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A Phase 2, Double-blind, Randomized Controlled Trial of PROSTVAC in Prostate Cancer Patients on Active Surveillance

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This randomized trial in prostate cancer patients on active surveillance did not show a favorable immunologic response to PROSTVAC, a prostate-specific antigen–based vaccine, in comparison to a control with empty viral vectors. The trial shows the acceptability of an immunotherapy intervention in this patient population.

Abstract

Background: There is an unmet clinical need for interventions to prevent disease progression in patients with localized prostate cancer on active surveillance (AS).

Objective: To determine the immunologic response to the PROSTVAC vaccine and the clinical indicators of disease progression in patients with localized prostate cancer on AS.

Design, setting, and participants: This was a phase 2, double-blind, randomized controlled trial in 154 men with low- or intermediate-risk prostate cancer on AS.

Intervention: Participants were randomized (2:1) to receive seven doses of subcutaneous PROSTVAC, a vaccinia/fowlpox viral vector–based immunotherapy containing a prostate-specific antigen (PSA) transgene and three T-cell co-stimulatory molecules, or an empty fowlpox vector (EV) over 140 d.

Outcome measurements and statistical analysis: The primary outcome was the change from baseline in CD4 and CD8 T-cell infiltration in biopsy tumor tissue. Key secondary outcomes were safety and changes in prostate biopsy tumor pathology, peripheral antigen-specific T cells, and serum PSA. Continuous variables were compared using nonparametric tests. Categorical variables were compared using Fisher's exact test.

Results and limitations: The PROSTVAC/EV vaccination was well tolerated. All except one participant completed the vaccination series. Changes in CD4 or CD8 density in biopsy tumor tissue did not differ between the PROSTVAC and EV arms. The proportions of patients with Gleason upgrading to grade group 3 after treatment was similar between the arms. There were no differences in postvaccination peripheral T-cell responses or the PSA change from baseline to 6-mo post-treatment follow-up between the groups.

Conclusions: In this first-of-kind trial of immunotherapy in patients on AS for prostate cancer, PROSTVAC did not elicit more favorable prostate tissue or peripheral T-cell responses than the EV. There was no difference between the arms in clinicopathologic effects. Despite the null findings, this is the first study reporting the feasibility and acceptability of an immunotherapy intervention in the AS setting.

Patient summary: We looked at responses after an experimental prostate cancer vaccine in patients with prostate cancer on active surveillance (AS). Participants who received the vaccine did not show more favorable outcomes than those receiving the control. Despite these findings, this is the first report showing the feasibility and acceptability of immunotherapy for prostate cancer in patients on AS.

1. Introduction

Active surveillance (AS) is a less morbid approach than immediate surgery or radiation therapy for localized, early-stage prostate cancer. There is an unmet clinical need for interventions to prevent disease progression in patients on AS. Immunomodulatory-based strategies could be a novel approach for preventing disease progression in men on AS [1]. In the past decade, a variety of vaccines against prostate cancer have been developed and tested in clinical trials involving patients with metastatic castration-resistant prostate cancer [2]. PROSTVAC is a poxviral vaccine that comprises a vaccinia virus vector for

priming and a fowlpox virus vector for boosting. Both vectors contain transgenes for human prostate-specific antigen (PSA) and three co-stimulatory molecules, collectively referred to as TRICOM (B7.1, ICAM-1, and LFA-3), to generate a T-cell response to cells expressing PSA. A phase 3 trial in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer showed that PROSTVAC had no effect on overall survival [3]. However, prior data suggested that patients with less aggressive disease and a lower tumor burden may disproportionately benefit from immunotherapy [4–6], supporting the evaluation of immunotherapy in early-stage prostate cancer.

We conducted a phase 2, double-blind, randomized controlled trial of PROSTVAC in patients with clinically localized prostate cancer on AS to determine immunologic responses and clinical indicators of disease progression. Changes in tumor CD4 and CD8 T-cell infiltration were selected as the primary study endpoints for determination of the prostate tissue bioactivity of PROSTVAC because prior studies have shown marked increases in CD4 and/or CD8 infiltrates in prostate tumors following PROSTVAC administration [7,8].

2. Patients and methods

2.1. Study design

This was a multicenter, phase 2, double-blind, randomized controlled trial of PROSTVAC in patients with clinically localized prostate cancer undergoing AS (NCT02326805 [9]). The study was approved by the institutional review board of each institution and was carried out in accordance with the Declaration of Helsinki and good clinical practice.

2.2. Study endpoints

The primary endpoint was the change from baseline in CD4-positive and CD8-positive cells in biopsies of prostate tumor tissue after the intervention. The secondary endpoints included the safety and feasibility of PROSTVAC administration and changes in the following measurements: PD-L1-positive cells in biopsy tumor and benign tissues; CD4-positive and CD8-positive cells in biopsy benign tissues; tumor pathology; antigen-specific T-cell responses in peripheral blood; serum PSA; and lower urinary tract symptoms as measured using the International Prostate Symptom Score (IPSS). We defined upgrading in post-treatment tumor biopsy tissue as Gleason score ≥ 3 + 4 = 7 (grade group ≥2) among participants with baseline Gleason score 6 (grade group 1), and Gleason score ≥ 4 + 3 = 7 (grade group ≥3) among participants with baseline Gleason score 3 + 4 = 7 (grade group 2).

2.3. Study drug

PROSTVAC vaccine and the empty viral vector (EV) used as the control were supplied by BN Immunotherapeutics (Bavarian Nordic, Morrisville, NC, USA) through the Division of Cancer Prevention of the National Cancer Institute (NCI). PROSTVAC vaccination consisted of priming with a recombinant vaccinia-based vaccine (PROSTVAC-V) followed by recombinant fowlpox-based vaccine (PROSTVAC-F) boosters. Both vaccine constructs contained a PSA transgene and three T-cell co-stimulatory molecules. An empty fowlpox vector was used for all control vaccinations, as it has minimal safety risks and its associated injection-site reactions are indistinguishable from those with PROSTVAC.

2.4. Study population

Key inclusion criteria were clinically localized, biopsy-proven adenocarcinoma of the prostate with ≤50% random biopsy cores positive for cancer; grade group ≤2; clinical stage ≤T2a; and serum PSA <20 ng/ml (PSA ≤10 ng/ml if on 5-α-reductase inhibitors). Key exclusion criteria were prior treatment for prostate cancer; prostate cancer with distant metastases; treatment with hormone therapy, immunotherapy, chemotherapy, and/or radiation therapy for any malignancies within the previous 2 yr; immunosuppressed/immunodeficient because of disease or medication; and a history of or active autoimmune disease. Written informed consent was obtained from all participants.

2.5. Study procedures

Eligible participants were randomized 2:1 to receive PROSTVAC or EV. Randomization was stratified according to the study site and the number of repeat biopsies following diagnosis (≤2 or >2). Participants received a priming vaccination with subcutaneous injection of PROSTVAC-V or EV at baseline and six boosters with subcutaneous injection of PROSTVAC-F or EV on days 14, 28, 56, 84, 112, and 140 following the priming vaccination. Participants returned 7–14 days after the last scheduled dose of vaccine for a standard-of-care surveillance transrectal ultrasound-guided prostate biopsy with targeted magnetic resonance imaging (MRI)-ultrasound fusion, as needed.

Blood was collected for a complete blood count with differential, comprehensive metabolic panel, and PSA at screening, on day 84, and at 7–14 d after the intervention. Additional PSA tests were collected at baseline (before the priming vaccination) and at the 6-mo follow-up visit. Blood was also collected at baseline and at 7–14 d after the intervention for immunologic studies. IPSS data were collected at screening, on day 84, and at 7–14 d and 6 mo after the intervention. Adverse events (AEs) were assessed according to the NCI Common Terminology Criteria for Adverse Events v4.0.

2.6. Immunohistochemistry assays

CD4, CD8, and PD-L1 positivity in cells in biopsy tissues was assessed via immunohistochemistry (IHC) using a Leica Bond RX system with the following primary antibodies: CD4 mouse anti-human predilute (4B12; Leica, catalog no. PA0427), CD8 mouse anti-human predilute (4B11; Leica, catalog no. PA0183), and PD-L1 rabbit anti-human with 1:25 dilution (E1L3N; Cell Signaling, catalog no. 13684S), respectively. Whole-slide scans of biopsies stained for CD4, CD8, or PD-L1 on IHC were analyzed using QuPath v0.2.0 (stable version). Scans were annotated by an expert pathologist to mark the various compartments (CT = tumor center; IM = invasive margin; NL = benign glands; and IT = isolated tumor) wherever feasible and present (Supplementary Fig. 1A). Data are reported as the number of positive cells ($CD4^+$ or $CD8^+$) per area of tissue in mm^2 (density) in each compartment (CA = compartmental analysis; Supplementary Fig. 1B). The average density of CD4 or CD8 in all tumor tissue compartments (CT, IM, and IT) was also calculated for noncompartmental analysis (NCA). The percentage of positive cells was assessed for PD-L1. Limited cases showed positive PD-L1 staining in the tumor, which precluded subsequent analysis.

2.7. Antigen-specific T-cell responses

Cryopreserved peripheral blood mononuclear cells (PBMCs) were assessed for peripheral T-cell responses to PSA, the target antigen encoded by the vaccine, and to the cascade antigens brachyury and MUC1, antigens not encoded by the vaccine, as a potential indicator of epitope spreading. This assay has been previously described and involves stimulating PBMCs with overlapping 15-mer peptide pools and evaluating CD4 and CD8 T cells for the production of cytokines (IFN-γ, TNF-α, IL-2) or for expression of a degranulation marker (CD107a) via flow cytometry [10]. All peptide pools were purchased from JPT Peptide Technologies; peptide pools encoding human leukocyte antigen and CEFT (a mixture of peptides of cytomegalovirus, Epstein-Barr virus, influenza, and tetanus toxin) were used as negative and positive controls, respectively.

2.8. Statistical analysis

The baseline demographic and disease characteristics were compared between the arms using a Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. The baseline CD4 and CD8 densities were compared between the arms using a Wilcoxon rank-sum test. The absolute and percentage changes in CD4 and CD8 density from baseline to post-treatment were compared between the arms using a Wilcoxon rank-sum test. The absolute and percentage changes in CD4 and CD8 density within each arm were assessed using a signed rank test. The proportion of participants with no tumor on postintervention biopsy and the proportion of participants with Gleason upgrading were compared between the two groups using Fisher's exact test. Changes in the percentage of positive random cores and in serum PSA were compared between the arms using a Wilcoxon rank-sum test. Descriptive statistics for the type and frequency of all AEs were generated, and Fisher's exact test was performed to compare the AE frequency between the two groups. For the primary endpoints, p values of <0.05 with Bonferroni correction (ie, a significance level of 2.5% for each) were deemed statistically significant. The secondary endpoints were considered exploratory and therefore no correction was performed for multiple comparisons; the results were interpreted with caution.

3. Results

The study opened to accrual in June 2014 and closed to accrual in December 2017. A total of 191 participants provided consent and 154 (103%) of the planned 150 participants were randomized to receive EV ($n = 48$) or PROSTVAC ($n = 106$; Fig. 1). All participants received the priming vaccination. One participant in the PROSTVAC arm received only one booster dose and declined further treatment because of AEs. One booster dose was held because of AEs for one participant in the EV arm and three participants in the PROSTVAC arm. All other participants received all six booster doses. The study was completed by 47 (98%) participants in the EV arm and 103 (97%) in the PROSTVAC arm.

3.1. Patient demographics

The baseline characteristics of the study participants by treatment arm are summarized in Table 1. The mean PSA (± standard deviation) at baseline was 6.9 ± 3.5 ng/ml. Some 66% of participants had grade group 1 prostate cancer at baseline and 34% had grade group 2. There

were no significant differences in demographic and disease characteristics between the study arms at baseline.

3.2. CD4 and CD8 density in biopsy tumor tissue

Table 2 summarizes the prevaccination CD4 and CD8 density in prostate biopsy tissue by arm. CD4 and CD8 density varied widely among individuals. Similar prevaccination CD4 and CD8 density in biopsy tumor tissue was observed between the EV and PROSTVAC arms in each tumor compartment and on NCA. The absolute and percentage changes in CD4 and CD8 density from baseline are shown in Figure 2. The change in CD4 and CD8 density varied widely among individuals. The absolute or percentage change in CD4 and CD8 density in biopsy tumor tissue did not differ significantly between the EV and PROSTVAC arms. The postvaccination percentage increase in CD4 density in IM tissue was significant in each arm ($p = 0.03$). The prevaccination CD4 and CD8 density in NL tissue did not differ significantly between the EV and PROSTVAC arms (Table 2). There were also no differences in the absolute or percentage change in CD4 and CD8 density in NL tissue between the EV and PROSTVAC arms (Fig. 2). The postvaccination percentage increase in CD4 density was significant in NL tissue in the PROSTVAC arm ($p < 0.01$).

3.3. Tumor pathology, PSA, and IPSS

Table 3 summarizes the change in tumor pathology, PSA, and IPSS. There was no difference between the arms in post-treatment biopsy Gleason upgrading to grade group 3, a prespecified analysis. Exploratory analyses revealed a marginally significant decrease in post-treatment biopsy upgrading favoring PROSTVAC among participants with baseline grade group 1 (21.6% vs 40.7%; $p = 0.08$) but not among participants with baseline grade group 2 disease (12.5% vs 21.1%; $p = 0.45$). The difference in post-treatment upgrading was attenuated in a subgroup of participants with MRI-guided targeted biopsy. There was no difference between the groups in the proportion of participants with no tumor found at postintervention biopsy ($p = 0.52$) or in the change in the percentage of positive random cores ($p = 0.28$). At 6-mo post-treatment follow-up, no between-group differences were observed for changes in serum PSA ($p = 0.30$) or IPSS ($p = 0.55$).

3.4. Antigen-specific and cascade T-cell responses in peripheral blood

A subset of peripheral blood samples was analyzed for the development of antigen- and cascade-specific T cells (Supplementary Table 1). Peripheral T-cell responses were observed in some of the participants in each arm, although there was no difference in the frequency of participants developing peripheral PSA-specific T cells ($p = 0.13$) or multifunctional PSA-specific T cells ($p > 0.99$) between the EV and PROSTVAC arms. There were also no differences in the development of T cells, including multifunctional cells, that target the cascade antigens brachyury and/or MUC1 not encoded by the vaccine between the EV and PROSTVAC arms.

3.5. Adverse events

The PROSTVAC vaccination was well tolerated in the study cohort. There was one death from a fall a month after completing the PROSTVAC vaccination believed to be unrelated

to the study agent. There were three grade 3 AEs reported during the intervention in the EV arm deemed unlikely to be related or unrelated to the intervention (syncope and hypertension in one participant each and scheduled knee surgery in another participant). The remaining AEs were of grade 1 or 2 (Supplementary Table 2).

4. Discussion

Prostate-focused immunotherapy able to generate localized and systemic antitumor immune responses could potentially prevent progression of localized disease and obviate the need for more morbid standard therapies. Tissue immune responses to PROSTVAC have been investigated in prior smaller, single-arm studies in localized prostate cancer. A phase 1 study of PROSTVAC with the priming vaccination administered subcutaneously and the booster given intraprostatically revealed a marked increase in tumor CD4 and CD8 T-cell infiltrates in patients with locally recurrent or progressive prostate cancer [7]. A recent phase 2a study showed that subcutaneous PROSTVAC priming with three boosters in patients with localized prostate cancer awaiting radical prostatectomy resulted in a significant increase in overall tumor $CD4^+$ T-cell infiltrates in postvaccination prostatectomy specimens in comparison to baseline biopsies [8]. Nevertheless, follow-up studies are needed to define the association between increases in tumor CD4/CD8 infiltrates and overall survival or progression. In our randomized controlled trial, PROSTVAC vaccination did not lead to more favorable changes in CD4 and CD8 T-cell infiltrates in comparison to EV. Our study used an empty fowlpox viral vector as the control to provide the blinded study evaluation. However, even if empty, the viral vector itself is also strongly immunogenic, as indicated by injection site reactions, flu-like symptoms, fatigue, headache, fever, and the development of peripheral T-cell responses in some participants. Use of an immunogenic control may have prevented us from observing differences between the study arms. In the exploratory analyses, both arms showed a significant percentage increase in CD4 density in IM tissue, and PROSTVAC vaccination led to a significant percent increase in CD4 density in NL tissue. More work is warranted to evaluate the effects of PROSTVAC on other immune targets to gain insights into its effects on the tumor immune microenvironment.

In comparison to the EV control, PROSTVAC did not lead to changes in PSA at 6 mo after completion of the vaccination series. There was no difference in postvaccination Gleason upgrading to grade group 3 between the arms. In an exploratory analysis, there was a numerical but nonsignificant difference between the study arms in post-treatment Gleason upgrading for participants with baseline grade group 1 favoring the PROSTVAC arm; no difference in Gleason upgrading was observed for participants with baseline grade group 2 cancer. The potentially favorable effect of PROSTVAC on upgrading among patients with low-risk disease was not seen in a subgroup of participants with MRI-guided targeted biopsies, a technique that minimizes biopsy sampling variability. However, the sample size for the MRI-targeted biopsy subgroup was too small to permit firm conclusions regarding this exploratory endpoint. In addition, we reviewed published work on pathologic outcomes for patients on AS to identify a historical control with similar patient demographics. The ENACT trial randomized patients with low-risk or intermediate-risk localized prostate cancer on AS, a cohort similar to ours, to enzalutamide or no treatment [11]. Some 23% of participants in the control arm of the ENACT trial had pathologic prostate cancer

progression at 12 mo. In our study, any Gleason upgrading was observed for 19% in the PROSTVAC arm and 33% in the EV arm. In comparison to the control arm of the ENACT trial, PROSTVAC did not seem to induce favorable pathologic outcomes. Nevertheless, there are limitations to such comparisons. Given the protracted nature of early-stage prostate cancer and the potential time needed to see the full effects of immune modulation in this disease setting, longer follow-up of the study participants may be required to identify any delayed clinical benefit.

5. Conclusions

In conclusion, PROSTVAC was well tolerated in patients undergoing AS for prostate cancer but did not elicit more favorable prostate tissue or peripheral T-cell responses than the EV. There was no difference between the arms in clinicopathologic effects in the primary analyses. Although our study did not show a favorable immunologic response to PROSTVAC in comparison to EV, we showed the feasibility and acceptability of intervening with immunotherapy in the AS setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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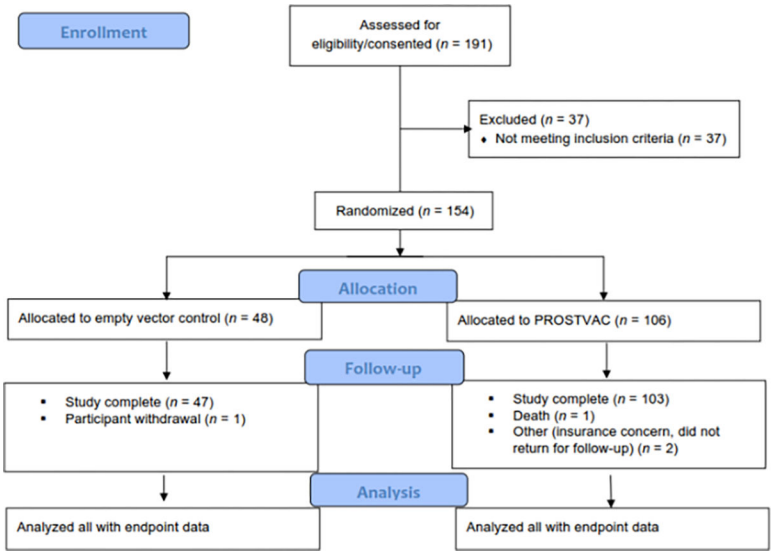

Fig. 1 –. CONSORT flow diagram.

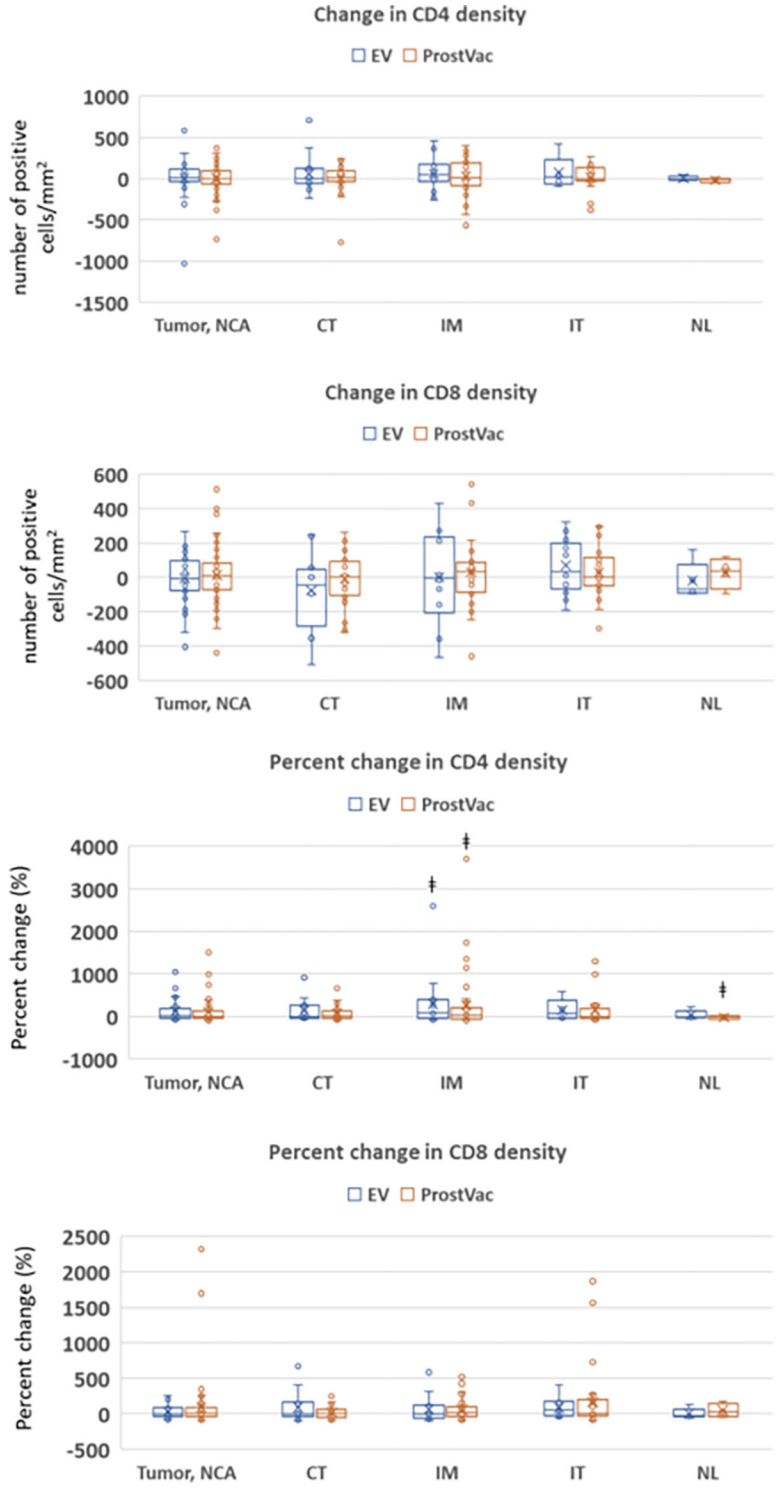

Fig. 2 –. Change in CD4 and CD8 density (number of positive cells per area of tissue) was assessed in various biopsy tissue compartments. CT = tumor center; IM = invasive margin; NL = benign glands; IT = isolated tumor. The average density in all biopsy tumor tissue compartments (CT, IM, and IT) was calculated for noncompartmental analysis (NCA). EV = empty vector control. ‡ Significant postintervention within-arm change versus baseline ($p < 0.05$).

Table 1 –

Baseline characteristics of the study participants by treatment assignment

Variable [a]	Overall (*n* = 154)	Empty vector (*n* = 48)	PROSTVAC (*n* = 106)	*p* value [b]
Demographics				
Age (yr)	64 ± 8	64 ± 8	65 ± 7	0.63
Body mass index (kg/m^2)	27.8 ± 4.3	27.8 ± 3.8	27.7 ± 4.5	0.81
Race, *n* (%)				0.40
White	134 (87.0)	43 (89.6)	91 (85.9)	
Black or African American	11 (7.1)	4 (8.3)	7 (6.6)	
Native Hawaiian or Pacific Islander	1 (0.7)	0 (0.0)	1 (0.9)	
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	
Asian	3 (2.0)	0 (0.0)	3 (2.8)	
More than one race	1 (0.6)	1 (2.1)	0 (0.0)	
Unknown	4 (2.6)	0 (0.0)	4 (3.8)	
Ethnicity, *n* (%)				
Hispanic/Latino	5 (3.3)	1 (2.1)	4 (3.8)	1.00
Not Hispanic or Latino	143 (92.9)	45 (93.8)	98 (92.5)	
Unknown	6 (3.9)	2 (4.2)	4 (3.8)	
Disease characteristics				
Prostate-specific antigen (ng/ml)	6.9 ± 3.5	6.9 ± 3.2	6.9 ± 3.7	0.86
Two or more repeat Bx since diagnosis, *n* (%)	132 (85.7)	40 (83.3)	92 (86.8)	0.62
Grade group, *n* (%)				0.20
1	102 (66.2)	28 (58.3)	74 (69.8)	
2	52 (33.8)	20 (41.7)	32 (30.2)	
Percent positive cores from random Bx (%)	19 ± 12	20 ± 11	18 ± 12	0.10

Bx = biopsy.

[a] Results for continuous variables are reported as the mean ± standard deviation.

[b] Derived from a Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Table 2 –

Prevaccination CD4 and CD8 density

Variable	Median number of positive cells/mm^2 (IQR)		*p* value [a]
	Empty vector	PROSTVAC	
CD4 density			
Tumor tissue via NCA	94 (44–184) (*n* = 37)	99 (52–200) (*n* = 79)	0.67
Tumor center	91 (45–269) (*n* = 24)	93 (62–157) (*n* = 53)	0.90
Invasive margin	75 (37–187) (*n* = 28)	96 (50–177) (*n* = 56)	0.80
Isolated tumor	71 (34–130) (*n* = 14)	88 (43–212) (*n* = 45)	0.56
Benign tissue	70 (32–140) (*n* = 39)	72 (45–137) (*n* = 86)	0.72
CD8 density			
Tumor tissue via NCA	189 (95–256) (*n* = 35)	153 (99–220) (*n* = 85)	0.31
Tumor center	171 (80–395) (*n* = 20)	129 (92–194) (*n* = 51)	0.25
Invasive margin	159 (113–383) (*n* = 29)	163 (114–244) (*n* = 64)	0.63
Isolated tumor	152 (87–208) (*n* = 22)	134 (81–189) (*n* = 48)	0.48
Benign tissue	152 (112–218) (*n* = 39)	168 (104–248) (*n* = 91)	0.69

IQR = interquartile range; NCA = noncompartmental analysis.

[a]Derived from a Wilcoxon rank-sum test for comparison of baseline CD4 and CD8 density between arms.

Table 3 –

Changes in Bx tumor pathology, PSA, and IPSS after the intervention

Variable [a]	Empty vector	PROSTVAC	*p* value [b]
No tumor found on postintervention Bx, *n* (%)	8 (17.4) (*n* = 46)	25 (23.6) (*n* = 106)	0.52
Gleason upgrading, *n* (%)			
Any GG → GG ≥3	6 (13.0) (*n* = 46)	8 (7.6) (*n* = 106)	0.36
GG 1 → GG ≥2	11 (40.7) (*n* = 27)	16 (21.6) (*n* = 74)	0.08
GG 2 → GG ≥3	4 (21.1) (*n* = 19)	4 (12.5) (*n* = 32)	0.45
Gleason upgrading on MRI-guided TBx, *n* (%)			
Any GG → GG ≥3	0 (0.0) (*n* = 17)	3 (7.5) (*n* = 40)	0.55
GG 1 → GG ≥2	2 (20.0) (*n* = 10)	6 (23.1) (*n* = 26)	1.00
GG 2 → GG ≥3	0 (0.0) (*n* = 7)	1 (7.1) (*n* = 14)	1.00
Change in percent positive random cores (%)	1.6 ± 15.2 (*n* = 46)	−1.7 ± 16.1 (*n* = 106)	0.28
Change in PSA (ng/ml) [c]	−0.66 ± 3.49 (*n* = 35)	0.26 ± 2.39 (*n* = 76)	0.30
Change in IPSS (points) [c]	0.87 ± 3.57 (*n* = 30)	−0.12 ± 4.67 (*n* = 58)	0.55

Bx = biopsy; GG = grade group; IPSS = International Prostate Symptom Score; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TBx = targeted biopsy.

[a] Results for continuous variables are reported as the mean ± standard deviation.

[b] Derived from a Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

[c] Change from baseline to 6-mo follow-up.