

Cancer Vaccines: Moving Beyond Current Paradigms

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Abstract The field of cancer vaccines is currently in an active state of preclinical and clinical investigations. Although no therapeutic cancer vaccine has to date been approved by the Food and Drug Administration, several new paradigms are emerging from recent clinical findings both in the use of combination therapy approaches and, perhaps more importantly, in clinical trial design and end point analyses. This article will review recent clinical trials involving several different cancer vaccines from which data are emerging contrasting classic “tumor response” (Response Evaluation Criteria in Solid Tumors) criteria with “patient response” in the manifestation of increased patient survival post-vaccine therapy. Also described are several strategies in which cancer vaccines can be exploited in combination with other agents and therapeutic modalities that are quite unique when compared with “conventional” combination therapies. This is most likely due to the phenomena that (a) cancer vaccines initiate a dynamic immune process that can be exploited in subsequent therapies and (b) both radiation and certain chemotherapeutic agents have been shown to alter the phenotype of tumor cells as to render them more susceptible to T-cell – mediated killing. Consequently, evidence is emerging from several studies in which patient cohorts who first receive a cancer vaccine (as contrasted with control cohorts) benefit clinically from subsequent therapies.

The field of cancer vaccines is currently in a state of active preclinical and clinical investigations. Although no therapeutic cancer vaccine has been approved to date by the Food and Drug Administration, recent preclinical and clinical findings have shown that appropriate clinical trial design and end points, and the use of vaccines in new paradigms of combination therapies may well lead to cancer vaccines ultimately being used for the therapy of several cancer types.

Cancer vaccines differ from other therapies in that they initiate a dynamic process of activating the host's own immune system. This process could potentially influence both how patient responses are evaluated and how responses to subsequent therapies post-vaccination are evaluated.

Evaluation of Cancer Vaccines: New Paradigms for Responses to Therapy

It is proposed that cancer vaccines are a therapeutic modality where one should evaluate “patient response” more so than “tumor response.” The two phenomena are not always mutually inclusive. Standardization of response criteria is of course critical for any given clinical trial, but one must be

aware that the use of only one criterion for all therapeutics, cancer types, and disease stages can be classic “paradigm paralysis.” Response Evaluation Criteria in Solid Tumors (RECIST; refs. 1, 2) has served the oncology community well in the evaluation of passive therapeutic modalities, such as chemotherapeutic agents and radiation therapy. With the advent of new targeted therapies, including cancer vaccines, however, the sole use of RECIST criteria as a clinical end point has now been called into question by, among others, several Cooperative Groups (2–5). An excellent example of this has been in the evaluation of sorafenib in clinical trials of patients with advanced renal cell carcinoma. In a randomized, placebo-controlled phase III trial involving 903 patients, progression-free survival doubled from 12 to 24 weeks ($P < 0.00001$) for patients on sorafenib. At 3 months, the response rate (partial response) was 10% with <1% complete response (1 of 451) using RECIST criteria (6). Another example of this phenomenon is in the evaluation of imatinib in patients with gastrointestinal stromal tumor (7). The converse of this phenomenon is also evident as seen, for example, in a trial in patients with metastatic renal cell carcinoma. A total of 306 patients were randomly assigned to high- versus low-dose interleukin (IL)-2 therapy. There was a higher response rate using RECIST criteria (with more toxicity) in the high-dose (21%) versus the low-dose (13%) IL-2 – treated cohorts ($P = 0.048$). However, there was no statistical difference in overall survival between the two groups (8). It is clear from these results and others that RECIST criteria do not always adequately assess patients' clinical benefit (i.e., survival and quality of life).

A study of contrasts. The paradigm shift in analysis of clinical benefit from immunotherapy is exemplified in comparing results using vaccines versus adoptive transfer of T cells (9).

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Dramatic tumor size reductions satisfying RECIST criteria have been observed in the elegant studies with adoptive transfer of T cells (10–12). Unfortunately, however, in the 20+ years of reporting these types of responses, no randomized trial has shown a statistical advantage in survival in patients receiving adoptive transfer of T cells over that seen with IL-2 alone (13–15). In contrast, although few responses satisfying RECIST were seen in vaccine trials, this article will review several recent trials where advantage in survival is being observed. Other contrasts are the reduced toxicities seen in vaccine therapy plus the potential for combination therapy, as will be discussed below.

Vaccine Clinical Trials

A prior review (16) listed 21 clinical trials in which a range of different cancer vaccines provided some evidence of clinical benefit in different patient populations. This article will review more recent clinical findings using five different types of vaccines in the therapy of prostate cancer patients. Prostate cancer is a disease well suited for the efficacy of vaccines for several reasons: (a) it is a relatively slow growing tumor, (b) recurrence is often diagnosed early in the disease state, (c) there is a surrogate marker for disease prognosis and outcome [i.e., serum prostate-specific antigen (PSA) doubling time¹; refs. 17, 18], and (d) after definitive primary therapy (surgery and/or radiation), there are few existing standard of care therapies that achieve long-lasting therapeutic effects.

Cell-based vaccines. One of these prostate cancer vaccines is Sipuleucel-T (i.e., Provenge, Dendreon, Inc.), which consists of autologous antigen-presenting cells and a fusion protein composed of prostatic acid phosphatase and granulocyte macrophage colony-stimulating factor (19). Early phase I/II trials showed increases in T-cell responses to the vaccine antigen, serum PSA declines in patients, and limited toxicity. A placebo-controlled randomized phase III trial in patients with metastatic asymptomatic androgen-independent prostate cancer using Sipuleucel-T has been reported recently (19). Patients were randomly assigned in a 2:1 ratio to receive vaccine ($n = 82$) or placebo ($n = 45$). The primary end point of this study, which was progression-free survival, did not achieve statistical significance ($P = 0.052$; Fig. 1A). Overall survival, however, was statistically significant (hazard ratio, 1.70; $P = 0.01$) between vaccine (25.9 months) versus placebo (21.4 months; Fig. 1B). A second randomized trial with Sipuleucel-T in this patient population showed a trend toward increased survival (19 months for vaccine versus 15.7 months for placebo) that did not reach statistical significance. Thirty-six-month survival was 32% for vaccine-treated patients versus 21% for placebo-treated patients. The integrated analysis of both of these randomized trials, vaccine ($n = 147$) versus placebo ($n = 78$), showed a statistically significant increase in overall survival (hazard ratio, 1.5; $P = 0.011$) in vaccine-treated patients. Thirty-six-month survival was 15% for placebo and 33% for vaccine. The survival advantages seen in these trials, as well as those described below, were obtained with little or no evidence of “objective” responses using RECIST criteria. A phase

III clinical trial using the Sipuleucel-T vaccine is currently ongoing using survival as a primary end point.

GVAX is another prostate cancer vaccine in advanced clinical trial testing. GVAX (Cell Genesys, Inc.) consists of two irradiated allogeneic prostate cancer cell lines engineered to secrete granulocyte macrophage colony-stimulating factor (20, 21). Two phase II clinical studies have now been completed in patients with asymptomatic metastatic androgen-independent prostate cancer. In the first trial ($n = 34$), GVAX was given at two dose levels. Decreases in PSA velocity were seen in 67% of patients given low-dose vaccine ($n = 24$) and in 90% of patients given high-dose vaccine ($n = 10$). This correlated with survival results, with a median survival of 24.0 months in the low-dose vaccine group and 34.9 months in the high-dose vaccine group. A second phase II trial in the same patient population ($n = 80$) used five vaccine dose levels: two low-dose ($n = 33$), one intermediate-dose ($n = 25$), and two high-dose ($n = 22$) cohorts. The median survival of patients in the low-dose and middle-dose cohorts was 23.1 and 20.0 months, respectively. The median survival of the high-dose cohorts has not yet been reached but will be ≥ 29.1 months (Fig. 2). Predicted survival was estimated for each patient using a nomogram; the median measured survival was >6 months longer than the predicted survival for the high-dose cohorts. There were no dose-limiting toxicities in either trial. These results have formed the basis for two ongoing phase III trials, with overall survival as the primary end points.

Another whole-tumor cell vaccine for prostate cancer is also showing promising clinical results. Onyvax-P vaccine (Onyvax Ltd.) consists of three irradiated allogeneic prostate cell lines, the first two vaccinations given with Bacillus Calmette-Guerin (BCG). A phase II Onyvax-P trial has now been completed in androgen-independent prostate cancer patients (22). Eleven of

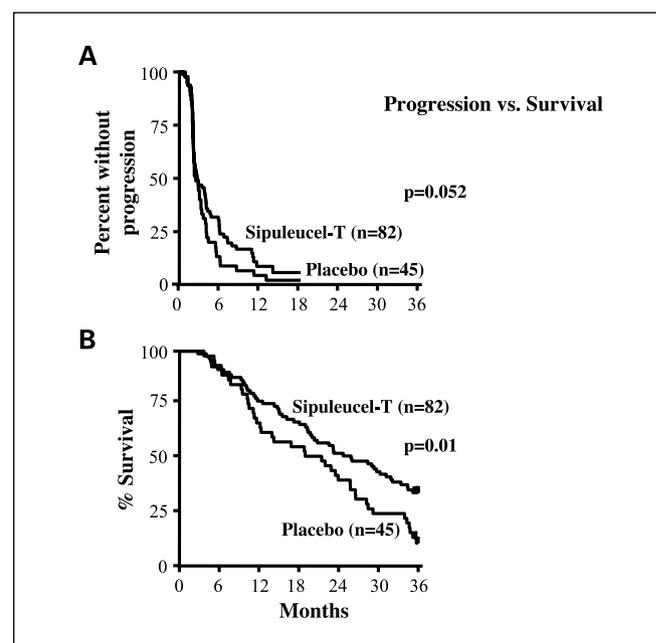


Fig. 1. Randomized, placebo-controlled, phase III trial of Sipuleucel-T vaccine (antigen-presenting cells with prostatic acid phosphatase – granulocyte macrophage colony-stimulating factor fusion protein) versus placebo in patients with metastatic asymptomatic hormone-refractory prostate cancer. *A*, time to progression (i.e., percentage without progression). *B*, overall survival (19).

¹ Arlen PM, Bianco F, Dahut WL, et al. Prostate-Specific Antigen Working Group's guidelines on PSA doubling time. Submitted to J Clin Oncol, 2007.

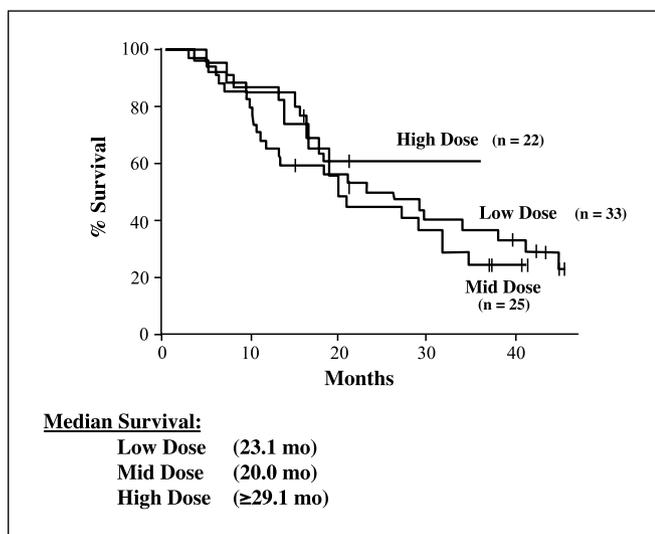


Fig. 2. Survival of patients with metastatic asymptomatic hormone-refractory prostate cancer receiving low-, mid-, or high-dose GVAX whole-tumor cell vaccine (20, 21).

26 patients showed statistically significant prolonged decrease in their PSA velocity with no patient having a statistically significant increase in PSA velocity post-vaccination. Mean time to tumor progression was 58 weeks compared with recent studies of other agents and historical control values of ~28 weeks. Immunologic profiles by artificial neural network analysis of cytokines correlated with PSA velocity responses. A multicenter phase IIb trial with Onyvox-P is currently under way.

Vector-based vaccines. There have also been several trials with poxviral vector-based vaccines with evidence of clinical benefit. Pox viruses [vaccinia (rV-), Modified Vaccinia Ankara (MVA), and fowlpox (rF-)] have the ability to accept and express multiple transgenes and can thus be engineered to express not only tumor-associated antigens but also various immunostimulatory molecules. TG4010 (Transgene) is a recombinant MVA expressing both MUC-1 tumor antigen and IL-2. MVA is a replication-incompetent vaccinia virus. A randomized phase II study has been completed with MVA-MUC-1-IL-2 in prostate cancer patients with biochemical progression and no evidence of metastatic disease after local therapy (23). Patients were vaccinated every week for 6 weeks and then every 3 weeks in arm I and every 3 weeks in arm II. Twenty-seven of 38 (71%) patients had lengthened PSA doubling time after vaccination. A statistically significant increase ($P < 0.001$) in PSA doubling time (mean increase, 3.8-fold) was observed in arm I, providing evidence that vaccine dose scheduling can be an important variable.

In a phase I study with recombinant vaccinia in prostate cancer patients, rV-PSA was administered to 33 patients with biochemical progression after local therapy or with metastatic disease (24). PSA levels in 13 of 33 men became stable for at least 6 months post-vaccination. Nine patients remained stable for 11 to 25 months and six remained progression-free with stable PSA. At the time of publication, several patients remained without evidence of clinical progression for up to 21 months. A National Cancer Institute-sponsored Eastern Cooperative Oncology Group randomized phase II trial was then carried out using two different PSA pox vectors in

different prime/boost regimens: rV-PSA(V) and/or rF-PSA(F) in patients ($n = 64$) with biochemical progression after local therapy for prostate cancer (25). At the 2-year follow-up (26), median time to PSA and/or clinical progression was 9.2 months in the FFFF cohort, 9.0 months in the FFFV cohort, and 18 months in the VFFF cohort. The National Cancer Institute has now developed rV- and rF- vectors containing the transgenes for PSA and three human costimulatory molecules (B7.1, intercellular adhesion molecule-1, and lymphocyte function-associated antigen-3, designated TRICOM; ref. 27). Recent phase I/II trials in patients with metastatic and locally advanced prostate cancer have shown clinical responses and drops in serum PSA (28). A company-sponsored multicenter randomized phase II study in 125 patients with metastatic androgen-independent asymptomatic prostate cancer did not meet its primary end point of progression-free survival (29). Patients' overall survival data are currently being accumulated, with provocative results. Median overall survival thus far is 16.3 months for the control cohort (wild-type vector; $n = 41$) versus 24.4 months for those patients receiving PSA-TRICOM vaccines ($n = 84$; Fig. 3).

This article has detailed vaccine trials in prostate cancer as one example of the progress being made in clinical vaccine therapy. Ongoing progress in pancreatic cancer, lymphoma, melanoma, lung cancer, and other tumor types is also providing evidence in clinical trials of vaccine efficacy.

Separating Vaccine Efficacy from Poor Clinical Trial Design

There is clinical evidence that the ability to mount an immune response to vaccine can be altered by prior chemotherapy. Studies in patients with metastatic cancer showed (30) that there was a negative correlation between the number of previous chemotherapy regimens and the magnitude of T-cell response to vaccine ($P = 0.032$). This same study also showed a positive correlation between the magnitude of a T-cell response to vaccine and time since last chemotherapy regimen ($P = 0.005$). Thus, patients who had received more

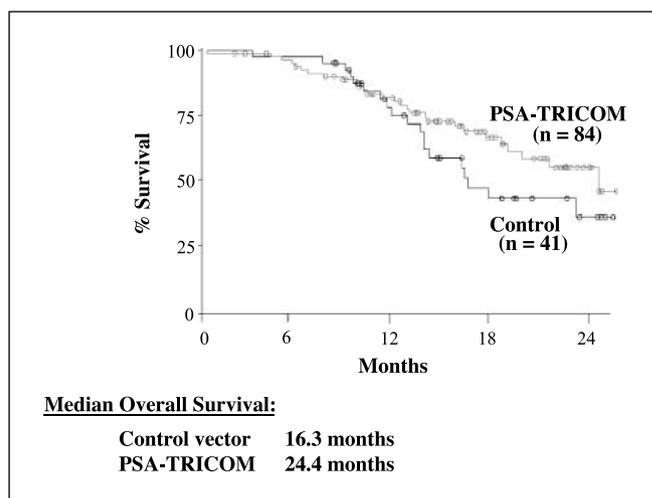


Fig. 3. Randomized phase II study in patients with metastatic androgen-independent asymptomatic prostate cancer receiving PSA-TRICOM vaccines ($n = 84$) versus control fowlpox vector ($n = 41$; ref. 29).

cycles of prior chemotherapy or who had received chemotherapy more recently were shown to mount less effective immune responses to vaccine.

New Paradigms for Combination Therapies

There are five different strategies of combination therapies that can and are being used with cancer vaccines. All have been validated in preclinical models and several have provided preliminary evidence of clinical benefit. As the field matures, progress in this area will undoubtedly be accelerated.

(a) Conventional combination therapy. In many cases of combination therapies using two or more chemotherapeutic agents or a chemotherapeutic agent and a targeted therapy (e.g., Herceptin and docetaxel), each agent works individually with the goal of additive antitumor effects. This too has been shown in numerous preclinical models using vaccines in combination with chemotherapeutic agents. Both preclinical and early clinical studies have highlighted the following important phenomena: although vaccines are less effective in patients heavily pretreated with chemotherapy before vaccine, no detrimental effects in immune responses to vaccines have been seen in patients when vaccine is given in combination with certain chemotherapeutic agents, such as 5-fluorouracil and docetaxel (31, 32). For example, in preclinical studies, it has even been shown that the cyclooxygenase-2 inhibitor celecoxib, an established anti-inflammatory, had no adverse effect on immune responses to vaccine and worked well in combination with vaccine to enhance antitumor effects (33).

(b) Vaccine in combination with agents that affect the host immune system. There now exist a plethora of reagents that can be used in combination with vaccines that act either as immune stimulants/adjuvants or inhibitors of immune regulatory cells or molecules. This phenomenon has been shown in multiple preclinical models. A major issue at this time, however, is that only a few of these agents have been approved by the Food and Drug Administration; sadly, there is still hesitancy on the part of many companies to use proprietary agents of another company to enhance their agent's efficacy.

Cytokines are well established for their ability to enhance immune response (see ref. 16 for review). As examples: granulocyte macrophage colony-stimulating factor (Food and Drug Administration approved) has now been shown in numerous clinical trials including several described above to enhance vaccine efficacy. IL-2 may not be as useful as thought due to its toxicity, its ability to induce apoptosis in activated T cells, and/or its ability to enhance regulatory T-cell activity. IL-15 and IL-7 both have the potential to be useful with vaccines in enhancing memory T-cell responses. Other immune stimulants, such as BCG, CpG motifs, and Aldara, are also currently being used clinically with vaccines (see ref. 16 for review).

One agent that is showing promise in patients with melanoma, ovarian cancer, and prostate cancer is the monoclonal antibody anti-CTLA-4 (34–37). Although the exact mechanism by which this agent works with vaccine has never been shown clinically, preclinical studies have clearly shown that anti-CTLA-4 renders higher avidity antigen-specific T cells when used with vaccines (38).

Still another paradigm to be exploited in the therapy of prostate cancer is the phenomenon that androgen deprivation therapy can enhance thymic regeneration. An elegant clinical study (39) has shown that biopsy samples of patients' prostates, post-androgen deprivation therapy versus pre-androgen deprivation therapy, have a substantial increase in CD3 T cells infiltrating their prostate. This can also be exploited in future vaccine/androgen deprivation therapy combination approaches.

It has become apparent from numerous preclinical studies and recent clinical studies that the control of immune inhibitory entities will play an important role in vaccine-mediated therapies. Preclinical and clinical studies have shown that the use of Ontak, a fusion protein consisting of diphtheria endotoxin and IL-2, can kill CD4/CD25/FOXP3 regulatory T cells and enhance vaccine efficacy in inducing greater T-cell responses (40). The chemotherapeutic agent Cyclophosphamide (cyclophosphamide) has been shown in preclinical studies to enhance vaccine efficacy. Cyclophosphamide reduces not only the number of regulatory T cells but also their functionality (41, 42). As the field matures, clinical application of agents that inhibit immunosuppressive molecules, such as transforming growth factor- β and IL-10, will more likely also add to vaccine effectiveness.

(c) Multiple vaccine therapies. This approach may ultimately prove advantageous because (a) different types of vaccines can augment different arms of the immune system, (b) each vaccine can carry different tumor-associated antigens, and (c) limited toxicities have been associated with vaccine therapy. Efficacy of this approach in clinical trials has been observed in cancer patients who have received a recombinant (r) vV-prime (V) and multiple fowlpox (F) boosts (25, 26). As the field matures, it is anticipated that more diverse vaccine combinations will be used.

(d) Dose scheduling of vaccine with other therapies. Perhaps the most unique feature of cancer vaccine therapy is the fact that a vaccine initiates a dynamic process of host immune responses that may be exploited in subsequent therapies. There are now several clinical studies that have provided evidence of this phenomenon.

In a phase I study, 17 patients with advanced stage progressive cancer received a plasmid/microparticle vaccine directed against cytochrome P4501B1. Most patients who developed immunity to vaccine, but required salvage therapy on progression, showed marked responses to their next treatment regimen, most of which lasted >1 year (43). In another study (44), 29 patients with extensive stage small-cell lung cancer received an adeno-p53 vaccine. A high rate (61.9%) of objective clinical responses was observed to chemotherapy that immediately followed vaccine therapy, and these clinical responses were also closely associated with induction or augmentation of immune response to vaccine.

Three randomized clinical trials in prostate cancer also provided evidence of this phenomenon. The National Cancer Institute has now completed studies with a diversified prime/boost strategy involving priming with rV-PSA + rV-B7.1 followed by rF-PSA booster vaccinations. In the first trial, 28 patients with metastatic androgen-independent prostate cancer were randomized to receive vaccine alone or vaccine plus weekly docetaxel (31). Patients on the vaccine arm alone were allowed to cross over to receive docetaxel at time of progression. After vaccine, median progression-free survival on

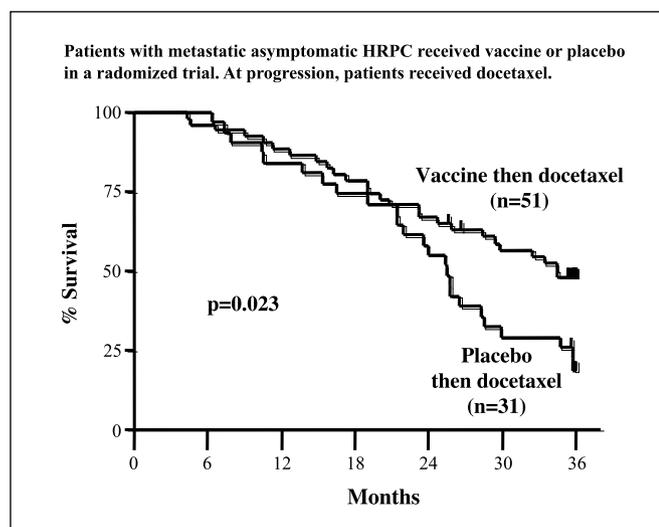


Fig. 4. Enhanced survival to docetaxel in patients having received prior vaccine. Overall survival in a randomized trial of patients with metastatic asymptomatic hormone-refractory prostate cancer receiving Sipuleucel-T vaccine or placebo. At progression, patients went on to receive docetaxel. There was a statistically significant increase in survival (hazard ratio, 1.9; $P = 0.023$) when patients received prior vaccine (45).

docetaxel was 6.1 months compared with a progression-free survival of 3.7 months with the same docetaxel regimen and patient population at the same institution. Similar findings were observed using the Sipuleucel vaccine (45). In the randomized multicenter Sipuleucel study described above, patients in both the vaccine arm ($n = 51$) and placebo arm ($n = 31$) went on to receive docetaxel at progression. There was a striking and statistically significant (hazard ratio, 1.90; $P = 0.023$) increase in overall survival with docetaxel treatment in patients having had prior vaccine versus placebo (Fig. 4).

In another phase II trial at the National Cancer Institute (46), 42 patients with nonmetastatic androgen-independent prostate cancer and rising serum PSA were randomized to receive either vaccine (rV-PSA/rV-B7.1 prime and rF-PSA boosts) or nilutamide, an androgen receptor antagonist. After 6 months, patients with a rising PSA were allowed to “cross over” and receive a combination of both therapies. Median time to treatment failure was similar in the vaccine (9.9 months) and androgen receptor antagonist (7.6 months) arms. However, for the patients who first received vaccine and then went on to receive vaccine plus androgen receptor antagonist, time to treatment failure was 13.9 months from the time of initiation of androgen receptor antagonist and the time to treatment failure from the initiation of any therapy was 25.9 months. Of the initial randomized population ($n = 21$ per cohort), for those patients who received nilutamide first (nilutamide alone or nilutamide and then vaccine), 5-year overall survival was 38% versus a median overall survival of 59% for those patients who received vaccine first (vaccine alone or nilutamide plus vaccine; Fig. 5; ref. 47).

All of the above trials have provided evidence of the same phenomenon: patients who receive vaccine (and mount immune responses to vaccine if monitored) have enhanced outcome to subsequent therapies. This is unlikely due to patient population selection because three of these trials described were randomized. This phenomenon may be due

to one or more factors: the subsequent therapy (*a*) may be reducing suppressor cell populations, allowing for enhancement of prior established T-cell responses, (*b*) may be lysing some tumor cells that are then, as a consequence of cross priming, activating relatively dormant T cells to elicit an anti-tumor response, (*c*) may enhance host T-cell activity, and/or (*d*) may alter the phenotype of tumor cells (see below).

(*e*) **Phenotype alterations in tumor cells.** Still another new paradigm to exploit in vaccine combination therapies is the phenomenon that certain standard of care therapeutics can actually alter the phenotype of tumor cells to render them more susceptible to T-cell-mediated lysis. This has been shown in a series of preclinical studies (48, 49). Sublethal doses of radiation delivered via external beam have been shown to up-regulate tumor-associated antigens, fas, and/or adhesion molecules and/or down-regulate antiapoptotic genes, subsequently rendering these phenotypically altered tumor cells more susceptible to antigen-specific T-cell-mediated lysis. Chemotherapeutic agents, such as 5-fluorouracil (50), cisplatin, and gemcitabine (48), have also been used in sublethal doses inducing similar alterations of tumor cell phenotype and subsequent susceptibility to T-cell-mediated lysis. This may ultimately lead to another paradigm shift in vaccine combination therapies (i.e., when a patient does not respond to a drug or radiation therapy due to its lack of ability to lyse tumor cells, it may continue to be used with vaccine therapy due to its ability to augment vaccine-induced T-cell lysis of tumor).

Immune Responses

Several clinical studies have reported statistical correlations between antigen-specific immune responses to vaccine and patient benefit, whereas others have not. These findings may be confounded by several phenomena: (*a*) the vast majority of studies have examined only T-cell or antibody responses in blood, which may not always correlate with their presence in tumor, and this may vary with tumor size, vasculature, etc.; (*b*) few studies, if any, have taken into consideration the presence

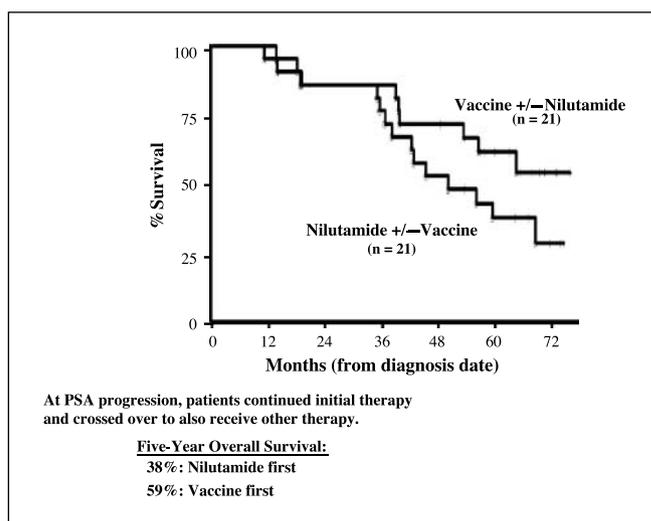


Fig. 5. Overall survival in a randomized trial of patients with hormone-refractory prostate cancer receiving vaccine (rV-PSA + rV-B7.1 prime and rF-PSA boosts; $n = 21$) versus nilutamide therapy ($n = 21$) with patients “crossing over” to receive both therapies at progression (46, 47).

of regulatory T cells and/or have analyzed multiple immune cell subsets (e.g., CD4, CD8, and natural killer responses from a given patient population); (c) virtually all studies have measured the level of antigen-specific T cells, but few studies have monitored avidity of antigen-specific T-cell subsets (51), which is, perhaps, the most important variable to measure; and (d) it has become apparent from preclinical studies that the more important antigen-specific T-cell subsets to monitor may not be those directed to the antigen in the vaccine. As a consequence of initial tumor cell disruption by vaccine-induced cytolytic T cells, cross priming will lead to the generation of T cells directed against other tumor-associated antigens. Preclinical studies (49) have shown that these "antigen cascade" T cells can be of greater magnitude and greater avidity than those directed against the antigen in the vaccine and are those that are principally responsible for tumor cure. Clinical studies (52–54) have also shown this phenomenon of "antigen cascade."

New Vaccine Strategies, New Targets, New Paradigms

This article has reviewed only a few of the vaccine vehicles that are currently being used with evidence of clinical benefit; allogeneic whole-tumor cells, peptide- or protein-pulsed antigen-presenting cells (including dendritic cells), recombi-

nant DNA and viral vectors, and recombinant *Saccharomyces* (yeast) are all currently in active clinical trial development. Moreover, there are a plethora of newly defined potential tumor-associated targets that are ripe for cancer vaccine development, including those involved in the neoplastic and/or tumor progression processes. As the field of cancer vaccine therapy matures, long-term safety profiles of several of these agents will most likely be realized. At that juncture, vaccines may well also be used in neoadjuvant settings and in certain preneoplastic conditions.

Skepticism is an important component of the scientific process and it should be an integral component in the development of any potential new therapy. Many are very much aware, for instance, of those skeptics and "naysayers" who, for a decade, dismissed monoclonal antibody-mediated cancer therapy (there are now seven monoclonals approved for cancer management). This too may well be the case for cancer vaccines. Although skepticism is important, there are also those who realize the need for paradigm shifts in both exploiting vaccine combination therapy and analysis of patient benefit in terms of survival (with minimal toxicity) as the appropriate clinical trial end point.

Acknowledgments

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