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A Randomized, Double-blind, Phase II Trial of PSA-TRICOM (PROSTVAC) in Patients with Localized Prostate Cancer: The Immunotherapy to Prevent Progression on Active Surveillance Study

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1. Introduction

A novel approach for preventing progression in prostate cancer patients on active surveillance (AS) is immunotherapy. PSA-TRICOM (PROSTVAC) is a prostate-specific antigen (PSA)-based pox-viral vaccine with the potential to induce antitumor T-cell responses. It contains PSA and three T-cell costimulatory molecules (B7.1, ICAM-1, and LFA-3). Although a phase III trial of PSA-TRICOM in patients with minimally symptomatic metastatic castrate-resistant prostate cancer did not demonstrate a significant survival advantage, other data suggest that PSA-TRICOM may have greater efficacy in earlier-stage disease [1–4].

We are conducting a randomized, phase II, placebo-controlled, double-blind trial of PSA-TRICOM in AS patients to determine its immunologic and clinical effects in patients with localized prostate cancer (ClinicalTrials.gov NCT02326805).

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Conflicts of interest: The authors have nothing to disclose.

2. Materials and methods

Participants were randomized (2:1) to receive seven doses of PSA-TRICOM or placebo SC over a 5-mo period. Postintervention prostate biopsy was performed 7–14 d after the last dose. PSA was evaluated every 3 mo starting from baseline; patients are followed for 6 mo after vaccine intervention.

2.1. Major inclusion and exclusion criteria

Eligible patients had clinically localized, biopsy-proven adenocarcinoma of the prostate with clinical stage ≤T2a and serum PSA of <20 ng/ml, diagnosed with an extended pattern (≥10 cores) biopsy with or without magnetic resonance imaging guidance, with ≤50% of the random biopsy cores positive for cancer and Gleason sum ≤3 + 4 = 7 (grade group [GG] 2).

Exclusion criteria included prior treatment for prostate cancer; history of human immunodeficiency virus, hepatitis B or C, solid organ or bone marrow transplant, immunodeficiency, splenectomy, autoimmune disease, eczema or other eczemoid skin disorders, and adverse reactions to smallpox vaccination; chronic immunosuppressive therapy; and chronic administration of systemic corticosteroids within 28 d of study entry.

2.2. Primary outcome

The primary outcome is the change in $CD8^+$ and $CD4^+$ expression within tumor and adjacent stromal tissue in the baseline versus postintervention biopsy tissue.

2.3. Secondary outcomes

Secondary immunologic outcomes include changes in PD-L1–positive cells; changes in $CD8^+$–, $CD4^+$–, and PD-L1–positive cells in benign biopsy tissue; changes in circulating 15-Mer PSA-specific T cells; and changes in soluble antibodies to tumor-associated antigens.

Other secondary outcomes include changes in PSA from baseline to 6 mo after intervention, pathologic progression defined as Gleason sum ≥4 + 3 = 7 (GG 3), changes in tumor extent (defined as percent of positive random biopsy cores), and the proportion of patients in each arm with no cancer on the postintervention biopsy.

2.4. Statistics

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. Pearson correlation coefficients will be derived to evaluate the correlation between the changes in $CD8^+$ and PSA for participants treated with PROSTVAC.

We conservatively estimated that at least 30% of patients would complete the intervention and postintervention biopsy and have tumor in the biopsy cores. Based on a sample size of at least 30 in the PSA-TRICOM group and 15 in the placebo group, and assuming that the standard deviation of the change in $CD8^+$- and $CD4^+$-positive cells for the PSA-TRICOM group is twice that for the placebo group, the power will be at least 90% to detect a Cohen's d effect size of ≥0.98 at a significance level of 5% by the Bonferroni correction.

A two-sided two-sample *t* test will be performed to compare each of the secondary endpoints between the intervention and placebo groups. Fisher's exact test will be performed to compare the proportion of patients with no cancer on the postintervention biopsy and the proportion of men with an increase in Gleason score to ≥4 + 3 (GG 3) from baseline to postintervention biopsy between the two groups.

3. Results

3.1. Randomization

From June 2015 to December 2017, 154 (103%) of a planned 150 participants were randomized at six US sites (Fig. 1).

3.2. Baseline characteristics

At baseline, mean (SD) age was 64 (8) yr and PSA 6.9 (3.4) ng/ml. Eleven (7%) participants were African American. There were no significant between-group differences for age (p = 0.63), race (p = 0.37), distribution of study groups among sites (p = 0.96), number of additional biopsies after prostate cancer diagnosis (p = 0.57), PSA (p = 0.96), or Gleason sum. Fifty-one (33%) of 154 participants had Gleason 3 + 4 = 7 (GG 2) disease (Table 1).

4. Discussion

The Immunotherapy to Prevent Progression on Active Surveillance Study (IPASS) is the first randomized clinical trial of immunotherapy for localized prostate cancer. Although AS provides an alternative to immediate treatment for some men with localized disease, approximately 30% of AS patients will undergo definitive treatment and/ or demonstrate pathologic disease progression within 3 yr [5–10]. Identification of interventions to prevent progression in AS would substantively inform care by reducing treatment incidence, minimizing morbidity, improving health-related quality of life, and tamping down health care costs.

Prostate-focused immunotherapy produces localized and systemic antitumor immune responses that might prevent progression of localized disease and obviate the need for treatment [4,11]. Practical, relatively inexpensive, and scalable to large populations, vaccine-based immunotherapy would be ideally suited for AS. PSA-TRICOM is administered intramuscularly and well tolerated. It can be manufactured in large quantities and stored frozen for years. In a phase 1 study of 21 patients who received PSA-TRICOM injections, who were either treatment naïve or had locally recurrent disease after primary radiotherapy, there were significant increases in $CD4^+$ and $CD8^+$ T-cell tumor infiltrates in post-treatment versus baseline tumor biopsies, and the majority of evaluable patients had improved PSA values and/or improved PSA doubling time, suggestive of a therapeutic effect [4].

In summary, IPASS is assessing the effects of PSA-TRICOM (PROSTVAC) on immune response and clinical progression in patients on AS. The final results are projected to be available in 2019.

Acknowledgments

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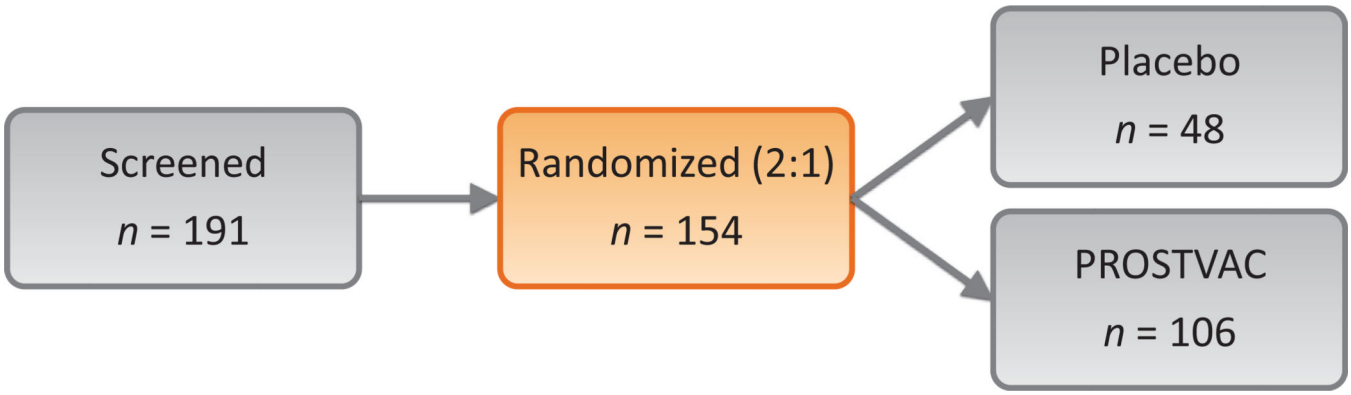

Fig. 1 –.

Screening and randomization of men enrolled in the Immunotherapy to Prevent Progression on Active Surveillance Study.

Table 1 –

Baseline characteristics of men enrolled in the Immunotherapy to Prevent Progression on Active Surveillance Study.

	Placebo (*N* = 48)	PROSTVAC (*N* = 106)	Total (*N* = 154)	*p* value
Age (yr)				0.626
N	48	106	154	
Mean (SD)	64.0 (8.4)	64.5 (7.4)	64.4 (7.7)	
Median	64	64	64	
Q1, Q3	59, 70	60, 70	59, 70	
Range	43, 82	45, 81	43, 82	
Race				
White	43 (89.58)	90 (84.91)	133 (86.36)	0.369
Black or African American	4 (8.33)	7 (6.60)	11 (7.14)	
Native Hawaiian or other Pacific islander	0 (0.00)	1 (0.94)	1 (0.65)	
Asian	0 (0.00)	3 (2.83)	3 (1.95)	
American Indian or Alaska Native	0 (0.00)	0 (0.00)	0 (0.00)	
>2	1 (2.08)	0 (0.00)	1 (0.65)	
Not reported	0 (0.00)	3 (2.83)	3 (1.95)	
Unknown	0 (0.00)	2 (1.89)	2 (1.30)	
Site				
UC San Diego	14 (29.17)	30 (28.30)	44 (28.57)	0.956
University of Southern California	2 (4.17)	7 (6.60)	9 (5.84)	
UC Irvine	8 (16.67)	14 (13.21)	22 (14.29)	
Cedars Sinai Hospital Los Angeles	1 (2.08)	4 (3.77)	5 (3.25)	
Johns Hopkins	12 (25.00)	24 (22.64)	36 (23.38)	
National Cancer Institute	11 (22.92)	27 (25.47)	38 (24.68)	
No. of biopsies after diagnosis				
≤2	40 (83.33)	92 (86.79)	132 (85.71)	0.570
>2	8 (16.67)	14 (13.21)	22 (14.29)	
PSA (ng/ml)				0.961
N	48	105	153	
Mean (SD)	6.9 (3.2)	7.0 (3.5)	6.9 (3.4)	

	Placebo (*N* = 48)	PROSTVAC (*N* = 106)	Total (*N* = 154)	*p* value
Median	6	6	6	
Q1, Q3	5, 8	5, 9	5, 9	
Range	1, 15	1, 19		
Gleason sum				
3 + 3 = 6	28 (58.33)	74 (69.81)	102 (66.23)	0.163
3 + 4 = 7	20 (41.67)	32(30.19)	52 (33.77)	

PSA = prostate-specific antigen; SD = standard deviation.