarrhea, cervical lymphadenopathy, paresthesia, and hypoesthesia (left facial numbness). One serious adverse event (SAE) of metastatic progressive disease occurred that was considered unrelated to vaccine.

In a randomized, controlled, and blinded Phase 2 study, PROSTVAC-VF treatment was evaluated for safety and for prolongation of progression-free survival (PFS) and overall survival (OS) [14]. In total, 125 patients were randomly assigned at multiple centers. Eligible patients had minimally symptomatic mCRPC. A vaccinia-based vector was used for priming followed by six planned fowlpox-based vector boosts. Patients were allocated (2:1) to PROSTVAC-VF plus GM-CSF or to control empty vectors plus saline injections. Eighty-two patients received PROSTVAC-VF and 40 received control vectors. Patient characteristics were

similar in both groups. In general PROSTVAC was well tolerated. Most AEs were injection site reactions with only a subset of patients experiencing associated systemic AEs such as fatigue, fevers, and nausea. Typical injection site reactions were mild, with only one clear grade 3 injection site reaction (injection site cellulitis). The AE profile of primary vaccinia immunization was equivalent to that induced by the fowlpox booster immunizations. Two PROSTVAC-treated patients discontinued therapy because of treatment-related AEs. One had recurrent lip edema after the second and third vaccinations; the other developed multiple AEs and SAEs associated with thrombotic thrombocytopenic purpura and myocardial infarction. The case was reported as possibly related to treatment. Thrombotic thrombocytopenic purpura has not been reported in association with vaccinia immunization [24].

A 3+3 Phase 1 dose-escalation study design of intraprostatic administration of PSA-TRICOM vaccine was performed in patients with locally recurrent or progressive prostate cancer [25]. Nineteen of 21 patients enrolled had locally recurrent prostate cancer after definitive radiation therapy, while two had no prior local therapy. All cohorts received initial subcutaneous vaccination with recombinant vaccinia (rV)-PSA-TRICOM and then intraprostatic booster vaccinations with recombinant fowlpox (rF)-PSA-TRICOM. Cohorts 3–5 also received intraprostatic rF-GM-CSF. Cohort 5 received additional subcutaneous boosters with rF-PSA-TRICOM and rF-GM-CSF. There were no DLTs, and the maximum tolerated dose was not reached. Twenty of 21 patients received all planned doses of vaccine, and no patient was discontinued for toxicity. The most common toxicity, subcutaneous injection site reaction, occurred with 47 % of administered doses. Fever, the second most common toxicity, occurred in 40.2 % of all treatment cycles. The most common grade 2 AEs were fever (38 %) and subcutaneous injection site reactions (33 %); the single grade 3 event was transient fever. Fevers generally occurred within hours of receiving the vaccine. None was serious enough to require intervention beyond acetaminophen, and all were transient.

A Phase I dose-escalation trial was performed to assess the safety and tolerability of escalating doses of ipilimumab in combination with a fixed dose of the PSA-Tricom vaccine [23]. Thirty patients with mCRPC received 2×10^8 plaque-forming units of recombinant vaccinia PSA-Tricom subcutaneously on day 1 of cycle 1, with subsequent monthly boosts of 1×10^9 plaque-forming units, starting on day 15. Intravenous ipilimumab was given monthly starting at day 15, at doses of 1, 3, 5, and 10 mg/kg. Twenty-four of the patients had not previously been treated with chemotherapy. A DLT for the vaccine and antibody combination was not identified during the period two weeks after the second infusion of ipilimumab. AEs were primarily local grade 1 and 2 injection-site reactions (three patients with grade 1 events, 26 with grade 2) and immune-related AEs. Rash was the most common immune-related AE, noted mostly in patients receiving 10 mg/ipilimumab kg. Endocrine immune-related AEs were more common at 5 and 10 mg/kg doses. However, grade 2 and 3 diarrhea or colitis were consistently noted at all doses beyond the lowest (1 mg/kg). Other uncommon immune-related AEs included raised concentrations of aminotransferases and neutropenia or leukopenia. Overall, 21 patients (70%) had a grade 2 or greater immune-related AE, and eight patients (27%) had grade 3 or 4 immune-related AEs.

There were no other non-immune-related grade 4 toxic effects, and the remaining grade 3 toxic effects were probably related to the accompanying immune-related AEs in the same patient, including dehydration (two patients), hypotension (two patients), fatigue (two patients), hyponatraemia (one), hypophosphataemia (one), and fever (one). One grade 3 thrombocytopenia occurred in a patient with colitis.

Overall, 14 patients discontinued ipilimumab because of disease progression (progressed before the planned initial six doses of ipilimumab), including seven of the nine patients in cohorts 1 and 2 (median 3 doses, range 1–4); 13 discontinued ipilimumab because of immune-related AEs (median 2 doses, range 1–3); and three received all six planned initial doses. Of these toxic effects, six patients had immune-related AEs in the first month of treatment. These AEs included rashes in four patients (all grade 2) and two cases of diarrhea or colitis (grade 2 and 3). With the exception of a rash at the 3 mg/kg dose, all other immune-related AEs in the first month were at the 10 mg/kg dose. The duration of all immune-related AEs varied on the basis of toxic effects and individual patients. For endocrine-related toxic effects, patients were placed indefinitely on replacement hormones. Two patients were weaned off these treatments. Rashes were treated

with supportive measures for a median of 27 days (range 6–138) for 10 patients who could be assessed. The duration of diarrhea or colitis varied from 2 to 98 days, with a median of 32 days until resolution of symptoms to grade 1 or less. The three episodes of raised aminotransferases lasted for 3, 25, and 28 days, respectively, and the single episode of grade 4 neutropenia lasted 6 days. The proportion of patients affected by grade 3–4 toxic effects was similar to previous Phase 1 trials involving ipilimumab [26-28]. The data suggest that the combination of PROSTVAC that enhances immune co-stimulation with an immune checkpoint inhibitor does not seem to be associated with increased immune-related AEs compared with ipilimumab alone.

6.3 Availability

PROSTVAC[®] and placebo will be supplied to the NCI, DCP agent repository by Bavarian Nordic, Inc. (Mountain View, CA) in single-use 2 mL glass injection vials with an available volume of 0.5 mL. The investigational vaccine will be supplied to investigators by the NCI, DCP agent repository.

6.4 Agent Distribution

PROSTVAC[®] and placebo will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied study agent will be requested by the UAZ Consortium Office for each Organization based on the randomization plan described in section 6.8. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Email: NCI.DCP@mriglobal.org
Emergency Telephone:(816) 360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator, or a responsible party designated by the Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility will be delegated to the research/investigational pharmacy staff at each site. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

DCP will package, label and distribute agent for all DCP-supplied agents.

6.7 Storage

Study agent will be stored in a secure location at -20 °C or below and then thawed for injection.

6.8 Registration/Randomization

Participants will be considered registered on the date they sign the approved informed consent document with a member of the study staff. The study coordinator will assign a participant identification number from a list of predetermined, site-specific numbers once the subject has been consented. After completion of final eligibility evaluation, the study coordinator will fax or email the registration CRF to the UAZ Consortium Office. If the participant is eligible for randomization, a randomization number will be assigned by the Consortium data manager and an agent request form will be forwarded by the UAZ Consortium Office to the DCP drug repository for shipment of study agent.

6.9 Blinding and Unblinding Methods

To retain the blind, the study products will not be identified by product names but by a unique randomization number. The randomization number is assigned to the subject upon completion of eligibility evaluation.

A list of randomization numbers linked to each study arm will be created and forwarded to the DCP drug repository. The DCP repository will ship the blinded agent to the study site by randomization number. The study products will be identified with the subject randomization number but with no product information on the label. The study staff will dispense the product to participants based on the assigned randomization number. None of the staff interacting with participants will know the link between randomization number and actual product. This process will allow the study to remain blinded to all study personnel and participants. The code that identifies the product will be kept by the UAZ Consortium Biometry Director, the study statistician or the data manager.

Unblinding is not expected to occur until all participants complete the intervention and data entry is complete. Study agents may be unblinded by the Principal Investigator or, in his absence, a Co-Investigator after discussion with the NCI medical monitor, if possible, in the event of a serious adverse event if deemed medically necessary. If the NCI medical monitor is not available and unblinding is deemed necessary, it should be done and the medical monitor can be notified subsequently. The investigator will notify the UAZ Consortium Biometry Director, the study statistician or the data manager that the blind is to be broken.

The NCI Medical Monitor must be notified that the blind has been broken.

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Phone (240) 276-7012
Fax (240) 276-7848
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6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be returned to THE NCI, DCP Repository according to the DCP “Guidelines for AGENT RETURNS” and using the DCP form “Return Drug List”.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Pre-Intervention ⁴		Intervention							Post Intervention (7-14 days after the last vaccine dose)	Safety Follow-Up ¹⁰	6-Month Follow-up Visit ^{11,13}
	Screening Visit	Randomization	Baseline Visit (Day 0)	Day 14 (±5)	Day 28 (±7)	Day 56 (±7)	Day 84 (±7)	Day 112 (±7)	Day 140 (±7)			
Informed Consent	X											
Assess Eligibility	X											
Medical History ¹	X											X
Vital Signs, Height ² and Weight	X		X	X	X	X	X	X	X	X		
Karnofsky performance status assessment	X											
Baseline signs and symptoms	X											
International Prostate Symptom Score (IPSS)	X						X			X		X
Digital rectal exam	X ⁵									X ⁶		X ⁶
Blood for CBC-diff, CMP ³	X						X ⁹			X		
Randomization		X										
Blood for PSA	X		X				X			X		X
Blood for PBMCs			X							X		
Blood for serum			X							X		
Release of Agent from Research Pharmacy			X	X	X	X	X	X	X			
Subcutaneous PROSTVAC-V or Placebo Injection			X									
Subcutaneous PROSTVAC-F or Placebo Injection ⁷				X	X	X	X	X	X			
Active Surveillance Status												X
Concomitant Medications	X		X	X	X	X	X	X	X	X		
Adverse Events			X	X	X	X	X	X	X		X	
Post-Intervention Prostate biopsy										X		
Request prostate biopsy reports	X									X		
Request prostate MRI reports ¹²	X											X
Telephone/email Contact ⁸									X		X	X

¹Includes history of autoimmune disease

²Height required at Screening only

³CMP includes serum glucose, urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, alkaline phosphatase, ALT, AST, total bilirubin.

⁴Screening visit Evaluation/Procedures performed within 90 days prior to the Baseline Visit (first vaccine injection) can be applied toward Screening/Eligibility evaluation.

⁵Digital rectal exam performed within 180 days prior to the Baseline Visit can be applied toward Screening/Eligibility evaluation.

⁶Performed at the discretion of the individual urologist.

⁷Vaccine injection may be omitted due to adverse events (see section 5.6).

⁸Participants will be contacted (by phone or email) periodically for evaluation of safety or changes in concomitant medications and to be reminded of 6-month follow-up visit.

⁹At the Day 84 visit, CBC-diff and CMP will need to be evaluated to determine whether the injection on that day may be given or omitted and whether there is the need to repeat the safety labs before the next scheduled injection. If needed, the labs can be done on a different day prior to the day for the vaccine injection, but the labs and the vaccine injection should fall within the window specified on the schedule of events.

¹⁰Subjects to be followed for 30 days after the last study dose is given. Participants will be asked to keep a 30-day diary and mail it back to the study staff in a pre-addressed, stamped envelope.

¹¹6 months (5-7 months) following the post-intervention biopsy or 6 months (5-7 months) after the last study dose is given, if no post-intervention biopsy was performed, to be performed as part of the standard-of-care.

¹²If available, reports from the prostate MRI scans (and companion pathology reports) performed from 3 years prior to and 6 months after the study intervention will be collected and submitted to the University of Arizona to capture the lesion size information.

¹³Patients who have undergone prostatectomy, radiation therapy or focal prostate cancer therapy are exempt from the six-month follow-up visit requirement.

7.2 Baseline Testing/Prestudy Evaluation

Participants will undergo a screening evaluation in which the informed consent form and medical records and tissue release form will be signed in order to obtain information from urologic assessment, biopsy pathology reports, PSA test results, and biopsy tissues. Participants will be interviewed for past medical history (including autoimmune disease) and concomitant medication use; and assessed for height, weight and vital signs (temperature, pulse, and blood pressure) and Karnofsky performance status. Subjects will be evaluated for baseline signs and symptoms. International Prostate Symptom Score will be obtained. Blood will be collected for complete blood count with differentiation (CBC-diff), comprehensive metabolic panel (CMP), and PSA. Evaluation/procedures performed within 90 days prior to the Baseline Visit can be applied toward Screening/Eligibility evaluation.

Participants will also undergo a digital rectal exam to confirm clinical stage at screening. A DRE performed within 180 days prior to the Baseline Visit can be applied toward Screening/Eligibility evaluation.

Following the screening evaluation, eligible participants will be randomized 2:1 to receive PROSTVAC® or placebo. Randomization will be stratified by the study site and the number of repeat biopsies following diagnosis (≤ 2 , or >2). The institutional code and the number of repeat biopsies following diagnosis for eligible participants will be captured on the registration CRF and submitted to the University of Arizona Early Phase Chemoprevention Consortium Office for randomization.

CRF Submission Information:

University of Arizona Early Phase Chemoprevention Consortium Office
Attn: Bonita Weible
1430 E. Fort Lowell, Suite 304
Tucson, AZ 85719
Phone: (520) 318-7178
Fax: (520) 514-6015
Email: UACC-CPRE@UACC.arizona.edu

7.3 Evaluation During Study Intervention

Following randomization, participants will return for a Baseline Visit and be evaluated for weight, vital signs, AEs and concomitant medications. Blood will be collected prior to administration of the vaccine injection and shipped overnight at ambient temperature to a central laboratory (see section 10.3) for peripheral blood mononuclear cells (PBMC) isolation. Blood will also be collected for PSA, performed as part of standard of care, and for serum soluble antibodies to tumor-specific antigens.

Participants will receive a priming vaccination with subcutaneous injection of PROSTVAC-V or placebo administered into the upper thigh. Because of the potential of shedding virus at the injection site and the potential of transmission of the vaccinia virus used in the priming vaccine, the injection site will be protected by gauze pads. Participants will be given instructions regarding care of vaccination site and necessary precautions regarding vulnerable populations and also supplies for taking care of the injection site and for disposing of used bandages. Participants will be reminded to avoid close contact or household contact with the following high-risk individuals for three weeks after the Day 1 vaccination or until the vaccination site heals completely: (a) children ≤ 3 years of age, (b) pregnant or nursing women, (c) individuals with prior or concurrent extensive eczema or other eczematoid skin disorders, (d) individuals with other acute, chronic, or exfoliative skin condition, or (e) immunocompromised or immunosuppressed persons (by disease or therapy).

Participants will be instructed to record adverse events and concomitant medications throughout the intervention. Participants will be contacted (by phone or email) periodically throughout the intervention for evaluation of safety, changes in concomitant medications, and to address questions or concerns of the

participant. AEs or new concomitant medications reported at this time will be reported on the appropriate CRF.

On 14, 28, 56, 84, 112, 140 days following the Baseline Visit, participants will return for interim study visits. Participants will receive booster vaccinations with subcutaneous injection of PROSTVAC-F or placebo, injected into the upper outer thigh or upper arm. It is recommended to alternate the injection sites. Prior to the first booster injection, participants will be evaluated for evidence of bacterial infection, blisters, vesicles or evidence of persistent infection. Weight, vital signs, AEs and conmed information will be collected at each interim visit. At the Day 84 visit, International Prostate Symptom Score will be obtained and blood will be drawn for PSA, CBC-diff, and CMP prior to administration of the vaccine injection. CBC-diff and CMP will need to be evaluated to determine whether the injection on that day may be given or omitted and whether there is the need to repeat safety labs before the next scheduled injection. If needed, the labs can be done on a different day prior to the day for the vaccine injection, but the labs and the vaccine injection should fall within the window specified on the schedule of events. The Day 14 visit can be scheduled +/- 5 days. The Day 28, 56, 84, 112, 140 interim visits can be scheduled +/- 7 days. The vaccine injection may be omitted due to adverse events (as described in section 5.6).

7.4 Evaluation at Completion of Study Intervention

Seven to fourteen days after the last scheduled vaccine dose, participants will return for the post-intervention visit. Blood will be collected for CBC-diff, CMP, PSA, PBMCs, and serum prior to the digital rectal exam and collection of the post-intervention biopsy. Participants will be evaluated for weight, vital signs, AEs and concomitant medications. International Prostate Symptom Score will be obtained. DRE will be performed at the discretion of the individual urologist. TRUS-guided prostate biopsy or targeted prostate biopsy using MR-US fusion will be performed as part of the routine care of patients on active surveillance.

Pre- and post-intervention biopsy pathology reports will be collected, de-identified, labeled with study ID and participant ID and submitted to the University of Arizona Early Phase Chemoprevention Consortium Office.

Report Submission Information:
University of Arizona Early Phase Chemoprevention Consortium Office
Attn: Bonita Weible
1430 E. Fort Lowell, Suite 304
Tucson, AZ 85719
Phone: (520) 318-7178
Fax: (520) 514-6015
Email: UACC-CPRE@UACC.arizona.edu

Unstained tissue slides from the pre- and post-intervention prostate biopsies will be requested from the institutional pathology lab for analysis of the immunologic response in the target tissue.

If available, reports from the prostate MRI scans (and companion pathology reports) performed from 3 years prior to and 6 months after the study intervention will be collected. Reports will be de-identified, labeled with study ID and participant ID and submitted to the University of Arizona Early Phase Chemoprevention Consortium Office to capture the lesion size information.

The results of all PSA tests performed throughout the intervention as part of the routine care of patients on active surveillance will be collected.

7.5 Post-intervention Follow-up Period

Study subjects will be followed for 30 days after the last study dose is given. Participants will continue to record adverse events during the 30-day follow-up period. The diary will be mailed back to the study staff in a pre-addressed, stamped envelope. Study staff will contact the subject by phone to clarify any of the diary entries, if necessary.

Participants will return for a follow-up visit 6 months (5-7 months) after the post-intervention biopsy or 6 (5-7 months) months after the last study dose is given, if no post-intervention biopsy was performed, as part of the standard-of-care. Blood will be collected for PSA. Participants will be interviewed for interval medical history including autoimmune disease. International Prostate Symptom Score will be assessed and active surveillance status will be documented. DRE will be performed at the discretion of the individual urologist. Patients who have undergone prostatectomy, radiation therapy or focal prostate cancer therapy are exempt from the six-month follow-up visit requirement.

7.6 Methods for Clinical Procedures

Not applicable.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

- 8.1.1 To determine the effect of PROSTVAC® on the change (pre to post-intervention) in CD8⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies. The change will be compared between participants treated with PROSTVAC® and those treated with placebo. A subgroup analysis will be performed to compare the change in CD8⁺ positive cells between study groups in specimens collected by targeted biopsy.
- 8.1.2 To determine the effect of PROSTVAC® on the change in CD4⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies. The change will be compared between participants treated with PROSTVAC® and those treated with placebo. A subgroup analysis will be performed to compare the change in CD4⁺ positive cells between study groups in specimens collected by targeted biopsy.

8.2 Secondary Endpoints

- 8.2.1 To assess the effect of PROSTVAC® on the change in PD-L1 positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies. The change will be compared between participants treated with PROSTVAC® and those treated with placebo. A subgroup analysis will be performed to compare the change in PD-L1 positive cells between study groups in specimens collected by targeted biopsy.
- 8.2.2 To assess the correlation between the change in CD8⁺ and the change in PSA. The correlation between the change in CD8⁺ in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies and the change in PSA (from baseline to 6 months (5-7 months) post-intervention) in participants treated with PROSTVAC® will be examined.
- 8.2.3 To assess the effect of PROSTVAC® on the change in CD8⁺, CD4⁺, and PD-L1 positive cells in the benign portion of the prostate biopsies. The change will be compared between participants treated with PROSTVAC® and those treated with placebo.
- 8.2.4 To assess the effect of PROSTVAC® on the change in PSA. The change in PSA from baseline to 6 months (5-7 months) post-intervention will be compared between participants treated with PROSTVAC® and those treated with placebo.
- 8.2.5 To assess the effect of PROSTVAC® on tumor grade progression, defined as a post-intervention

- Gleason score of $\geq 4+3$ using all biopsy data, i.e., from random and target biopsy cores. Proportion of men with post-intervention Gleason score of $\geq 4+3$ will be compared between the treatment groups. In addition, this endpoint will be evaluated in the subgroup of patients in whom MRI-targeted biopsies were obtained pre- and post-intervention.
- 8.2.6 To assess the effect of PROSTVAC on tumor extent based on the percent of positive random biopsy cores. The change in tumor extent will be compared between the treatment groups.
 - 8.2.7 To assess the proportion of men with no cancer in the post-intervention biopsy between participants treated with PROSTVAC® and those treated with placebo. This analysis will utilize all biopsy data, i.e., from random and target biopsy cores.
 - 8.2.8 To assess the effect of PROSTVAC on the size of the dominant lesion on MRI (largest histopathologically confirmed lesion) in the subgroup of patients with MRIs pre and post-intervention.
 - 8.2.9 To determine the safety and feasibility of PROSTVAC® in patients with clinically localized prostate cancer undergoing active surveillance.
 - 8.2.10 To assess the change in circulating 15-Mer PSA-specific T cells.
 - 8.2.11 To assess the change in soluble antibodies to tumor-associated antigens.
 - 8.2.12 To assess the immunologic effects of PROSTVAC® on the target organ using multiplex immunofluorescence.
 - 8.2.13 To assess the effects of PROSTVAC on LUTS by evaluating changes in International Prostate Symptom Score from baseline to 6 months (5-7 months) post-intervention.

If feasible, change in tumor grade and extent will be assessed by central pathology review.

8.3 Off-Agent Criteria

Participants may stop receiving study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible and appropriate, for safety reasons and in order to collect endpoint data according to the schedule of events. Vaccine injections may be held at the discretion of the patient and/or investigator for any concerns related to drug toxicity.

8.4 Off-Study Criteria

Participants may go ‘off-study’ for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, and determination of ineligibility (including screen failure). Study subjects will be followed for 30 days after the last study dose is given.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

The immunologic response to PROSTVAC® in the target tissue will be evaluated by immunohistochemistry (IHC) to assess the CD8⁺, CD4⁺, and PD-L1 positive cells. Immunohistochemistry

is the best and most validated technique for measuring protein levels of the biomarkers of interest in paraffin-embedded tissue. It allows analyses of relative expression levels of each biomarker and determination of localization of each marker. The study will also explore the potential of assessing immunologic response in the target tissue using multiplex immunofluorescence assay. This will allow for the measurement of multiple protein biomarkers in the same tissue section.

Multi-color flow cytometry analysis will be used to analyze the circulating immune cell subsets. The multi-color flow cytometry is a powerful tool that can separate a heterogenous mixture of cells and has been used in prior trials with PROSTVAC®.

9.2 Comparable Methods

Proposed methods are standard methodologies used in published research studies. The resulting data will be able to be compared to existing data.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

Clinical chemistry, hematology, and PSA will be performed at the institutional or commercial diagnostic laboratories.

Dr. Sherry Chow's laboratory will serve as a central repository for the receipt, storage, and distribution of the tissue sections and serum samples collected from this trial.

The immunohistochemistry analysis (IHC) of immune infiltrates in the prostate biopsies will be performed by the University of Arizona Cancer Center Tissue Acquisition and Cellular/Molecular Analysis Shared Resource under the supervision of Dr. Ray Nagle. Following the IHC staining of the immune infiltrates, scanned digital images of the de-identified tissue slides will be sent to Dr. James Gulley's research group at the NCI for quantitative scoring of the immune infiltrates.

Dr. Christina Jamieson's laboratory will serve as the central laboratory for PBMC processing, storage, and distribution.

Dr. Schlom's laboratory at the NCI will perform the 15-Mer prostate specific T-cell assay and the analysis on soluble antibodies to tumor associated antigens.

10.2 Collection and Handling Procedures

Blood Samples

Clinical labs

Approximately 10 ml of blood will be drawn to one 3 ml EDTA and one 7 ml SST or tiger top Vacutainer tubes at screening, Day 84, and at the post intervention for CBC with differentials and CMP. The EDTA tube will be gently inverted to mix for anticoagulation. The SST tube will be held at room temperature for 30 min and then centrifuged. Blood tubes will be prepped, labeled, and packaged according to the recommendations from the diagnostic laboratory.

PSA

Approximately 4 ml of blood will be drawn into one SST or tiger top Vacutainer tube at screening, baseline, Day 84, and at the end of intervention. The SST tube will be held at room temperature for 30 min and then centrifuged. Blood tubes will be prepped, labeled, and packaged according to the recommendations from the diagnostic laboratory.

PBMC

Approximately 60 ml of blood will be drawn into multiple Heparin Vacutainer tubes at baseline and at the end of intervention. The tubes will be labeled with study ID, subject ID, and visit date. The tubes will be gently inverted to mix for anticoagulation and shipped overnight at ambient temperature to a central laboratory for PBMC isolation.

Serum

Approximately 5 ml of blood will be drawn into a SST or tiger top Vacutainer tube at baseline and at the end of intervention. The SST tube will be held at room temperature for 30 min and then centrifuged. Serum will be aliquoted evenly into ten cryovials (~200 µl each) and stored at -80°C. The cryovials will be labeled with study ID, subject ID, and visit date.

Tissue Sections

Unstained tissue slides from pre and post intervention prostate biopsies will be requested from each institution's pathology department for measurement of tissue biomarkers. One to two tissue blocks with tumor from pre-intervention biopsy and same number of tissue blocks with tumor from post-intervention biopsy will be selected to cut the tissue slides. If no tumor was present in the post-intervention biopsy, block(s) from the same tissue region as the pre-intervention block(s) with tumor will be selected. Five to 10 unstained slides will be requested from each block.

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Whole blood will be shipped overnight at room temperature. Tissue sections will be shipped in batches at room temperature. Banked serum cryovials will be shipped in batches overnight on dry ice. Current shipper and institutional procedures must be followed. Biologic specimens (Category B, UN3373) will be in leak-proof primary and secondary receptacles with puncture resistant packaging and absorbent material. Shipments are to be preceded with phone contact to the receiving lab to assure the shipment will be met and processed promptly. The NCI Clinical Center for Cancer Research will retain pre and post-intervention serum and internally transport to NCI Laboratory of Tumor Immunology and Biology.

Tissue sections and serum cryovials:
Catherine Cordova c/o Chow Laboratory
University of Arizona Cancer Center, Room 4971
1515 N. Campbell Ave.
Tucson, AZ 85724
(520) 626-5433
ccordova@uacc.arizona.edu

Whole blood:
University of California, San Diego
Christina Jamieson/ Michelle Muldong
Moores Cancer Center, Room 4359, Bay 4KK
3855 Health Sciences Drive
La Jolla, CA 92093
Telephone: (858) 534-2921
Fax: (858) 822-6288
CAMJamieson@ucsd.edu

Upon completion of the study, all pre- and post-intervention serum will be sent from University of Arizona to the following NCI lab for analysis of soluble antibodies to tumor associated antigens. Pre- and post-intervention cryopreserved PBMCs (25×10^6 PMBCs) will be sent from UCSD to the NCI for 15-Mer prostate specific T-cell assay.

Caroline Jochems M.D., Ph.D.
Laboratory of Tumor Immunology and Biology NCI, National Institutes of Health
Attn: Caroline Jochems
10, Center Drive, Room 8B08
Bethesda, MD 20892
Tel: (301) 402-6274
Fax: (301) 496-2756

Following the IHC staining of the immune infiltrates, scanned digital images of the de-identified tissue slides will be uploaded onto password-protected portable flash drives and sent via FedEx to Dr. James Gulley's research group at the following address for quantitative scoring of the immune infiltrates.

Houssein Abdul Sater, M.D.
Center for Cancer Research
National Cancer Institute
Building 10, Room 6B12
Bethesda, MD 20892
Telephone: 240-858-3384

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in §6.2, Pharmaceutical Information, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for adverse event reporting.

- AE verbatim term
- System Organ Class (SOC)
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc.*

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed for at least 30 days according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE form found at http://prevention.cancer.gov/files/clinical-trials/SAE_form.doc.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

Malgorzata (Margaret) Wojtowicz, MD
Lung and Upper Aerodigestive Cancer Research Group
Division of Cancer Prevention, NCI, NIH
9609 Medical Center Dr., Room 5E-104, MSC 9781
Bethesda, MD 20892 (For FedEx use Rockville, MD 20850)
Phone (240) 276-7012
Fax (240) 276-7848
wojtowim@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

11.2.2.3 The Lead Organization and all Participating Organizations will FAX or email written SAE reports to the DCP Medical Monitor within 48 hours of learning of the event using the paper SAE form. The written SAE reports will also be faxed (650-691-4410) or emailed (safety@ccsainc.com) to DCP's Regulatory Contractor, CCS Associates (phone: 650-691-4400).

11.2.2.4 The DCP Medical Monitor and regulatory staff will determine which SAEs require FDA submission.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE form in the appropriate format. Follow-up information should be sent to DCP as soon as available. SAE related to the study agent will be followed until resolved, or deemed unlikely to further resolved by the Protocol Chair, or until the subject withdraws consent for further follow-up. SAE unrelated or unlikely to be related to study agent will be followed for at least 30 days after the last dose of study agent.

12. STUDY MONITORING

12.1 Data Management

This study will report clinical data using the OnCore application from Forte Research Systems, Inc., as stated in the Master Data Management Plan. All users of the database will have appropriate education, training and experience to perform assigned tasks. The data collection and management will be done according to the Consortia 2012 DMP.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDE). The approved CRFs will be used to create the electronic CRF (e-CRF) screens in the OnCore application. Consortia site staff will enter data into the e-CRF for transmission to DCP according to pre-established DCP standards and procedures. Amended CRF will be submitted to the DCP Protocol Information Office for review and approval. Approved changes will be programmed into the OnCore database by the Consortium Data Management staff.

CRF Submission Information:

University of Arizona Early Phase Chemoprevention Consortium Office
Attn: Bonita Weible
1430 E. Fort Lowell, Suite 304
Tucson, AZ 85719
Phone: (520) 318-7178
Fax: (520) 514-6015
Email: UACC-CPRE@UACC.arizona.edu

12.3 Source Documents

Source documentation for this trial will consist of protocol-specific source documents as well as clinical and research laboratory reports. In the event of a Serious Adverse Event, medical records related to the event will be sought for source documentation of the event and its treatment, if any.

12.4 Data and Safety Monitoring Plan

The University of Arizona Cancer Center (UACC) Data and Safety Monitoring Board (DSMB) will provide oversight for subject safety for all UA Consortium clinical trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998; further guidance statement issued by the NIH on June 5, 2000, and the policy for Data and Safety Monitoring by Data and Safety Monitoring Boards. The UACC DSMB meets quarterly.

Regular monthly meetings of the UA Consortium, are used as a forum to review accrual rates, problematic issues relating to accrual and protocol implementation, adverse events occurrence, follow-up, and reporting; submission of all required study reports; and progress and outcomes of laboratory analyses.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc.*), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This study utilizes a Phase II double-blind, randomized, placebo controlled design to assess the effect of PROSTVAC® in patients with clinically localized prostate cancer undergoing active surveillance. Each eligible participant will be randomly assigned to receive either PROSTVAC® or matched placebo. Due to potential withdrawals and the absence of tumor in the post-intervention biopsy, 25% or more participants may not provide endpoint data. All of the statistical analysis (both primary and secondary analysis) will be based on the intent-to-treat principle. Multiple imputation (MI) techniques will be applied, as necessary, for participants without endpoint data. The statistical analysis based on Rubin's rules will be performed on the imputed datasets, if MI is performed.

13.2 Randomization/Stratification

We plan to randomize 150 eligible participants to receive either PROSTVAC® or matched placebo at a 2:1 ratio (i.e. 100 receiving PROSTVAC® and 50 receiving placebo) based on a random allocation rule. Blocking technique with a size of 3 or 6 will be used to assure a 2:1 ratio between PROSTVAC® and placebo. In addition, randomization will be stratified by the study site and the number of repeat biopsy following diagnosis (≤ 2 or > 2).

13.3 Accrual and Feasibility

We plan to randomize 150 eligible participants. We anticipate to enroll 6-8 participants/per month and estimate that it will take approximately 20-25 months to complete accrual.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objectives of this study are to determine the effects of PROSTVAC® on the change (from pre- to post-intervention) in CD8⁺ and CD4⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies.

The primary endpoints are the change in CD8⁺ and CD4⁺ positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies. The change in CD8⁺ and CD4⁺ positive cells will be compared between participants treated with PROSTVAC® and those treated with placebo. We project an attrition rate of 10% (with respect to completing the intervention and providing post intervention biopsy) and 70% of the post intervention biopsy would have tumor. We plan to randomize 150 eligible participants to receive PROSTVAC® or placebo at a 2:1 ratio to have 63 and 31 subjects in the PROSTVAC® group and the placebo group, respectively, with primary endpoint data. A two-sided two-sample t test will be used to compare the change in CD4⁺ and CD8⁺ positive cells in tumor tissue between the treatment and placebo groups. Based on a sample size of 63 in the PROSTVAC® group and 31 in the placebo group and assuming that the standard deviation of the change in CD8⁺ and CD4⁺ positive cells for the PROSTVAC group is twice that of the placebo group, the power will be at least 90% to detect a Cohen's d effect size (i.e. the difference between the two groups divided by the pooled standard deviation) of ≥ 0.63 at a significance level of 5% by the Bonferroni correction (i.e., a significance level of 2.5% for each). MI techniques will be performed, as needed, for the participants without endpoint data. If MI is deemed necessary, the variables that are predictive of missing endpoint data will be incorporated into MI. The "available" sample size after MI is expected to be larger than the estimated sample size. Hence, we are confident of detecting effect sizes smaller than the above effect sizes after applying the Rubin's rules since the predictive variables used in MI can improve efficiency and reduce potential bias due to missing data.

13.5 Secondary Objectives, Endpoints, Analysis Plans

The secondary objectives are to determine the effects of PROSTVAC® on the change in PD-L1 positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies, the correlation between the change in CD8⁺ and the change in PSA, to determine the effect of PROSTVAC® on the change in CD8⁺, CD4⁺, and PD-L1 positive cells in the benign portion of the prostate biopsies, to determine the effect of PROSTVAC® on the change in PSA, to assess the effect of PROSTVAC® on tumor grade and tumor extent, to assess the proportion of men with no cancer on the post-intervention biopsy, to assess the safety and feasibility of PROSTVAC®, and to assess the effects of PROSTVAC® on LUTS.

The secondary endpoints include the change in PD-L1 positive cells in the stroma adjacent to tumor and within the malignant portion of the prostate biopsies, the correlation between the change in CD8⁺ and the

change in PSA, the change in CD8⁺, CD4⁺, and PD-L1 positive cells in the benign portion of the prostate biopsies, the change in PSA, the tumor grade progression, the change in tumor extent, safety and feasibility, and the change in International Prostate Symptom Score. In addition, a comparison will be made between the two study arms on the proportion of patients with no cancer on the post-intervention biopsy. Similarly, MI techniques will be performed, as necessary. A two-sided two-sample t test at a significance level of 5% will be performed to compare each of the secondary endpoints between the PROSTVAC® and placebo groups. Pearson correlation coefficient will be derived to evaluate the correlation between the change in CD8⁺ and the change in PSA for participants treated with PROSTVAC®. Fisher's exact test will be performed to compare the proportion of patients with no cancer on the post-intervention biopsy and the proportion of men with an increase in Gleason score to $\geq 4+3$ between the two groups. These secondary analyses are considered exploratory, therefore, no correction will be performed for multiple comparisons.

For both primary and secondary endpoints, data will be tested for non-normality and outliers. If the normality assumption is violated, a potential transformation will be sought. If no suitable transformations can be found, nonparametric tests (e.g. Wilcoxon Rank Sum test and Spearman correlation coefficient) will be used. If outliers are detected, sensitivity analysis will be performed to evaluate the impact of the outliers on the effects of PROSTVAC®. In addition, we anticipate observing a missing rate of 25% or greater for both primary and secondary endpoints. The missing rates for both PROSTVAC® and placebo groups will be reported and compared. Also, regression models will be performed to identify the potential variables that are predictive of the missing endpoints or probabilities.

Descriptive statistics of the type and frequency of all adverse events will be generated, including 95% confidence intervals. For each type of the adverse events, a Fisher's exact test will be performed to compare the frequency of the adverse event between the two groups.

13.6 Reporting and Exclusions

The reporting will be based on the intent-to-treat principle in which the intent-to-treat population will be used for data analysis and reporting.

Explanatory analyses will evaluate endpoints in those participants who received 2 or more doses of PROSTVAC-F (boost).

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study agent.

13.8 Evaluation of Response

Evaluation of response will be based on the intent-to-treat principle in which the intent-to-treat population will be used for data analysis.

Subanalyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, subanalyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported.

13.9 Interim Analysis

No formal interim analysis for futility is planned because the primary endpoints will be analyzed in batches at the end of the study. Accrual, data collection, and any adverse events will be monitored on a regular basis.

13.10 Ancillary Studies

None.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Signed and dated current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in “Protection of Human Research Subjects” for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator’s Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the

study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to the DCP Regulatory Contractor:

Paper Document/CD-ROM Submissions:

Regulatory Affairs Department
CCS Associates
20001 Gateway Place
Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:

regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to the DCP Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

Study procedures performed during study visits will be covered by the study budget. Research tests will not be billed to the subject. Subjects may incur minimal out-of-pocket expenses for transportation but will not be charged for study agent or any study-related activities. Subjects will receive monetary compensation which they may use at their discretion for out of pocket cost such as transportation. If injury occurs, medical care will be provided and charged to the subject's insurer.

REFERENCES

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CONSENT FORM

Study Title for Study Participants:

Testing PROSTVAC® to prevent disease progression in prostate cancer patients on active surveillance

Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>:

Protocol UAZ2014-03-01 Phase II randomized, placebo-controlled trial of PROSTVAC® (PSA-TRICOM) in patients with clinically localized prostate cancer undergoing active surveillance

What is the usual approach to my prostate cancer?

Treatment options for your prostate cancer include active surveillance, surgery, and radiation therapy. Active surveillance refers to close monitoring for changes in your cancer with biopsies and prostate-specific antigen (PSA) blood tests and, if it appears your cancer is becoming more aggressive, to offer surgery or radiation therapy at that time. Active surveillance is a reasonable option for many men with low-risk prostate cancer and for some men with intermediate risk prostate cancer, because prostate cancer often grows so slowly that it does not require treatment.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above,
- you may choose to take part in a different study, if one is available,
- or you may choose to do nothing.

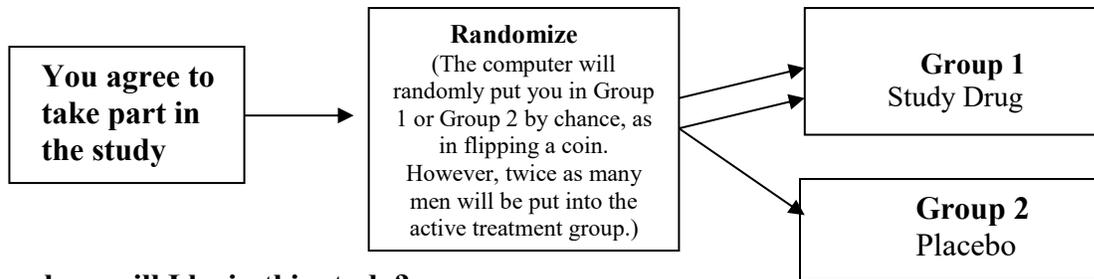
Why is this study being done?

The purpose of this study is to compare the safety and effects of PROSTVAC® with placebo. PROSTVAC® is a prostate cancer vaccine designed to stimulate immune responses to prevent the prostate cancer from getting worse. Placebo is a product that looks like the study vaccine but does not contain the active vaccine. PROSTVAC® is considered investigational because it is not yet approved for marketing by the FDA, however, the vaccine has been used in clinical trials of over 1,000 patients and has been well tolerated without major side effects. There will be about 150 people taking part in this study.

What are the study groups?

This study has two study groups. Group 1 will receive the study vaccine PROSTVAC® and Group 2 will receive a placebo.

A computer will randomly put you in a study group—like a coin toss—to decide what group you get placed into. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group. Neither you nor your doctor will know if you are receiving the study drug or placebo. Your doctor cannot choose which group you will be in. Two-thirds of the participants will be placed in Group 1 and one-third in Group 2.



How long will I be in this study?

You will be in the study for about seven months and will receive seven doses of the study vaccine or placebo over 20 weeks. You will undergo a prostate biopsy 1-2 weeks after the last dose of the study vaccine or placebo. You will be asked to continue to keep a diary of any illness or injury for 30 days after the end-of-study biopsy or 30 days after the last dose of study vaccine or placebo, if no biopsy was done.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and/or procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra tests, and/or procedures in a Screening Visit to find out if you can be in the study.

- The study staff will discuss this consent form with you and answer any questions you may have. Once you have signed it, the following procedures will be done.
- A brief physical exam including height, weight, and vital signs (blood pressure, pulse, and temperature).
- Collection of 3 teaspoons of blood for routine blood tests (a complete blood count and a group of blood tests of your body's chemical balance and metabolism) and PSA, if you have not had this done recently.
- Digital rectal exam, if you have not had this done recently.
- A review of your medical history and current medications, including any symptoms you may be currently experiencing.
- You will be asked to complete an 8-question survey about your urinary symptoms (International Prostate Symptom Score Survey).
- Completion of medical release form to allow the study staff to obtain your prior prostate exams, prostate biopsy reports, prostate MRI reports, and biopsy samples for the study.

Once you are determined to be eligible, you will return to the clinic for a Baseline Visit. Tests and procedures include:

- Measurement of weight, and vital signs (blood pressure, pulse, and temperature).
- Collection of 5 tablespoons of blood for research tests (analysis of circulating immune cells and immune response).
- You will receive an injection of the priming vaccine or placebo. The PROSTVAC® priming vaccine uses vaccinia virus (the virus used in current small pox vaccines) that has been artificially weakened. The vaccinia virus can be accidentally spread to another area of

your body such as your eye and mucous membranes (inner lining) of the nose, mouth or genitals by scratching the vaccination site and then rubbing the eye or an open skin area. Also vaccinia virus can multiply in human cells, very rarely, and can cause complications and infect people who are in close contact with you. You should avoid close contact with the following individuals for three weeks after the priming vaccine injection: children ≤ 3 years of age, immunocompromised individuals, individuals with skin disorders, and pregnant or breast feeding women. You will be given an instruction sheet that describes the general precautions for caring for the injection site to ensure your safety and the safety of those around you. You will also be given supplies for taking care of the injection site and for disposing of used bandages.

- You will be given a diary to record any illness or injury (adverse events) during the study and all medications you take during the study.

During the study, you will return to the clinic at 2, 4, 8, 12, 16 and 20 weeks after the Baseline Visit. Tests and procedures at these interim visits include:

- Measurement of weight, and vital signs at each visit.
- You will receive an injection of the booster vaccine or placebo. The PROSTVAC® booster vaccine uses fowlpox virus (a virus that can be found in birds) that has been artificially weakened. Fowlpox virus cannot multiply in human cells so it cannot cause humans to become infected with the fowlpox virus. There is no danger of infecting other parts of your body or other people, so there are no restrictions on contact with immune-compromised individuals, individuals with skin disorders, pregnant or breastfeeding women, or children ≤ 3 years of age.
- Your diary of adverse events and medications will be reviewed.
- At week 12, three teaspoons of blood for routine blood tests and PSA will be collected and you will be asked to complete the International Prostate Symptom Score Survey.

You will return to the clinic 1 to 2 weeks after the last vaccine dose. Tests and procedures at this End of Study Visit include:

- Measurement of weight, and vital signs.
- Collection of 6 tablespoons of blood for routine blood tests, PSA and research tests.
- Your diary of adverse events and current medications will be reviewed.
- You will be asked to complete the International Prostate Symptom Score survey.
- You may undergo a digital rectal exam at the discretion of the urologist.
- You will undergo the end of study prostate biopsy as part of your routine care.

You will continue to keep a diary of any illness or injury for 30 days after the last dose of vaccine and mail the diary back to the study office in a pre-stamped envelope provided by the study office. After the diary is returned, the study staff may contact you to clarify any of the diary entries.

As part of your routine care, you will return to the clinic 6 months (range 5-7 months) after the end of study biopsy or after the last dose of vaccine for a follow-up visit. Tests and procedures at this visit include:

- Collection of approximately 1 teaspoon of blood for PSA.
- You will be asked to complete the International Prostate Symptom Score survey.
- You may undergo a digital rectal exam at the discretion of the urologist.
- A review of your medical history.

If you have had prostatectomy, radiation therapy or focal prostate cancer therapy treatment after completing the study vaccine injections and before the 6 month follow up visit, you will not be required to complete the 6 month follow up visit.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may lose time at work or home and spend more time in the hospital or doctor's office than usual.

There is also a risk that you could have side effects. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away. Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

Risks to be considered with PROSTVAC®

PROSTVAC® priming vaccine (the vaccine used in the first injection) uses vaccinia virus. Vaccinia virus has been given to hundreds of millions of people worldwide to prevent the disease smallpox. Vaccinia immunization has resulted in the worldwide elimination of smallpox. It is a live replicating virus that infects large mammals and rodents, and usually causes only a self-limited skin infection in humans. The virus stimulates a strong immune response, which results in the body eliminating the virus. However, caution is required in its use, in that subjects or their contacts may experience inadvertent spread of vaccinia, or worse may experience more severe rare infections. The potential for these risks, and the precautions necessary to minimize these risks, are discussed further below.

In clinical studies of PROSTVAC®, the vaccine is given by injection under the skin. Most subjects experience some redness and diffuse swelling in the surrounding area, approximately 1-4 inches (2-10 centimeters) in diameter. This lasts for 7-14 days and may be accompanied by itching and soreness. There is typically full healing and no residual scarring from subcutaneous administration. On average, vaccinia stays active in your body for approximately 10-14 days. Prior to receiving your next vaccine, you will be evaluated for evidence of bacterial infection, blisters, vesicles (lesions seen on your skin at or around your vaccine site) or evidence of persistent vaccinia infection.

A potential problem associated with vaccinia vaccination is accidental spread of the virus to another area of your body. This occurs rarely (incidence 1 in 4000 in some reports), however, it is very important to protect against. You can transfer the virus to your eye and mucous membranes (inner lining) of the nose, mouth or genitals by scratching the vaccination site and then rubbing the eye or an open skin area. If you participate in this study you will have to take special care of your vaccination site and wash your hands often to prevent spreading of the virus. Because you may "shed" live virus from the vaccination site after vaccination until the vaccination site heals

completely, and could spread the virus to others, you must avoid close contact with the following people for approximately 3 weeks after the first vaccination only:

- Persons with weak or suppressed immune systems such as individuals with leukemia or lymphoma, individuals with AIDS, or those receiving treatment to suppress their immune system (for example, after organ transplantation).
- Individuals with eczema or other significant skin rashes, itching infections, burns, chicken pox, or skin injury
- Pregnant or breast-feeding women or
- Children ≤ 3 years of age

“Close contact” means that these people share your house with you, are in physical contact with you, come in contact with your bed linens or clothes, and/or you take care of them and touch them. A dressing will be placed over the vaccination site to reduce the risk of accidental spreading. It is very important that you keep the vaccination site covered. Hand washing is also necessary.

Possible adverse reactions can also be related to allergic responses to the vaccine itself. An allergic reaction to the study vaccine may be development of a rash or hives within 7 to 10 days of vaccination, which usually gets better within 2 to 4 days. Rarely, a serious allergic reaction requiring hospitalization may occur.

Generalized vaccinia infection may be characterized by several small blisters around the vaccination site or by widely distributed lesions developing 7-12 days after immunization. This is also known as a disseminated vaccinia infection. These tend to follow a course of healing similar to that of the inoculation site.

Serious side effects from the vaccinia vaccine are most common in children ≤ 3 years of age, subjects with disorders of the immune system, and individuals with skin disorders. That is why precautions are taken to exclude such individuals from exposure.

Serious reactions such as post-vaccinia encephalomyelitis (“brain inflammation”), which can lead to coma and death, or progressive vaccinia infection which leads to a large unhealing sore and death are the most severe complications after vaccination. They occur almost exclusively in very young children who are exposed to vaccinia for the first time, or in subjects with impaired immunity; such individuals are not eligible for this study and must be avoided after vaccination. The death rate for people receiving revaccination with vaccinia for smallpox is about 1 in 10 million. These serious reactions have not been seen in any subjects treated with PROSTVAC-V to date.

The tables below show the side effects that are seen more often in PROSTVAC®-treated patients than placebo-treated patients. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS
In 100 people receiving PROSTVAC®, more than 20 may have:
<ul style="list-style-type: none">• Injection site reactions (redness, pain, swelling, and itching)• Tiredness• Nausea• Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving PROSTVAC®, from 4 to 20 may have:
<ul style="list-style-type: none">• Diarrhea• Swollen glands• Swelling of the arm that got the injection• Tickling or burning or numbness sensation in the hands, feet or face• Flu-like symptoms including joint or muscle pain

RARE, SOME MAY BE SERIOUS In 100 people receiving PROSTVAC®, 3 or fewer may have:
<ul style="list-style-type: none">• Skin infection at the injection site• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat, and may be life-threatening• Abnormal lab test result for liver function and white blood counts (cells that help fight infection)• Blood clots (If in the arms or legs, symptoms may be pain, redness, swelling; in the lungs, symptoms may be chest pain, rapid heartbeat and difficulty breathing; if in the brain, symptoms may include difficulty talking, loss of vision, or weakness on one side of the body; if in the heart, symptoms of heart attack which may be chest pain, shortness of breath, nausea, indigestion, and sweating)• Decreased ability for the blood to clot (stop bleeding)• Diarrhea which may be severe enough to cause dehydration (excess loss of water from the body) or abnormally low lab tests results of electrolytes, which are chemicals required for the cells in your body to work (symptoms may include dark urine, fatigue, tiredness, nausea or vomiting, abdominal cramping, or less commonly an irregular heartbeat)

Other Potential Side Effects

Additional adverse effects could be related to the immune response to the proteins that are part of the vaccines. Some normal human cells (such as normal prostate cells) have these proteins on their surface. If the vaccine causes an immune reaction against these normal cells, you could develop swelling or inflammation of these tissues. While unlikely, it is also possible that if you develop a very active antibody (immune) reaction after the vaccination, you could develop an immune complex disease (or serum sickness) which can cause fevers, rashes, joint pains, and less commonly, kidney failure and severe allergic reaction inside blood vessels (vasculitis) or any part of your body. None of these symptoms have been observed to date in the approximately 1,000 subjects receiving PROSTVAC®, but the possibility of their occurrence exists.

Reproductive risks: You should not father a baby while on this study because PROSTVAC® may affect an unborn baby. It is important you understand that you need to use birth control while on this study and for at least one month after the last study injection. You must agree to use a medically acceptable method of contraception unless you have had a vasectomy. Participants with partners of childbearing potential must be willing to use barrier contraception (condom or diaphragm) plus another method. If your partner becomes pregnant while you are in the study, you must notify the study physician immediately. The study sponsor may request additional information regarding the course of the pregnancy and the outcome of the pregnancy. For more information about risks and side effects, ask your study doctor.

There may be a small risk in the process of drawing blood. You may faint or become dizzy. You may feel a little pain or discomfort as the needle goes through the skin. Some bleeding or bruising may occur at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent this. Very rarely, your arm may swell or become infected.

What possible benefits can I expect from taking part in this study?

This study may or may not help you because we do not know how the study agent will compare to the usual approach for your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor, Institutional Review Board (IRB) or Food and Drug Administration (FDA).

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ (*insert name of center*) Institutional Review Board at _____ (*insert telephone number*). (*Note to Site Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.*)

What are the costs of taking part in this study?

The study agent will be supplied at no charge while you take part in this study. The cost of study-specific tests and procedures will be paid for by the study.

Some costs associated with your care such as PSA tests and end of study prostate biopsy are considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will receive \$500 at the end of the study upon completion of all the required visits and tests. This money is to reimburse you for your time and help cover any cost you may have in being on the study. If for any reason you are unable to complete the entire study, the amount of compensation will be less. It will be based on how long you are in the study.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor, the National Cancer Institute (NCI) and NCI agents and partners, and the study Coordinating Center, the University of Arizona Cancer Center.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The U.S. Food and Drug Administration.

Where can I get more information?

The National Cancer Institute will obtain information from this clinical trial under data collection authority Title 42 U.S.C. 285.

You may visit the NCI website at <http://cancer.gov/> for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ (*insert name of study doctor[s]*) at _____ (*insert telephone number*).

This section is about optional studies you can choose to take part in.

The National Cancer Institute is conducting a long-term follow up study on subjects who have previously participated in immunotherapy studies and requests your permission to contact you with information about the study. At the end of this consent form you will have the opportunity to indicate your permission to be contacted.

There may be some specimens (biopsy tissue, blood cells, and blood serum) remaining once the study is complete. The researchers ask your permission to store and use your remaining samples and health information for future medical research. These samples may be stored indefinitely. You can take part in the main research study described above without giving your consent for your samples to be stored. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

- **What are the possible risks?**

There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by

May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

- **How will information about me be kept private?**

When your sample(s) is sent to the researchers, no information identifying you (such as your name or social security number) will be sent. Samples will be identified by a unique study code only. Researchers receiving your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are. Information that identifies you will not be given to anyone, unless required by law. If research results are published, your name and other personal information will not be used.

- **What are the possible benefits?**

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

- **Are there any costs or payments?**

There are no costs to you or your insurance. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

- **What if I change my mind?**

If you decide you no longer want your samples to be used, you can call the study doctor, _____, (*insert name of study doctor for main trial*) at _____ (*insert telephone number of study doctor for main trial*) who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

If you allow the remaining specimens to be used for future medical research, you can specify your consent below. Consent for future use of your remaining samples is entirely voluntary and may be withdrawn at any time. If you have any questions, please talk to the study staff or the investigator.

My biopsy tissue may be kept for use in future medical research. Yes No
(circle one)

My blood cells may be kept for use in future medical research. Yes No
(circle one)

My blood serum may be kept for use in future medical research. Yes No
(circle one)

I may be contacted regarding a long term follow-up study. Yes No
(circle one)

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

Date of signature _____

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.