

## REVIEW

# Is there a role for immune checkpoint blockade with ipilimumab in prostate cancer?

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**Abstract**

Treatment for advanced prostate cancer has and will continue to grow increasingly complex, owing to the introduction of multiple new therapeutic approaches with the potential to substantially improve outcomes for this disease. Agents that modulate the patient's immune system to fight prostate cancer – immunotherapeutics – are among the most exciting of these new approaches. The addition of antigen-specific immunotherapy to the treatment of castration-resistant prostate cancer (CRPC) has paved the way for additional research that seeks to augment the activity of the immune system itself. The monoclonal antibody ipilimumab, approved in over 40 countries to treat advanced melanoma and currently under phase 2 and 3 investigation in prostate cancer, is thought to act by augmenting immune responses to tumors through blockade of cytotoxic T-lymphocyte antigen 4, an inhibitory immune checkpoint molecule. Ipilimumab has been studied in seven phase 1 and 2 clinical trials that evaluated various doses, schedules, and combinations across the spectrum of patients with advanced prostate cancer. The CRPC studies of ipilimumab to date suggest that the agent is active in prostate cancer as monotherapy or in combination with radiotherapy, docetaxel, or other immunotherapeutics, and that the adverse event profile is as expected given the safety data in advanced melanoma. The ongoing phase 3 program will further characterize the risk/benefit profile of ipilimumab in chemotherapy-naïve and -pretreated CRPC.

## Rationale for Immunotherapy in Prostate Cancer

For men across the world, prostate cancer is the second most common cancer diagnosis and the sixth leading cause of cancer-related death [1]. Most diagnoses (approximately 71%) occur in developed countries where routine prostate-specific antigen (PSA) screening is practiced; thus, the disease is frequently diagnosed in the asymptomatic stage [1, 2]. Even before the appearance of clinical symptoms, immune responses against prostate tumors are evidenced by intratumoral leukocyte infiltration and inflammatory pathway activation [3, 4]. Analyses of tissue samples from prostate tumors have revealed infiltrating leukocytes with a role in innate immunity (i.e., natural killer cells), as well as those with antigen-specific activity (i.e., effector and regulatory T cells), suggesting that the host immune system can mount a natural

antitumor response that employs both the innate and adaptive branches [3, 4]. Persistence and progressive growth of the tumor in an immunocompetent environment suggests that, as has been shown for many solid tumors, at least some prostate cancer cells develop the ability to avoid or suppress the host immune response [4, 5]. This body of evidence supports the rationale for combating prostate cancer with immunotherapy, with the goal of promoting more effective tumor control by encouraging the host to mount an immunogenic response to prostate tumor cells [4, 6].

Because tumor-associated antigens may not be adequately recognized by the immune system for a productive immune response to result [3, 5], antigen-specific anti-cancer immunotherapy (tumor vaccines) is designed to enhance the immunogenicity of known tumor-associated antigens, with the goal of promoting a productive anti-tumor immune response. Tumor vaccines may or may not

employ an adjuvant component to enhance the function of antigen presenting cells (APCs) and immune effectors such as T cells [7]. In 2010, sipuleucel-T (PROVENGE<sup>®</sup>; Dendreon, Seattle, WA) garnered the first national regulatory approval (by the United States Food and Drug Administration [FDA]) of a tumor vaccine and is now indicated for treatment of castration-resistant prostate cancer (CRPC) in patients with asymptomatic or minimally symptomatic disease [8, 9]. For prostate cancer oncologists and urologists, this approval helped to validate immunotherapy as a treatment approach with the potential to provide significant clinical benefits, and several other tumor vaccines are now under investigation for CRPC.

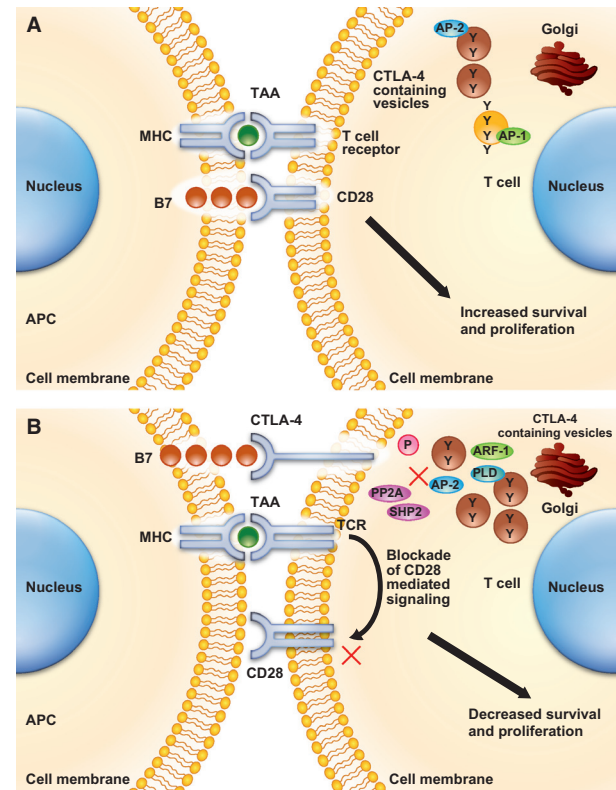
Targeting specific tumor-associated antigens is only one therapeutic approach with the potential to tip the balance from immune tolerance to immune activation against the tumor. Some preclinical and clinical evidence suggests that the CRPC tumor cells or the surrounding micro-environment are capable of suppressing the activity of infiltrating T effector cells, leading to immune tolerance toward the tumor in spite of an antigen-specific immune response [7, 10, 11]. With the aim of overcoming this tolerance and augmenting immune responses to CRPC tumors, cancer researchers are investigating inhibition of molecules or pathways that dampen immune responses (so-called immune checkpoint receptors), in an effort to modulate the immune system itself to fight cancer [4, 6].

Interestingly, standards of care like androgen deprivation therapy, radiotherapy, and chemotherapy [12] have been observed to alter the immune milieu of prostate cancer or the host, although the underlying pathways are not completely understood [4, 6, 7, 10, 13]. Preclinical and preliminary clinical evidence suggest that radiotherapy and/or chemotherapy may augment immunotherapy-induced immunologic responses on a molecular level, possibly through antigen release from dying tumor cells [14–16] or by direct modulation of immune effector molecules [17]. This evidence for synergy supports the rationale for investigating multimodal therapies involving immunotherapy and other anticancer agents with potentially immunosupportive mechanisms of action. Whether a particular combination, timing, or schedule maximizes clinical benefit of immunotherapy-containing regimens is a subject of ongoing research.

## CTLA-4 Blockade in Prostate Cancer

When APCs present antigens to T cells, the costimulatory interaction between APC-expressed B7 and T-cell-expressed CD28 is indispensable for a productive immune response to the antigen. To keep these responses in check, T-cell activation induces cell surface expression of

immune checkpoint receptors, which has the net effect of downregulating T-cell activity [18–20]. This process is thought to underlie the induction of peripheral tolerance. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), the most extensively studied of these immune checkpoint receptors, binds to B7 with higher avidity than does CD28; thus, CTLA-4 competitively inhibits CD28-mediated T-cell activation and subsequently dampens the T-cell response (Fig. 1) [18]. Blockade of CTLA-4 signaling preserves the CD28-B7 costimulatory signal and thus the T-cell activation signal, which augments the resulting T-cell-mediated immune responses.



**Figure 1.** Role of CTLA-4 in T-cell activation and molecular consequence of CTLA-4 blockade. AP, adapter protein; APC, antigen presenting cell; ARF-1, ADP ribosylation factor 1; BCL-2, B cell lymphoma-associated protein 2; BCL-XL, B cell lymphoma-associated extra large protein; CTLA-4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; NF- $\kappa$ B, nuclear factor kappa light-chain enhancer of activated B cells; P, phosphorylation (of the indicated target); PI3K, phosphoinositide 3 kinase; PLD, phospholipase D; PP2A, protein phosphatase 2A; SHP2, SH2 domain-containing protein tyrosine phosphatase 2; TAA, tumor-associated antigen. Reprinted from Salama A. K., Hodi F. S. Cytotoxic T-lymphocyte-associated antigen 4 [18]. Reprinted from *Clinical Cancer Research*, 2011, Vol. 17/Issue 14, 4622–4628, April K. S. Salama et al., "Is there a role for immune checkpoint blockage with ipilimumab in prostate cancer?", with permission from AACR.

Ipilimumab (YERVOY™; Bristol-Myers Squibb, Princeton, NJ) is a fully human IgG<sub>1</sub> monoclonal antibody against CTLA-4 [21]. Two randomized phase 3 trials of ipilimumab in advanced melanoma have reported overall survival benefit over control arms, with a side-effect profile that was managed with proactive treatment guidelines as outlined in the individual protocols [22–24]. In 2011, the agent was approved in the United States as monotherapy at a dose of 3 mg/kg for treatment of unresectable or metastatic melanoma [24]. The agent has since been approved as an advanced melanoma treatment in over 40 countries.

Due to its potentially broadly applicable mechanism of action, ipilimumab has also been under investigation in several other solid tumor settings, including CRPC. In fact, the first in-human study of ipilimumab was in prostate cancer: an investigation of a single 3 mg/kg dose of ipilimumab in 14 patients with hormone-refractory prostate cancer [25]. Ipilimumab as a single dose had acceptable pharmacokinetic and safety profiles, but only two of the 14 patients experienced PSA declines of >50%. Results have since been reported for six other clinical studies of ipilimumab in CRPC. Together, these seven trials encompassed 240 patients across multiple settings of advanced CRPC, roughly 20% of whom had progressed on or relapsed after docetaxel (Table 1) [25–35].

Reflecting the dose-finding nature of many of these trials, the studies utilized multiple doses (ranging from 0.5 to 10 mg/kg as either monotherapy or in combination studies) and schedules (ranging from a single dose of ipilimumab to recurring doses every 3 weeks for four cycles). In the phase 1 and 2 trials in CRPC, ipilimumab was active whether used as monotherapy [25, 28] or with other interventions such as radiotherapy [26], docetaxel [27], or other immunotherapeutics with different mechanisms of action [29–35]. Notably, one study in 43 chemotherapy-eligible patients compared ipilimumab monotherapy (3 mg/kg, every 4 weeks, for four doses) with ipilimumab plus a single 75 mg/m<sup>2</sup> dose of docetaxel on day 1; this small study did not reveal a clear difference in safety or PSA response (around 15%) between the two groups [27].

Clinical investigation in CRPC with the antigen-specific therapies sipuleucel-T [9] and PROSTVAC® (Bavarian Nordic, Kvistgaard, Denmark) [36] revealed little overall impact on delaying progression of disease, but the reported benefits in overall survival may represent a slowing of tumor growth [7, 26]. In phase 2 reports of ipilimumab, although efficacy endpoints also varied amongst the studies, declines in PSA were consistently noted (15–20%) at doses of  $\geq 3$  mg/kg. All trials utilized the PSA Working Group 2 criteria [37]. These response rates suggest that a subset of patients with CRPC may be

responsive to therapy with ipilimumab, although none of the data reported to date have revealed specific characteristics of this subset. However, these studies did report various patterns of PSA declines, occurring at treatment onset, after a short period of stable disease, or within 6 months after an initial rise in PSA levels. Some immediate responses (within 1 month of initiating treatment) were noted, and some late responses (after 6 months of treatment) were also observed [26, 27]. In some cases, responses to ipilimumab lasted for 1 year or more [26, 27]. Although these phase 2 data require further verification in phase 3 trials, these observed patterns do suggest that an individual's immune response to cancerous cells may be dynamic and, in a select number of patients, durable over the course of disease.

In the CRPC trials, the side effects associated with ipilimumab therapy were common and inflammatory in nature (reflective of the immunologic mechanism of action). Table 2 provides incidences of these immune-related adverse events (irAEs) from the largest phase 2 trial, in which ipilimumab was used as monotherapy at 10 mg/kg (CA184-017) [26]. Commonly reported side effects in the CRPC studies included gastrointestinal events such as colitis, diarrhea, rash or pruritus, hepatitis, or endocrinopathies. These endocrinopathies included adrenal insufficiency, hyper- or hypothyroidism, hypophysitis, or hypopituitarism. Interestingly, endocrinopathies leading to adrenally insufficient states (and suppressed androgen production) may also provide an indirect mechanism for tumor control, but as PSA responses to ipilimumab have been reported in the absence of changes in adrenal hormones [30], it is more likely that tumor responses are directly mediated by an ipilimumab-induced immune response. The phase 1 and 2 studies in CRPC did not report any safety issues that were unexpected given the safety data previously reported for ipilimumab [22, 23]. Though these side effects were severe in some instances, they were typically addressed through interventions outlined in the individual trial protocols, as was done in the melanoma studies. In study CA184-017, corticosteroids and other immunosuppressive agents, as well as hormone replacement therapy for endocrine side effects, were utilized at the discretion of the investigators [26].

Only one of the phase 2 studies in CRPC reported a dose-limiting toxicity (one case of grade 4 sarcoid alveolitis in a patient who received 5 mg/kg of ipilimumab and GVAX) [35], but this has not been recapitulated in other studies of ipilimumab monotherapy or combination therapy at 10 mg/kg [26, 29–31, 33–35]. Phase 2 dose-ranging studies for ipilimumab in advanced melanoma suggested that the risk/benefit profile was more favorable at 10 mg/kg than it was for 3 mg/kg [16]. Although it is not known whether these results are translatable to pros-

**Table 1.** Summary of phase 1/2 data for ipilimumab in CRPC.

Study/phase	Population (n) <sup>1</sup>	Regimen	Dose/schedule	Endpoints	Efficacy results <sup>3</sup>	Safety results <sup>3</sup>	Reference(s)
CA184-017 <sup>2</sup> NCT00323882 (Phase 2)	Metastatic CRPC, pre- and postdocetaxel (70)	Monotherapy or with one prior dose of XRT	3, 5, or 10 mg/kg monotherapy, 3 or 10 mg/kg with prior XRT, q3w × 4	Primary: safety Secondary: PSA responses, metabolic bone activity	21% (15 pts) had PSA responses (15.4% in chemo-naïve; 9.5% in chemo-pretreated)	11 pts with 13 grade ≥3 irAEs; no DLTs observed, no MTD or DLT	Slovin et al. [26]
CA184-019 <sup>2</sup> NCT00050596 (Phase 2)	HRPC, docetaxel eligible (43)	Monotherapy or with docetaxel	3 mg/kg, monthly × 4	Safety and activity between arms	Two pts who received ipilimumab monotherapy and one pt who received ipilimumab + docetaxel had confirmed PSA responses	18 pts experienced 52 SAEs, 10 of which were attributed to ipilimumab	Small et al. [27]
CA184-009 <sup>2</sup> (Phase 1)	Advanced HRPC; pre- and postchemo (14)	Monotherapy	3 mg/kg, one dose (two retreated at progression)	Safety, PK, PSA, objective responses (per reference at right)	Two pts had PSA declines of ≥ 50%	One pt experienced grade 3 rash/pruritus	Small et al. [25]
CA184-118 NCT00170157 (Phase 2)	Advanced chemo-naïve CRPC (108)	With AA versus AA alone	3 mg/kg, one dose	Primary: percent without progression at 18 months Secondary: PSA responses	55% versus 38% undetectable PSA by 3 months	In combination arm, grade ≥ 3 irAEs included colitis (4.5%) and diarrhea (4.5%)	Tollefson et al. [28]
CA184-098 NCT00064129 (Phase 1/2)	Metastatic CRPC, docetaxel eligible (24) (36)	With GM-CSF	Phase 1: 0.5, 1.5, 3, 5, or 10 mg/kg, monthly; expansion: 3 mg/kg monthly × 6	Primary for phase 1: MTD and safety; primary for expansion: PSA response Secondary for phase 1: T-cell immunity/response, PK, PSA response, ORR; secondary for expansion: percent activated naive/memory T cells, epitopes for prostate	At 3 mg/kg, 50% (three pts) had PSA declines of ≥ 50%, 1 PR; at 10 mg/kg, 17% (one pt) had PSA declines of ≥ 50%	irAEs correlated with dose (≥3 mg/kg) and PSA response	Small et al. [29]; Fong et al. [30]; Harzstark et al. [31]

Table 1. Continued.

Study/phase	Population (n) <sup>1</sup>	Regimen	Dose/schedule	Endpoints	Efficacy results <sup>3</sup>	Safety results <sup>3</sup>	Reference(s)
CA184-119 (Phase 1)	Metastatic chemo-naïve HRPC (12 escalation, 16 expansion)	With GVAX	0.3, 1, 3, or 5 mg/kg, monthly; expansion = 3 mg/kg	antigens, T-cell response in HLA <sup>+</sup> pts, safety, PSA response, ORR Primary: safety, MTD Secondary: TTP, PSA response, immune response, reduction in metabolic bone activity, survival	Six pts (five in escalation, one in expansion) receiving $\geq 3$ mg/kg had PSA declines of $\geq 50\%$	Escalation cohort: five pts who received 3 or 5 mg/kg had grade $\geq 2$ irAEs (four had hypophysitis, one had sarcoid alveolitis [DLT]; expansion cohort: two pts had grade 2 hypophysitis, three pts had grade 1 or 2 colitis, and one pt had grade 3 hepatitis	van den Eertwegh et al. [32]
CA184-100 NCT00124670 (Phase 1)	Metastatic CRPC, chemo-naïve (24) and postdocetaxel (6)	With PSA-Tricom/ PROSTVAC + GM-CSF	1, 3, 5, or 10 mg/kg, monthly $\times$ 6	Primary: MTD of regimen, safety Secondary: PSA and RECIST responses in HLA-A2 <sup>+</sup> pts; immunologic response (increase in PSA-specific T cells	15 pts had PSA declines (14 chemo-naïve, one pt postdocetaxel, all 3, 5, or 10 mg/kg), six were $\geq 50\%$ ; median PFS in chemo-naïve and postdocetaxel pts was 5.9 and 2.4 months; 3/12 unconfirmed PRs; median OS 34.4 months; 2-year OS 73%	No DLTs; most common AE was grade 1/2 site reaction; 8 (0/3, 2/6, 2/6 and 4/15 events in 1, 3, 5, or 10 mg/kg cohorts, respectively) grade $\geq 3$ irAEs: 3 endocrinopathies, 2 rash, 1 diarrhea, 1 neutropenia, 1 elevated liver enzymes	Mohebtash et al. [33]; Mohebtash et al. [34]; Madan et al. [35]

AA, androgen ablation; AE, adverse event; chemo, chemotherapy; CRPC, castration-resistant prostate cancer; DLT, dose-limiting toxicity; GM-CSF, granulocyte macrophage colony-stimulating growth factor; HLA, human leukocyte antigen; HRPC, hormone-refractory prostate cancer; irAEs, immune-related adverse events; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PSA, prostate-specific antigen; pt, patient; qXw, every X weeks; SAEs, serious (grade  $\geq 3$ ) adverse events; TTP, time to progression; XRT, radiotherapy.

<sup>1</sup>Population descriptors are listed as defined in publication of data.

<sup>2</sup>Trial sponsored by Bristol-Myers Squibb.

<sup>3</sup>Results as reported in publicly available materials; most recent publicly available reports may be of interim data.

**Table 2.** Common treatment-related adverse events observed with ipilimumab monotherapy at 10 mg/kg in a phase 2 study [26].

	Ipilimumab -XRT <i>n</i> = 16 (%)	Ipilimumab +XRT <i>n</i> = 34 (%)	Ipilimumab overall ( $\pm$ XRT) <i>n</i> = 50 (%)
Any treatment-related AE			
Any Grade	16 (100)	29 (85)	45 (90)
Grade 3	7 (44)	13 (38)	20 (40)
Grade 4	3 (19)	0	3 (6)
Any immune-related AE (irAE)			
Any Grade	16 (100)	29 (85)	45 (90)
Grade 3	7 (44)	13 (38)	20 (40)
Grade 4	3 (19)	0	3 (6)
Common <sup>1</sup> irAEs: any grade; Grade 3			
Colitis	7 (44); 6 (38)	4 (12); 2 (6)	11 (22); 8 (16)
Diarrhea	13 (81); 2(13)	14 (41); 2 (6)	27 (54); 4 (8)
Rash	9 (56); 0	7 (21); 0	16 (32); 0
Pruritus	6 (38); 1 (6)	4 (12); 0	10 (20); 1 (2)
Common <sup>1</sup> laboratory abnormalities <sup>2</sup> : any grade; Grade 3; Grade 4			
Evaluable patients	15	34	49
Hemoglobin	12 (80); 1 (7); 0	28 (82); 6 (18); 0	40 (82); 7 (14); 0
Lymphocytes	12 (80); 2 (13); 0	31 (91); 3 (9); 0	43 (88); 5 (10); 0
ALT	7 (47); 1 (7); 1 (7)	10 (29); 1 (3); 0	17 (35); 2 (4); 1 (2)
AST	6 (40); 1 (7); 1 (7)	8 (24); 0; 0	14 (29); 1 (2); 1 (2)
AP	7 (47); 1 (7); 0	21 (62); 4 (12); 1 (3)	28 (57); 5 (10); 1 (2)
Amylase	4 (27); 0; 0	4 (12); 1 (3); 0	8 (16); 1 (2); 0

XRT, radiotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; irAE, immune-related adverse event. Data from Slovin et al. [26].

<sup>1</sup>Defined as AE or laboratory abnormality of any grade in  $\geq 15\%$  of patients in the 10 mg/kg  $\pm$  XRT group.

<sup>2</sup>Calculated from laboratory values.

tate cancer, when taken together, the reports in melanoma, and the overall tolerability of the 10-mg/kg dose in CRPC trials where it was evaluated, suggest that 10 mg/kg is appropriate for further study of ipilimumab in CRPC.

## Open Questions, Ongoing Trials, and Future Directions

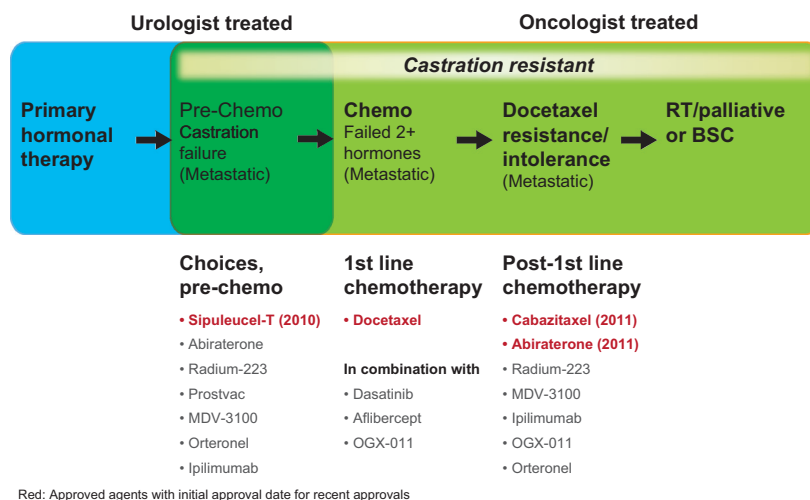
Ongoing research in prostate cancer has broadened, and it is continuing to augment the therapeutic choices available to treat this disease. Immunotherapy is a promising but relatively recent addition, and while the concept of immunotherapy in CRPC was solidified with the US approval of sipuleucel-T, the ideal fit for immunotherapy in the CRPC treatment paradigm is a matter of continued study (Fig. 2) [38–40].

In an effort to understand in which settings ipilimumab might provide benefit in CRPC, it is under phase 2 and 3 investigation in both the chemotherapy-naïve and -pretreated settings (Table 3). In addition, other antigen-specific approaches are the subjects of ongoing clinical investigation (reviewed in Cha 2011 [7]). It is hoped that these studies will help answer some of

the questions that the medical community has regarding immunotherapy in CRPC.

Treating physicians must always consider the question of risk/benefit when considering a therapeutic approach, and for immunotherapy, more data is needed to firmly address this issue. In the case of ipilimumab, phase 2 studies in CRPC suggest that PSA declines may occur in roughly 15–20% of patients. However, in the phase 3 trials of ipilimumab in melanoma, some responses to ipilimumab therapy initially appeared as disease progression (e.g., increases in total tumor burden or number of lesions) [16, 22, 23]. If the response patterns seen in the phase 3 studies are suggestive of what can be expected in CRPC, it is possible that in some cases the benefit with ipilimumab may not be readily apparent for several weeks or months. It is for this reason that the phase 3 clinical trials of ipilimumab specify confirmation of disease progression [41, 42].

The experience with irAEs associated with ipilimumab therapy in CRPC is limited to phase 1 and 2 data, but the agent's clinical development in melanoma has provided more extensive characterization of side effects and how to proactively manage them [22, 23]. Prompt treatment with corticosteroids or other immunosuppressive therapy, skip-



**Figure 2.** Anticancer agents US- or EU-approved or under phase 3 investigation for castration-resistant prostate cancer (CRPC). Data from [www.fda.gov](http://www.fda.gov) [38], [www.ema.europa.eu](http://www.ema.europa.eu) [39], and [www.clinical.trials.gov](http://www.clinical.trials.gov) [40].

**Table 3.** Summary of ipilimumab clinical trials in CRPC.

Study	Phase/setting	Design [Primary endpoint]	Site(s)
NCT01057810	Phase 3 1st line CRPC	Ipilimumab (10 mg/kg q3w × 4 → q12w) versus placebo [OS]	International
NCT00861614	Phase 3 2nd+ line CRPC	Single-dose XRT → randomization to ipilimumab (10 mg/kg q3w × 4 → q12w) versus placebo [OS]	International
NCT01194271	Phase 2 Neoadjuvant	Ipilimumab (10 mg/kg q3w × 3) + hormone ablation → radical prostatectomy [safety]	US
NCT01377389	Phase 2 1st line HS	Ipilimumab (10 mg/kg q4w × 4) + leuprolide acetate (7.5 mg/month × 8) [response by PSA]	US
NCT00170157	Phase 2 1st line HS	Ipilimumab (3 mg/kg once) + leuprolide (7.5 mg/month × 3) + bicalutamide (50 mg/day × 3 months) versus leuprolide + bicalutamide alone [PFS]	US
NCT01530984	Phase 2 1st line CRPC	Ipilimumab (10 mg/kg q4w × 6) + GM-CSF (250 mcg/m <sup>2</sup> days 1–14 × 6) versus ipilimumab alone [response by PSA]	US
NCT00064129	Phase 1 1st line CRPC	Ipilimumab (0.5–3 mg/kg q4w) + GM-CSF (250 mcg/m <sup>2</sup> days 1–14 × 4) [MTD, safety, reduction in PSA]	US

CRPC, castration-resistant prostate cancer; GM-CSF, granulocyte macrophage colony-stimulating growth factor; HS, hormone sensitive; MTD, maximum-tolerated dose; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; qXw, every X weeks; XRT, radiotherapy.

ping a dose of ipilimumab, or in some cases discontinuation of ipilimumab therapy permitted resolution of the majority of severe events in a matter of days to weeks [22]. It was also noted that prophylactic budesonide does not reduce the incidence of grade  $\geq 2$  diarrhea during therapy with ipilimumab for advanced melanoma [17]. In the phase 1/2 reports for CRPC, ipilimumab's side-effect profile did not greatly differ from that reported for melanoma, but there is always a potential for patients with CRPC to experience side effect incidence or severity not anticipated from experience in other tumor types; for

example, pelvic irradiation in older patients with CRPC might predispose them to side effects such as colitis. The phase 3 clinical trials in CRPC will help answer these questions and clarify whether the current side effect management guidelines, established in the phase 3 melanoma trials, will benefit patients with CRPC.

Finally, even though the phase 2 data in CRPC supports the use of 10 mg/kg as the phase 3 investigational dose, it is not yet clear whether this dose provides the ideal risk/benefit profile for CRPC. The phase 3 trials in CRPC will not utilize doses lower than 10 mg/kg, and it

is uncertain what the risk/benefit profile of a lower dose would be.

Physicians must also consider whether a given therapy is the right choice for an individual patient. Currently, the prostate cancer community does not know to what extent different types of immunotherapy will be best suited for different subsets of patients, as heretofore no clinical or molecular parameters have clearly emerged as biomarkers. Encouragingly, however, studies of ipilimumab and ipilimumab-based combination therapy in melanoma and CRPC have identified new leads. Antibody and T-cell responses to NY-ESO-1 [43], high baseline expression of immune markers such as FoxP3 and indoleamine 2,3-dioxygenase [44], increases in tumor-infiltrating lymphocytes, and changes in expression of immune-related genes [44] have all been correlated with clinical activity or benefit of ipilimumab. High baseline frequency of differentiated CD8<sup>+</sup> T cells, high baseline frequency of CD4<sup>+</sup> T cells that express CTLA-4 or PD-1, and low pre-treatment frequencies of differentiated CD4<sup>+</sup> or regulatory T cells have been associated with significantly longer survival following ipilimumab therapy [45]. Furthermore, analysis of CD4<sup>+</sup> and CD8<sup>+</sup> T cells from ipilimumab-treated patients correlated low baseline expression of Ki67, a marker for T-cell proliferation, and eomesodermin, a transcription factor associated with effector T-cell function, with relapse or irAEs from ipilimumab therapy [46]. Ongoing ipilimumab studies in multiple tumor types are evaluating various clinical and molecular parameters as biomarkers for survival or other clinical benefit, safety, or immunologic competence.

Chronic use of immunosuppressive corticosteroids, a therapeutic option among solid tumors unique to prostate cancer, may also be detrimental to ipilimumab's activity, and sustaining an active and durable immune response after ipilimumab treatment may benefit from delaying the initiation of corticosteroid-heavy regimens. There is currently no appropriate analysis to determine to what extent prolonged corticosteroid use and its sequence in CRPC treatment affect ipilimumab activity.

As mentioned above, their nonoverlapping mechanisms of action suggest the potential for combination therapy between multiple immunotherapy approaches, particularly antigen-specific therapies such as sipuleucel-T and antigen-independent therapies such as ipilimumab. To further explore the utility of such combinations, phase 1 or 2 studies pairing ipilimumab in regimens with sipuleucel-T, off-the-shelf prostate cancer vaccines, and/or adjuvants such as granulocyte macrophage colony-stimulating growth factor (GM-CSF) are complete or underway [31, 32]. One recent study, a phase 1 dose escalation trial of ipilimumab given concurrently with a fixed dose of GM-CSF-transduced allogeneic prostate cancer cells, reported

that the higher doses (3 mg/kg and 5 mg/kg) were tolerated well in most patients and produced some PSA declines of >50% in seven patients (25% of patients in the 3 mg/kg or 5 mg/kg cohorts) [32]. Although these trials have not and will not directly address how the sequence of therapies may affect results, as data from these studies and the phase 3 trials mature, clarification of issues above will further our understanding of the ideal placement for ipilimumab, and possibly other immunotherapy, into the CRPC treatment paradigm.

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## Conflict of Interest

None declared.

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