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Review article

Immunotherapy for castration-resistant prostate cancer: Progress and new paradigms

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Abstract

Background: The approval of sipuleucel-T in conjunction with data from other immunotherapeutic trials for prostate cancer and other solid tumors demonstrates the potential of harnessing the patient's immune system for long-term survival. Thus, a range of therapeutic approaches are under evaluation. This review describes the rationale for immunotherapy for prostate cancer, summarizes the approaches under evaluation, and discusses sequencing options for immunotherapy in the current treatment paradigm.

Design: References for this review were identified through searches of PubMed with the search terms "prostate cancer," "immune system," "vaccine," "immunotherapy," and "T cells." Articles were also identified through searches of the authors' own files. The final reference list was generated based on originality and relevance.

Results: The immune system can recognize and respond to prostate tumor antigens, effected through tumor-associated antigens and tumor infiltration of immune effector cells. However, evidence also suggests that prostate tumors are adept at escaping immunological recognition, thus hypothesizing multiple therapeutic strategies. Therapeutic approaches could include vaccination and modulation of T-cell function via the blockade of checkpoint receptors such as cytotoxic T-lymphocyte antigen-4 and programmed death 1. In phase III trials, sipuleucel-T improved overall survival for an M1 patient population with castration-resistant prostate cancer and ipilimumab also did so when given after radiotherapy in a subset of better risk patients. In randomized phase II trials, prostate-specific antigen-TRICOM improved overall survival and tasquinimod improved progression-free survival.

Conclusion: Although immunotherapy has the potential to affect advanced prostate cancer, additional research is needed to (1) identify predictive or surrogate markers of activity, (2) understand which agents are clinically effective alone or in combination with other therapies, and (3) define the optimal timing for an immunotherapy to achieve maximal benefit.

Keywords: Prostate cancer; Immunotherapy; Vaccine; T cell; Immune system

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1. Introduction

Prostate cancer is the most common cancer among men worldwide and a leading cause of cancer deaths among them [1]. Early-stage prostate cancer can be managed with an "active surveillance" approach, brachytherapy, external beam radiotherapy (RT), and radical prostatectomy, with a minority of patients eventually developing metastatic disease. Patients whose disease recurs after interventional treatment or for those with de novo metastatic disease are often treated with androgen deprivation therapy (ADT). Disease that progresses despite ADT is referred to as castration-resistant prostate cancer (CRPC). Until relatively recently, the prognosis of patients with metastatic CRPC (mCRPC) was poor, with a median survival for docetaxel-based therapy of less than 2 years and no viable treatment options for patients ineligible or progressing on or after treatment with docetaxel [1].

During the past 3 years, progress has been made with drugs such as cabazitaxel, abiraterone, enzalutamide, and radium-223, thus improving the overall survival (OS) of patients who were previously treated with docetaxel [1,2]. Abiraterone plus prednisone significantly improved progression-free survival (PFS) when compared with prednisone alone in chemotherapy-naïve patients with mCRPC (16.5 vs. 8.3 mo; the median OS with abiraterone was not reached after 22.2 mo of follow-up) [3], and sipuleucel-T extends survival in men with asymptomatic or minimally symptomatic mCRPC (25.8 vs. 21.7 mo with placebo) [4]. Results of an interim analysis from the phase III PREVAIL trial were recently reported, showing a 29% reduction in the risk of death with enzalutamide over placebo ($P < 0.001$) in men with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC [5].

Although metastatic prostate cancer is invariably a lethal outcome, it offers multiple opportunities for therapeutic intervention. Recent improvements in the understanding of tumor-host interactions have led to numerous immunotherapeutic approaches with the potential to complement, and synergize with, other approved treatment modalities. This review presents the rationale for using immunotherapy to treat CRPC, summarizes recent clinical and trial progress, and discusses sequencing strategies for immunotherapy regarding CRPC treatment paradigms.

2. Immune cells and the tumor microenvironment

The immune system's ability to respond to the biology of neoplasia has been well documented. Cell types central to the recognition and destruction of tumor cells include macrophages/antigen-presenting cells (APCs), $CD8^+$ cytotoxic T cells, and natural killer cells. Pathophysiologically, tumors are adept at developing pathways to suppress immune responses and escape from immune destruction, culminating with evasion and clinical progression. Potential mechanisms of evasion include the modulation of immune-inhibitory (checkpoint) pathways to suppress T-cell activity and the disruption of antigen processing and presentation. Tumors can also recruit and promote the development of immunosuppressive cell types, in particular regulatory T cells (Tregs). Tumors may directly or indirectly mediate the release of immunosuppressive factors, such as transforming growth factor β and interleukin (IL)-10, which contribute to the development of an immunosuppressive microenvironment in and around the tumor [2,6].

As in other tumor types, clinical trial data have demonstrated that the immune system can recognize and respond to prostate cancer cells. Spontaneous or endogenous immunity to prostate cancer cells is because of adaptive as well as innate immunity. Indeed, data suggest that both the innate and the adaptive immune systems are modulated or dysregulated in patients with prostate cancer, which thereby presents an opportunity to target multiple molecules within immune regulatory pathways [2].

To understand the involvement of the immune system in various tumor types, the presence of tumor-infiltrating cells and their correlation with clinical outcomes is important. For example, in advanced ovarian carcinoma, the duration of OS and PFS was significantly longer in patients with tumor-infiltrating T cells [7]. Similar data have been reported in a range of tumor types, including prostate cancer, where although the data are more limited and somewhat inconclusive, there is evidence to suggest that the infiltration of prostate tumors by certain immune cells is associated with prognosis (data are summarized in Table 1) [8–14]. In a joint international initiative, several national and international cancer and immunotherapy associations have initiated a protocol for developing and validating an immune score based on the type and the density of immune cells in tumor infiltrates [15]. Initially evaluated in colorectal cancer, such "immune profiling" of the tumor immune microenvironment appears to be one of the strongest

Table 1
The immune system in prostate cancer [8–14]

Evidence of a protective immune response
Presence of effector T cells specific to TAAs [8]
Presence of effector T cells specific for epitopes on the androgen receptor [9]
Presence of antibodies against NY-ESO-1, a TAA [10]
NK cell tumor infiltration (potential protective role—correlated with a lower risk of progression after ADT) [11]
Potential mechanisms of prostate cancer immune escape
Impaired NK cells (altered activating and inhibitory receptor profiles and decreased cytolytic function) [12]
Increased levels of circulating and tumor-infiltrating immunosuppressive Tregs (associated with a poorer prognosis) [13]
Infiltration of macrophages (after ADT) associated with an increased risk of recurrence [11]
High PD-1 expression on tumor-infiltrating CD8 T-cells indicating inactivity/exhaustion [14]

NK = natural killer.

prognostic factors for disease-free survival and OS. Researchers are now evaluating whether immune profiling may serve as a tool to help guide decision making and for evaluating novel therapies, including immunotherapy, in other solid tumor types, including prostate cancer. Hence, immunotherapies are predicated on the potential to leverage and amplify existing immune mechanisms (i.e., break tolerization and stimulate apoptosis) and thus provide an effective antitumor response.

3. Immunotherapy treatment strategies for prostate cancer

Considering the immune system's ability to respond to prostate cancer antigens, a range of immunotherapeutic strategies are being developed and evaluated with the goal of inducing de novo or reactivating antitumor immune responses or both. A key component to this strategy is to overcome the mechanisms tumors use to escape detection and destruction by the immune system. These escape mechanisms are mediated by various factors including immunosuppressive cells (e.g., Tregs), soluble factors (e.g., tumor growth factor β1), and immune checkpoint inhibitors (e.g., programmed death 1 [PD-1]) [6]. An overview of the key complete and ongoing trials with immunotherapies in mCRPC is provided in Tables 2 [4,16–35] and 3, respectively.

3.1. Vaccines

"Vaccines" is a broad term encompassing various approaches to elicit and enhance an immune response to tumor-associated antigens (TAAs). Antitumor vaccines can be generic (i.e., created or engineered to deliver selected TAAs known to be immunogenic) or personalized (i.e., generated from the patient's own tumor-reactive immune cells) (Table 2). Several prostate TAAs have been identified that may form the basis of immunotherapeutic approaches (Table 4) [10,36]. Of the peptide vaccines, prostate-specific antigen (PSA)-TRICOM (PROSTVAC; Bavarian Nordic, Kvistgaard, Denmark) has shown promising efficacy and tolerability in a phase II trial. Although there was no improvement in PFS—the primary end point of the study—and PSA responses were infrequent, the vaccine improved OS when compared with placebo (25.1 vs. 16.6 mo, $P = 0.006$) [16]. It is unclear whether the OS benefit reported in the absence of a PFS improvement or responses is because of the unique patterns of response reported with some immunotherapies (as discussed in Section 4.2) or because of a confounding factor, as has been proposed as occurring in the sipuleucel-T Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) (discussed later) [37]. Nevertheless, these data led to the opening of the phase III PROSPECT trial (NCT01322490) to evaluate whether PSA-TRICOM, with or without granulocyte-macrophage colony-stimulating factor (GM-CSF), can prolong survival in chemotherapy-naïve patients with mCRPC. PSA-TRICOM is also being studied in a phase II trial (NCT01145508) as an add-on to a chemotherapy doublet of docetaxel with prednisone (Table 4). However, thorough analysis of data from these ongoing trials is needed to demonstrate unequivocally that any benefit is because of the vaccine.

Personalized peptide vaccine (PPV), an approach that "screens" patients for their immunoreactivity against a panel of epitopes from TAAs before vaccinating them with up to 4 peptides to which they had reacted most strongly, improved PFS when added to low-dose estramustine therapy (Table 2) [17]. PPV plus low-dose estramustine was well tolerated and increased levels of immunoglobulin G (IgG) and cytotoxic T-cell responses to the vaccinated peptides. A prospective cohort trial comparing PPV in patients in whom treatment with docetaxel had failed and patients who had not received docetaxel showed a significant survival benefit for the latter group (Table 2), and there was a nonsignificant survival benefit of 7.3 months (17.8 [95% CI: 14.9–20.6] vs. 10.5 [95% CI: 7.1–14.0]) for PPV-treated patients in whom previous treatment with docetaxel had failed when compared with matched historical controls who did not receive PPV [18].

Vaccines based on nucleic material from TAAs have also been studied in prostate cancer. For example, DNA vaccine pTVG-HP has produced immunological responses in patients with recurrent, localized prostate cancer and some evidence of clinical responses (Table 2) [19]. Of 8 patients who had a $\geq$200% increase in PSA doubling time, 6 had detectable long-term prostatic acid phosphatase–specific interferon-γ–secreting T-cell responses [36]. An ongoing phase II trial (NCT00849121) evaluating the immunogenicity of pTVG-HP with GM-CSF as an adjuvant is ongoing. CV9103 (RNActive; CureVac GmbH, Tübingen, Germany), an RNA vaccine encoding for PSA, prostate stem cell antigen, prostate-specific membrane antigen, and six transmembrane epithelial antigen of the prostate 1, was safe and well tolerated in a phase I/IIa study and had encouraging signs of clinical efficacy (Table 2) [20]. A phase IIb trial is ongoing (NCT01817738).

Another type of anticancer vaccine was derived from whole tumor cells modified genetically to coexpress another molecule, an adjuvant such as GM-CSF. GVAX, a whole-cell vaccine expressing GM-CSF, had shown promising clinical activity in phase I when combined with ipilimumab, a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4) (Table 2) [33]. However, 2 phase III trials using GVAX alone and in combination with docetaxel were stopped early because of a lack of efficacy and increased mortality [38,39].

A growing area of interest is the use of "cell-based vaccines" made from a patient's own APCs and precursors, which are activated ex vivo with TAA and reinfused into the patient. The best known of these is sipuleucel-T, which

Table 2
Immunotherapeutic treatment strategies for prostate cancer [4,16–35]

Agent(s)	Description	Key studies	Key outcomes	Reference
Peptide vaccines				
PSA-TRICOM (PROSTVAC)	PSA + 3 T-cell costimulatory molecules (B7-1, LFA-3, and ICAM-1)	A phase II RCT in 125 patients with mCRPC randomized 2:1 to receive 1 priming dose (2×10^8 pfu) and 6 booster doses (1×10^9 pfu) of PSA-TRICOM + GM-CSF or control vector + saline injections	Patients receiving PSA-TRICOM had longer median OS by 8.5 mo (25.1 vs. 16.6 for controls; HR = 0.56, 95% CI: 0.37–0.85, $P = 0.006$) and better 3-y survival rates (25/82 [30%] vs. 7/40 [17%])	Kantoff et al. [16]
Personalized peptide vaccine (PPV)	Vaccine prepared with ≤4 peptides according to each patient's immunoreactivity profile; peptides derived from various TAAs (including PSA, PAP, PSMA, and MDRP)	A phase II trial in 57 patients with CRPC randomized to treatment with PPV and either low- or standard-dose EMP (280 vs. 560 mg/d, respectively)	PPV/low-dose EMP: 6/27 patients (21%) PR; 15/27 patients (54%) SD as best responses PPV/standard-dose EMP: 6/28 patients (20%) PR; 8/28 patients (28%) SD as best responses Median PFS was 8.5 mo (95% CI: 4.7–8.8) vs. 2.8 mo for PPV/low-dose EMP vs. PPV/standard-dose EMP, respectively (HR = 0.28, 95% CI: 0.14–0.61, $P = 0.001$) Median OS was undefined (95% CI: 11.7–17.4) vs. 16.1 mo (95% CI: 8.0–13.4) for PPV/low-dose EMP vs. PPV/standard-dose EMP, respectively (HR = 0.30, 95% CI: 0.10–0.91, $P = 0.033$)	Noguchi et al. [17]
		A phase II open-label study comparing PPV in 20 patients in whom treatment with docetaxel had failed and 22 patients who had not received docetaxel	Median OS was 14 · 8 mo (95% CI: 9.7–20.0) for PPV after treatment with docetaxel vs. not reached within 22 mo for PPV without treatment with docetaxel (HR = 0 · 38, 95% CI: 0.13–1.13, $P = 0.081$)	Noguchi et al. [18]
DNA/RNA vaccines				
pTVG-HP PAP vaccine	PAP-encoding plasmid DNA	A phase I/IIa single-arm, dose-escalation study (100, 500, or 1,500 μg) in 22 patients with recurrent stage D0 prostate cancer receiving pTVG-HP coadministered with GM-CSF 6 times at 14-d intervals	Immunological responses: 6/22 patients (27.3%, 95% CI: 13.1–48.2) developed at least a 3-fold increase in PAP-specific $CD4^+$ proliferative T cells, and 3/22 patients (13.6%, 95% CI: 4.7–33.3) developed at least a 3-fold increase in $CD8^+$ proliferative T cells Clinical responses: 7/22 patients experienced at least a doubling of the PSA doubling time; median increase in PSA doubling time from the pretreatment to the on-treatment period was 1.3 mo (4.4–24.0 mo, $P = 0.033$)	McNeel et al. [19]
CV9103 (RNActive)	PSA, PSCA, PSMA, and STEAP1 as self-adjuvanted full-length mRNAs	A phase I/IIa single-arm, dose-escalation study (256, 640, or 1,280 μg total mRNA) in 44 patients with CRPC (>80% mCRPC) with increasing PSA levels received CV9103 at 1, 3, 7, 15, and 23 wk	Immunomonitoring performed in 33/38 patients in the high-dose cohort; induction of antigen-specific T cells in 79% of patients, more than half of whom developed immune responses to >2 antigens	Kübler et al. [20]

Cell-based vaccines				
Sipuleucel-T	Autologous PBMCs (including APCs) activated ex vivo with a recombinant fusion protein (PA2024) comprising PAP fused to GM-CSF	A phase III RCT (IMPACT) in 512 men with mCRPC randomized 2:1 to receive sipuleucel-T or placebo Q2W for 3 infusions; OS was the primary end point	Patients receiving sipuleucel-T had a relative reduction in risk of death of 22.0% ($P = 0.03$) vs. placebo (HR = 0.78, 95% CI: 0.61–0.98); this represented a 4.1-mo improvement in median OS (25.8 mo) vs. placebo (21.7 mo) There was no effect of treatment on objective or clinical TTP Sipuleucel-T was well tolerated; infusional AEs, including fever/chills, mainly grade 1/2	Kantoff et al. [4]
		A phase III RCT in 127 men with asymptomatic mCRPC randomized 2:1 to receive sipuleucel-T or placebo every 2 wk for 3 infusions; TTP was the primary end point	TTP did not improve significantly after sipuleucel-T; 11.7 wk (95% CI: 9.1–16.6) vs. 10.0 wk (95% CI: 8.7–13.1) for placebo (HR = 1.45, 95% CI: 0.99–2.11, $P = 0.052$) Possible survival advantage after treatment with sipuleucel-T; median OS was 25.9 mo (95% CI: 20.0–31.9) vs. 21.4 mo (95% CI: 12.3–25.8) for placebo (HR = 1.70, 95% CI: 1.13–2.56, $P = 0.01$) In a patient subset, median ratio of T-cell stimulation index at 8 wk was approximately 8-fold higher vs. preinfusion after treatment with sipuleucel-T (16.91 vs. 1.99, $P = 0.001$) Treatment was well tolerated; rigors (59.8% vs. 8.9%) and pyrexia (29.3% vs. 2.2%) for treatment vs. placebo, respectively, were the most common AEs, both primarily infusion reactions	Small et al. [21]
		Sequential phase I and II trials to determine the safety, efficacy, and capacity to break immune tolerance to PAP in 31 patients with mCRPC who received sipuleucel-T for 3 infusions every 4 wk; patients improving or with SD had a fourth infusion in week 24	There was a >50% decrease in PSA level in 3 patients, and another 3 had 25%–49% decreases in PSA levels Of 26 patients, 10 (38%) developed immune responses to PAP Median TTP: 34 wk for patients who developed immune response ($n = 20$) vs. 13 wk for patients who did not ($n = 11$); $P = 0.027$ Treatment was well tolerated; fever was the most common AE, after 15 infusions (14.7%)	Small et al. [22]
DCVAC/Pa	Dendritic cells pulsed with killed LNCap prostate cancer cell line	A phase I/II trial using DCVAC/Pa for patients with biochemical failure after prostatectomy or primary radiotherapy. Patients received 12 doses of vaccine at 4-wk intervals	Of 20 treated patients, all had a significantly prolonged PSA doubling time; 7 had stable PSA levels during the treatment. Mean PSA doubling time increased from 8.15 mo before therapy to 52.64 mo after 12 doses ($P < 0.0015$). Treatment did not lead to any significant side effects	Spisek et al. [23]
T-cell modulators				
Ipilimumab	Fully human monoclonal antibody against CTLA-4 with chemotherapy	A phase I study of a single, 3 mg/kg dose of ipilimumab in 14 patients with mCRPC	There was a ≥50% decrease in PSA level in 2 patients; treatment was well tolerated	Small et al. [24]
Ipilimumab following radiotherapy	As above	A phase III trial comparing ipilimumab vs. placebo following radiotherapy in patients with mCRCP previously treated with docetaxel	The primary end point was not met (OS: ipilimumab, 11.2 mo; placebo, 10.0 mo; HR = 0.85; $P = 0.053$); the safety profile was consistent with prior studies. Post hoc subgroup analysis showed that ipilimumab improved OS in patients with a better prognostic profile (median OS: ipilimumab [$n = 146$], 22.7 mo; placebo, 15.8 mo [$n = 142$])	Kwon et al. [25]
Ipilimumab with GM-CSF	As above, with adjuvant	A phase I study of ipilimumab (0.5–10 mg/kg on day 1 of each 28-d cycle × 6) with GM-CSF (250 μg/m^2/d) on days 1–14 of each 28-d cycle in 36 patients with mCRPC	Of 6 patients treated at 3 mg/kg, 3 (50%) had confirmed decreases in PSA levels of ≥50%, with TTP of 22, 26, and 103 wk; 1 patient had a PR in hepatic metastases	Harzstark et al. [26]

Table 2
Continued

Agent(s)	Description	Key studies	Key outcomes	Reference
Other immunomodulators				
Tasquinimod	Quinoline-3-carboxamide with antiangiogenic and, potentially, immunomodulatory activity	Phase I, dose-escalation studies in patients with chemotherapy-naïve CRPC. Patients ($n = 32$) received tasquinimod for up to 1 y at fixed doses of 0.5 or 1.0 mg/d, or an initial dose of 0.25 mg/d that was escalated to 1.0 mg/d	The maximum tolerated dose was 0.5 mg/d, but using intrapatient dose escalation, 1.0 mg/d was well tolerated. DLT was sinus tachycardia and asymptomatic amylase elevation There was a ≥50% decrease of PSA levels in 2 patients, and the median time to PSA progression (>25%) was 19 wk. Of 15 patients, 3 developed new bone lesions on study (median time on study 34 wk)	Bratt et al. [27]
		A randomized, phase II study comparing tasquinimod (0.25 mg/d escalating to 1.0 mg/d over 4 wk) and placebo in men with chemotherapy-naïve, minimally symptomatic mCRPC ($n = 134$ in tasquinimod arm; $n = 67$ in placebo)	The 6-mo progression-free proportions were 69% and 37% in the tasquinimod and placebo arms, respectively ($P < 0.001$). Median PFS was 7.6 vs. 3.3 mo ($P = 0.0042$) AEs that were more frequent in the tasquinimod arm included gastrointestinal disorders, fatigue, musculoskeletal pain, and elevations of pancreatic and inflammatory biomarkers. The incidence of grade 3/4 adverse events was 40% with tasquinimod vs. 10% with placebo	Pili et al. [28]
Lenalidomide	Oral thalidomide analogue with antiangiogenic and immunomodulatory properties	A phase II, single-institution study of lenalidomide in patients with chemotherapy-naïve CRPC. Patients ($n = 32$) received lenalidomide orally (25 mg/d) for 21 d in 28-d cycles	The rate of clinical benefit (SD/CR/PR) was 63%, the median time to radiographic progression was 4 mo, and median OS was 20 mo. Of 27 PSA-evaluable patients, 13 (48%) had a decrease in PSA level and 3 patients (11%) had a decrease of ≥50% Grade 3/4 hematologic toxicities were the most common AEs. Serious AEs occurred in 14 patients (44%), including 1 patient with a rash definitely related to lenalidomide	Nabhan et al. [34]
Multimodal combinations				
Ipilimumab with or without docetaxel	As above	A randomized, phase II study comparing ipilimumab (3 mg/kg every 4 wk for 4 cycles) alone (A) or with 1 dose of docetaxel (B; 75 mg/m^2 on day 1) in 43 chemotherapy-naïve patients with CRPC	Coadministration of docetaxel did not enhance activity: 6 patients (3 in each arm) had a decrease of >50% in PSA levels; 3 patients (2 in arm A and 1 in arm B) had confirmed PSA responses (79+, 169+, and 280 d) There were no radiologic responses with PSA responses Of 43 patients, 36 (84%) had ≥1 AE related to ipilimumab; the most common included fatigue (44%) and pruritus (26%) Of 43 patients, 3 (6%) experienced an immune breakthrough event	Small et al. [29]
Ipilimumab with ADT	Fully human monoclonal antibody against CTLA-4 with ADT	A randomized, phase II study comparing a single dose of ipilimumab (3 mg/kg) with ADT, with ADT only, in 108 patients with advanced prostate cancer; on progression, those in the latter group were allowed to cross over to the ipilimumab group	Patients receiving ipilimumab with ADT were more likely to have undetectable PSA levels by 3 mo (55% vs. 38%) Some patients treated with ipilimumab had significant clinical response and disease downstaging Of the patients treated with ipilimumab, 15 (27.7%) had cutaneous changes, including localized vitiligo and previously unreported desquamation of atypical nevi	Tollefson et al. [30]

Ipilimumab with or without RT	Fully human monoclonal antibody against CTLA-4 with/without RT	A phase I/II study to assess safety of ipilimumab (3, 5, or 10 mg/kg every 3 wk for 4 cycles) alone or with RT at 3 or 10 mg/kg in 71 patients with mCRPC with/without prior chemotherapy; single-dose RT (8 Gy/lesion, up to 3 lesions per patient) given 24–48 h before first ipilimumab dose	Of 28 tumor-evaluable patients receiving 10 mg/kg of ipilimumab ± RT, 1 had CR and 6 had SD No DLTs; treatment-related AEs and irAEs common across all cohorts with or without RT; irAEs generally responsive to immunosuppressives	Slovin et al. [31]
Ipilimumab with PSA-TRICOM	Fully human monoclonal antibody against CTLA-4 with peptide vaccine	A phase I dose-escalation trial assessing safety/tolerability of ipilimumab (1, 3, 5, or 10 mg/kg every month starting at day 15) with PSA-TRICOM (2×10^8 pfu day 1 then booster doses of 1×10^9 pfu every month starting at day 15) in 30 patients with mCRPC	In 24 chemotherapy-naïve patients, median OS was not reached at publication, and 3-y OS was 52.6% (range: 31.4–72.9); 6 patients with prior chemotherapy had median OS of 31.3 mo (range: 4.8–41.4) and 3-y OS of 16.7% (range: 3.0–56.4) Of 6 patients who received prior chemotherapy, 1 had PSA level decrease from baseline; 14/24 patients (58%) in 3.0-, 5.0-, and 10.0-mg/kg cohorts who were chemotherapy naïve had a PSA level decrease; 6 (25%) had >50% decrease AEs were primarily local grade 1/2 injection-site reactions and irAEs (most commonly rash) No DLTs; combination not associated with increased irAEs compared with ipilimumab alone	Madan et al. [32]
Ipilimumab and GVAX	Fully human monoclonal antibody against CTLA-4 with irradiated allogeneic prostate cancer cells engineered to produce GM-CSF	A phase I dose-escalation trial using 1 GVAX priming dose (5×10^8 cells) with subsequent booster doses (3×10^8 cells) every 2 wk for 24 wk combined with ipilimumab (0.3, 1.0, 3.0, or 5.0 mg/kg) every 4 wk in 28 patients with mCRPC	The 3.0-mg/kg ipilimumab cohort expanded because of serious toxicity/DLT in the 5.0-mg/kg cohort; treatment otherwise tolerable Of 28 patients, 7 (25%) had >50% decrease in PSA levels No PSA responses in the 0.3-/1.0-mg/kg cohorts but 5 of 22 patients (23%) in the 3.0-/5.0-mg/kg cohorts had a confirmed PSA PR (>50% decrease from baseline); all patients with an irAE had PSA PR Median OS of all patients was 29.2 mo; patients who developed PSMA-specific antibody responses had longer median OS than patients who did not (46.5 mo [95% CI: 30.2–62.8] vs. 20.6 mo [95% CI: 19.0–22.2]; $P = 0.028$); 15 patients had SD (duration: 3–27 mo)	van den Eertwegh et al. [33]
Lenalidomide and GM-CSF	Oral thalidomide analogue with an immunostimulatory cytokine	A phase I/II trial in patients with CRPC who has not received prior immunotherapy or chemotherapy ($n = 32$). All patients received 250 ug of GM-CSF given subcutaneously 3 times weekly with lenalidomide given orally 25 mg/d on days 1–21 of a 28-d cycle	The response rate among the 11 evaluable patients was 18%; 81% of patients had a decrease in PSA level, but this was only ≥50% in 4 patients The most common grade 1 and 2 AEs included fatigue (69% of the patients), nausea/vomiting (34%), and diarrhea (28%). Grade 3 or 4 AEs occurred in 22% of the patients and were primarily thrombocytopenia (9%) or neutropenia (19%) or both	Garcia et al. [35]

AEs = adverse events; CR = complete response; DC = dendritic cell; DLT = dose-limiting toxicity; EMP = estramustine phosphate; HR = hazard ratio; ICAM-1 = intercellular adhesion molecule-1; IMPACT = Immunotherapy for Prostate Adenocarcinoma Treatment; irAE = immune-related adverse event; LFA-3 = leukocyte function–associated antigen-3; MDRP = multidrug resistance protein; mRNA = messenger RNA; PAP = prostatic acid phosphatase; PBMCs = peripheral blood mononuclear cells; pfu = plaque-forming units; PR = partial response; PSCA = prostate stem cell antigen; PSMA = prostate-specific membrane antigen; Q2W = every 2 wk; RCT = randomized controlled trial; SD = stable disease; STEAP1 = six transmembrane epithelial antigen of the prostate 1; TTP = time to progression.

Table 3
Selected ongoing studies of immunotherapy in prostate cancer

Therapy	Phase	Description	Study identifier	Latest status[a]
Vaccines				
PSA-TRICOM with or without GM-CSF	III	An RCT evaluating efficacy in asymptomatic/minimally symptomatic patients with mCRPC Primary outcome: OS Secondary outcomes: proportion of event-free patients vs. placebo	NCT01322490	Recruiting; estimated study completion date, August 2016
pTVG-HP with GM-CSF	II	A randomized, open-label, 2-arm study comparing different dosing schedules (one schedule adaptable based on immune responses) in patients with nonmetastatic CRPC Primary outcomes: safety and immune responses Secondary outcomes: PSA doubling time and 1-y metastasis-free survival	NCT00849121	Ongoing; estimated study completion date, September 2014
Sipuleucel-T with pTVG-HP DNA booster vaccine	II	An open-label, randomized, efficacy study in patients with mCRPC Primary outcome: immune response Secondary outcomes: PFS, TTP, and PSA doubling time	NCT01706458	Recruiting; estimated study completion date, June 2015
Mixed 20 peptides vaccine	I	An exploratory randomized, open-label, dose-ranging study in patients with CRPC Primary outcome: safety Secondary outcomes: immune responses/minimum immunological effective dose and PSA responses	UMIN000008209	Recruitment completed
T-cell modulators				
Ipilimumab	III	An RCT in chemotherapy-naïve patients with asymptomatic/minimally symptomatic mCRPC comparing ipilimumab with placebo Primary outcome: OS Secondary outcomes: PFS, time to pain progression, time to subsequent nonhormonal systemic therapy, and safety	NCT01057810	Ongoing; estimated study completion date, February 2016
Ipilimumab with or without GM-CSF[b]	II	A randomized, open-label study in chemotherapy-naïve patients with mCRPC Primary outcomes: PSA response, PSA decrease Secondary outcomes: duration of PSA response, time to PSA progression, frequency of immune toxicities, T-cell activation, and objective responses	NCT01530984	Not yet recruiting; estimated study completion date, December 2018
Ipilimumab with GM-CSF[b]	I	An open-label, single-arm, dose-escalation study in patients with mCRPC Primary outcome: MTD that results in that results in $<33\%$ DLT Secondary outcomes: adaptive immunity, PSA and objective responses, safety, anti-idiotype antibody, and PK	NCT00064129	Ongoing
AMG-212—T-cell–engaging, bispecific antibody	I	A first-in-man, open-label, single-arm, dose-escalation study Primary outcomes: safety and MTD Secondary outcomes: PK, tumor responses, and PSA responses	NCT01723475	Recruiting; estimated study completion date, December 2015
Other immunomodulators				
Tasquinimod	III	A randomized, placebo-controlled study of tasquinimod in men with mCRPC Primary outcome: PFS	NCT01234311	Ongoing; estimated study completion date, January 2016
Tasquinimod	II	A randomized, proof-of-concept study of maintenance tasquinimod in patients with mCRPC who are not progressing after first-line, docetaxel-based chemotherapy Primary outcome: radiologic PFS Secondary outcomes: OS, TTP on next therapy, symptomatic PFS, and safety	NCT01732549	Recruiting; estimated study completion date, February 2016

Table 3
Continued

Therapy	Phase	Description	Study identifier	Latest status[a]
Lenalidomide	I/II	A randomized study of 2 different doses of lenalidomide in biochemically relapsed patients with prostate cancer (M0) after local treatment Primary outcomes: safety, tolerance, and rate of PSA progression Secondary outcome: effects on PSA constructs	NCT00348595	Ongoing; estimated study completion date, July 2015
Multimodal combinations				
Enzalutamide with or without PSA-TRICOM	II	A randomized trial combining vaccine therapy and enzalutamide in patients with mCPRC Primary outcome: TTP Secondary outcomes: OS, time to PSA progression, and immune response	NCT01867333	Ongoing; estimated final collection date for primary outcome, June 2016
PSA-TRICOM with docetaxel and prednisone or docetaxel and prednisone alone	II	A randomized, open-label study in patients with mCRPC comparing chemotherapy with or without vaccine Primary outcome: OS Secondary outcomes: TTP, ORs, PSA responses, and immune responses before/after docetaxel; association between PSA-specific immune responses, TTP, and OS, association between predicted and actual survival	NCT01145508	Ongoing; estimated final collection date for primary outcome, June 2013
Sipuleucel-T with indoximod	II	An RCT in patients with mCRPC evaluating addition of IDO inhibitor (indoximod 1,200 mg/d in 2 doses) to vaccine therapy Primary outcome: immune response to vaccine Secondary outcomes: TTP, PFS, ORR, OS, and QoL	NCT01560923	Recruiting; estimate study completion date, July 2015
Sipuleucel-T with enzalutamide	II	Sipuleucel-T with concurrent or sequential enzalutamide in patients with mCRPC Primary Outcome: PA2024-specific T-cell immune response to sipuleucel-T over time Secondary outcomes include time to PSA progression, OS, and safety	NCT01981122	Ongoing; estimated final collection date for primary outcome, September 2015
Sipuleucel-T with abiraterone acetate and prednisone	II	Sipuleucel-T with concurrent or sequential abiraterone acetate plus prednisone (starting next day after first vaccine infusion or 6 wk after last vaccine infusion, respectively) in patients with mCRPC Primary outcome: immune response to vaccine (APC activation) Secondary outcomes: immune response (various parameters); safety	NCT01487863	Ongoing; estimated final collection date for primary outcome, July 2015
Sipuleucel-T and ipilimumab given immediately or delayed	II	A randomized trial to determine the effects of ipilimumab, as an immediate or delayed treatment, following completion of sipuleucel-T in patients with mCRPC Primary outcome: safety and effect of the timing of ipilimumab administration on sipuleucel-T immune responses	NCT01804465	Active; estimated study completion date, December 2016
Sipuleucel-T and ipilimumab	I	A phase I trial in patients with advanced CRPC Primary outcome: antigen-specific memory T-cell response, antigen-specific memory T-cell proliferation, and antibody responses against PA2024 and PAP	NCT01832870	Recruiting; estimated study completion date, December 2015
GVAX with low-dose cyclophosphamide and degarelix acetate, or degarelix acetate alone	I/II	A randomized, open-label study in neoadjuvant setting in patients with high-risk localized prostate cancer	NCT01696877	Recruiting; estimated study completion date October 2015

Table 3
Continued

Therapy	Phase	Description	Study identifier	Latest status[a]
		Primary outcomes: $CD8^+$ T-cell infiltration into the prostate, safety, and tolerability Secondary outcomes: $CD4^+$ T-cell and Treg infiltration into the prostate and their ratio, tissue androgen concentrations/AR expression, markers of apoptosis in prostate tissue, pathological CR, antibodies to prostate-associated antigens, PSA response rate, and time-to-PSA-recurrence		
Ipilimumab with abiraterone acetate and prednisone	I/II	An open-label, single-group study in chemotherapy and immunotherapy-naïve patients with progressive mCRPC Primary objectives: safety and PFS Secondary objectives: PSA kinetics, measurable disease, and radionuclide bone scan	NCT01688492	Recruiting; estimated study completion date, September 2015
Ipilimumab with leuprolide acetate	II	An open-label, single-arm study in a neoadjuvant setting in patients with high-risk localized prostate cancer Primary outcome: immunological measures	NCT01194271	Recruiting; estimated final collection date for primary outcome, September 2015
Ipilimumab with leuprolide, goserelin, or degarelix	II	An open-label study in patients with castration-sensitive prostate cancer Primary outcomes: proportion of patients achieving PSA level $\leq$0.2 ng/ml at the seventh month	NCT01377389	Recruiting; estimated study completion date for primary outcome, June 2016
Ipilimumab with leuprolide acetate, bicalutamide, or ADT alone	II	A randomized, open-label, crossover study comparing ipilimumab with concurrent androgen ablative therapy with an initial phase of ADT alone in patients with CRPC/mCRPC Primary outcome: proportion of patients remaining progression free Secondary outcome: initial PSA response	NCT00170157	Completed, November 2010
CT-011 with sipuleucel-T or with sipuleucel-T and low-dose cyclophosphamide	II	A randomized, open-label pilot study in patients with chemotherapy-naïve mCRPC Primary outcome: feasibility and immune efficacy Secondary outcomes: PFS and OS	NCT01420965	Recruiting; estimated study completion date, December 2017
Lenalidomide with bevacizumab, docetaxel, and prednisone	II	Trial using bevacizumab, lenalidomide, docetaxel, and prednisone in patients with CPRC Primary outcome: safety Secondary outcomes: OS	NCT00942578	Ongoing; estimated study completion date, July 2015
Lenalidomide plus paclitaxel	I/II	A modular trial using lenalidomide and paclitaxel in patients with CRPC and lymph node–dominant metastases Primary outcome: MTD Secondary outcomes: PFS	NCT00933426	Ongoing; estimated study completion date, August 2016

AR = androgen receptor; CR = complete response; DLT = dose-limiting toxicity; IDO = indoleamine 2,3-dioxygenase; MTD = maximum tolerated dose; OR = objective response; ORR = objective response rate; PK = pharmacokinetics; QoL = quality of life; RCT = randomized controlled trial; TTP = time to progression.

[a]Per http://clinicaltrials.gov July 2014.

[b]Given as an adjuvant.

was the first anticancer immunotherapy to be approved by the US Food and Drug Administration. In the landmark phase III Immunotherapy for Prostate Adenocarcinoma Treatment study, sipuleucel-T prolonged survival in men with asymptomatic or minimally symptomatic mCRPC (hazard ratio = 0.78, 95% CI: 0.61–0.98) but had no effect on time to progression [4]. Despite the approval of sipuleucel-T based on these data, concerns were raised that the survival benefit reported in the trial, which was not accompanied by evidence of a measurable antitumor effect, may be because of either an imbalance in unmeasured prognostic variables or a flaw in the trial design [37]. A potentially relevant factor that has been proposed is the different treatment of cells harvested from patients in the placebo arm compared with those in the sipuleucel-T arm. In the placebo arm, two-thirds of the cells harvested were frozen and not reinfused; this large cell loss could have had a detrimental effect on patient survival, potentially

Table 4
TAAs as targets for future prostate cancer vaccines [10,36]

TAA	Description
Prostate stem cell antigen	Expressed in a subset of basal and secretory cells in normal prostate and overexpressed in CRPC and bone metastatic prostate cancers
Prostate cancer membrane antigen	Abundantly expressed at all stages of disease and up-regulated in CRPC and mCRPC
MUC-1	Overexpression of MUC-1 has been related to tumor angiogenesis, proliferation, metastasis, and immunosuppression. Expression of MUC-1 appears different in normal, benign, and cancerous prostate tissues, although further evaluation is needed
uPA and its receptor	The uPA system has a key role in angiogenesis, cancer invasion, and metastasis; it has been strongly associated with prostate cancer metastasis. uPA plasma levels are higher in men with prostate cancer than in normal controls and are reported to be increased in patients with metastatic vs. nonmetastatic disease
EMMPRIN	EMMPRIN can modulate the tumor microenvironment by inducing angiogenic factors and regulating the growth and survival of tumor cells. Data suggest that EMMPRIN has a crucial role in prostate cancer progression
Epidermal growth factor receptor (EGFR)	Increased EGFR expression has been reported for many tumor types. Studies in prostate cancer also showed increased expression, with an association between EGFR expression and tumor progression or the development of androgen independence. Additionally, EGFR overexpression has been associated with an increased rate of relapse after therapy
Platelet-derived growth factor receptor (PDGFR)	PDGFR is expressed by many primary and metastatic prostate tumors and across various stages of disease
NY-ESO-1	NY-ESO-1 is widely expressed by cancers and may elicit spontaneous humoral and cellular immune responses

EMMPRIN = extracellular matrix metalloproteinase inducer protein; MUC-1 = mucin-1; uPA = urokinase plasminogen activator.

accounting for some or all of the OS benefit observed [37]. The alternative explanations proposed for the outcome of the Immunotherapy for Prostate Adenocarcinoma Treatment study were not given credence during an Food and Drug Administration review of the data [40], but they do provide insight relevant for the design of future trials with immunotherapeutics, such as sipuleucel-T and other modalities.

In men with progressing mCRPC, treatment with an autologous, genetically modified dendritic cell vaccine BPX-101 and its chemical activating agent AP1903 elicited measurable clinical responses in some patients, including in those who had visceral metastatic disease (Table 2) [41]. In addition, data suggested a potential synergy between BPX-101 and docetaxel. Another cell-based vaccine under phase III evaluation is DCVAC/Pa (www.clinicaltrialsregister.eu/ctr-search/trial/2012-002814-38/HU). DCVAC/Pa is composed of dendritic cells pulsed with killed LNCap, a prostate cancer cell line. Phase I/II data showed delayed PSA doubling time in all patients, evidence of sustained T-cell responses against prostate cancer antigens, and no significant side effects [23].

3.2. Immunotherapies modulating T-cell function

Ipilimumab is an anti–CTLA-4 monoclonal antibody approved for the treatment of metastatic melanoma. CTLA-4 is an inhibitory immune checkpoint receptor that acts to fine-tune the immune response, preventing autoimmunity. Several phase I and II clinical trials have evaluated different doses, schedules, and combinations in patients with mCRPC (Table 2). In preliminary trials, decreases in PSA levels of $\geq$50% were observed with a single dose of ipilimumab (3 mg/kg), ipilimumab monotherapy (3 mg/kg every 4 wk in chemotherapy-naïve patients), and ipilimumab (0.5–10 mg/kg every 4 wk) in combination with GM-CSF; the results also suggested that ipilimumab could be administered safely, supporting further evaluation [24,26,29]. Data from a small trial using ipilimumab plus docetaxel vs. ipilimumab alone did not suggest that this combination improved the activity of ipilimumab [29]. However, small trials using ipilimumab in combination with ADT or RT showed encouraging clinical activity, supporting further evaluation [30,31].

Combining ipilimumab with a vaccine to enhance costimulation of the immune system has been evaluated using PSA-TRICOM and GVAX. Findings showed that the combinations were feasible [32,33]. Based on data to date, new trials with ipilimumab alone and in combination are planned or ongoing, including a phase III trial in treatment-naïve patients (NCT01057810) (Table 3). Recent data from a phase III trial of a single dose of RT followed by ipilimumab or placebo in previously treated patients showed the primary end point, i.e., OS, was not met (ipilimumab vs. placebo, 11.2 vs. 10.0 mo, respectively; hazard ratio = 0.85; P = 0.053); however, there was an improvement in PFS and PSA responses. The safety profile was consistent with that found in previous ipilimumab studies. Findings from a post hoc, exploratory subgroup analysis showed that ipilimumab did improve OS in patients with a better prognostic profile (no visceral metastases, alkaline phosphatase $<$1.5 times the upper limit of the normal range, and hemoglobin $\geq$11 g/dl), supporting further evaluation of ipilimumab in patients with a lower disease burden (median OS: ipilimumab [n = 146] vs. placebo [n = 142], 22.7 vs. 15.8 mo, respectively) [25]. Another phase III trial has completed enrolling patients with less advanced, chemotherapy-naïve CRPC (Table 3).

Nivolumab is an anti–PD-1 antibody that has been evaluated in a range of solid tumors [42]. Although there were objective responses in patients with other solid tumors, there were no responses in patients with CRPC, although only 17 patients were enrolled. Given the PD-1$^+$ status of

tumor-infiltrating cytotoxic T cells in men with prostate cancer [14], it may be appropriate to investigate PD-1 blockade alone and in combination with other therapies, perhaps for patients with a high level of PD-1^+ T cells in their tissue specimen. CT-011, another anti–PD-1 antibody, is being evaluated in a phase II trial in combination with sipuleucel-T and low-dose cyclophosphamide (NCT01420965). Another T-cell–targeted agent AMG-212, a T-cell–engaging, bispecific antibody, is in early development for treatment of prostate cancer (NCT01723475; Table 3).

3.3. Other immunomodulatory agents

In addition to the therapies discussed, tasquinimod, a quinolone-3-carboxamide, may also have an immunomodulatory effect. A molecular target for tasquinimod is S100A9, an immunomodulatory protein expressed on myeloid-derived suppressor cells. In a phase II trial, in patients with minimally symptomatic mCRPC, tasquinimod significantly slowed progression and improved PFS (6-mo progression-free proportions were 69% with tasquinimod vs. 37% in placebo, $P < 0.001$; Table 2). Adverse events included gastrointestinal disorders, fatigue, and musculoskeletal pain [28]. A phase III trial is ongoing (Table 3).

Lenalidomide is an oral thalidomide analogue that has antiangiogenic, anti-inflammatory, and immunomodulatory effects; it is under evaluation alone and in combination for treatment of prostate cancer [43]. Findings from studies evaluating lenalidomide alone in mCRPC showed evidence of clinical activity (Table 2) [43]. Recent data from a phase II trial in patients with chemotherapy-naïve CRPC showed a PSA level decline in 13 of 27 evaluable patients (48%), with serious adverse events in 44% of patients [34]. Modest antitumor activity was also reported from a phase II trial using lenalidomide plus GM-CSF in patients with CRPC; 81% of the 31 evaluable patients had a PSA decline, and 4 had a decline $\geq$50%. Grade 3 or 4 toxicities occurred in 22% of patients [35]. However, in a phase III trial (MAINSAIL), lenalidomide in combination with docetaxel and prednisone failed to improve survival and increased toxicity in patients with CRPC [44]. Despite the poor outcome with lenalidomide in combination with chemotherapy, phase I and II trials are ongoing to further evaluate the potential of lenalidomide alone and in combination with chemotherapy or targeted therapies or both (Table 3).

4. Integrating immunotherapy into clinical practice

Current evidence demonstrates the potential for immunotherapy to augment advanced prostate cancer treatment. However, the most efficient integration of this approach into clinical practice requires further investigation.

4.1. Optimal use of immunotherapies

A fundamental question arises regarding the optimal timing of immunotherapy. Because OS is the regulatory end point for registrational approval, immunotherapies, as with most new cancer therapies, are initially evaluated in previously treated patients with significantly advanced disease. Nonetheless, the integrity and functional status of the immune system at the time of therapy is an extremely important consideration, as it may be suppressed by previous treatment (e.g., chemotherapy or corticosteroids), extent of tumor burden, and age and associated comorbidities. Hence, immunotherapies may be most effective when administered earlier in the disease paradigm when tumor burden is low (e.g., after debulking therapy).

In support of earlier treatment, a post hoc analysis of data from a trial using sipuleucel-T in patients with symptomatic or minimally symptomatic mCRPC suggested that patients with a lower serum PSA level, and presumably lower disease burden, derived a larger survival benefit when compared with those with higher PSA levels and greater disease burden [45]. Phase III data of ipilimumab in advanced mCRPC suggest that ipilimumab may be more active in patients with a lower tumor burden (i.e., no visceral metastases) [25]. Interestingly, a preclinical study has shown an advantage of administering immunotherapy before castration [46], and in a clinical trial, sipuleucel-T was shown to increase PSA doubling time, consistent with a biological effect, in patients with hormone-sensitive disease [47]. These data support further investigation of immunotherapies in earlier stages of prostate cancer, perhaps as early as the initial hormone-sensitive therapy setting.

Another important consideration is whether the activity of an immunotherapy can be improved by using it in combination or sequentially with another immunotherapy, ADT, or cytotoxic agents such as chemotherapy and RT. The combination of immunotherapy with ADT is being evaluated in several trials, and initial data are encouraging (Tables 2 and 3). In patients receiving ADT, there is evidence of persistent changes in the adaptive immune response and T-cell infiltration into the prostate, providing rationale for combining with immunotherapy [48,49]. Preliminary data from patients treated with sipuleucel-T in concurrent or sequential combination with enzalutamide support the potential of this combination. In 1 case, a patient with rising PSA response on treatment with enzalutamide received sipuleucel-T in addition to enzalutamide; the combination resulted in a complete PSA response, and the timing of the response supported an immune mechanism [50]. The mechanism of action may involve the release of secondary antigens that prime subsequent immune response (antigen spread), as reported recently with sipuleucel-T [51]. Initial data from another trial evaluating sipuleucel-T given concurrently with or before enzalutamide showed that the concurrent approach is feasible and achieves an immunological prime boost [52]. Data from a study of patients who were given sipuleucel-T

before enzalutamide showed encouraging antitumor activity, including a case of radiographic full regression of metastatic lesions in the lung, bones, and lymph nodes [53]. Data from a trial using sipuleucel-T and abiraterone also suggest that this type of combination approach is feasible [54].

Combining immunotherapies with chemotherapy may also be effective, as some cytotoxic agents can stimulate the immune system by either inducing the immunogenic death of tumor cells or engaging immune effector mechanisms [55]. In particular, platinum-based chemotherapies can enhance the immunostimulatory potential of dendritic cells and decrease the immunosuppressive capacity of tumor cells [56]. However, experience shows that the choice of chemotherapy, dose, and scheduling of the agents are all key, unresolved factors. Scheduling may also be an important consideration for RT, which alone has been shown to stimulate the immune system. In transgenic mice that spontaneously develop prostate cancer, the combination of immunotherapy and RT was shown to result in antitumor T-cell activation, but the effect was observed when immunotherapy was given 3 to 5 weeks after RT and not earlier or later [57].

There is a clear rationale for combining immunotherapies that target different components of the immune system, and several trials are in progress (Table 3). Data from a phase I trial showed that ipilimumab in combination with GM-CSF for mCRPC induced clinical responses, warranting further evaluation [26]. One of the most promising approaches is the combination of immune checkpoint inhibitors, given the distinct roles that immune checkpoint molecules play in immune regulatory pathways. In a clinical study of patients with advanced melanoma, the combination of ipilimumab and nivolumab produced rapid and deep tumor responses that appeared to be greater than that with either agent alone [58]. Clinical activity was observed both when the agents were given concurrently and when patients who progressed on treatment with ipilimumab subsequently received nivolumab.

The studies with ipilimumab and nivolumab in combination in advanced melanoma suggest the potential use of these agents in combination or in sequence, and similar studies are ongoing in other tumor types. However, the concurrent administration of immunotherapies and other types of agents may be limited by toxicities, as highlighted by studies with molecularly targeted agents. For example, in a phase I study of concurrent ipilimumab and vemurafenib in BRAF-mutant advanced melanoma, dose-limiting toxicities in the liver were observed, which caused patient enrollment to be stopped [59]. Overall, the results of these studies highlight the importance of carefully optimizing treatment regimens with immunotherapies to minimize patient risk while maximizing benefit.

4.2. Response patterns and safety profile

The collective experience with immunotherapies in the treatment of cancer has revealed that they can produce different response patterns and have a safety profile that is distinct from other therapies. Because immunotherapies produce antitumor effects by inducing or enhancing immune responses, such effects can be delayed and may manifest as a gradual reduction in tumor growth, ultimately resulting in prolonged OS that is not necessarily accompanied by objective tumor responses. For example, studies of ipilimumab monotherapy in advanced melanoma have shown that some tumor responses characterized as "progressive disease" by the standard response criteria may actually be responses to treatment [60]. These "unconventional" responses include the growth of existing, target lesions before a response occurs (resulting initially in an apparent increase in total tumor burden) and the development of new lesions while others are responding ("mixed responses"). Thus, in some patients who ultimately benefit from immunotherapy, the disease may progress before antitumor effects are detected.

These unconventional response patterns are not observed with cytotoxic agents and may reflect the time taken to build antitumor immunity in patients treated with immunotherapy. This may also be reflected in the delayed separation of Kaplan-Meier survival curves observed in immunotherapy trials (e.g., sipuleucel-T in mCRPC and ipilimumab in advanced melanoma) [60]. Contrary to immunotherapies, cytotoxic agents (chemotherapy and RT) elicit their effects directly on tumor cells and cause a rapid reduction in tumor volume in responding patients. These rapid effects can improve PFS but are not always accompanied by an OS benefit. Conversely, immunotherapies may prolong OS without an effect on measures of tumor response [60,61]. This can present a challenge to clinicians evaluating the efficacy of immunotherapies in individual patients, and it may explain why PSA-TRICOM and sipuleucel-T trials in prostate cancer demonstrated an improvement in OS but not improved PFS or PSA responses [4,16,61].

The safety profile of immunotherapies likely also reflects their unique mechanisms of action. For example, with ipilimumab, adverse events consistent with enhanced immune activity are the most common drug-related toxicities observed in patients [24–26]. These have been described as "immune-related adverse events," as they are inflammatory in nature and consistent with immune phenomena. Although immune-related adverse events can be severe and life threatening, most are manageable when treatment guidelines are followed, which include vigilant patient follow-up and the use of corticosteroids. Thus, the recognition of different response patterns and safety profiles, along with their appropriate management, are keys to the successful use of immunotherapies in prostate cancer.

4.3. Potential immune-based predictive and prognostic biomarkers

As discussed in the previous section, one of the challenges in the development of immunotherapies is the accurate assessment of clinical benefit, given the potential

Table 5
Potential immune-based biomarkers in cancer [51,62–66]

Types of candidate biomarkers under evaluation
Immune-gene signatures and genetic profiles [62,63]
Parameters related to the interaction of the immune system and tumor
Immune cell populations including TILs, e.g., ALC [64]
Antibody or T-cell responses to cancer antigens (e.g., NY-ESO-1 [65], KRAS, and PSA) [51]
Soluble factors (e.g., ICOS and IDO) [64,66]
Cell-signalling molecules, including T-cell checkpoint pathways (e.g., PD-L1) [66]

ALC = absolute lymphocyte count; ICOS = inducible T-cell costimulator; IDO = indoleamine 2,3-dioxygenase; PD-L1 = programmed death ligand-1; TILs = tumor-infiltrating lymphocytes.

for different response patterns and delayed effects. Another challenge is the identification of patients who are most likely to benefit from treatment and, in particular, to experience a durable survival benefit. Addressing both will enable the optimal use and integration of immunotherapies into the mCRPC treatment paradigm. Because of the different patterns of clinical activity that can be associated with immunotherapies, using predictive, prognostic, pharmacodynamic, or surrogate biomarkers of activity may enable a better assessment of clinical benefit. Such markers could aid in decision making regarding when to stop or change therapy, something that is becoming increasingly relevant with the number of new drugs. This is an area of active investigation, with potential biomarker candidates being identified, which ultimately have to be validated in prospective studies. An overview of the key areas under investigation for immune-based biomarkers in cancer is provided in Table 5 [51,62–66].

Some proposed biomarkers for prostate cancer include absolute lymphocyte count, T-cell activation and differentiation (e.g., expression of PD-1, CTLA-4, forkhead box P3, and inducible T-cell costimulator), and T-cell activity (e.g., interferon-γ secretion, cytotoxicity, and proliferation). Analysis of data with sipuleucel-T showed that markers of an antigen-specific immune response (APC numbers, APC activation [CD54 up-regulation], and total nucleated cell numbers) correlated with OS, demonstrating immune activation as a mechanism of action for sipuleucel-T and also as potential biomarkers [67,68]. In a trial using ipilimumab and GVAX, high pretreatment frequencies of $CD4^+$/CTLA-4^+, $CD4^+$/PD-1^+, or differentiated (i.e., nonnaïve) CD8 T cells, or low pretreatment frequencies of differentiated CD4 or Tregs, were associated with significantly prolonged OS [67]. Finally, in patients with prostate cancer, data show that a gene signature associated with an adaptive immune response is correlated with a good prognosis [69].

5. Conclusions

It is evident that prostate cancer has the potential to elicit immune responses, and clinical data have proven the principle that immune modulation can prolong survival [4]. However, the development and evaluation of immunotherapies for prostate cancer is in its infancy; perhaps, immunotherapies may be most effective when used earlier in, or throughout, the course of disease or with a combination that is yet to be discovered and schedule of several agents with different, complimentary mechanisms of action. Another important consideration for immunotherapy is that development of an antitumor immune response is likely to be effective irrespective of androgen receptor status [47].

There is also the possibility of identifying patients who are most likely to benefit from therapy. Most intriguing is the possibility of identifying patients with high-risk, localized prostate cancer, screening them for markers indicative of a pre-existing antitumor immune response, and treating them with immunotherapy in a neoadjuvant or adjuvant setting. There is currently substantial evidence that immunotherapy may be of benefit to patients with prostate cancer, either in combination or in sequence with newer agents, and at different disease stages. The continued evaluation of immunotherapy for the treatment of prostate cancer engenders ongoing future promise.

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