Immunotherapeutic Approaches in Prostate Cancer: Combinations and Clinical Integration

Susan F. Slovin, MD, PhD

OVERVIEW

Despite multiple immunologic approaches with peptide, protein, and DNA vaccines, no single therapy has induced complete remission or maintained durability of response in patients with castration-resistant prostate cancer (CRPC). Historically, immunotherapy has had limited effect on solid tumors with the exception of melanoma and renal cell carcinomas, which have been deemed as immunologic cancers given their potential for remissions either spontaneously or after removal of the primary lesion. There is considerable excitement about using an immunotherapy in combination with biologic agents such as checkpoint inhibitors, cytokines, other vaccines, or chemotherapy. Sipuleucel-T represents one of several novel immunologic therapeutic approaches to treat prostate cancer in addition to other solid tumors. It is the first in its class of autologous cellular therapies to demonstrate safety and an overall survival benefit in patients with asymptomatic or minimally symptomatic CRPC and represents a unique treatment method that may be further enhanced with other agents. Although sipuleucel-T can be used as a foundation on which to build and enhance future immunologic clinical trials, other exciting strategies are in development that may be easily integrated into the algorithm of current care.

The introduction of immunotherapy for the treatment of CRPC has been transformative in that it has revitalized an area of research that had waned for many years. Although there are five new therapies that have changed the standard treatment algorithms used for treating CRPC, a personalized medicine approach is now being embraced as a means of developing and directing therapies based on unique patient molecular profiling and the ability to target actionable mutations with specific drugs. Despite the enthusiasm held for immunotherapy, there are still concerns about how to best integrate a specific type of immunotherapy into the current treatment algorithm and whether combinatorial approaches will improve antitumor responses. Jerome Groopman, MD, a well-known physician who on occasion presents his views on controversial medical issues in The New Yorker magazine, has noted that there are many new oncology drugs now available to patients with different cancers, but the question remains whether it is possible to “control cancer without killing it.” Immunotherapy may in fact provide sufficient control in prostate cancer that may minimize the need for immediate cytotoxic agents.

Immunotherapy for solid tumors is not new; preclinical studies have suggested that animals can be cured with a wide variety of approaches from conjugate and DNA vaccines, to combinatorial schemes with chemotherapy or biologic modifiers. However, stunningly successful preclinical vaccine strategies have not successfully translated into similar results in humans. Each of the five new drugs approved for prostate cancer—sipuleucel-T, enzalutamide, abiraterone, cabazitaxel, and radium 223 dichloride—has shown a survival benefit, benefits in pain control, and quality of life, but sipuleucel-T has revitalized the role of immunotherapy in treating a solid tumor. Sipuleucel-T stands out as the first immunotherapy approved by the U.S. Food and Drug Administration (FDA) for prostate cancer with the added benefit of improvement in overall survival (OS). Its approval was determined by the results of a placebo-controlled, randomized trial (the IMPACT trial), conducted in 512 asymptomatic or minimally symptomatic men with metastatic CRPC. Although no difference in time to progression or prostate-specific antigen (PSA) response rate was reported, a significant 4.1-month improvement in median survival was achieved in the active arm compared with the placebo arm (25.8 vs. 21.7 months; p < 0.005). The survival benefit was comparable to that seen with other standard agents. In fact, given how many of the androgen receptor (AR)-directed therapies have been introduced earlier in the treatment paradigm, the same may prove beneficial with immune-based therapies. Although sipuleucel-T’s indication is for patients with asymptomatic or minimally symptomatic CRPC, it has broad applicability to all clinical states of the disease, that is, from neoadjuvant, to biochemical relapse post-primary therapy, to castrate nonmetastatic disease, and castrate metastatic disease.
CHANGING THE TREATMENT PARADIGM

Sipuleucel-T is an autologous cellular product vaccine that mandates that patients undergo leukapheresis to obtain peripheral blood mononuclear cells that are processed, expanded, and incubated with a prostatic acid phosphatase (PAP)/granulocyte macrophage-colony stimulating factor (GM-CSF) fusion protein within a 48-hour window. The cells are divided into three reinfusions, one given every 2 weeks. In clinical trials, patients were then monitored per clinical practice with imaging and PSAs. Overall, the treatment was well tolerated with expected transfusion-associated side effects such as fever and chills. Since the FDA approval of sipuleucel-T, additional studies have sought to expand its use and to identify in which patients the greatest clinical benefits may be derived. A retrospective analysis of the IMPACT trial found that patients in the lowest quartile of PSA values derived a greater benefit from sipuleucel-T with a 13-month improvement in OS (41.3 months with sipuleucel-T compared with 28.3 months with placebo; [HR 0.51; 95% CI, 0.35 to 0.85]). However, for those patients in the highest baseline PSA quartile, the median OS was 18.4 months compared with 15.6 months for placebo (HR 0.84; 95% CI, 0.55 to 1.29), with an improvement of only 2.8 months. Most of the studies of sipuleucel-T have been retrospective and its mechanism of action is still controversial. A report by Drake et al9 postulated that antigen cascade (Fig. 1) may be responsible for its mechanism of action. This also is thought to be a key factor for ProstVAC.10 Though antibodies to PAP were generated, and a robust ki57 proliferative response was induced, this may be suggestive of an adaptive immune response. Additional evaluation of retrospective studies by Drake et al9 suggested that OS was improved in patients who received sipuleucel-T and had immunoglobin G antibody responses to greater than two secondary antigens compared with those patients who did generate antibodies. It should be noted that the term response should be used within the context of an association of antibody induction with a change in biology of the cancer, that is, clinical outcome, and not the generation of the antibody in response to an immunogen per se. Similarly, a caveat in determining whether there is an effect of the immune therapy on either the humoral or cellular compartments is that any induction of a component of either compartment, that is, antibody or T cell population, should correlate with a biologic change in the cancer.

Sipuleucel-T has been met with enthusiasm as the first immunotherapy approved for a solid tumor malignancy; the observation that OS was improved in the absence of significant clinical benefit has encouraged further evaluation of the mechanism for survival benefit and whether, over time, a significant antitumor response could be induced. Many physicians in the field felt that knowing the mechanism of action was important for future clinical trial development; whereas, others felt that knowing the mechanism of action made little difference in their use of the drug as long as the drug provided some clinical benefit. As such, investigators have sought to identify a biomarker that may indicate that a target has been hit or that the immune system has been stimulated. Because of mixed cellular nature of the autologous mononuclear cell product, it was unclear as to the nature of the effector population that may have been relevant in inducing a potential antitumor effect, and ultimately survival. Other than T-cell-proliferation assays, no other cellular marker was indicative of this product inducing immunogenicity. The working premise has always been that the cellular product was enriched with antigen presenting cells (APC). This was confirmed by the observation by flow cytometry that CD54+ cells were responsible for antigen uptake and that CD54+ cells harbored the PAP-specific antigen presentation activity as assayed using a PAP-specific HLA-DRβ1-restricted T cell hybridoma.11 The marker CD54 or intracellular adhesion molecule-1 (ICAM-1) serves as a ligand for the CD11a/CD18 (LFA-1) leukocyte integrin complex, and its interaction with other cells types is thought to be relevant in its role as a potential costimulatory receptor.11,13,14 In the setting of sipuleucel-T, the fusion protein, PA2024, comprised of PAP fused to GM-CSF was used as the immunogen, with the PAP portion of the molecule providing the necessary immunogenicity and the GM-CSF serving to activate the APC. Studies confirmed that the isolated CD54+ cells took up the antigen as well as presented and processed the antigen in an MHC-restricted manner.11 Similar results were obtained with an HLA-DRβ1 restricted T cell hybridoma specific for a different PAP-derived peptide. These findings provided some insight to how the product might work in vivo but still required validation. This was later confirmed. The opportunity to further validate the earlier role of CD54+ cells was provided by the availability of cellular products from three phase III double-blind, placebo-controlled trials in patients with metastatic CRPC including the IMPACT trial, which led to the product’s FDA approval. Patients were randomly selected 2:1 in favor of sipuleucel-T or to control. This included a minimum of at least one treatment with the cellular product as

KEY POINTS

- Sipuleucel-T remains a standard for patients with asymptomatic or minimally symptomatic castration-resistant prostate cancer.
- The checkpoint inhibitor ipilimumab has shown activity in phase I, II, and III trials in patients with prostate cancer with durable responses; however, the phase III trial did not show a survival benefit.
- A subset analysis of patients with castration-resistant prostate cancer who had visceral metastases did not show a survival benefit with ipilimumab and radiation, suggesting that there may be some advantage to patients without visceral metastases.
- Future work with combination approaches with immunotherapy, including chimeric antigen receptor-directed T lymphocytes, represents novel approaches.
- Establishment of appropriate immunologic biomarkers that are associated with disease response/outcome is needed.
well as additional information provided from the product prepared at the primary manufacturing facility in Seattle. APC number, APC activation, and total nucleated cells (TNC) were assessed in both the control and investigational product. Also assessed were T cell proliferation and interferon-gamma secretion by ELISPOT at treatment weeks 0, 2, and 4 in the IMPACT trial. In the three trials, ex vivo APC activation was greater with sipuleucel-T relative to the control at weeks 0, 2, and 4 with the median APC activation increased approximately 6.2 fold. The median cumulative APC activation with sipuleucel-T alone across the three dose preparations was 26.7 (21.5 to 33.6). Elevated levels of T-cell activation-associated cytokines were noted during manufacture but not induced before and after exposure to GM-CSF alone. The treatment generated PA2024- and/or PAP-specific humoral responses in 68% (102/151) of patients compared with 3% (2/27) of control patients. The anti-PA2024 and anti-PAP antibody titers were greater in the sipuleucel-T arm compared with controls at all time points post-therapy, and a persistent response detectable 26 weeks after initial post-treatment baseline. It should be noted that overall product activation was confirmed by TH1 cytokines (IFN-gamma, TNF-alpha); TH2 cytokines (interleukin [IL]-5, IL-13) were also present implying that both TH1 and TH2 cells were activated in an antigen-specific manner. IL-10 was less detectable relative to those cytokines that facilitate T cell expansion such as IL-2, IFN-gamma, TNF-alpha. There also appeared to be a correlation between OS and T-cell secretion of IFN-gamma by ELISPOT and PA2024-specific antibody.

Can reducing or limiting the regulatory T-cell population improve the vaccine response? Apart from chemotherapy, improving vaccine response by inactivating T-regulatory (Treg) cells has been attempted through the specific targeting of the T-cell cytotoxic T-lymphocyte associated (CTLA)-4 receptor with a monoclonal antibody such as

![FIGURE 1. Graphic Describing Antigen Spreading by Banderlugt and Miller](image)
ipilimumab.17-19 Preliminary clinical trials suggest that administering a therapeutic vaccine followed by ipilimumab enhances immune responses and tumor reduction in prostate and ovarian cancers as well as melanoma.20-23 In a non-comparative phase I trial (30 patients) of ipilimumab plus the PSA-TRICOM24 vaccine in prostate cancer, OS was 31.8 months compared with an expected survival of 18.5 months based on baseline factors (Halabi nomogram–predicted survival [HPS]).25 Fong et al26 used microarrays spotted with more than 8,000 human proteins to assess the diversity of antibody responses modulated by treatment with CTLA-4 blockade and GM-CSF. Patients with advanced prostate cancer who had clinical responses developed robust antibody responses to a higher number of antigens than nonresponders. The antibody responses appeared to target antigens on which preexisting antibodies were likely to be present in patients who responded compared with nonresponders. Although the majority of antibody responses were patient-specific, there appeared to be a commonality of immune responses to shared antigens within the responder population. They identified one shared antigen, PAK6, which is also expressed in prostate cancer and to which CD4+ T cell responses were induced.

THE CHECKPOINT INHIBITORS: DOES ONE SIZE FIT ALL?

Although sipuleucel-T still remains an active choice for patients with asymptomatic or minimally symptomatic CRPC, the stunning and durable responses seen by the checkpoint inhibitors, ipilimumab26-28 and nivolumab,29,30 in prostate,27,28 melanoma,26,29,30 non–small cell lung,29,30 renal,29,30 and bladder29,30 cancers, have provided rationale for their investigation in CRPC. The phase I/II report of a dose-escalating study of ipilimumab with and without radiation therapy to a single site in bone showed stable disease and severe dramatic and durable responses. This provided the impetus for the recently reported phase III trial29 for patients who progressed after docetaxel treatment and were randomly assigned 1:1 to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. Nonprogressing patients could continue to receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 months until disease progression, unacceptable toxic effect, or death. This came close to, but did not meet, its endpoint of OS. An exploratory and post-hoc subgroup analysis, noted an OS benefit for ipilimumab in a subset of patients without visceral metastases, with normal or mildly elevated alkaline phosphatase, and without anemia. This suggested that ipilimumab may still be effective but in patients with more favorable prognostic features. Unlike melanoma, a highly mutated disease,31 for which ipilimumab has been shown to have favorable effects, this has not been the case for prostate cancer. Similarly, nivolumab (anti-programmed death [PD]-1),29,30 and its ligand (anti-PD-L1) have shown robust activity in melanoma, renal cell, non-small lung cancers, and now bladder cancer but minimal activity in prostate cancer. Despite this, there is still consideration to trying to maximize their effectiveness in prostate cancer via other combinatorial approaches.

DNA VACCINES

For the first time in CRPC, a phase III clinical trial of a viral-based vaccine, rilimogene galvacirepvec/rilimogene glafolivec (PROSTVAC),32-34 Many viral-based cancer vaccines are produced via the insertion of a plasmid encoding tumor proteins (i.e., PSA, prostate-specific membrane antigen [PSMA]) into a viral vector, often a poxvirus (e.g., vaccinia, fowlpox).35-37 After administration, host epithelial cells are infected and can, on lysis, continue to release a variety of encoded antigens that are taken up and processed by APCs for presentation to the T cell. This is accompanied by activation of CD4+ and CD8+ T cells. Alternatively, as in PROSTVAC, not only are plasmids used that encode tumor-associated antigens (i.e., PSA) but there is inclusion of costimulatory molecules. In the case of PROSTVAC, three T-cell costimulatory molecules, that is, B7.1, intercellular adhesion molecule-1 (ICAM) and leukocyte function-associated antigen-3 (LFA-3) are included. As in all vaccine strategies, there are limitations especially when preclinical studies showed marked tumor regressions but the responses in man are disappointing. One shortcoming of the viral-based vaccine preparation lies in that the antibody response to vector antigens may be more exaggerated compared with the response to the plasmid encoded tumor antigens. This can induce neutralization of the vaccine with recurrent administrations.38 PROSTVAC circumvents this by using an immunologic prime boost that by sequencing two different viruses, a vaccinia virus prime followed by a fowlpox virus boost, results in potent immune responses. Although there has been an effect on cancer cellular proliferation, the cancer cell rate of growth was also affected.39 The authors suggest that this may provide an alternative explanation to why vaccines that yield an improved OS are not accompanied by a delayed time to progression.

A recent paper by Madan et al40 showed that ipilimumab could be safely combined with the PSA-targeted vaccine PSA-Tricom without significantly exacerbating the agent’s immune-related adverse event profile. Those patients who were chemotherapy-naïve experienced a PSA decrease from baseline levels. In support of this approach, another phase I study also confirmed that ipilimumab could safely be combined with GVAX prostate.41 Preclinical models continue to be performed to assess the translatable of these combinatorial approaches. A combination of GVAX and anti-CTLA-4 in an autochthonous prostate cancer model expressing hyaluronic acid in a prostate-restricted manner reported on the importance of timing and dosage in this kind of regimen, which may have importance in future trials with ipilimumab combinations.42 GVAX plus anti-CTLA-4 combination therapy reduced peripheral tolerance and promoted...
TABLE 1. Rationale for Combinatorial Strategies

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<tr>
<th>Pros</th>
<th>Concerns</th>
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<td>Metastatic tumors develop highly sophisticated strategies for derailing immune defenses. Therapeutic vaccines, therefore, need support that sets the tumors back and/or resets the immune system.</td>
<td>Patients status post standard chemotherapy have resistant tumor cells, a shorter survival, and more suppressed immune systems. This population may not be optimal for evaluation of a novel vaccine.</td>
</tr>
<tr>
<td>Chemotherapy, if not myeloablative, has immunomodulatory effects that help restore antitumor immunity while affecting the tumor microenvironment.</td>
<td>Timing of chemotherapy relative to therapeutic immunization may be a critical factor in the success of a combination regimen. Is chemotherapy being used to debulk tumor burden or to improve synergism with the therapy?</td>
</tr>
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<td>Moving forward, optimization of the effectiveness of vaccine/chemotherapy regimens requires the development of clear endpoints that include biomarkers that reflect the effect of the therapy on the biology of the disease.</td>
<td>Basic questions remain unanswered, including the dose and timing of chemo-therapy when used in conjunction with therapeutic vaccines. It is unclear how to design trials with viable endpoints for patients with biochemical relapse or nonmetastatic castration-resistant disease.</td>
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The genetic engineering of T cells is a novel strategy designed to accelerate the generation of tumor-specific T cells and remedy the biologic limitations that constrain the antitumoral functions of normal T cells. Unlike the physiologic T-cell antigen receptor (TCR), chimeric antigen receptors (CARs) encompass immunoglobulin variable regions or receptor ligands as antigen-recognition elements, thus, permitting T cells to recognize cell surface tumor antigens in the absence of HLA expression (Fig. 1). T-cell activation is mediated by the cytoplasmic domain of the CAR, which is typically derived from the CD3-zeta chain or the FcR1-gamma.

T-CELL STRATEGIES: CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS

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On the contrary, initiation of chemotherapy during or after vaccination would be an option if the strategy was to impede the tumor and potentiate or broaden the vaccine-induced responses.

The question of which patient, clinical state, and treatment history is most appropriate for therapeutic vaccine schemes also arises. Patients with late-stage disease may have had their immune systems compromised by extensive chemotherapy and the evolving tumor escape strategies. One implication is that the patients with shorter life expectancies will not benefit from vaccine therapy, as demonstrated in the GVAX/docetaxel combination results. The original phase III trial of GVAX compared with docetaxel enrolled patients with less-advanced disease. A trend toward superior survival in the GVAX recipients after 22 months follow-up was already emerging. In another vaccine example, in a phase II study of PSA-TRICOM (32 patients), patients with HPS of 18 months or longer lived significantly longer than expected (p = 0.035). Median survival was 14.6 months for patients with HPS less than 18 months and was 37.3 months or longer for those patients with an HPS of 18 months or longer. Considering the safety of vaccines relative to standard chemotherapy, clinical trials could justify enrolling patients in earlier stages of disease in lieu of conventional chemotherapy alone.

the activation and proliferation of tumor antigen-specific CD8 T cells.
chain (Table 2, Figs. 2 and 3). Our group has shown that the zeta chain–based CARs could induce strong activation capable of sustaining T-cell proliferation and permitting secondary antigenic restimulation in vitro provided that antigen was presented in the context of CD28-mediated costimulation. In an effort to determine if T cells—particularly human T cells—expanded in this manner could mediate tumor eradication in vivo and if further in vivo costimulation would be needed to sustain their function, three tumors models using severe combined immunodeficiency-beige/beige mice were developed that showed that PSMA-targeted T cells could effectively eliminate prostate cancer. T cells were transduced with Pz1, a CAR-targeting human PSMA. The Pz1 receptor encompasses the zeta chain of the CD3 complex as its activation domain and specifically redirects in vitro cytolyis against PSMA-positive tumor cells lines. The tumor models included orthotopic, subcutaneous, and pulmonary diseases; tumor eradication was directly proportional to the in vivo effector-to-tumor cell ratio. Serial imaging studies revealed that the T cells had to survive for at least 1 week to induce durable remissions. The administration of Pz1-transduced T cells induced objective responses in all mice and cured a substantial fraction of them. Based on the favorable responses, several clinical trials have been actively pursuing this approach using unique combinations with constructs that encompass unique vectors or are given in combination with cytokines. Although these approaches have been well-tolerated—stable disease has been seen but in a majority of cases—a cytokine release syndrome is observed following administration of the cells suggesting T cell activation. Achievement of maximal responses in solid tumor may depend on the nature of the vector, the ability of cells to migrate to and persist at the tumor site, incorporation of a multiantigen construct with molecules such as PSA, PAP, PSMA, or prostate stem cell antigen or delivering a sufficient number of cells to reach the tumor site without causing worsening toxicities.

**TABLE 2. Target Molecules and Their Respective Constructs Used in Preclinical/Clinical Trials**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Malignancy</th>
<th>Receptor Type</th>
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<tbody>
<tr>
<td>CD19, 20</td>
<td>B-cell malignancies</td>
<td>scFv-CD3zeta</td>
</tr>
<tr>
<td>PSMA</td>
<td>Tumor neovasculature</td>
<td>scFv-CD3zeta</td>
</tr>
<tr>
<td>PSCA</td>
<td>Pan-carcinoma</td>
<td>scFv-CD28-CD3zeta</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Breast and others</td>
<td>scFv-CD28-CD3zeta</td>
</tr>
<tr>
<td>GD2</td>
<td>Neuroblastoma</td>
<td>scFv-CD3zeta, scFv-CD28</td>
</tr>
<tr>
<td>MDM2</td>
<td>Pan-carcinomas</td>
<td>alpha beta TCR</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal cancer</td>
<td>scFv-CD28-CD3zeta</td>
</tr>
<tr>
<td>VEGF-R2</td>
<td>Tumor neovasculature</td>
<td>scFv-CD3zeta</td>
</tr>
<tr>
<td>KDR</td>
<td>Tumor neovasculature</td>
<td>scFv-Fc XI RI gamma</td>
</tr>
<tr>
<td>EGP2</td>
<td>Colorectal cancer</td>
<td>scFv-CD3zeta, scFv-Fc XI RI gamma</td>
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**HEREIN LIES THE FUTURE**

Although prostate cancer is a suitable target for immunotherapy given the variety of prostate cell surface antigens that can serve as immune targets, the availability of a serum biomarker, that is, PSA, and the fact that immunotherapy is a reasonable treatment for all clinical states of the disease, how to build on current therapies remains a challenge. Alternative strategies include OX40 and its ligand OX40L, which are members of the tumor necrosis factor (TNF) superfamily and can augment T-cell expansion, cytokine production, and survival. OX40 signaling also controls regulatory T cell differentiation and suppressive function. OX40 agonists have...
been shown to enhance antitumor immunity in preclinical models using immunogenic tumors. A recent phase I trial in patients with metastatic castration- and chemotherapy-resistant prostate cancer evaluated the toxicity and the effect of cyclophosphamide combined with radiotherapy and an anti-OX40 agonist on peripheral blood lymphocytes (PBLs). There was no effect of the combination on the degree of proliferation of PBLs. There was no change in the proliferation of CD4+ FoxP3+ T cells (Treg), but there was a trend toward a higher percentage of cycling CD8+ T cells expressing activation markers CD38 and HLA-DR. OX40 and its ligand remain interesting targets for future development.

Clinical trials in the castration-resistant nonmetastatic state evaluating combinations of the antiandrogen flutamide with or without the addition of PROSTVAC/PSA-TRICOM in delaying disease progression are ongoing [NCT00450463]. Another randomized phase II trial is examining the combination of PROSTVAC/TRICOM and the AR-directed agent enzalutamide to determine if the combination will increase time to progression (as defined by Prostate Cancer Clinical Trials Working Group 2 criteria [NCT01867333]). The results of the phase III multinational randomized trial of PROSTVAC in patients with asymptomatic or minimally symptomatic CRPC are eagerly awaited. This 800-patient trial has reached its target accrual and is comparing the OS and proportion of patients who remain event-free (radiological or pain progression, initiation of chemotherapy, or death) at 6 months.

CONCLUSION

The mix and match approach—that is, combining immunologic agents with different mechanisms of action or even within the same class—supports the rationale for continuing research in immunotherapy for prostate cancer. While understanding mechanistically how antitumor effects may occur, it is important to keep in mind that the manner in which a therapy induces an antitumor response may be unclear, and as such should not deter investigators from using the drug.

Disclosures of Potential Conflicts of Interest

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References


