original reports

Phase II Trial of a DNA Vaccine Encoding Prostatic Acid Phosphatase (pTVG-HP [MVI-816]) in Patients With Progressive, Nonmetastatic, Castration-Sensitive Prostate Cancer

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abstract

PURPOSE We previously reported the safety and immunologic effects of a DNA vaccine (pTVG-HP [MVI-816]) encoding prostatic acid phosphatase (PAP) in patients with recurrent, nonmetastatic prostate cancer. The current trial evaluated the effects of this vaccine on metastatic progression.

PATIENTS AND METHODS Ninety-nine patients with castration-sensitive prostate cancer and prostate-specific antigen (PSA) doubling time (DT) of less than 12 months were randomly assigned to treatment with either pTVG-HP co-administered intradermally with 200 μg granulocyte-macrophage colony-stimulating factor (GM-CSF) adjuvant or 200 μg GM-CSF alone six times at 14-day intervals and then quarterly for 2 years. The primary end point was 2-year metastasis-free survival (MFS). Secondary and exploratory end points were median MFS, changes in PSA DT, immunologic effects, and changes in quantitative ^{18}F-sodium fluoride (NaF) positron emission tomography/computed tomography (PET/CT) imaging.

RESULTS Two-year MFS was not different between study arms (41.8% vaccine *v* 42.3%; $P = .97$). Changes in PSA DT and median MFS were not different between study arms (18.9 *v* 18.3 months; hazard ratio [HR], 1.6; $P = .13$). Preplanned subset analysis identified longer MFS in vaccine-treated patients with rapid (< 3 months) pretreatment PSA DT (12.0 *v* 6.1 months; n = 21; HR, 4.4; $P = .03$). PAP-specific T cells were detected in both cohorts, including multifunctional PAP-specific T-helper 1–biased T cells. Changes in total activity (total standardized uptake value) on ^{18}F-NaF PET/CT from months 3 to 6 increased 50% in patients treated with GM-CSF alone and decreased 23% in patients treated with pTVG-HP (n = 31; $P = .07$).

CONCLUSION pTVG-HP treatment did not demonstrate an overall increase in 2-year MFS in patients with castration-sensitive prostate cancer, with the possible exception of a subgroup with rapidly progressive disease. Prespecified ^{18}F-NaF PET/CT imaging conducted in a subset of patients suggests that vaccination had detectable effects on micrometastatic bone disease. Additional trials using pTVG-HP in combination with PD-1 blockade are under way.

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INTRODUCTION

Approximately one third of patients with prostate cancer will have a recurrence after definitive surgery or radiation therapy.[1] The first evidence of recurrence before developing radiographically detectable metastases is usually an increase in serum prostate-specific antigen (PSA). The rate of increase, or PSA doubling time (DT), has been demonstrated to be prognostic of the time to radiographic evidence of metastases and death.[2-4] Although early androgen deprivation is an option for biochemically recurrent prostate cancer, therapies that could delay the progression of disease and avoid the treatment-related adverse effects from castration therapies are desirable.

The goal of antitumor vaccines is to elicit tumor-specific immunity capable of eliminating tumors or slowing their growth. Conceptually, these should be most effective in earlier stages of disease when tumor volume and mechanisms of immune escape are minimal. Hence, this treatment approach is attractive for patients with early recurrent prostate cancer. We initially studied vaccines that target prostatic acid phosphatase (PAP) because a rodent homolog of this prostate-specific protein exists, which enables preclinical studies.[5-7]

PAP is also the target antigen of sipuleucel-T, the only US Food and Drug Administration–approved antitumor vaccine, which validates PAP as a relevant prostate tumor antigen.[8] However, the use of autologous cellular vaccines is cumbersome and costly. Hence, we have focused on simpler genetic vaccine methods that favor the induction of antigen-specific cytolytic $CD8^+$ T cells.[6,7] We previously evaluated a DNA vaccine (pTVG-HP [MVI-816]) that encodes PAP in phase I/II clinical trials in men with nonmetastatic, PSA-recurrent prostate cancer.[9,10] These trials demonstrated safety and immunologic activity. Moreover, the development of persistent, PAP-specific T-helper 1 (Th1)–biased immunity was associated with a prolonged PSA DT, which suggests a possible clinical effect.[9,11]

We report here the results from a multicenter, randomized, phase II clinical trial using this DNA vaccine with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) as a vaccine adjuvant, versus GM-CSF adjuvant alone, in patients with castration-sensitive, nonmetastatic, PSA-recurrent prostate cancer with rapid PSA DT. This represents the first randomized placebo-controlled clinical trial using an antitumor DNA vaccine to our knowledge. The primary end point was 2-year metastasis-free survival (MFS) on the basis of conventional imaging.

PATIENTS AND METHODS

Study Agent and Regulatory Information

The pTVG-HP (MVI-816, Madison Vaccines, Madison, WI) vaccine is a plasmid DNA that encodes the full-length human PAP cDNA downstream of a eukaryotic promoter.[5] The study protocol was reviewed and approved by all local and federal (US Food and Drug Administration, National Institutes of Health Recombinant DNA Advisory Committee) entities. All patients gave written institutional review board–approved consent for participation.

Patient Population

Male patients with adenocarcinoma of the prostate and biochemical (serum PSA) recurrence after definitive surgery and/or radiation therapy were eligible provided that there was no evidence of suspected lymph node, bone, or visceral metastatic disease on ^{99m}Tc-methylene diphosphonate planar scintigraphy (bone scans) or computed tomography (CT) scans. Patients were required to have at least four serum PSA values collected from the same clinical laboratory at least 2 weeks apart over a 3- to 6-month period before study entry, with a final PSA of 2 ng/mL or more and a calculated DT of less than 12 months. Patients were required to have an Eastern Cooperative Oncology Group performance score of 1 or lower and normal bone marrow, liver, and renal function. Prior androgen deprivation was prohibited unless used for less than 24 months with radiation therapy.

Study Design

This randomized, double-blind, multi-institutional, phase II trial was designed to evaluate the effect of pTVG-HP plus GM-CSF adjuvant on time to radiographic progression compared with GM-CSF alone. Patients were stratified by pretreatment PSA DT (0 to 3 months, 3 to 6 months, or 6 to 12 months), Gleason score (≤ 7 or > 7), and baseline PSA at the time of screening (≤ 10 or > 10 ng/mL). The study began as a 56-patient two-institution trial in 2011 and was expanded in 2014 to add an additional 50 patients, a clinical trial site, and biomarker assessments (biomarker cohort). With 106 planned participants, the study was designed to have greater than 90% power to detect a difference of 40% versus 70% in 2-year MFS at a one-sided 5% significance level and assuming an attrition rate of 15%. No interim analyses were planned.

Study Procedures

Patients were treated intradermally six times at 14-day intervals and then quarterly for up to 2 years with 200 μg GM-CSF (sargramostim) admixed or not with 100 μg pTVG-HP plasmid DNA (Fig 1). Safety laboratory studies were performed at week 6 and quarterly. All toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4). CT scans of the abdomen and pelvis and bone scintigraphy were performed every 6 months or at any additional time per physician discretion. Patients came off the trial at the time of metastatic disease as determined using these conventional scans; patients were discouraged from discontinuing as a result of PSA rise alone.

Clinical Response Evaluation

Time to metastasis was determined from the date of registration to the first CT or bone scan that demonstrated metastatic disease. PSA DT was calculated using all serum PSA values available from the same clinical laboratory for the specified period by the equation $\log 2 / b$, where b denotes the least-squares estimator of the linear regression model of the log-transformed PSA values on time. For the pretreatment PSA DT, a period of 3 to 6 months was used before treatment, including day 1, with a minimum of four values. The on-treatment PSA DT was determined using values from month 3 to month 9.

Immunologic Response Evaluation

All immune analyses were performed while blinded to study arm assignment. Cryopreserved peripheral blood mononuclear cells were stimulated in vitro for 9 days with 0.5 μg/mL of a pool of 15-mer peptides that span the amino acid sequence of PAP. Cells were washed and restimulated with PAP protein, phytohemaglutinin, or media alone, and evaluated for interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), and granzyme B release by FluoroSpot (Cellular Technology Limited, Shaker Heights, OH) as previously

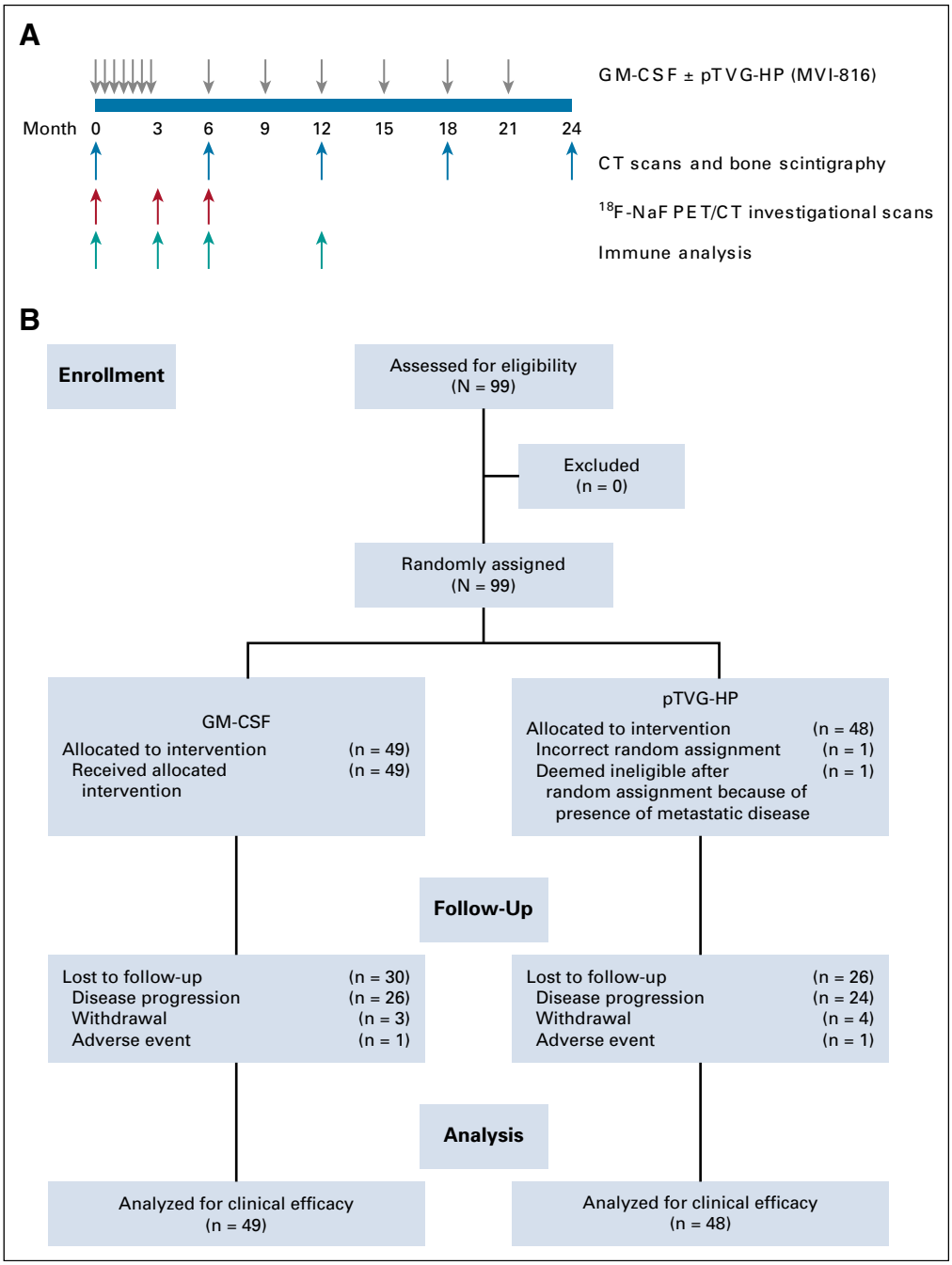

FIG 1. Schema and patient allocation. (A) Treatment schema and (B) CONSORT diagram. ^{18}F-NaF, ^{18}F-sodium fluoride; CT, computed tomography; GM-CSF, granulocyte-macrophage colony-stimulating factor; PET, positron emission tomography.

reported.[9,12] IFN-γ alone (or IFN-γ, TNF-α, and granzyme B) spots per well were counted by an automated ELISPOT reader (Cellular Technology Limited). Antigen-specific spot-forming units were determined by subtracting spot-forming units from media-alone wells.

^{18}F-Sodium Fluoride Positron Emission Tomography/CT Imaging

Patients at two centers in the biomarker cohort received investigational ^{18}F-sodium fluoride (NaF) positron emission tomography (PET)/CT scans at baseline, month 3, and month 6. A qualification PET scan using the American College of Radiology phantom was performed at each site, and reconstructions were selected to minimize differences between maximum standardized uptake values (SUVs). Patients were injected with 110 to 185 MBq (3 to 5 mCi) ^{18}F-NaF and imaged 60 minutes postinjection. All scans were performed on the same qualified PET/CT scanner (GE Discovery RX [GE Healthcare, Chicago, IL] at Johns Hopkins University or GE Discovery ST at the University of Wisconsin) for each participant. Post-treatment scans were acquired within 5 minutes of the postinjection time from the baseline scan. Image reconstruction parameters provided from the American College of Radiology qualification scan analysis were used.

^{18}F-NaF PET/CT images were analyzed semi-automatically using Quantitative Total Bone Imaging (QTBI) software.[13] The performance characteristics for this method were established in a prior trial that included test-retest imaging to establish limits of agreement for significant changes in NaF PET/CT measurements.[14] Changes detected by QTBI have been associated previously with clinical outcome.[13] Lesions were identified and segmented using statistically optimized regional thresholds adjusted for patient-specific background.[15] Lesions were classified as malignant or benign automatically by a previously trained and tested random forest machine learning model on the basis of lesion location, PET features, and CT features.[16] The number of lesions and patient disease burden (sum of individual lesion uptakes [SUV_{total}]) were extracted and while blinded to study arm assignment, evaluated as the percent change relative to baseline.

Statistical Analysis

Baseline characteristics were summarized as frequencies and percentages or medians and ranges. MFS was analyzed using the Kaplan-Meier method and compared between arms using the unstratified log-rank test and Cox proportional hazards regression model. PSA DT was summarized by medians and ranges and compared between study arms using the nonparametric Wilcoxon rank sum test. Preplanned exploratory comparisons of clinical end points between arms were conducted by stratification factors. Changes in quantitative bone imaging and immune response parameters within each arm were evaluated using a nonparametric Wilcoxon signed rank test. Analogously, changes in quantitative bone imaging and immune response parameters between arms were evaluated using a nonparametric Wilcoxon rank sum test. All reported P values are two-sided, and $P < .05$ was used to define statistical significance. Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

TABLE 1. Patient Demographics

Characteristic	Study Arm, No. (%)	
	GM-CSF	pTVG-HP
No. of patients	49	48
Age, years		
Median	71	71
Range	56-86	46-82
Race		
White	46 (94)	43 (90)
Black	1 (2)	1 (2)
Asian/Pacific Islander	0 (0)	1 (2)
American Indian/Alaska Native	0 (0)	1 (2)
Unknown	2 (4)	2 (4)
Prior treatment		
Prostatectomy	34 (69)	41 (85)
Radiation therapy		
Primary treatment	20 (41)	12 (25)
Adjuvant/salvage	28 (57)	31 (65)
Androgen deprivation	13 (27)	15 (31)
Chemotherapy	1 (2)	1 (2)
Gleason score		
≤ 7	34 (69)	32 (67)
> 7	15 (31)	16 (33)
Baseline PSA, ng/mL		
2.0-10.0	42 (86)	40 (83)
> 10	7 (14)	8 (17)
Baseline PSA DT, months		
< 3	10 (20)	11 (23)
3-6	22 (45)	21 (44)
6-12	17 (35)	16 (33)

Abbreviations: DT, doubling time; GM-CSF, granulocyte-macrophage colony-stimulating factor; PSA, prostate-specific antigen.

RESULTS

Patient Population and Course of Study

Ninety-nine patients were enrolled between 2011 and 2016 at the University of Wisconsin; University of California, San Francisco; and Johns Hopkins University (Fig 1). The median age of participants was 71 years (range, 46 to 86 years). The median PSA before treatment of all patients was 4.3 ng/mL (range, 2.1 to 55.4 ng/mL; Table 1). The original accrual goal was 106 patients; however, the trial was stopped after 99 patients were enrolled given a lower attrition rate than anticipated. Of these 99, two patients were excluded from the final intention-to-treat analysis because one was subsequently determined to be ineligible and the other was not randomly assigned correctly. Among the final 97 participants, one grade 4 neutropenia event was observed (Table 2). Five grade 3 events were observed, including hypertension, syncope, neutropenia, and allergic reaction. Both cases of neutropenia were attributed to known transient effects of GM-CSF.[17] Grade 1/2 events that occurred in more than 10% of patients included injection site reactions, fatigue, flu-like symptoms, and headache. Two patients discontinued treatment because of adverse effects: one with syncope and one with an allergic reaction with tongue swelling. Adverse events were not significantly more common in the vaccine treatment arm (Table 2).

Clinical Response

The primary end point of the trial was 2-year MFS, with the development of metastases by conventional imaging used to define progression. The 2-year MFS rate was 41.8% in the vaccine arm and 42.3% in the GM-CSF arm ($P = .97$). The median MFS was 18.9 months in the vaccine arm and 18.3 months in the GM-CSF arm ($P = .14$; Fig 2A). In a prespecified analysis of patients separated with respect to

TABLE 2. Adverse Events

	Grade 2, No. (%)		Grade 3, No. (%)		Grade 4, No. (%)	
Adverse Event	**GM-CSF**	**pTVG-HP**	**GM-CSF**	**pTVG-HP**	**GM-CSF**	**pTVG-HP**
General/constitutional						
Chills	2 (4)	1 (2)				
Fatigue	2 (4)	1 (2)				
Injection site reaction	2 (4)	2 (4)				
GI						
Nausea		1 (2)				
Immune system						
Allergic reaction	3 (6)			1 (2)		
Infections						
Shingles		1 (2)				
Sinusitis		1 (2)				
Musculoskeletal						
Arthritis	2 (4)					
Generalized muscle weakness		1 (2)				
Myalgia		1 (2)				
Nervous system						
Headache	1 (2)	1 (2)				
Paresthesia		1 (2)				
Syncope				1 (2)		
Skin						
Rash		1 (2)				
Skin swelling		1 (2)				
Vascular						
Hot flashes		1 (2)				
Hypertension	1 (2)	1 (2)		2 (4)		
Laboratory investigations						
Increased ALT		1 (2)				
Increased AST		1 (2)				
Decreased ANC				1 (2)		1 (2)
Decreased WBC		1 (2)				

NOTE. Listed are the number of patients who experienced any adverse events greater than grade 1 that were determined to be at least possibly related to treatment and with the highest grade reported per patient.

Abbreviations: ANC, absolute neutrophil count; GM-CSF, granulocyte-macrophage colony-stimulating factor.

pretreatment PSA DT, the median MFS of patients with a pretreatment PSA DT < 3 months was 12.0 months in patients treated with vaccine *v* 6.1 months in patients treated with GM-CSF (hazard ratio [HR], 4.4; 95% CI, 1.2 to 16.8; $P = .028$). No differences in MFS were observed for patients with longer pretreatment PSA DT (Fig 2B).

No significant changes in PSA DT were observed. The median PSA DT pretreatment for patients treated with vaccine was 4.5 months (range, 1.5 to 11.6 months) and for patients treated with GM-CSF, 4.7 months (range, 1.1 to 11.9 months). The median on-treatment PSA DT was 5.4 months (range, 1.8 to 77.9 months) for patients treated with vaccine and 8.9 months (range, 1.6 to 77.9 months) for patients treated with GM-CSF (or a 1.3-fold change for patients treated with vaccine *v* a 1.7-fold change for patients treated with GM-CSF; $P = .08$). There were no significant differences in the fold changes detected between arms when stratified by pretreatment PSA DT. Of note, for patients with a PSA DT of less than 3 months at baseline, the median on-treatment PSA DT was 4.1 months for

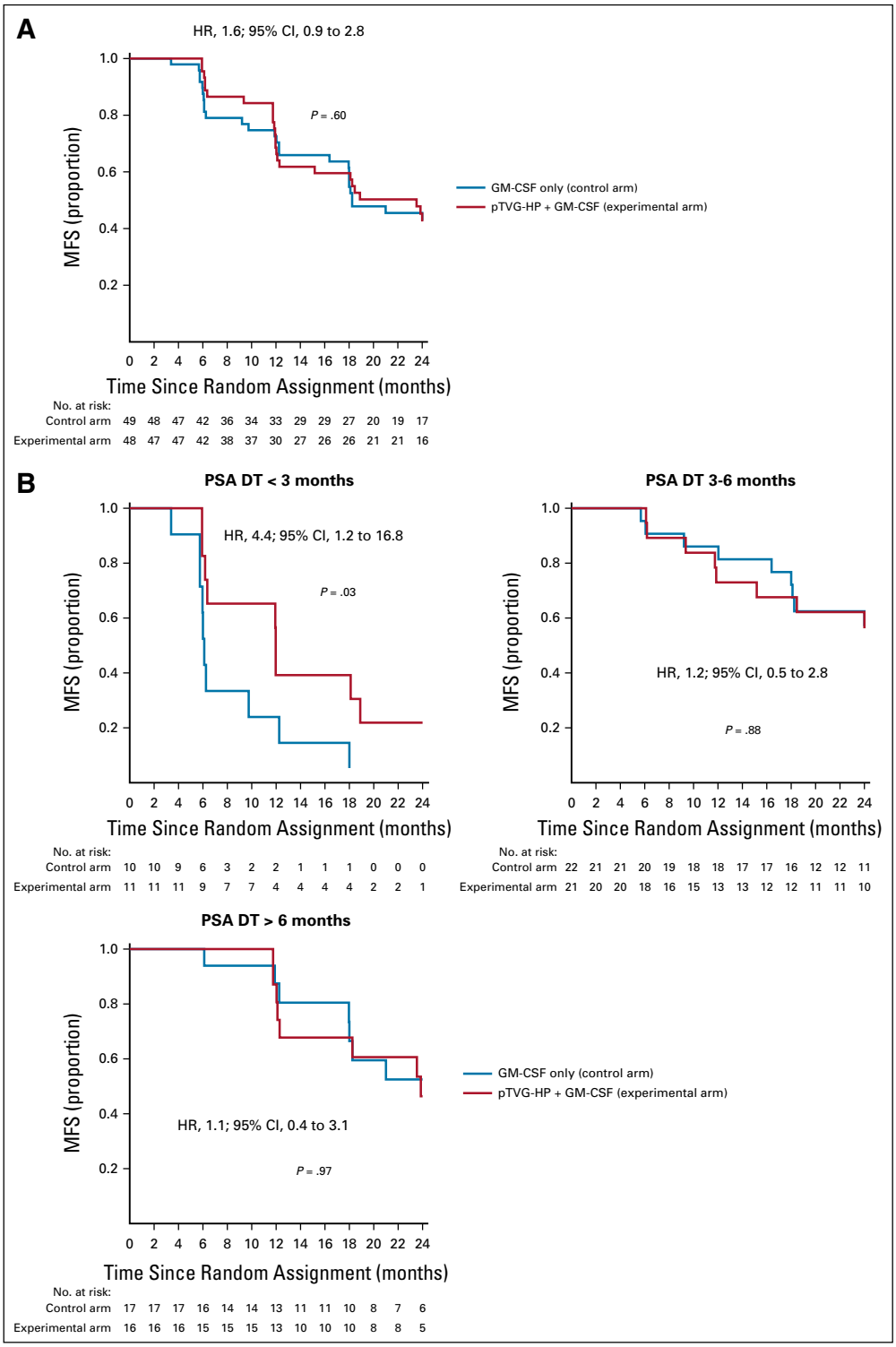

FIG 2. Metastasis-free survival (MFS). (A) Kaplan-Meier plot of time to radiographic progression. Time to radiographic regression was defined as the time from random assignment to the date of documented radiographic progression or last available follow-up date. (B) Kaplan-Meier plots of time to radiographic progression for stratification cohorts of patients with pretreatment prostate-specific antigen (PSA) doubling time (DT) of less than 3 months, 3 to 6 months, and 6 to 12 months. Comparisons made by log-rank test, with $P < .05$ considered statistically significant. GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio.

patients treated with vaccine and 2.8 months for patients treated with GM-CSF ($P = .3619$).

Immunologic Response

FluoroSpot was used to identify PAP-specific cytokine-secreting T cells from cryopreserved blood samples from 98 of 99 participants collected at baseline, 3 months, 6 months, and 1 year. As shown in Figure 3A, no significant differences in PAP-specific IFN-γ release were observed over time in vaccine-treated patients; however, the change from month 3 to month 6 was greater in vaccine-treated patients. PAP-specific multifunctional Th1-biased T cells (secreting IFN-γ, TNF-α, and granzyme B) were significantly increased at month 3 in patients who received pTVG-HP but not detectably greater at month 6 (Fig 3B).

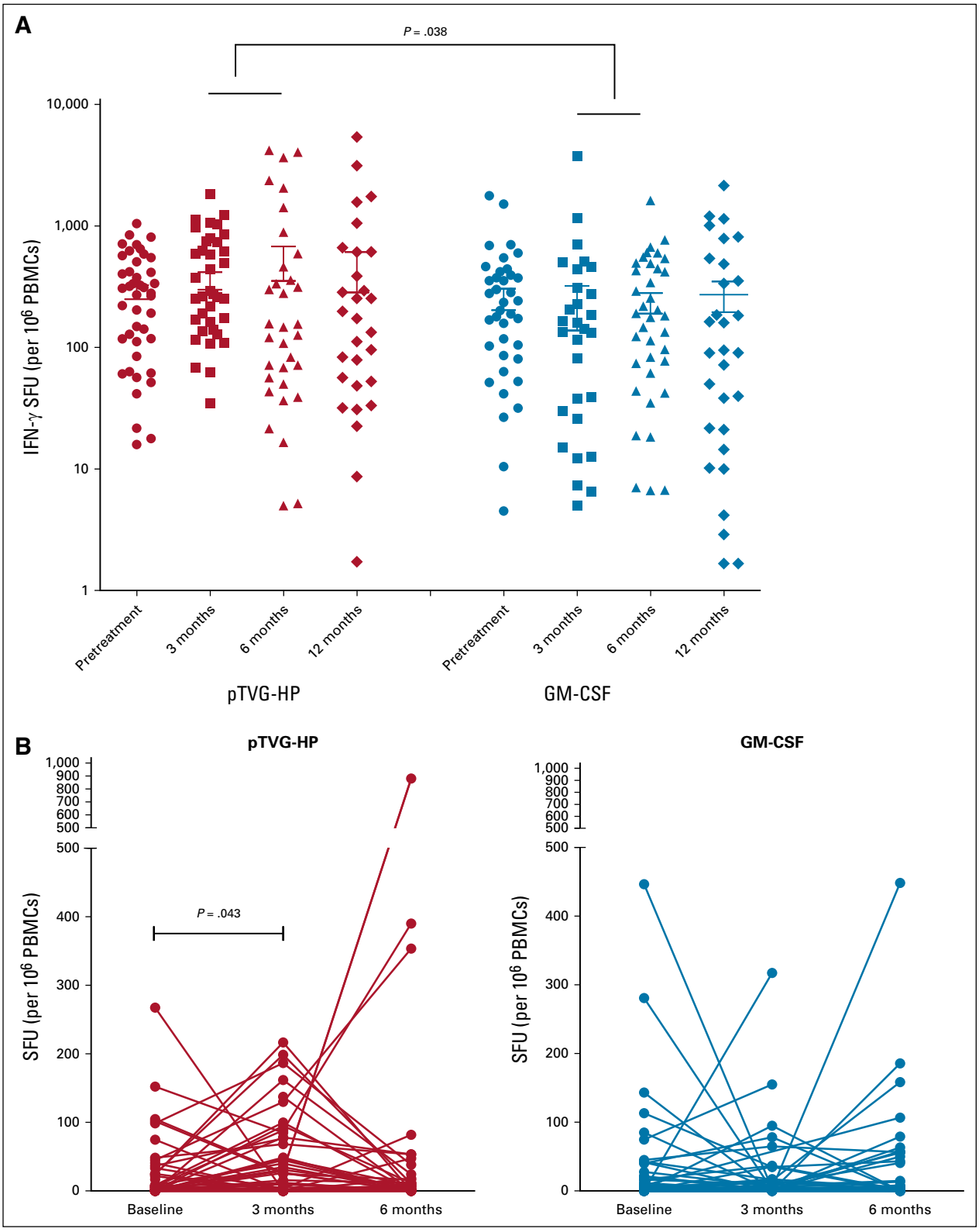

FIG 3. Immunologic response: FluoroSpot (Cellular Technology Limited, Shaker Heights, OH) analysis. Cryopreserved peripheral blood mononuclear cells (PBMCs) from patients obtained at the indicated time points were stimulated in vitro with prostatic acid phosphatase (PAP) protein and evaluated by FluoroSpot for (A) PAP-specific interferon γ (IFN-γ) secretion or (B) PAP-specific secretion of IFN-γ, tumor necrosis factor-α, and granzyme B. Comparisons within treatment arms are made by nonparametric Wilcoxon signed rank test and between arms by nonparametric Wilcoxon rank sum test. All comparisons with $P < .05$ are shown. GM-CSF, granulocyte-macrophage colony-stimulating factor; SUV, standardized uptake value.

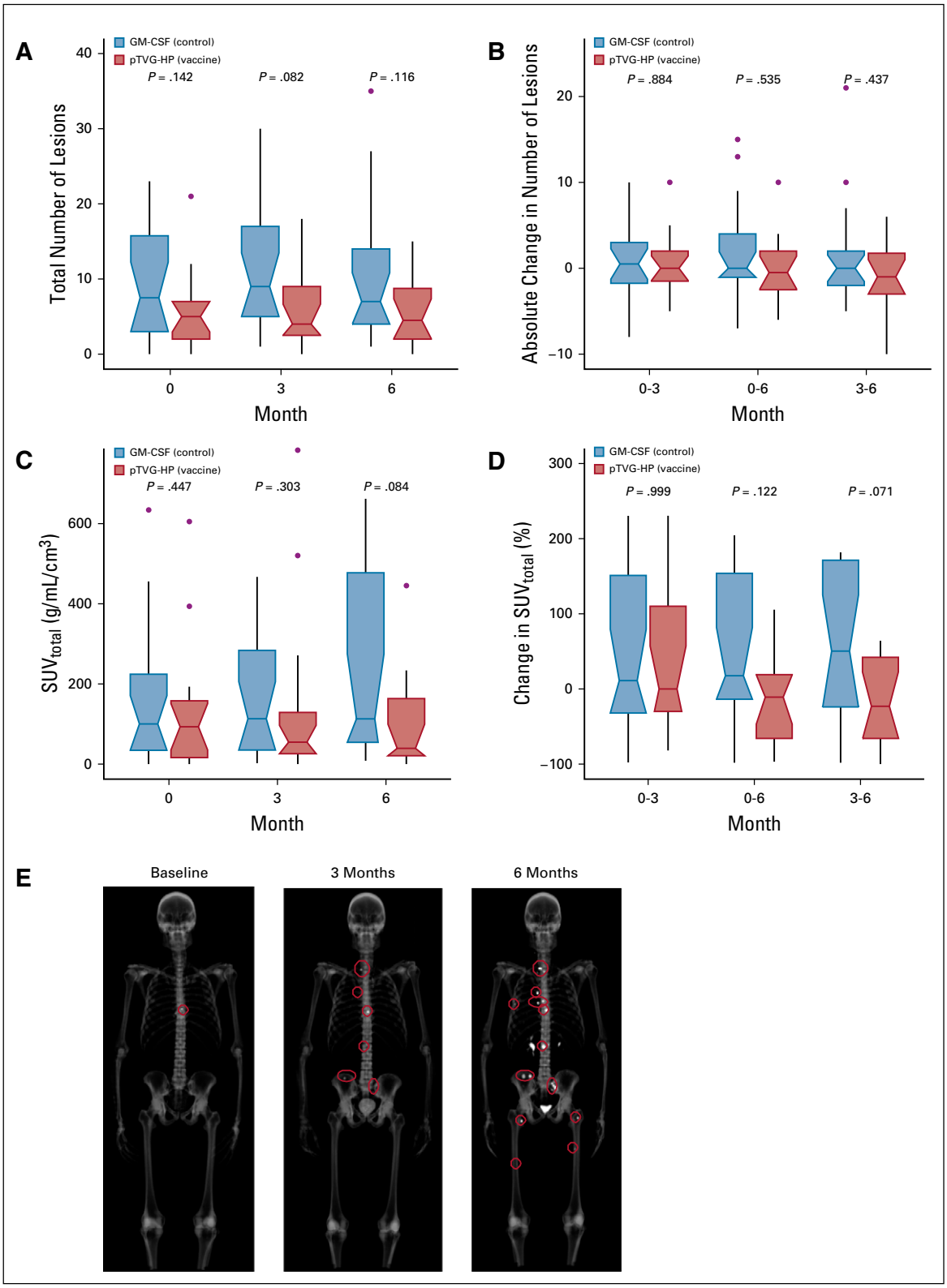

FIG 4. ^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET)/computed tomography (CT) analysis. Box and whisker plots (median and interquartile range) for the (A) total number of lesions identified at each time point by ^{18}F-NaF PET/CT, (B) numerical change in number of lesions detected between time points indicated, (C) total standardized uptake value (SUV_{total}) of identified bone lesions at each time point, and (D) percent change in SUV_{total} between the time points indicated. Comparisons were made by nonparametric Wilcoxon rank sum test. (E) Representative ^{14}F-NaF PET/CT images from one patient. GM-CSF, granulocyte-macrophage colony-stimulating factor.

QTBI

Thirty-four patients were evaluated by ^{18}F-NaF PET/CT imaging at baseline, 3 months, and 6 months. The hypothesis was that ^{18}F-NaF PET/CT would detect bone metastases not detectable by standard bone scintigraphy, and hence, this might identify patients at greater risk for progression and permit evaluation of micrometastatic lesions. The number of lesions and SUV_{total} at each time point were evaluated in blinded fashion. Thirty of 34 patients had lesions identified at baseline. Only one of the 34 patients had no lesions at any time point. At baseline, there was no statistical difference between the arms for number of lesions (P = .142; Fig 4A) or SUV_{total} (P = .447; Fig 4C). Over time, the median number of lesions detected was not statistically different between treatment arms (Fig 4B). However, the median SUV_{total} increased 50.4% (interquartile range, −23.9%-171.3%) in the GM-CSF arm and decreased 23.0% in the pTVG-HP arm (interquartile range, −67.6%-53%; P = .071) from month 3 to month 6 (Fig 4D).

DISCUSSION

Patients with rapidly rising serum PSA after definitive surgery or radiation therapy for prostate cancer are at increased risk of developing radiographic recurrence and death as a result of prostate cancer within 10 years.[3] Although androgen deprivation commonly is used, the optimal timing for initiating treatment and whether particular subsets of patients benefit from earlier treatment remain unknown.[18,19] With the advent of newer, more sensitive imaging methods, many patients currently undergo ablation of oligometastases; however, there is no evidence of long-term benefit from this approach. Many patients elect to postpone the start of androgen deprivation given its adverse effects.[19] We and others have evaluated antitumor vaccines in this stage of disease with the goal of prolonging the time to radiographic metastases and the start of androgen deprivation.[10,20] The current randomized trial was designed to determine prospectively whether pTVG-HP could delay disease progression in this setting. As expected, treatment was not associated with significant adverse events. The primary end point, difference in 2-year MFS, was not met. Median MFS was not longer in patients treated with vaccine, except in a subgroup of patients with the most rapidly progressive disease. Multifunctional Th1-biased immunity, detected by FluoroSpot, was elicited shortly after pTVG-HP immunization but was not detectable later. Exploratory studies using quantitative imaging suggested that vaccination induced subtle changes in bone metastases identified by changes in SUV_{total}. Together, these findings have implications for future studies that will evaluate antitumor vaccines for PSA-recurrent prostate cancer.

The overall MFS observed was similar to what has been previously reported in this population of patients. Specifically, Slovin et al[2] reported a median MFS of 19 months in patients with a rising PSA and DT of less than 12 months. Freedland et al[21] similarly reported a 2-year median MFS in patients with rising PSA after prostatectomy. However, as described, a planned subgroup analysis demonstrated an increase in MFS in the group of patients with the shortest pretreatment PSA DT. This was unexpected because we anticipated that a greater difference might be observed in patients with slower-growing disease. This observation suggests that the frequency of immunizations might need to be increased in the time period beyond 3 months. This is supported by the observation that PAP-specific multifunctional Th1-biased T cells were detected early at 3 months (during which time patients received vaccinations biweekly) but not at 6 months (when booster immunizations were given every 3 months). The traditional schedules used for preventive vaccines, in which a limited number of treatments are used to establish long-term memory, is likely different in the setting of cancer that expresses the target antigen, in which T cells become dysregulated or tolerized. Future trials will evaluate different booster treatment schedules.

In this trial, no significant difference was found between study arms with respect to change of PSA DT, although there was a nonsignificant trend toward increased fold change in the GM-CSF control arm (1.5-fold median change; range, 0.4- to 16.2-fold). Although changes in PSA DT have been previously reported after other treatments for this stage of disease,[4] our findings suggest that this measure of clinical effect is imperfect given the large natural variability observed in the control group.

QTBI revealed that the majority (30 of 34; 88%) of patients with PSA-recurrent prostate cancer and PSA DT of less than 1 year had evidence of bone metastases not detectable by conventional bone scintigraphy. This finding was surprising because we expected to observe these only in patients with the most rapid PSA DTs. Our intent was to determine whether QTBI with ^{18}F-NaF PET/CT imaging could detect changes in lesions over time. Although we did not observe differences in the development of new lesions, our findings suggest that pTVG-HP had a measurable effect on existing bone metastases as reflected by decreases in total disease burden (SUV_{total}) over the first 6 months. Future studies will use quantitative ^{18}F-NaF PET/CT imaging to evaluate the effect of pTVG-HP, in combination with other agents, on bone metastases.

Using IFN-γ FluoroSpot, we did not detect a substantial increase in immune response to PAP in the treatment arm relative to the control arm and found no association with longer MFS (data not shown). This was unexpected on the basis of our previous studies.[9,11] The analysis was performed with cryopreserved specimens after in vitro stimulation using a fluorescent ELISPOT method. Hence, these methodological differences may have accounted for some discrepancy with our prior results. PAP-specific multifunctional T cells, which secrete multiple cytokines,

were detected after vaccination but did not persist. This also suggests that the vaccination schedule may have been suboptimal and may require more frequent immunization beyond 12 weeks. Additional analysis is ongoing to determine whether release of other cytokines, cytolytic proteins, or detection of antigen spread[22] serve as better measures of systemic immunity and are associated with prolonged MFS.

To our knowledge, this study represents the first phase II trial conducted with a DNA vaccine that targets a tumor-associated self-antigen for the treatment of existing cancer. DNA vaccines have been perceived as less immunogenic than some other vaccine approaches. Notwithstanding, a previous phase II trial evaluated a DNA vaccine that targeted human papillomavirus 16 and 18 E6 and E7 proteins as treatment of premalignant cervical intraepithelial neoplasia.[23] That trial confirmed that DNA vaccines can elicit therapeutic immunity in humans. Our current trial also suggests that DNA vaccines can elicit biologic effects in established tumors but may be insufficient as single agents to mediate meaningful changes for the majority of patients. We have previously reported that the combination of vaccination with PD-1 blockade to prevent tumor-mediated dysregulation of vaccine-activated $CD8^+$ T cells that express PD-1 results in PSA declines and objective tumor changes.[12] In the future, we believe that combination therapies will be required. A clinical trial that is evaluating pTVG-HP with PD-1 blockade in patients with castration-sensitive, PSA-recurrent prostate cancer is currently under way (ClinicalTrials.gov identifier: NCT03600350).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01701.

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Provision of study material or patients: Lawrence Fong, Emmanuel S. Antonarakis, Glenn Liu
Collection and assembly of data: Laura E. Johnson, Lawrence Fong, Emmanuel S. Antonarakis, Ellen Wargowski, Robert Jeraj, Glenn Liu
Data analysis and interpretation: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Trial of a DNA Vaccine Encoding Prostatic Acid Phosphatase (pTVG-HP [MVI-816]) in Patients With Progressive, Nonmetastatic, Castration-Sensitive Prostate Cancer

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