REVIEW

Immunotherapy in the treatment of advanced prostate cancer

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Prostate cancer is a complex disease, and treatment selection is informed by numerous variables depending on the stage of disease. Moreover, patient expectations and the impact of treatment-related adverse events may influence treatment choices. Available treatment options over the course of the disease have included surgery, radiation therapy, hormonal therapy, immunotherapy, and chemotherapy. This complexity requires an understanding of a wide range of treatment options and the support of a multidisciplinary team that involves urologists, radiation oncologists, diagnostic radiologists, pathologists, and medical oncologists. Collaboration among these physicians allows for a comprehensive treatment strategy that addresses the individual needs of the patient throughout the course of his disease.

Prior to 2004, treatment options for metastatic castrate-resistant prostate cancer (CRPC) were limited to therapies for palliation of pain and reduction of skeletal-related events. Over the past 7 years, four therapeutic options—three within the last 2 years—that provide a survival benefit in this setting have been approved. These therapies have diverse mechanisms, perhaps reflecting the complex nature of advanced prostate cancer. Among them is sipuleucel-T, the first autologous immunotherapy approved for any cancer. This review will discuss the rapidly changing treatment environment for metastatic CRPC and the increased exploration of immunotherapeutic approaches to advanced prostate cancer.

Key Words: immunotherapy, metastatic castrate-resistant prostate cancer, advanced prostate cancer, sipuleucel-T, abiraterone, docetaxel, cabazitaxel, PSA-TRICOM, ipilimumab, autologous cellular immunotherapy, active immunotherapy, GVAX

Disease state overview

Prostate cancer is the most commonly diagnosed malignancy, excluding skin cancer, and the second leading cause of death from cancer among men in the United States.[1] As a result of the introduction of widespread prostate-specific antigen (PSA) screening approximately 20 years ago, prostate cancer is now diagnosed predominantly as local/regional disease, Figure 1.[1] This change is also reflected in the dramatic stage migration that has occurred, both in the United States and Europe,[2,3] such that about 84% of cases of prostate cancer in the United States are low or intermediate risk at diagnosis.[2]

The 10 year survival rate for low risk, clinically localized disease is approximately 95% with definitive treatment (surgery or radiation therapy).[4,5] However, nearly one-third of the subset of men with intermediate to high risk disease who receive definitive treatment will develop progressive disease that requires additional therapy.[6] A subgroup of these men experience local recurrence that can be treated with adjuvant or salvage radiation therapy following a radical prostatectomy or with cryotherapy if they have received radiation therapy.[7-10]

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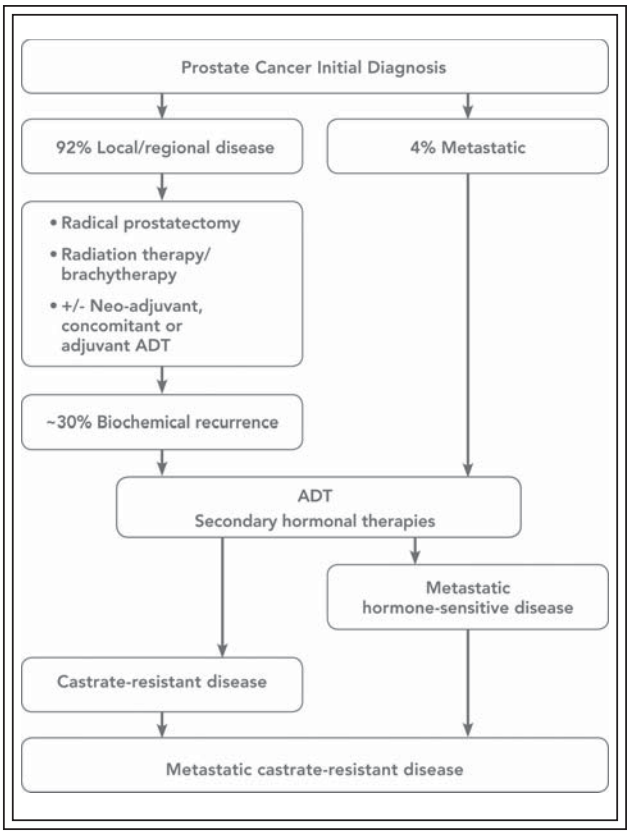

Figure 1. Prostate cancer disease progression.

A considerable body of evidence has been developed defining clinical parameters that can serve as guides for physicians in determining treatment for patients with biochemical recurrence after definitive therapies.[11-15] These parameters include Gleason score, time to biochemical recurrence, tumor stage, and PSA doubling time (PSADT). PSADT after local therapy has been validated to be the most predictive marker of survival[12-14] and is currently used in clinical trials to select patients with biochemical failure for new treatment modalities as well as to define the need to initiate androgen deprivation therapy (ADT).

ADT has been the cornerstone of treatment for men whose disease progresses after all forms of definitive therapy have been exhausted and for those men who present with de novo metastatic disease.[16,17] Although ADT is highly effective in reducing tumor burden and PSA levels, its use in patients with rising PSA has been controversial given the effects associated with long term use, including reduced quality of life, increased risk of incident diabetes and cardiovascular disease, metabolic syndrome, and fractures.[18-20] ADT is used in the following settings: as neoadjuvant and adjuvant therapy with primary radiation therapy for high risk disease, where it offers a survival advantage over radiation alone; in locally advanced disease not amenable to definitive local therapy, where it has been shown to increase time to progression; in the case of lymph node metastases, after radical prostatectomy; and for the palliation of symptomatic metastases.[17,21,22]

Although the median duration of response is approximately 10 years,[23,24] nearly all men receiving ADT will eventually develop progressive disease. Some men will respond to secondary hormonal manipulations, including addition or withdrawal of antiandrogens, adrenal androgen inhibitors such as ketoconazole, or estrogens; however, their disease will inevitably progress to castration resistant prostate cancer (CRPC).[16]

Unlike early prostate cancer, CRPC is an aggressive disease. Progression to overtly metastatic disease is relatively rapid among men with progressive nonmetastatic CRPC, with median bone-metastasis-free survival of 25 months to 30 months.[25,26] Men with metastatic CRPC have had a poor prognosis, with median survival of only 16 to 20 months,[27-29] although patients treated with docetaxel and/or other active treatments now available for this disease may live significantly longer. Optimizing survival may require the use of multiple lines of therapy, elevating the importance of tolerability when introducing new therapies. The goal is to maintain quality of life while simultaneously increasing survival.

Treatment of metastatic CRPC

Prior to 2004, treatment options such as mitoxantrone provided palliation of pain for patients with metastatic CRPC, but did not extend survival.[30,31] Two landmark trials, SWOG-9916 and TAX327, were the first studies to demonstrate a survival benefit for patients with metastatic CRPC.[27,28] In SWOG-9916, docetaxel (Taxotere: sanofi-aventis) in combination with estramustine was compared with mitoxantrone plus prednisone. An improvement in survival of 1.9 months (17.5 months versus 15.6 months, p = .002) was observed, along with improvements in progression-free survival (PFS) and objective response rates (ORR).[27] In this trial, progression was defined as tumor progression, PSA progression, or death.

In TAX327, patients with metastatic CRPC received two different schedules of docetaxel plus prednisone compared with mitoxantrone plus prednisone, Table 1.[28] An overall survival benefit from docetaxel every 3 weeks was seen (18.9 months versus 16.5 months), but no significant survival difference was seen with weekly

docetaxel. Pain control and PSA-ORR were also higher with docetaxel. Common toxicities included nausea, vomiting, diarrhea, and sensory neuropathy, as well as Grade 3/4 neutropenia in 32% of patients. Although these studies disproved the notion that metastatic CRPC was refractory to chemotherapy, the survival benefit was modest and came at the expense of considerable toxicity. Often, physicians will not recommend chemotherapy for men with metastatic CRPC until they develop symptomatic pain.[32]

In 2010, another chemotherapeutic agent, cabazitaxel (Jevtana: sanofi-aventis), was approved after having demonstrated a survival advantage in the postdocetaxel setting. Like docetaxel, cabazitaxel is a cytotoxic agent that inhibits microtubule activity, but cabazitaxel was shown to have activity in docetaxel-resistant preclinical models. The phase III TROPIC trial compared cabazitaxel plus prednisone with mitoxantrone plus prednisone in patients who had progressed after first-line docetaxel therapy, Table 1.[33] There was a 2.4 month improvement in median overall survival with cabazitaxel (15.1 months versus 12.7 months). Grade 3/4 adverse events included febrile neutropenia and diarrhea, as well as neutropenia in 81.7% of patients. In addition, more deaths from neutropenia and its consequences and cardiac causes occurred in the cabazitaxel group than in the mitoxantrone comparator group, leading to the recommendation for careful monitoring of blood counts, especially in the elderly and in patients with underlying cardiac disease.[34]

In 2011, abiraterone (Zytiga: Centocor Ortho Biotech), an additional option shown to have a survival benefit in the postdocetaxel setting, was approved. Abiraterone is a potent inhibitor of the

TABLE 1. **Current therapeutic options for treatment of metastatic CRPC**

Therapy	Approval	Pivotal trial name	Pivotal trial design	Outcomes	
				Primary	Secondary
Docetaxel	2004	TAX327[28]	Docetaxel plus prednisone every 3 weeks vs. mitoxantrone plus prednisone in metastatic CRPC	OS: 18.9 months vs. 16.5 months in the control group; HR 0.76 (95% CI 0.62 to 0.94) p = .009	PSA response: 45% vs. 32 p < .001 Pain response: 22% vs. 13% p = .009
Sipuleucel-T	2010	IMPACT[39]	Sipuleucel-T vs. control in asymptomatic or minimally symptomatic metastatic CRPC	OS: 25.8 months vs. 21.7 months in the control group; HR 0.77 (95% CI 0.61 to 0.97) p = .03	TTP 3.7 months vs. 3.6 months HR 0.95 (95% CI 0.77 to 1.17) p = .063
Cabazitaxel	2010	TROPIC[33]	Cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in metastatic CRPC following docetaxel therapy	OS: 15.1 months vs. 12.7 months in the control group; HR 0.70 (95% CI 0.59 to 0.83) p < .0001	PFS 2.8 months vs. 1.4 months HR 0.74 (95% CI 0.64 to 0.86) p < .0001
Abiraterone	2011	COU-AA-301[36]	Abiraterone plus prednisone vs. placebo plus prednisone in metastatic CRPC following docetaxel therapy	OS: 14.8 months vs. 10.9 months in the placebo group; HR 0.65 (95% CI 0.54 to 0.77) p < .001	TTPSAP 10.2 months vs. 6.6 months p < .001 PFS 5.6 months vs 3.6 months p < .001 PSA response rate 29% vs. 6% p < .001

OS = overall survival; TTP = time to progression; TTPSAP = time to PSA progression; PFS = progression-free survival

androgen biosynthesis enzyme CYP17, which has been shown to dramatically reduce both adrenal and intratumoral androgen production.[35] In the phase III trial COU-AA-301 in men with metastatic CRPC that had progressed with docetaxel therapy, a survival benefit of 3.9 months in favor of abiraterone plus prednisone compared with prednisone alone was shown (14.8 months versus 10.9 months, $p < .001$); Table 1.[36] Secondary endpoints, including time to PSA progression, PFS, and PSA response rate, also showed a benefit with abiraterone. In this trial, PFS was a composite endpoint that included a 25% increase in PSA over the patient's baseline/nadir and protocol-defined radiographic progression as well as symptomatic or clinical progression. Adverse events were mainly related to mineralcorticoid excess, including hypokalemia (17%) and fluid retention (31%); Grade 3/4 hypokalemia and hypertension were infrequent. Abiraterone is given with prednisone (5 mg BID) to help mitigate adverse effects; however, the effects of long term use of prednisone in this population have not been studied.

Immunotherapy presents a new approach to the treatment of advanced prostate cancer. Although the clinical benefits of passive immunotherapy using monoclonal antibodies are established in other cancers, it has not been shown to be an effective approach in prostate cancer.[37] The approval of sipuleucel-T (Provenge: Dendreon) in 2010 marks the first active immunotherapy ever to demonstrate significant clinical benefit in any solid tumor in a large, controlled, randomized phase III clinical trial, Table 1. Sipuleucel-T is indicated for patients with asymptomatic or minimally symptomatic metastatic CRPC—a patient population that typically has not been offered docetaxel-based chemotherapy until their disease progresses to the onset of symptoms.[38]

Autologous cellular immunotherapy in prostate cancer

Sipuleucel-T is an autologous cellular immunotherapy designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous

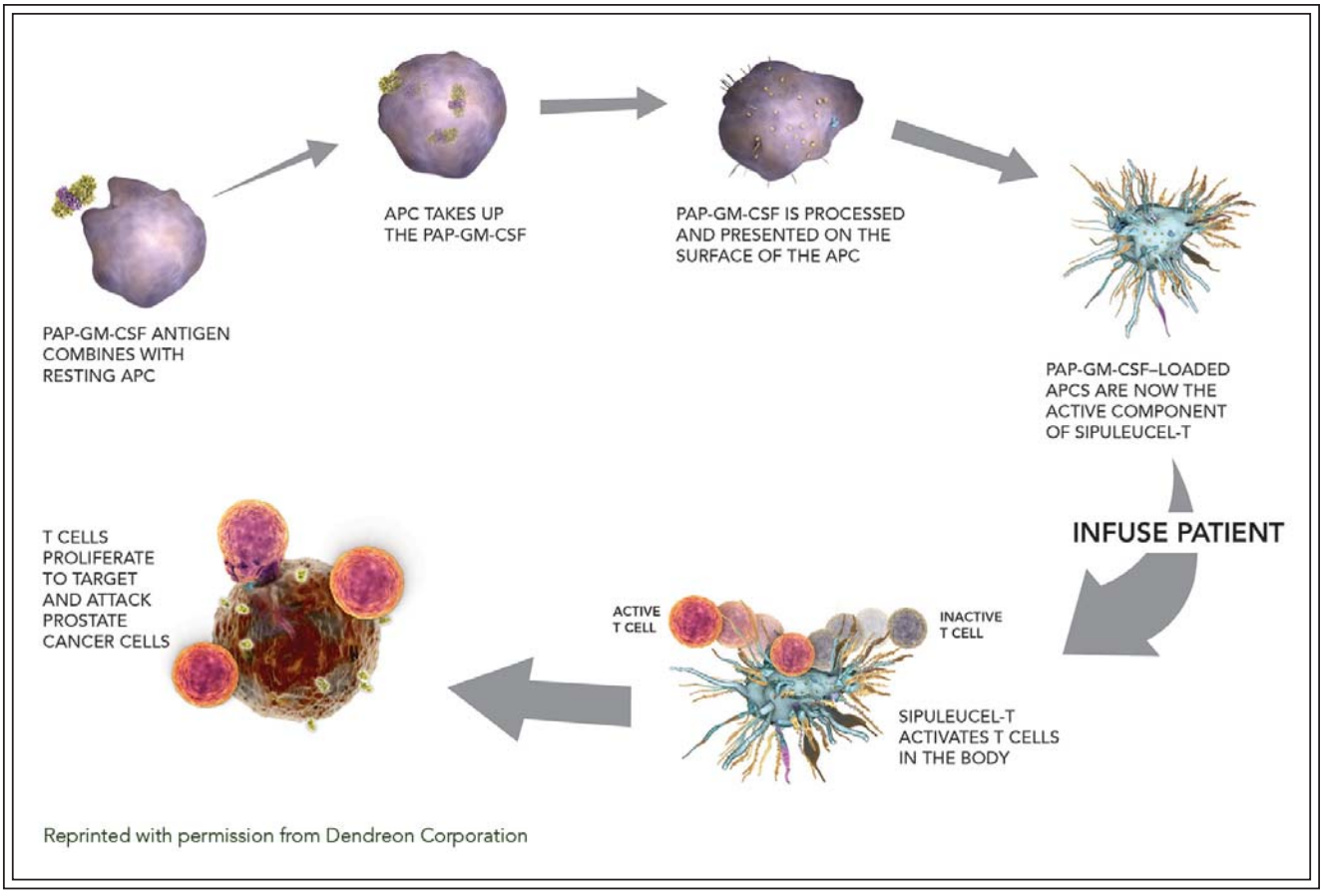

Figure 2. Sipuleucel-T proposed mechanism of action.

peripheral blood mononuclear cells, including antigen-presenting cells (APCs), that are activated ex vivo by culture with a recombinant protein consisting of prostatic acid phosphatase (PAP), an antigen expressed in more than 95% of prostate tumors, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator, Figure 2.[39,40]

During ex vivo culture with the PAP-GM-CSF antigen, APCs take up and process the recombinant antigen into small peptides that are then displayed on the APC surface. These antigen-loaded APCs have the ability to initiate an adaptive immune response by activating antigen-specific T cells.[41] In the pivotal trial of sipuleucel-T, immune responses were assessed in a subset of patients.[39] In the sipuleucel-T group, antibody and T-cell responses against the immunizing antigen were observed in 66.2% and 73.0% of patients, respectively, compared with 2.9% and 12.1% of patients in the control group. Patients in the sipuleucel-T group who had an antibody titer > 400 against the immunizing antigen at any time after baseline lived longer than those who had an antibody titer ≤ 400 ($p < .001$).

Sipuleucel-T was initially evaluated in two phase III clinical trials involving men with metastatic CRPC and no cancer-related pain.[42,43] At the time these trials were developed, there were no approved therapies for men with metastatic CRPC. The primary endpoint in both trials was time to progression (TTP). Disease progression was defined as radiographic evidence of progressive disease, or new cancer-related pain associated with a radiographic anatomical correlation, or other clinical events consistent with progression.

In trial D9901, 127 patients were randomized, 82 patients in the sipuleucel-T group and 45 patients in the control group. Median TTP was 11.7 weeks in the sipuleucel-T group compared with 10.0 weeks in the control group ($p = .052$).[42] Although this trial did not meet its primary endpoint, a planned survival analysis demonstrated a significant survival benefit for treatment with sipuleucel-T (median survival 25.9 weeks versus 21.4 weeks in the control group [$p = .010$]).[42,43] The second trial, D9902A, also showed no benefit in terms of TTP.[43]

Based on the findings from these two trials, a larger trial, IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment), was initiated and overall survival was reported as the primary endpoint, Table 1. The IMPACT trial randomized 512 men with asymptomatic or minimally symptomatic (not needing opioids for cancer-related pain) metastatic CRPC to the sipuleucel-T group (n = 341) or the control group (n = 171).[39]

The median survival was 25.8 months in the sipuleucel-T group compared with 21.7 months in the control group (HR = 0.78 (95% CI 0.61, 0.98 [$p = .03$])), and the 36 month survival probability was 31.7% versus 23% in the control group.[39] As observed in the previous trials, TTP was not significantly different in the two groups. In the IMPACT trial, TTP was defined as radiographic evidence of progressive disease. On determination of objective disease progression, patients were treated at the discretion of their physicians, including docetaxel-based therapy (57.2% of patients in the sipuleucel-T group). Sensitivity analyses adjusting for the use and timing of docetaxel in the IMPACT trial and in an analysis of all three phase III trials of sipuleucel-T showed a consistent treatment effect for sipuleucel-T, confirming that the survival benefit is independent of the effects of subsequent docetaxel therapy.[39,44]

Adverse events were mild to moderate in 65.2% of patients.[39] Adverse events that were more frequently reported in the sipuleucel-T group included chills, fever, and headache. These data were the basis for the approval of sipuleucel-T for men with asymptomatic or minimally symptomatic metastatic CRPC.

The survival benefit of 4.1 months in the IMPACT trial and 4.5 months in the D9901 trial may underrepresent the survival benefit of therapy with sipuleucel-T. On determination of objective disease progression, patients in the control arm had the option of receiving 3 infusions of an autologous immunotherapy made from cells cryopreserved at the time of control generation (APC8015F).[39,42,43] In an integrated analysis, 66.3% (165/249) received APC8015F. APC8015F-treated patients had improved postprogression survival compared with untreated controls (HR = 0.52 (95% CI 0.37, 0.73 [$p = .0001$])).[45] Thus, postprogression treatment with APC8015F may have extended survival in the control group, potentially reducing the magnitude of the survival difference observed between the sipuleucel-T group and the control group.

Sequencing available treatment options

With the rapidly changing treatment landscape for metastatic CRPC, it is important to integrate these new therapeutic options to ensure that patients have the opportunity to take advantage of agents providing a survival benefit. For men with metastatic CRPC, the course of their disease may have extended over 10 to 15 years,[4,5] and they may have received multiple therapies, including surgery, radiation therapy, and various hormonal therapies. Given that most of these men are older and dealing with medical comorbidities

and the toxicities associated with the long term use of ADT, their ability to tolerate additional treatment for metastatic CRPC might be compromised.

Sipuleucel-T expands treatment options by providing a significant clinical benefit for men with asymptomatic or minimally symptomatic metastatic CRPC. Patients with metastatic CRPC who benefit most are those who do not need opioids or steroids for cancer-related pain and who have a good performance status, with life expectancy greater than 6 months. The goal is to provide maximum time to achieve an immune response before moving on to subsequent therapies. Docetaxel-based chemotherapy is considered the best option for men with metastasis who develop symptoms such as pain, and therefore have a more clinically advanced stage of the disease.[38] However, patients with asymptomatic or minimally symptomatic disease who had prior exposure to chemotherapy also benefited from sipuleucel-T despite more clinically advanced disease.[39]

Intriguing emerging data suggest that subsequent therapies may combine with the induced immune response from active immunotherapies, resulting in a combination that is more effective than either treatment alone.[46,47] Analyses of studies of other active immunotherapies have found that patients who received an active immunotherapy did better than expected on subsequent chemotherapy.[48,49] Whether sipuleucel-T induces an immune response that augments subsequent therapies awaits further studies.

Other immunotherapies in development for the treatment of advanced prostate cancer

The approval of sipuleucel-T seems to have invigorated efforts to leverage the immune system against cancer. Three agents in development are GVAX (BioSante, United States), ipilimumab (Yervoy: Bristol-Myers Squibb, United States), and PSA-TRICOM (Prostvac: Bavarian Nordic ImmunoTherapeutics, United States).

GVAX is a granulocyte-macrophage colony-stimulating factor (GM-CSF)–secreting, allogeneic cellular immunotherapy based on two prostate cancer cell lines that were genetically modified with the gene that encodes human GM-CSF and then irradiated to prevent cell division. Treatment with GVAX involves injection of whole tumor cells to provoke an immune response to prostate cancer. The rationale for this therapy is that the multiple antigens expressed by the tumor cells coupled with GM-CSF to induce growth, maturation, and recruitment of dendritic cells to process and present the antigens would increase the likelihood of a robust immune response to the diverse antigens in cancer cells in advanced disease.[50,51]

Two phase I/II trials of GVAX in men with asymptomatic metastatic CRPC showed promising clinical activity and provided a foundation for two phase III trials, one of GVAX versus docetaxel plus prednisone in men with asymptomatic metastatic CRPC and the other of GVAX plus docetaxel versus docetaxel plus prednisone in men with symptomatic metastatic CRPC, Table 2.[51-55] The first trial was prematurely terminated for lack of efficacy based on an interim analysis.[52] The second trial was also prematurely terminated, but in this case due to an excess of deaths in the treatment arm.[54] Only recently has clinical development of GVAX been reinitiated.

Ipilimumab is a fully human monoclonal antibody that binds to cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). CTLA-4 is a molecule expressed by T cells after they have been activated. The binding of these T cells to APCs through CTLA-4 is a mechanism to down-regulate T-cell activation. Ipilimumab, by blocking this interaction, is thought to prolong and enhance T–cell-mediated immune activity—releasing the brake on the immune system.[55]

Ipilimumab has been studied most extensively in metastatic melanoma where it was shown to provide improved overall survival compared with an active control.[56] Early work in metastatic CRPC demonstrated PSA-modulating effects.[57] In a phase II study, patients with nonmetastatic disease treated with androgen ablation and ipilimumab were more likely to have undetectable PSA levels at 3 months (55% compared with 38% with androgen ablation alone).[58] Ipilimumab is currently being evaluated in two phase III clinical trials with overall survival as the primary endpoint, Table 2.[59,60] The first trial compares ipilimumab with placebo in men with asymptomatic or minimally symptomatic metastatic CRPC, and the second compares ipilimumab with placebo following radiotherapy in men with metastatic CRPC who have received prior docetaxel therapy.

PSA-TRICOM is a prostate cancer vaccine regimen that consists of a primary vaccination with a recombinant vaccinia virus vector followed by several booster vaccinations with a recombinant fowlpox virus vector. Both vectors contain transgenes for human PSA and 3 T-cell costimulatory molecules. PSA-TRICOM was designed to enhance and sustain an antitumor immune response. The vaccines are given subcutaneously where they infect APCs and generate proteins on the surface of the APCs. Interaction of these APCs with T cells initiates an immune response targeted to prostate cancer.[61]

TABLE 2. **Immunotherapies in development in metastatic CRPC**

Immunotherapy	Clinical development	Trial design	Results
GVAX	Phase III	GVAX vs. docetaxel plus prednisone in asymptomatic metastatic CRPC	Prematurely terminated for lack of efficacy
	Phase III	GVAX plus docetaxel vs. docetaxel plus prednisone in symptomatic metastatic CRPC	Prematurely terminated due to survival advantage in the control group: 12.2 months in the treatment group vs. 14.1 months in the control group
Ipilimumab	Phase III	Ipilimumab vs. placebo in asymptomatic or minimally symptomatic metastatic CRPC	Ongoing
	Phase III	Ipilimumab vs. placebo following radiotherapy in metastatic CRPC post-docetaxel	Ongoing
PSA-TRICOM	Phase II	PSA-TRICOM vs. control in minimally symptomatic CRPC	Primary endpoint PFS: 3.8 months vs. 3.7 months in the control group At 3 years, OS 25.1 months vs. 16.6 months; HR 0.56 (95% CI, 0.37 to 0.85)

In a randomized phase II trial of PSA-TRICOM in men with minimally symptomatic (not requiring narcotics for cancer-related pain) metastatic CRPC, an overall survival benefit of 8.5 months (25.1 months in the PSA-TRICOM group compared with 16.6 months in the placebo group) was seen at 3 years post-study, Table 2. Overall survival, however, was not the primary endpoint in this trial. Similar to the initial phase III trials of sipuleucel-T, the primary endpoint was PFS, and no difference between the two groups was found.[62]

Discussion

Sipuleucel-T represents the first active immunotherapy approach to the treatment of prostate cancer and solid tumors in general. The survival benefit paired with a lack of effect on disease progression is perplexing for many. This discordance between survival and disease progression also has been observed with PSA-TRICOM and ipilimumab. The randomized phase II trial of PSA-TRICOM in men with metastatic CRPC showed a significant survival advantage with similar PFS in the two groups.[62] In metastatic melanoma, ipilimumab demonstrated a survival benefit without any improvement in median PFS compared with an active control.[56]

Thus, a survival benefit without an impact on PFS may be a feature of immunotherapies. This phenomenon may reflect the time it takes to generate an immune response. Unlike cytotoxic therapies, which have their greatest effects soon after initiation of therapy, immunotherapies engage the immune system to generate a response—a process that may take months. Madan et al[63] proposed a model in which immunotherapy induces an active antitumor immune response that produces a continued cumulative slowing pressure on tumor growth rate rather than an immediate or dramatic change in tumor burden. These changes may lead to substantially longer overall survival. Whether conventional response measures can adequately capture clinical benefit for immunotherapies remains to be proven.

The relatively short duration of therapy and the absence of an effect on disease progression present a dilemma for physicians seeking to understand how to sequence therapies. Since patients are maintained on ADT during therapy with sipuleucel-T, secondary hormonal manipulations may be a strategy for managing PSA. Changes in symptoms or dramatic

changes in PSA or PSA velocity serve as indicators to perform repeat imaging to determine if objective disease progression has occurred and whether or not to introduce subsequent therapies. The decision to recommend additional therapeutic options should be based on clinical judgment; however, delaying therapies such as chemotherapy or corticosteroids for as long as possible will minimize the negative impact of their immunosuppressive effects on the induced immune response.[64]

Efforts to identify markers of response are ongoing. A recent report on the effect of sipuleucel-T on time to disease-related pain in patients with asymptomatic metastatic CRPC indicated 12 month pain-free estimates at 39.3% for sipuleucel-T compared with 18.9% for control.[65] There was a trend toward a delay in time to disease-related pain beginning 6 months after randomization, which is consistent with a potentially delayed antitumor effect of immunotherapy.

Current data demonstrate that sipuleucel-T is a viable treatment option for men with asymptomatic or minimally symptomatic metastatic CRPC. Research related to optimal timing of immunosuppressive agents following treatment with sipuleucel-T as well as ongoing research in earlier stages of disease and in combination with other new treatment options will help realize the full potential of immunotherapy in the treatment of prostate cancer.

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