Clinical Cancer Research

Sequencing of Sipuleucel-T and Androgen Deprivation Therapy in Men with Hormone-Sensitive Biochemically Recurrent Prostate Cancer: A Phase II Randomized Trial

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Abstract

Purpose: STAND, a randomized, phase II, open-label trial (NCT01431391), assessed sequencing of sipuleucel-T (an autologous cellular immunotherapy) with androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC) patients at high risk for metastasis.

Experimental Design: Men with BRPC following prostatectomy and/or radiotherapy, a PSA doubling time ≤12 months, and no metastasis were enrolled. Patients were randomized (34/arm) to sipuleucel-T followed by ADT (started 2 weeks after sipuleucel-T completion), or ADT followed by sipuleucel-T (started 12 weeks after ADT initiation); ADT continued for 12 months in both arms. The primary endpoint was PA2024-specific T-cell response [enzyme-linked immunospot (ELISPOT)] over time.

Results: PA2024-specific ELISPOT responses over time were similar between groups, except at week 6, where responses were higher with sipuleucel-T→ADT versus ADT→sipuleucel-T ($P = 0.013$). PA2024-specific T-cell proliferation responses, averaged across time points, were approximately 2-fold higher with sipuleucel-T→ADT versus ADT→sipuleucel-T ($P = 0.001$). PA2024-specific cellular and humoral responses and prostatic acid phosphatase–specific humoral responses increased significantly versus baseline ($P < 0.001$) and were maintained for 24 months (both arms). Median time-to-PSA recurrence was similar between arms (21.8 vs. 22.6 months, $P = 0.357$). Development of a PA2024-specific humoral response correlated with prolonged time-to-PSA progression (HR, 0.22; 95% CI, 0.08–0.67; $P = 0.007$). Sipuleucel-T with ADT was generally well tolerated.

Conclusions: Sipuleucel-T→ADT appears to induce greater antitumor immune responses than the reverse sequence. These results warrant further investigation to determine whether this sequence leads to improved clinical outcomes, as well as the independent contribution of ADT alone in terms of immune activation. *Clin Cancer Res; 23(10); 2451–9. ©2016 AACR.*

Introduction

Following primary treatment for localized prostate cancer, approximately 20% to 40% of patients will develop biochemically recurrent prostate cancer (BRPC; ref. 1). Many of these men will eventually develop metastatic progression, particularly those with a PSA doubling time (PSADT) <12 months (2). Androgen deprivation therapy (ADT), commonly used to delay disease progression in men with BRPC (3), has not been shown to extend overall survival (4). Hence, there remains a need to improve outcomes in these patients. ADT has been shown to augment

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Translational Relevance

The findings of STAND, a randomized, phase II, open-label trial that assessed the effect of treatment sequence with sipuleucel-T (an autologous cellular immunotherapy) and androgen deprivation therapy (ADT) on immune responses, may inform the design of future clinical trials and shape clinical practice across a broad spectrum of prostate cancer care. In biochemically recurrent prostate cancer (BRPC) patients at high risk for metastasis in STAND, T-cell immune responses were generally greater when sipuleucel-T was administered prior to ADT compared with the reverse sequence. After treatment, cellular and humoral responses against target antigens were increased significantly versus baseline and remained for 24 months (both arms). Further investigation is needed to determine whether this sequence leads to improved clinical outcomes. However, in BRPC and perhaps in advanced hormone-sensitive prostate cancer settings, future research on the combined use of immunotherapy and androgen-directed therapies may be optimized by sequencing sipuleucel-T prior to androgen deprivation.

antitumor immune responses in animal models (5–7) and in patients with prostate cancer (6, 8–10), especially when combined with immunotherapies (11). Several (but not all) studies have shown superior immunologic and antitumor responses when immunotherapy was administered prior to ADT (7, 12, 13). However, although there is a clear rationale for combining ADT with immunologic therapies in men with prostate cancer (14), optimal sequencing remains unresolved.

Sipuleucel-T, an autologous cellular immunotherapy targeting prostatic acid phosphatase (PAP), is FDA approved for treating asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (mCRPC; ref. 15). In the phase III, IMPACT trial (NCT01133704), sipuleucel-T significantly reduced the risk of death by 22% versus control in men with mCRPC (16). In localized prostate cancer, sipuleucel-T induces T-cell and B-cell trafficking to the tumor margin when administered prior to prostatectomy (17). Sipuleucel-T also elicits sustained immune responses in patients with BRPC (18).

We conducted a randomized, phase II trial (STAND) combining ADT with sipuleucel-T (in alternate sequences) in patients with BRPC at high risk of metastatic progression. The primary endpoint was a comparison of cellular immune responses between arms, as measured by antigen-specific IFNγ enzyme-linked immunospot (ELISPOT) response. This endpoint was chosen as possibly the most relevant assessment of the ability of ADT to augment the mobilization of a T-cell–mediated antitumor immune response initiated by sipuleucel-T (19). The identification of a superior sequence could inform the design of future trials. A variety of other exploratory measures of immune response and clinical outcome were also assessed.

Materials and Methods

Patients

Eligible men aged ≥18 years had confirmed prostatic adenocarcinoma previously treated with local therapy (prostatectomy and/or radiotherapy), a rising PSA, defined as two consecutive values >0.2 ng/mL taken ≥3 weeks apart (after primary prostatectomy) or two rising values ≥2.0 ng/mL above the PSA nadir (after primary radiotherapy), a PSADT ≤12 months (using ≥3 PSA values each collected ≥4 weeks apart), plasma testosterone ≥200 ng/dL, and nonmetastatic disease (technetium-99 bone scans and CT scans). Key exclusion criteria included inadequate end-organ function, requirement for systemic corticosteroids or immunosuppressive therapies, prior sipuleucel-T, prior ADT (neoadjuvant/adjuvant setting) for ≥6 months or within 6 months of registration, or prior experimental immunotherapies within ≤1 year. All patients provided written informed consent.

Study design and treatment

STAND (NCT01431391) was a multicenter, randomized, open-label, phase II study conducted at 11 U.S. centers. Sixty-eight patients were randomized (using a computer-aided permuted block scheme) 1:1 to two groups, sipuleucel-T→ADT or ADT→sipuleucel-T (Supplementary Fig. S1). Stratification was based on PSADT (≤3 months vs. >3 to ≤12 months) and primary treatment (prostatectomy vs. radiotherapy vs. both). The study was compliant with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from central or local ethics committees at all centers. All national, state, and local laws of appropriate regulatory authorities were followed.

In the sipuleucel-T→ADT group, patients received three sipuleucel-T intravenous infusions (one every 2 weeks), followed by 12 months of ADT [45 mg leuprolide acetate (Eligard) subcutaneous injection every 6 months, for two doses] starting 2 weeks after the third sipuleucel-T infusion. In the ADT→sipuleucel-T group, patients received 12 months of ADT with sipuleucel-T treatment beginning 12 weeks after the first leuprolide injection. For each sipuleucel-T treatment, patients underwent a standard 1.5 to 2.0 blood volume leukapheresis and received the sipuleucel-T infusion approximately 3 days later (16). Blood sampling times are shown in Supplementary Fig. S1. Final follow-up visits were at months 27 (sipuleucel-T→ADT) and 24 (ADT→sipuleucel-T).

Endpoints

The primary endpoint was PA2024-specific T-cell response over time assessed by IFNγ ELISPOT, a functional assay. PA2024, the immunogen used to manufacture sipuleucel-T, is a recombinant fusion protein of PAP and granulocyte macrophage colony-stimulating factor. Secondary protocol–specified endpoints included additional immune response assessments (PAP-specific ELISPOT, PA2024- and PAP-specific T-cell proliferation, PA2024 and PAP humoral responses), PSA assessments, safety, and product characterization (including APC activation, a measure of sipuleucel-T potency). Several *post hoc* endpoints were evaluated: humoral responses to secondary antigens (antigen spread), time-to-testosterone recovery, incidence of metastases, time-to-next anticancer intervention, correlation between immune response and time-to-PSA recurrence, comparison of APC activation with IMPACT (16), and comparison of humoral antigen spread with IMPACT and STAMP (NCT01487863; ref. 20).

Assessments

All PA2024-specific and PAP-specific cellular and humoral immune parameters were assessed as described previously

(19). Immune responses were defined as responses >95th percentile of baseline values. Humoral antigen spread was assessed as described previously (21).

The protocol-defined PSA recurrence endpoint (Supplementary Material; ref. 22) only captured a limited number of events. Thus, a *post hoc* definition, more consistent with current clinical practice, was also used, that is, the first of at least two serial rises in PSA ($\geq$2 weeks apart) with a PSA $\geq$0.2 ng/mL (prior prostatectomy; ref. 23) or $\geq$2.0 ng/mL (prior radiotherapy alone; ref. 24) measured from the first ADT injection. Time-to-PSA recurrence starting from the time of testosterone recovery ($\geq$175 ng/dL) was also assessed. Details of time-to-testosterone recovery, time-to-next anticancer treatment, incidence of metastases, and evaluation of sipuleucel-T product parameters are in the Supplementary Material.

Safety assessments (Supplementary Material) were conducted at every study visit. These included adverse event (AE) monitoring (NCI's Common Terminology Criteria for AEs, version 4.03) in all patients receiving at least one leukapheresis.

Statistical analyses

For the primary endpoint, 27 patients per arm provide 90% power to detect a 2.5-fold difference in mean PA2024 ELISPOT counts between arms with a two-sided 0.05-level *t* test. Allowing for drop-outs and patients not receiving three sipuleucel-T infusions, the target enrolment was 60 patients. The immune and clinical response study populations included all randomized patients receiving three sipuleucel-T infusions. The safety population was all patients undergoing at least one leukapheresis. Data were analyzed using SAS V9.3 software.

Immune responses were analyzed with a repeated measures model using the variables as fixed effects: treatment allocation, visit time point, and interaction between treatment and visit (to determine whether a difference in treatment effect was observed at specific time points; Supplementary Material). Comparison of the arms at specific time points and comparison of postbaseline versus baseline response were evaluated using a linear contrast statement if the *P* value for the treatment-by-visit interaction was <0.05. The rank of PA2024 IFNγ ELISPOT counts was used for the primary analysis. Immune responses were evaluated categorically (occurrence of a response or not, with response defined as >95th percentile of baseline values prior to first leukapheresis). Comparison between arms was performed using a Fisher exact test for a response at any time point postbaseline and by time point. Humoral antigen spread was statistically analyzed as described previously (21).

Time-to-event endpoints were analyzed using the Kaplan–Meier method and the log-rank test. A Cox regression analysis with treatment group as a predictor variable was used to compute HR (ADT→sipuleucel-T vs. sipuleucel-T→ADT) and 95% confidence interval (CI). Statistical analyses of cumulative product characteristics (including APC activation) are shown in the Supplementary Material.

Correlations between categorical immune response endpoints and time-to-PSA recurrence were evaluated using a Cox regression model (pooled over arms), with each categorical immune response variable considered as a predictor variable in the model. Safety data were summarized descriptively.

For comparison of APC activation to IMPACT data (16) at infusions 1, 2, and 3, a repeated measures model was used to compare the natural log-transformed values (terms for study, infusion number, and study by infusion number interaction). A *t* test was used to compare the natural log-transformed cumulative APC activation values for the comparison of the cumulative values (summed across all infusions for each patient). Humoral antigen spread magnitudes from STAND, STAMP (20), and IMPACT (16) were compared between studies for secondary antigens: ERAS, KLK2, KRAS, LGALS3, and LGALS8. Pairwise *t* tests between data ($\log_2$ difference relative to baseline) from all three trials were performed to evaluate differences between study pairs. As different methods for ELISPOT, T-cell proliferation, and humoral responses were used in IMPACT versus STAND, no comparisons were made between studies for these endpoints.

Results

Patients

From September 2011 to August 2012, 68 patients were enrolled: 34 were randomized to each arm (Fig. 1). All patients received three sipuleucel-T infusions. Almost all received 12 months of ADT (sipuleucel-T→ADT: 33/34; ADT→sipuleucel-T: 32/34). Three men received only 6 months of ADT (two refused the second dose; one changed therapy due to disease progression). Baseline patient characteristics were well balanced between arms (Table 1).

Immune responses

Analysis of the primary endpoint showed mean PA2024-specific ELISPOT counts (averaged over time) were numerically but not statistically higher with sipuleucel-T→ADT compared with the alternative sequence [47 spots (sipuleucel-T→ADT) vs. 25 spots (ADT→sipuleucel-T); $P = 0.235$]. At 6 weeks following the third sipuleucel-T infusion, mean PA2024-specific ELISPOT counts were significantly higher with sipuleucel-T→ADT versus ADT→sipuleucel-T (71 vs. 16 spots, $P = 0.013$). In both arms, PA2024-specific ELISPOT counts were significantly increased versus baseline at each postbaseline visit through month 24 ($P < 0.001$; Fig. 2A). The percentage of PA2024-specific ELISPOT responders was similar in both arms [sipuleucel-T→ADT: 29/33 (88%); ADT→sipuleucel-T: 29/34 (85%); $P = 1.00$].

PA2024-specific T-cell proliferation responses, averaged across all time points, were approximately 2-fold higher with sipuleucel-T→ADT versus ADT→sipuleucel-T ($P = 0.001$; Fig. 2B). At all time points through month 24, PA2024-specific T-cell proliferation responses were significantly higher versus baseline in both arms ($P < 0.001$). Nearly all patients developed PA2024-specific T-cell proliferation responses [sipuleucel-T→ADT: 30/32 (94%); ADT→sipuleucel-T: 33/34 (97%); $P = 0.61$].

PA2024 antibody titers after sipuleucel-T treatment were 25 times higher on average versus baseline in both arms ($P < 0.001$; Fig. 2C), and similar between arms, remaining significantly elevated through 24 months. The number of PA2024 antibody responders was 30/34 (88%; sipuleucel-T→ADT) and 33/34 (97%; ADT→sipuleucel-T; $P = 0.356$).

PAP-specific IFNγ ELISPOT and T-cell proliferation responses did not change significantly posttreatment versus baseline [$P = 0.22$ (ELISPOT); $P = 0.39$ (T-cell proliferation)] and were not different between arms [$P = 0.63$ (ELISPOT); $P = 0.70$ (T-cell proliferation); data not shown]. Anti-PAP antibody titers were

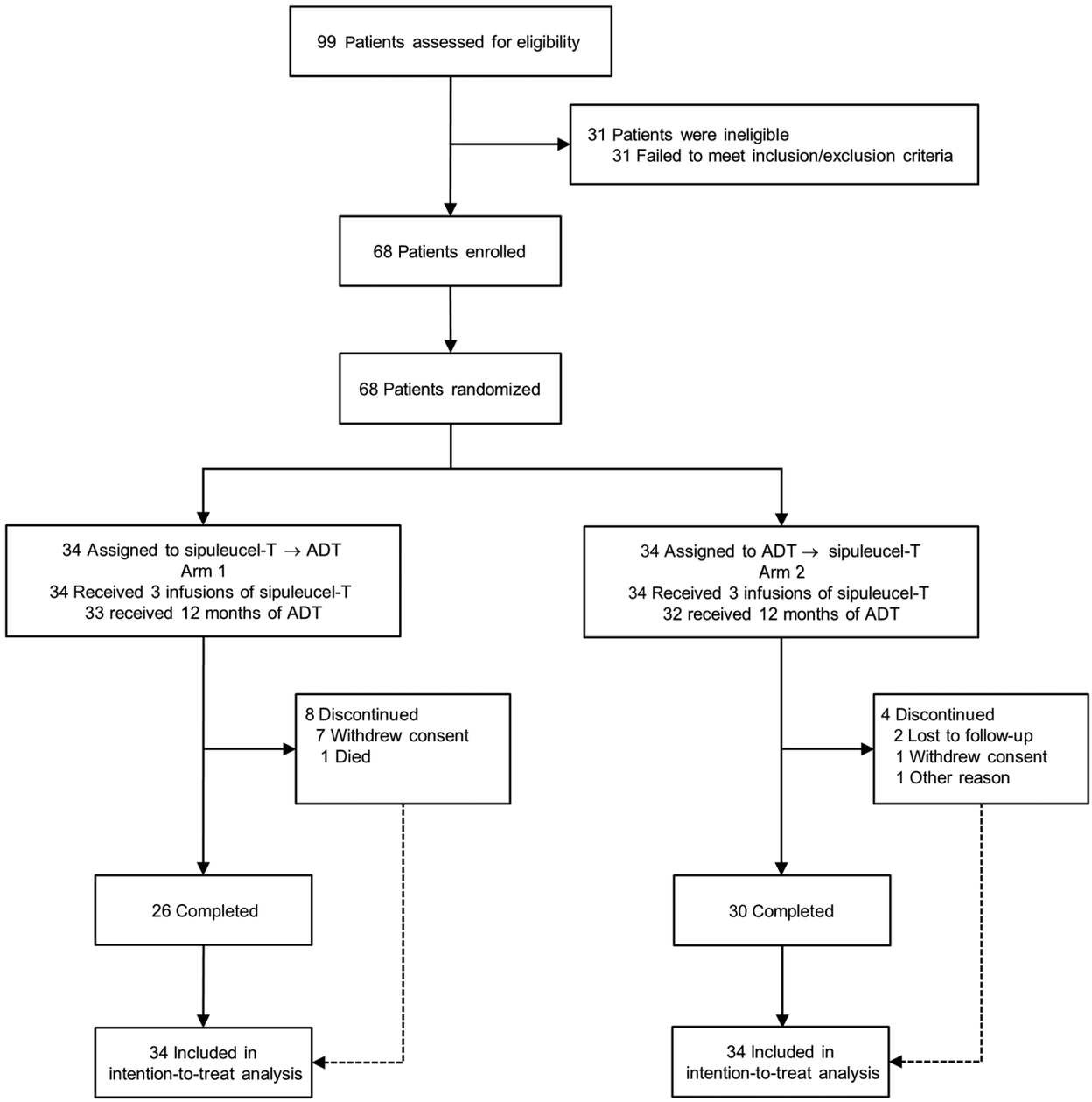

Figure 1.
Patient disposition.

significantly higher following sipuleucel-T treatment versus baseline (~12 times higher on average vs. baseline; $P < 0.001$) and remained elevated through 24 months in both arms, with no differences between arms (data not shown). The overall percentage of patients with PAP-specific humoral responses was 82%.

There was no correlation of baseline PSA with the magnitude of immune response (by T-cell proliferation, IFNγ ELISPOT, and antibody titers) to both PAP and PA2024, adjusting for treatment arm and visit time point, and treatment by visit interaction (data not shown).

Clinical outcomes

Five (15%) and 11 (32%) PSA recurrence events (protocol-defined analysis) occurred with sipuleucel-T→ADT and ADT→sipuleucel-T, respectively (HR, 2.26; 95% CI, 0.78–6.49; $P = 0.121$); median time-to-PSA progression was not reached in either arm. Median time-to-PSA recurrence (*post hoc* definition) from first ADT injection was similar for sipuleucel-T→ADT and ADT→sipuleucel-T (21.8 and 22.6 months, respectively, $P = 0.357$; Fig. 3A). PSA recurrence occurred in 71% of patients in each arm after a median follow-up of 26.8 months. No differences

Table 1. Patient baseline demographics and disease characteristics

	Sipuleucel-T→ADT ($N = 34$)	ADT→Sipuleucel-T ($N = 34$)
Median age (range), years	64 (48–90)	67 (52–79)
Gleason sum, *n* (%)		
≥8	8 (23.5)	9 (26.5)
≤7	26 (76.5)	25 (73.5)
ECOG PS, *n* (%)		
0	33 (97.1)	34 (100.0)
1	1 (2.9)	0
Median time from initial PC diagnosis to randomization (range), years	5.3 (0.5–15.8)	4.5 (0.6–14.2)
Median serum PSA (IQR), ng/mL	3.5 (1.4–7.8)	2.3 (1.1–8.2)
Median PSADT (IQR), months	5.0 (3.3–7.2)	5.1 (2.9–8.7)
PSADT, *n* (%)		
≤3 months	9 (26.5)	8 (23.5)
>3 to ≤12 months	25 (73.5)	26 (76.5)
Primary treatment, *n* (%)		
Radical prostatectomy alone	5 (14.7)	5 (14.7)
Radiation alone	6 (17.6)	4 (11.8)
Radical prostatectomy + radiation	23 (67.6)	25 (73.5)
Median time from radical prostatectomy to randomization (range), years	5.2 (0.4–15.7)	4.2 (0.4–13.2)
Median time from radiation to randomization (range), years	2.9 (0.4–12.3)	2.5 (0.6–14.0)
Prior adjuvant/neoadjuvant hormone therapy, *n* (%)	9 (26.5)	13 (38.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PC, prostate cancer.

were seen between arms in time-to-PSA recurrence after testosterone recovery to ≥175 ng/dL ($P = 0.151$, Supplementary Fig. S2). Of the 48 patients with testosterone recovery, three men (6%; $n = 1$ sipuleucel-T→ADT; $n = 2$ ADT→sipuleucel-T) maintained undetectable PSA levels at the end of the study. In particular, two of these patients had prolonged periods of undetectable PSA lasting more than 7.6, and 17.5 months following testosterone recovery.

There were no differences between arms in time-to-testosterone recovery (≥175 ng/dL; Supplementary Fig. S3), time-to next anticancer intervention (Supplementary Fig. S4), or the rate of metastatic progression (Supplementary Material).

Correlative analyses

When combining data across arms, PA2024-specific antibody responses were significantly correlated with a longer time-to-PSA progression (HR, 0.22; 95% CI, 0.08–0.67; $P = 0.007$; Fig. 3B). Nonsignificant trends were observed for PA2024-specific ELISPOT and proliferation responses correlating with longer time-to-PSA recurrence (Fig. 3B). No correlations between PAP-specific cellular or humoral responses and time-to-PSA recurrence were observed (data not shown).

Safety and tolerability

Sipuleucel-T and ADT were generally tolerated well in both arms, with no new safety signals. AEs were comparable between arms (Supplementary Table S1). One patient receiving sipuleucel-T→ADT died from endocarditis and sepsis 7 months after his last sipuleucel-T infusion (considered unrelated to treatment).

Comparison of antigen spread and APC activation with castration-resistant prostate cancer (IMPACT and STAMP)

Following sipuleucel-T administration, humoral antigen spread (IgG responses to secondary antigens: E-RAS, KLK2, K-RAS, LGALS3, and LGALS8) was similar between arms at weeks 2, 6, 12, and months 6, 9, and 12 (all $P > 0.25$; data not shown). The magnitude of IgG responses at week 2 to each antigen in STAND (BRPC patients) was significantly higher than in two prior trials [IMPACT (16) and STAMP (20), mCRPC patients; $P < 0.01$ or $P \leq 0.001$ for E-RAS, KLK2, K-RAS, LGALS3, and LGALS8; Supplementary Fig. S5].

There were no significant differences between arms in sipuleucel-T product parameters (Supplementary Fig. S6). The magnitude of APC activation in STAND was higher than in the pivotal phase III IMPACT trial (Supplementary Fig. S7; ref. 16). APC activation values were 24%, 43%, and 41% higher on average in STAND versus IMPACT for infusions 1, 2, and 3, respectively (all $P < 0.001$). The ratio of cumulative APC activation across all infusions in STAND was greater than in IMPACT (ratio of geometric means 1.37; 95% CI, 1.27–1.48; $P < 0.001$).

Discussion

Immune response parameters that best correlate with clinical outcomes are of particular interest for immunotherapies like sipuleucel-T that improve long-term overall survival without affecting proximal endpoints of disease progression. To date, clinically meaningful immune response endpoints have not been definitively established and represent an area of active research. However, there is some evidence with sipuleucel-T in mCRPC patients that suggests that immune responses may be relevant to clinical efficacy. Exploratory analyses of the phase III IMPACT study showed that at least one postbaseline immune response to PA2024 or PAP (i.e., IFNγ ELISPOT, T-cell proliferation response, or antibody responses) was significantly correlated with overall survival (19). The strongest correlation was seen between PA2024 antibody responses and overall survival (19). Moreover, immune responses to secondary tumor antigens (antigen spread) induced by sipuleucel-T were also significantly correlated with overall survival (21).

STAND, a randomized, phase II trial, provided an opportunity to further explore the utility of different measures of cellular and humoral immunity in an earlier disease setting. PA2024-specifc ELISPOT was chosen as the primary endpoint based on the understanding of immune monitoring at the time of trial design.

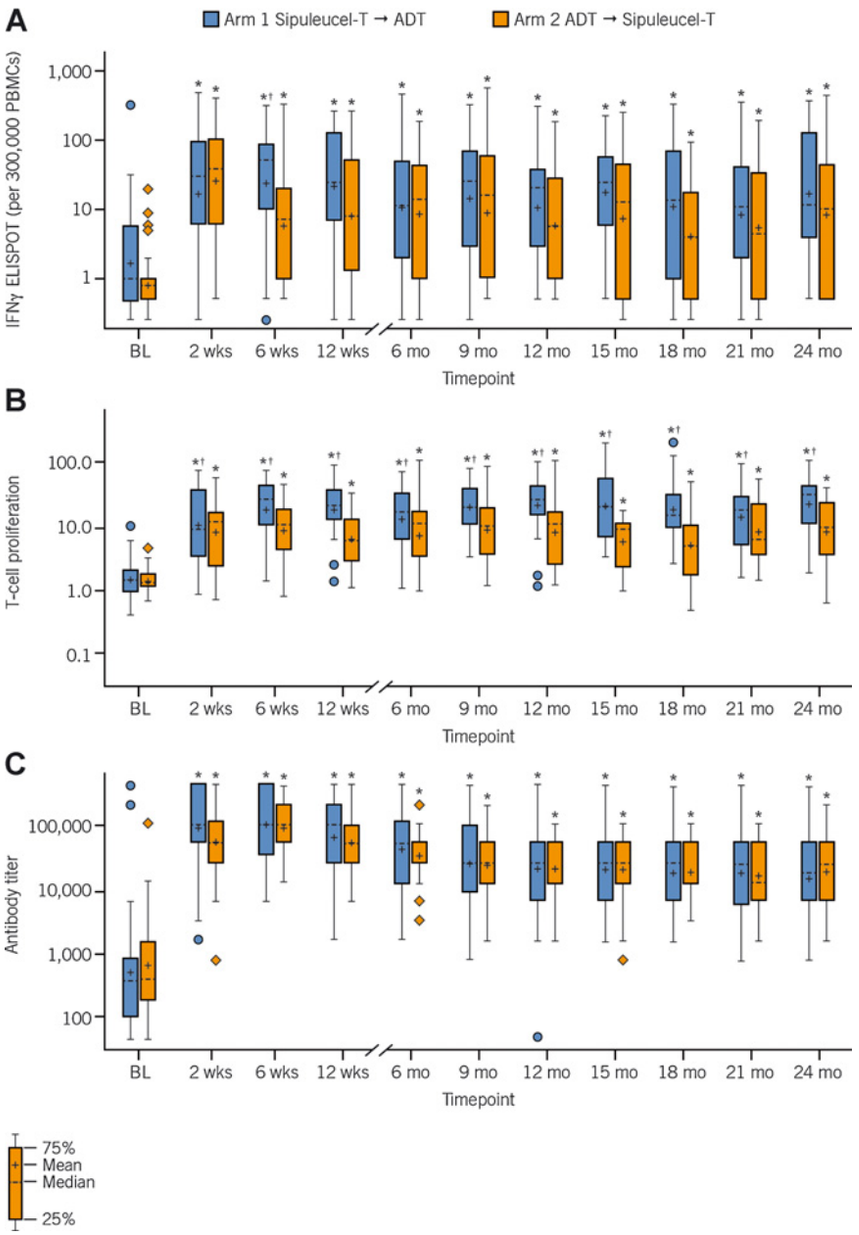

Figure 2.
PA2024 antigen-specific immune responses to sipuleucel-T.

	P value from repeated measures model		
	Treatment	**Visit**	**Treatment by visit interaction**
ELISPOT (A)	0.235	<0.001	0.047
Proliferation (B)	0.001	<0.001	0.022
Humoral (C)	0.976	<0.001	0.636

Small circles and diamonds show outliers. **A,** PA2024 T cell IFNγ ELISPOT count; *, $P < 0.001$ versus baseline at all time points in both arms; †, $P = 0.013$. **B,** PA2024 antigen-specific T-cell proliferation responses (response measured as stimulation index); *, $P < 0.001$ versus baseline for all time points in both arms; †, $P < 0.001$ sipuleucel-T→ADT versus ADT→sipuleucel-T; responses in the sipuleucel-T→ADT arm were approximately 2-fold higher versus the ADT→sipuleucel-T arm. Stimulation index is the ratio of tritiated thymidine incorporation in antigen-treated T cells versus controls. **C,** The amount of antigen-specific antibodies in serum was expressed as a reciprocal of the last dilution that yielded a signal equivalent to the assay control. PA2024 antibody titer responses (IgG + IgM); *, $P < 0.001$ versus baseline through month 24 in both arms. Patient numbers per arm were 19 to 33 (IFNγ ELISPOT T-cell immune responses), 16 to 31 (T-cell proliferation), and 14 to 33 (PA2024 antibody titer). BL, baseline; IgM, immunoglobulin M; mo, months; PBMC, peripheral blood mononuclear cell; wks, weeks.

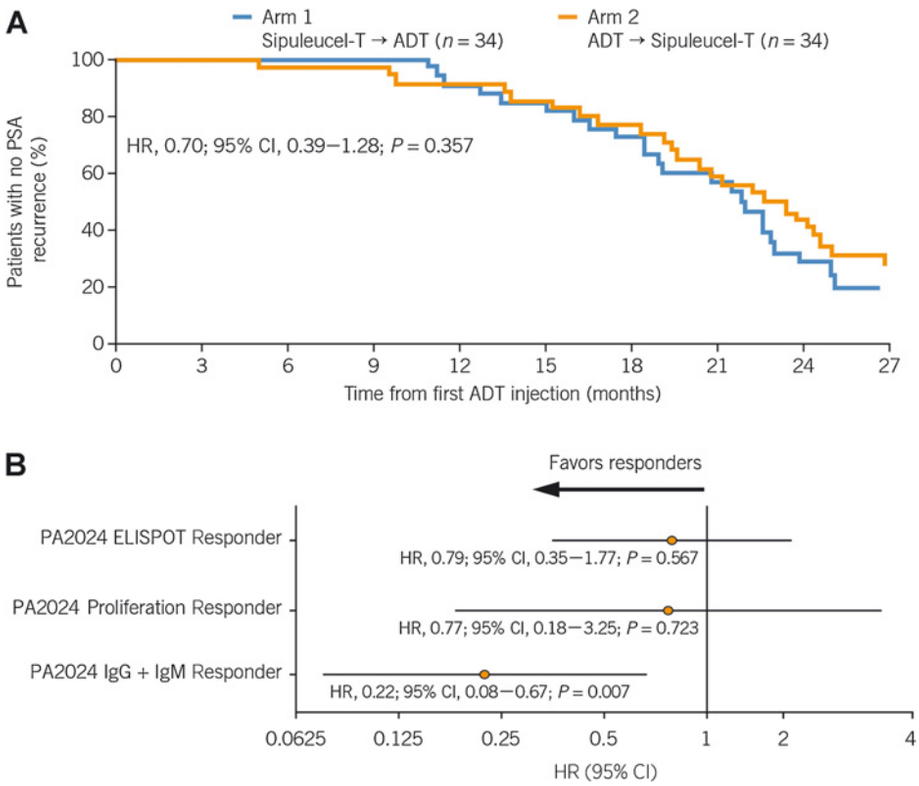

Figure 3.

A and **B,** Time-to-PSA progression* (**A**), and correlations between PA2024-specific immune responses and time-to-PSA progression* (**B**). *Defined as the first of two consecutive PSA measures ≥2 weeks apart > nadir and ≥2.0 ng/mL for radiation alone, ≥0.2 ng/mL for radical prostatectomy, measured from the day of the first ADT injection. **B,** data from both arms were combined and 58 to 68 patients were included in the analyses. A patient was defined as a PA2024 ELISPOT responder if they had a postbaseline count >18. A patient was defined as a PA2024 proliferation responder if they had a postbaseline stimulation index >5.0. A patient was defined as a PA2024 IgG + IgM responder if they had a postbaseline antibody titer ≥25,600. IgM, immunoglobulin M; PA2024, a recombinant protein comprising PAP fused to granulocyte macrophage colony-stimulating factor.

In STAND, although the primary endpoint was not statistically different between treatment arms, there was evidence that sipuleucel-T followed by ADT appears to induce greater PA2024-specific cellular immune responses than ADT→sipuleucel-T in men with hormone-sensitive BRPC. PA2024-specific T-cell responses as measured by IFNγ ELISPOT did not differ significantly between arms over time but were greater in the sipuleucel-T→ADT arm at 8 of 10 posttreatment time points. PA2024-specific T-cell proliferation, which was greater in the sipuleucel-T→ADT sequence at every measured time point, was, on average, approximately 2-fold higher. These results are in broad agreement with the ELISPOT data.

The findings of this study are consistent with preclinical prostate cancer models (7, 12) and a small randomized trial involving men with nonmetastatic castrate-resistant prostate cancer, in which survival was longer in patients vaccinated with a PSA-encoding poxviral vaccine prior to second-line ADT (nilutamide) versus those receiving ADT prior to vaccination (13).

In STAND, both sequences resulted in similarly robust and sustained PA2024 cellular responses, PA2024 and PAP humoral responses, and humoral antigen spread to secondary antigens. STAND was also the first trial to demonstrate long-term antitumor immunity lasting for 2 years following sipuleucel-T administration. Sipuleucel-T combined with ADT (in either sequence) was generally well tolerated, with no new emerging toxicities.

Low cellular immune responses to PAP, a self-antigen (25), were not unexpected because activated effector T cells might be expected to concentrate at the tumor site or in lymph nodes, not in the blood compartment from which samples were taken. However, antibodies circulate in the blood, and the observation that sipuleucel-T induced strong PAP-specific humoral responses in both arms of STAND, was an important finding that suggests the ability of sipuleucel-T to break humoral immune tolerance.

Biologically, using cancer immunotherapy earlier is logical because immunotherapy may be more effective when tumor burden is low (26) and the immune system is more intact (27). As tumors progress, the microenvironment becomes increasingly resistant to an immune response (28). An exploratory analysis of IMPACT suggested greater survival benefit from sipuleucel-T when given to patients with lower PSA values (29). Indeed, exploratory analyses in STAND support the notion that immune responses to sipuleucel-T may be greater when administered in less-advanced disease states as cumulative APC activation across the three doses of sipuleucel-T (a measure of product potency and immune activation) was significantly higher in STAND versus IMPACT (16). Although such studies must be regarded as hypothesis generating, this observation is noteworthy as higher cumulative APC activation has been shown to significantly correlate with survival in mCRPC (19). With the same measure of caution when comparing across studies, it can be noted that the magnitude of IgG responses to secondary antigens (i.e., antigen spread) was higher in STAND than in mCRPC patients from IMPACT (16) and STAMP (20). Importantly, antibody responses to certain secondary antigens (e.g., LGALS3 and PSA), and the breadth of IgG responses to multiple key secondary antigens with biologic relevance in cancer, were significantly correlated with survival in IMPACT (21). Collectively, the potentially augmented immune responses (cumulative APC activation and antigen spread) in STAND compared with trials in mCRPC patients may reflect either the earlier disease stage in STAND (BRPC) or could be due to the ADT in STAND, which, itself, may act as an immune adjuvant.

STAND had several limitations. First, it was powered to detect differences in PA2024-specific IFNγ ELISPOT responses, which may or may not have been the most relevant immune endpoint for assessing whether timing of ADT could augment sipuleucel-T–induced antitumor responses. STAND was also not powered to compare clinically meaningful endpoints, such as time-to-PSA progression or metastasis-free survival, which was further compounded by the relatively short follow-up. Finally, STAND was not designed with a true control arm (an ADT only arm), so our ability to draw conclusions about the relative efficacy of sipuleucel-T + ADT versus ADT alone in BRPC patients is limited.

In conclusion, although the results presented here should be regarded as hypothesis generating, STAND suggests that sipuleucel-T administered prior to ADT in men with hormone-sensitive BRPC may yield superior cellular immune responses than the reverse sequence. Furthermore, sipuleucel-T may lead to greater immune responses in less advanced stages of prostate cancer; these responses are sustained for at least 2 years following sipuleucel-T administration. These findings will inform potential future studies with the aim of evaluating whether sipuleucel-T, when utilized in earlier disease, improves long-term clinical outcomes.

Disclosure of Potential Conflicts of Interest

E.S. Antonarakis reports receiving commercial research grants from Dendreon, Genentech, Janssen, Johnson & Johnson, Novartis, Sanofi, and Tokai and is a consultant/advisory board member for Astellas, Dendreon, ESSA, Janssen, Medivation, and Sanofi. A.S. Kibel and E.Y. Yu are consultant/advisory board members for Dendreon. L.I. Karsh reports receiving speakers bureau honoraria from Amgen, Astellas/Medivation, Bayer, Dendreon, and Janssen and is a consultant/advisory board member for Abbvie, Astellas/Medivation, Bayer, Dendreon, Ferring, Janssen, Sanofi, and Spectrum Pharma. N.D. Shore is a consultant/advisory board member for Amgen, Astellas, Bayer, Dendreon, Janssen, and Sanofi. N.N. Chang holds ownership interest in Valeant. C.G. Drake reports receiving commercial research grants from Aduro Biotech, Bristol Myers Squibb, and Janssen, holds ownership interest (including patents) in Compugen and Potenza Therapeutics, and is a consultant/advisory board member for Agenus, Compugen, Dendreon, Janssen, Merck, Potenza, Roche Genentech, and Tizona Therapeutics. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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