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Ipilimumab in prostate cancer

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Abstract

Introduction: Immune checkpoint inhibitors, such as ipilimumab, are a new class of immunotherapeutic agents that have shown significant efficacy in melanoma. A number of ongoing clinical trials are investigating the role of ipilimumab in prostate cancer, either alone or in combination with immunomodulating agents such as radiation and chemotherapy, and in combination with cancer vaccines.

Areas covered: This article reviews the molecular basis, preclinical and clinical evidence on the safety and efficacy of ipilimumab in prostate cancer. Medical literature search using MEDLINE and online abstracts database of national meetings form the basis of this article.

A number of preliminary clinical studies suggest the potential therapeutic utility of immune checkpoint inhibitors such as ipilimumab in prostate cancer. Pending the results of large-scale studies, the rationale of combining ipilimumab with standard anticancer therapeutics such as radiation, cytotoxic chemotherapy and other immunotherapeutic agents can be of great value in reducing mortality and morbidity in prostate cancer.

Keywords

checkpoint inhibitors; chemotherapy; immunotherapy; ipilimumab; prostate cancer; radiation

1. Introduction

The scientific community's painstaking efforts to break the immune system's tolerance to tumors have finally borne fruit. The first breakthrough came in the form of sipuleucel-T (PROVENGE®, Dendreon Corp.), which in 2010 became the first therapeutic vaccine approved by US Food and Drug Administration (FDA) for the treatment of prostate cancer. To create the vaccine, a patient's autologous peripheral blood mononuclear cells are isolated and co-cultured *ex vivo* for 36 to 44 h with a fusion protein of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor (GM-CSF), then reinfused back into the patient. The efficacy of this innovative approach was established in the Phase III IMPACT trial, which showed a 22% relative reduction in risk of death (HR [hazard ratio] = 0.78; 95%

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Declaration of interest

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confidence interval [CI], 0.61 – 0.98; $p = 0.03$) in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) [1]. An alternative strategy currently being studied in a Phase III trial involves a prime-boost regimen using the prostate-specific antigen (PSA)-expressing PROSTVAC-VF vaccine [2]. PROSTVAC-VF (PSA-TRICOM, BN ImmunoTherapeutics) is a poxvirus-based vaccine engineered to contain PSA and three immune costimulatory molecules (B7.1, ICAM-1 and LFA-3) within a vaccinia virus prime and fowlpox virus vector boost. The vaccine has been tested in several Phase II trials. In one such trial involving 125 patients with asymptomatic or minimally symptomatic mCRPC, PROSTVAC-VF showed an improved 3-year survival rate of 30 vs 17% and a median survival of 25.1 vs 16.6 months compared with an empty vector [3,4].

Overall, prostate cancer is the second most common cause of death from cancer in men in the United States (28,170 estimated deaths in 2012) [5,6]. A number of anticancer immunotherapy strategies have shown preclinical and clinical efficacy either as monotherapies or, more recently, in combination strategies (Table 1). However, once prostate cancer has metastasized, it can be only transiently controlled by androgen-deprivation therapy (ADT), and the 5-year relative survival rate is 27.8%, fueling an urgent search for more effective, durable treatments for mCRPC. With the proven success of ipilimumab in melanoma, a number of completed and ongoing clinical studies are investigating the potential role of immune checkpoint inhibitors in prostate cancer therapies.

Ipilimumab (Yervoy®; Bristol-Myers Squibb), a fully human IgG1 κ monoclonal antibody (mAb) that targets cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), see Drug summary Box 1, is the first in a class of therapies targeting T-cell activation and regulation to be licensed in the broad category of agents known as immune checkpoint blockers/inhibitors. It has an approximate molecular weight of 148 kDa and is produced in mammalian (Chinese hamster ovary) cell culture [7]. Tremelimumab (Pfizer) is another fully human IgG2 mAb that targets CTLA-4 and blocks its functionality. As a group, the immune checkpoint inhibitors block diverse pathways involved in moderating an evolving antitumor immune response, thereby abrogating tolerance. CTLA-4 is one of the best studied molecules that acts as a check on specific effector and regulatory immune cells [8]. Programmed cell death protein-1 (PD-1) and its ligand PD-ligand-1 (PD-L-1), a different set of immune checkpoint molecules, have also been studied extensively. Anti-PD-1 and anti-PD-L-1 treatments have been shown to have antitumor activity in solid tumors [9,10]. Novel agents that target other checkpoint molecules, such as lymphocyte activation gene 3 (LAG3) and B7-H3, are in clinical trials, while B7-H4 and T-cell membrane protein 3 (TIM3) inhibitors are in preclinical development [8,11].

2. Molecular function of CTLA-4

In order to initiate an adaptive response, immune T cells require two separate signals from an antigen-presenting cell (APC). The first signal involves the interaction of a T-cell receptor (TCR) with an antigenic peptide–MHC ligand complex. The best characterized costimulatory signal involves the interaction of B7 with CD28. The combination of the two signals determines subsequent effector cell activation or anergy. There are also naturally occurring CD4⁺CD25⁺ regulatory T cells (Tregs) that specifically express the transcription

factor forkhead box P3 (FOXP3) and are essential for maintaining immunological self-tolerance and homeostasis [12], the latter of which provides checks and balances between tolerance and autoimmunity.

CTLA-4 is a CD28 protein homologue that participates in peripheral tolerance, along with FOXP3 and transforming growth factor- β (TGF- β) [13–16]. Despite their structural similarity and shared genes on human chromosome 2q33, there are a number of differences between CTLA-4 and CD28. CTLA-4 and CD28 share the same B7 ligands (CD80 and CD86), but CTLA-4 can bind the ligands with higher affinity and avidity and is thought to act as a competitive antagonist for CD28 [17]. CD28 is constitutively expressed on the plasma membrane of both resting and activated naïve T cells, whereas CTLA-4 is not expressed by resting naïve T cells, but becomes detectable 2 days after activation [18]. TCR stimulation leads to the trafficking of CTLA-4 from the Golgi apparatus to the plasma membrane [19]. However, ongoing constitutive endocytosis keeps its expression level very low compared to CD28 [20].

The role of CTLA-4 as a regulator of immune tolerance and autoimmunity was described in preclinical studies for the first time in the mid-1990s. Investigators noted that CTLA-4 knockout mice died just 3 weeks after birth from massive post-thymic lymphoproliferation and autoimmunity [16,21,22]. Subsequently, it was shown that CTLA-4 blockade with antagonistic mAbs broke immune tolerance, resulting in effective antitumor immunity and autoimmunity [23]. Several pivotal observations followed the discovery of CTLA-4; however, the exact role of the CTLA-4 receptor in negative immune regulation is still the subject of considerable debate. The finding that CTLA-4 expression is controlled by both intracellular trafficking and transcription, the discovery of three different isoforms and the observation that the binding of CTLA-4 to its ligands on effector T cells initiates extrinsic cell signals have given rise to a multitude of models describing the role of CTLA-4 in the immune response [24]. CTLA-4 exerts negative regulation on CD28 costimulation through the upregulation and cell-autonomous engagement of CTLA-4 on activated effector T cells that leads to downregulation of IL-2 production, thereby terminating the immune response [25]. On the other hand, CTLA-4 can inhibit T cells by involving others cells (the extrinsic model). The extrinsic path involves release of immune-inhibitory cytokines by the CTLA-4-bearing cell and several pathways of B7 ligand sequestration (Figure 1).

The presence of CTLA-4 has also been described on CD4⁺CD25⁺FOXP3⁺ Tregs [24]. The CTLA-4 molecule seems to be essential to Tregs' suppressive function, where it is constitutively expressed [26]. These observations are not definitive proof of the role of CTLA-4 in Treg suppressive function; in fact, contradictory evidence exists in both murine and human models [27–30].

Anti-CTLA-4 antibody may also enhance the avidity of cytotoxic T lymphocytes (CTLs), thus making them more effective [31,32]. To test this hypothesis, investigators determined an optimum dosing schedule for combining an anti-CTLA-4 mAb and with a viral vector consisting of live recombinant vaccinia (rV) [33]. This poxviral-based vaccine was designed to express the transgene for carcinoembryonic antigen (CEA) plus TRICOM (rV-CEA/TRICOM). Tetramer dissociation and cytotoxicity assays measured T-cell avidity. There was

a profound difference in tetramer dissociation and a 10-fold difference in T-cell functional avidity in mice receiving both rV-CEA/TRICOM and anti-CTLA-4 compared to mice treated with vaccine alone. These findings raised the possibility that CTLA-4 blockade could have a potentiating effect on T-cell avidity against tumors.

3. Ipilimumab in prostate cancer: preclinical studies

The earliest evidence that ipilimumab showed promise in antitumor immunotherapy was published in 1994. Using murine fibrosarcoma Sal N and murine colon adenocarcinoma 51BLimlO cells in mice, Leach *et al.* demonstrated for the first time the permissive role of CTLA-4 antibodies in the rejection of established tumors [23]. Tumor rejection was also associated with immunity to tumor rechallenge.

In preclinical studies with a transplantable prostate cancer cell line (pTC1) derived from TRAMP (transgenic adenocarcinoma of the mouse prostate) mice, Kwon *et al.* modified pTC1 to express the murine B7.1 costimulatory ligand [34]. Their results showed that this led to tumor rejection in syngeneic mice, proving that the rejection was T-cell-mediated. They showed that *in vivo* antibody-mediated blockade of CTLA-4 led to wild-type (unmodified) tumor rejection.

Following radiation, chemotherapy, cryoablation or immunotherapy, dead or dying tumor cells can release an 'antigen cascade'. Through cross-presentation, these peripherally released antigens may gain entry into the MHC class I pathway, where APCs can present them to CD8⁺ T cells as a priming step in the immune response (Figure 2) [35–37]. Cross-presentation may act synergistically with immune-based therapies, augmenting their antitumor effect. Using poorly immunogenic metastatic mouse mammary carcinoma 4T1, Demaria *et al.* showed that combination therapy with anti-CTLA-4 antibody and radiation was associated with a significant survival advantage compared to control mice [37]. The improved survival correlated with inhibition of lung metastases and required CD8⁺ but not CD4⁺ T cells.

The combined effect of CTLA-4 blockade and tumor cryoablation demonstrated synergy in a transplantable TRAMP C2 prostate cancer mouse model [38]. TRAMP C2 tumor cells were injected on the left flank of male B6 mice. The mice were treated with tumor cryoablation and/or anti-CTLA-4 antibody when tumors reached 5 to 8 mm in diameter, about 28 days after tumor cells were injected. As evidence of synergy, at tumor rechallenge, there was a rejection rate of 44% in mice treated with cryoablation and anti-CTLA-4 antibody alone, compared to no rejection in controls. Preclinical studies in mice bearing non-prostatic, poorly immunogenic tumors also support the use of ipilimumab in novel combinatorial approaches in humans [39,40].

Hurwitz *et al.* examined the combined effect of whole tumor cell vaccine and anti-CTLA-4 antibody in 14- to 16-week-old male TRAMP mice that spontaneously develop prostatic adenocarcinoma as a consequence of expression of the SV40 TAg oncogene [41]. They found that only the combination therapy resulted in a significant reduction in tumors.

There is emerging evidence that ADT and cytotoxic chemotherapy can enhance antitumor immunity by acting directly on the immune system or by immunogenic modulation [42–44]. The biological mechanism may involve alteration of subpopulations of CD4⁺ and CD8⁺ cells, inhibition of Tregs, increased thymic output of T cells, increased intratumoral trafficking of effector cells and decreased tolerance of tumor cells [45–50]. A chemotherapeutic agent such as docetaxel can upregulate one or more surface molecules (Fas, ICAM-1, MUC-1, CEA and MHC class I) in both sensitive and resistant human carcinoma cell lines [42,43]. Radiation can have a similar effect on the phenotype of tumor cells, as demonstrated by clinical trials in prostate cancer that showed clinical evidence of epitope expansion and antitumor immunity [51,52].

4. Anti-CTLA-4 antibody in prostate cancer: clinical evidence

The success of ipilimumab in advanced melanoma is highlighted by its approval by the FDA in 2010. A unique set of toxicities referred to as immune-related adverse events (irAEs) has been seen with the use of anti-CTLA-4 antibodies. These irAEs include skin and mucosal rash (47 – 68%), diarrhea/colitis (all grades, 44%), hepatotoxicity (3 – 9%), hypophysitis (1 – 6%), episcleritis/uveitis (< 1%), immune-related pancreatitis (< 1.5%), lymphadenopathy/sarcoid-like syndrome (anecdotal) and transient peripheral neuropathies (< 1%) [53]. The events are typically dose-dependent and dermatological toxicities tend to occur before the visceral manifestations. It is mechanism-based as the CTLA-4 blockade leads to a compromised immune tolerance to selected normal tissue antigens [54]. Discontinuation of immune checkpoint inhibitor and immunosuppressive medications is standard treatment for irAEs [53]. Neither our experience nor published reports show a consistent correlation between irAEs and dose or tumor response. Risk evaluation and mitigation strategy (REMS) for ipilimumab, prepared by Bristol-Myers Squibb in conjunction with FDA, should be referred to in managing patients with moderate to severe irAEs. REMS consists of a communication plan to inform healthcare professionals of the serious risks, early identification and an overview of recommended management.

A pilot study with safety as the primary endpoint used a single 3 mg/kg i.v. dose of ipilimumab as monotherapy in 14 patients with mCRPC [55]. Overall, ipilimumab was well tolerated, with attributable irAEs noted in one patient who developed grade 2 pruritus and grade 3 rash that responded to steroids. Of the 14 patients, 2 had a decline in PSA of > 50% that lasted 135 and 60 days, respectively; 8 of 14 patients had a < 50% decline in PSA. Two patients with bidimensionally measurable disease who had baseline and follow-up imaging showed no radiographic objective response. Since this pilot trial was completed, more than 10 clinical trials exploring the role of ipilimumab in prostate cancer, including two Phase III trials, have been completed or are ongoing (Tables 2 and 3). The two ongoing Phase III studies will address overall survival (OS) as the primary endpoints. One Phase III, randomized, placebo-controlled trial (clinical trials.gov identifier: NCT00861614) that is open to recruitment aims to enroll 800 patients with mCRPC who have been exposed to docetaxel [56]. Ipilimumab at 10 mg/kg will be used as induction–maintenance strategy in the treatment group following radiation therapy. The second randomized, placebo-controlled clinical trial (clinical trials.gov identifier: NCT01057810) will look into the survival impact of ipilimumab in patients with asymptomatic or minimally symptomatic chemo-naïve

mCRPC [57]. The projected enrollment for the trial is 600 and a 10 mg/kg dose of ipilimumab will be employed in an induction–maintenance strategy.

Numerous clinical trials have suggested the effectiveness of combining multiple modalities to obtain synergy with anti-CTLA-4 mAbs. The results of a Phase I/II clinical trial of ipilimumab and radiation in mCRPC (in chemo naïve subjects and those with prior docetaxel) have been reported [58]. Patients (n = 33) received dose-escalated ipilimumab with or without a single dose of radiation (8 Gy/lesion, up to three lesions per patient). Later, the cohort receiving 10 mg/kg of ipilimumab was expanded to 50 patients, 34 of whom received radiation. Of the 50 PSA-evaluable patients in the 10 mg/kg ± radiation group, 8 patients had a PSA decline of ≥ 50%.

A randomized Phase II trial of 3 mg/kg ipilimumab with or without concurrent docetaxel in mCRPC showed a confirmed PSA decline of ≥ 50% in 3 of 43 patients, with no objective responses [59]. Of 52 severe adverse events, 5 (reported in 3 patients) were irAEs. In this study, the 6% rate of irAEs was less than the 10 to 15% rate of grade ≥ 3 irAEs noted in a Phase III study of ipilimumab (3 mg/kg) in melanoma [60].

The combination of ipilimumab and ADT has also shown clinical activity. A Phase II trial randomized patients newly diagnosed with locally advanced prostate cancer to receive ADT with or without a single dose of ipilimumab (3 mg/kg). At 3 months, 55% of patients in the combination group had undetectable PSA as against 38% in patients receiving ADT alone [61].

A Phase I dose-escalation trial of another anti-CTLA-4 antibody, tremelimumab, in combination with androgen receptor blockade (high-dose bicalutamide) in patients (n = 11) with biochemically recurrent prostate cancer was recently reported [62]. With safety as the endpoint, the trial reported three grade 3 irAEs: two patients receiving 6 mg/kg tremelimumab had diarrhea and rash; one patient receiving 3 mg/kg tremelimumab had colitis. In a follow-up period of 12 to 18 months, two patients had asymptomatic disease progression, and three reported improvements in PSA doubling time of 23.4 to 41.8 months (baseline for the group was 6.3 months; range: 2.7 – 11.3).

Ipilimumab has also been clinically tested in combination with immune adjuvants such as GM-CSF. A Phase I trial combined GM-CSF with escalating doses (0.5 – 10 mg/kg) of i.v. ipilimumab on day 1 of each cycle × 6 cycles in 36 patients with mCRPC [63]. The combination was well tolerated, with 10 reporting irAEs (rash, panhypopituitarism, temporal arteritis and diarrhea). Notably, 3 of 6 patients treated with 3 mg/kg had PSA declines of ≥ 50%.

CTLA-4 blockade increases T-cell avidity, raising the possibility of synergy with a therapeutic cancer vaccine [32]. This strategy was tested in a Phase I study that combined GVAX with escalating doses of ipilimumab (0.3 – 5 mg/kg) in patients with mCRPC [64]. A total of 12 patients were enrolled in the dose-escalation cohort. At the 3 mg/kg dose level, three patients had grade 2 hypophysitis; two had grade 3 hypophysitis; three had colitis (one grade 1 and two grade 2) and one had grade 3 hepatitis. At the 5 mg/kg dose level, two patients had grade 3 hypophysitis and one patient had grade 4 sarcoid alveolitis (a dose-

limiting toxicity). Seven patients (25%) who received either 3 or 5 mg/kg ipilimumab had PSA declines of $\geq 50\%$. A strong association between irAEs and PSA response was noted in the dose-escalation cohort, but not in the expansion cohort. Two patients in the dose-escalation cohort showed a clear regression of bone metastases. Complete regression of abdominal lymphadenopathy was seen in one of four patients with measurable disease at baseline. Stable bone metastases lasting 3 to 27 months were seen in 15 patients in the escalation and expansion cohorts.

In a trial involving patients with mCRPC, PSA-TRICOM was tested in combination with an initial six planned cycles of ipilimumab in escalating doses of 1 to 10 mg/kg and expansion cohorts of 3 and 5 mg/kg [65]. Of the 30 patients enrolled (80% chemotherapy naïve), 14 patients discontinued ipilimumab because of disease progression, while no dose-limiting toxicities were reported. Grade 3 or grade 4 irAEs were identified at all doses above 1 mg/kg, including diarrhea or colitis ($n = 4$), grade 3 rash ($n = 2$), grade 3 raised aminotransferases ($n = 2$), grade 3 endocrine irAEs ($n = 2$) and grade 4 neutropenia ($n = 1$). Of the 24 chemotherapy-naïve patients, 14 (58%) had PSA declines, 6 (25%) of which were $> 50\%$ (2 of these 6 declines were $> 90\%$). Of 12 patients, 3 with measurable disease had unconfirmed partial responses on CT imaging. The actual median OS for all patients was 34.4 months (95% CI: 29.6 – > 41), with a 2-year OS of 73% (95% CI: 55.6 – 85.8). In the two combination trials involving ipilimumab, the median OS of 29.2 months in combination with GVAX (95% CI: 9.6 – 48.8) and 34.4 months in combination with PSA-TRICOM (95% CI: 29.6 – > 41) suggests the promise of improved outcomes over vaccine alone in mCRPC [64,65]. Together, these trials suggest that, when used in combination, vaccine does not enhance the toxicity of anti-CTLA-4 antibody. Preliminary evidence of efficacy for this combination strategy needs to be confirmed in large randomized studies.

Ongoing experience, in general with immunotherapeutic agents, has revealed a unique characteristic of clinical response as opposed to the standard cytoreductive therapies [66–68]. Vaccines such as sipuleucel-T and PROSTVAC-VF generate an immune response that grows significantly over time. Due to delayed response, the resultant antitumor effect is not amenable to prediction with standard PSA kinetics model and PFS is relatively unaffected compared to the OS as randomized data show [60,69]. Ipilimumab, in metastatic melanoma patients, demonstrated an OS advantage without a change in disease progression. Decreased reliance on PSA for response (as suggested by most recent Prostate Cancer Clinical Trials Working Group criteria) [70], development of new immune biomarkers and their validation are thus paramount in future trials involving immunotherapeutic agents.

5. Expert opinion

The traditional view that prostate cancer is poorly immunogenic has been challenged by the approval of sipuleucel-T and by preliminary studies of vaccines and immune checkpoint inhibitors. Recent studies have shown acceptable safety for the combination of vaccine and ipilimumab, as well as encouraging clinical outcomes (25% of patients showed PSA declines of $\geq 50\%$ in vaccine combination studies) [64,65]. Larger combination studies will be required to confirm this observed impact on OS.

Given the encouraging safety data on novel immune checkpoint inhibitors, such as anti-PD-1, combination studies of anti-PD-1 with vaccines such as PSA-TRICOM or sipuleucel-T may be the next logical step [3]. The rationale for combination studies with immune checkpoint inhibitors could also be extended to include combinations with standard anticancer agents, such as chemotherapy, radiation and small molecular inhibitors. Optimum sequencing of the various treatment modalities would need to be determined. For patients with bone metastases, once radiation has exposed endogenous cancer-specific antigens by inducing tumor necrosis and expansion of the T-cell repertoire through crosstalk, an immune checkpoint inhibitor may help to sustain or even enhance the antitumor immune response. The efficacy of ipilimumab alone or in combinatorial testing remains to be tested in large-scale setting and the results of the two ongoing Phase III trials [56,57] are eagerly awaited.

Acknowledgments

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Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22 [PubMed: 20818862]
2. Madan RA, Arlen PM, Mohebtash M, et al. Prostavac-VF: a vector-based vaccine targeting PSA in prostate cancer. *Expert Opin Investig Drugs* 2009;18:1001–11
3. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010;28:1099–105 [PubMed: 20100959]
4. Stein WD, Gulley JL, Schlom J, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. *Clin Cancer Res* 2011;17:907–17 [PubMed: 21106727]
5. [[Cited September 2012]] SEER Cancer Statistics Review 1975 – 2009 (Vintage 2009 Populations). Available from: http://seer.cancer.gov/csr/1975_2009_pops09/
6. American Cancer Society: Cancer Facts & Figures 2012 Available from: <http://www.cancer.org/Research/CancerFactsFigures/index> [Cited September 2012]
7. Yervoy* ipilimumab product monograph 2012 Available from: http://www.bmscanada.ca/static/products/en/pm_pdf/Yervoy_EN_PM.pdf
8. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–64 [PubMed: 22437870]
9. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54 [PubMed: 22658127]
10. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455–65 [PubMed: 22658128]
11. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* 2012;72:917–27 [PubMed: 22186141]
12. Wing K, Sakaguchi S. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat Immunol* 2010;11:7–13 [PubMed: 20016504]
13. Brunkow ME, Jeffery EW, Hjerrild KA, et al. Disruption of a new forkhead/winged-helix protein, scurfy, results in the fatal lymphoproliferative disorder of the scurfy mouse. *Nat Genet* 2001;27:68–73 [PubMed: 11138001]

14. Wahl SM, Orenstein JM, Chen W. TGF-beta influences the life and death decisions of T lymphocytes. *Cytokine Growth Factor Rev* 2000;11:71–9 [PubMed: 10708954]
15. Fehervari Z, Yamaguchi T, Sakaguchi S. The dichotomous role of IL-2: tolerance versus immunity. *Trends Immunol* 2006;27:109–11 [PubMed: 16459146]
16. Tivol EA, Borriello F, Schweitzer AN, et al. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* 1995;3:541–7 [PubMed: 7584144]
17. Collins AV, Brodie DW, Gilbert RJ, et al. The interaction properties of costimulatory molecules revisited. *Immunity* 2002;17:201–10 [PubMed: 12196291]
18. Walunas TL, Lenschow DJ, Bakker CY, et al. CTLA-4 can function as a negative regulator of T cell activation. *Immunity* 1994;1:405–13 [PubMed: 7882171]
19. Egen JG, Allison JP. Cytotoxic T lymphocyte antigen-4 accumulation in the immunological synapse is regulated by TCR signal strength. *Immunity* 2002;16:23–35 [PubMed: 11825563]
20. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. *Nat Rev Immunol* 2011;11:852–63 [PubMed: 22116087]
21. Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. *Science* 1995;270:985–8 [PubMed: 7481803]
22. Chambers CA, Cado D, Truong T, Allison JP. Thymocyte development is normal in CTLA-4-deficient mice. *Proc Natl Acad Sci USA* 1997;94:9296–301 [PubMed: 9256476]
23. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996;271:1734–6 [PubMed: 8596936]
24. Read S, Malmstrom V, Powrie F. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+)CD4(+) regulatory cells that control intestinal inflammation. *J Exp Med* 2000;192:295–302 [PubMed: 10899916]
25. Wing K, Yamaguchi T, Sakaguchi S. Cell-autonomous and -non-autonomous roles of CTLA-4 in immune regulation. *Trends Immunol* 2011;32:428–33 [PubMed: 21723783]
26. Metzler B, Burkhart C, Wraith DC. Phenotypic analysis of CTLA-4 and CD28 expression during transient peptide-induced T cell activation in vivo. *Int Immunol* 1999;11:667–75 [PubMed: 10330272]
27. Wing K, Onishi Y, Prieto-Martin P, et al. CTLA-4 control over Foxp3+ regulatory T cell function. *Science* 2008;322:271–5 [PubMed: 18845758]
28. Quezada SA, Peggs KS, Curran MA, Allison JP. CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells. *J Clin Invest* 2006;116:1935–45 [PubMed: 16778987]
29. Kavanagh B, O'Brien S, Lee D, et al. CTLA4 blockade expands FoxP3+ regulatory and activated effector CD4+ T cells in a dose-dependent fashion. *Blood* 2008;112:1175–83 [PubMed: 18523152]
30. Read S, Greenwald R, Izcue A, et al. Blockade of CTLA-4 on CD4+CD25+ regulatory T cells abrogates their function in vivo. *J Immunol* 2006;177:4376–83 [PubMed: 16982872]
31. Zeh HJ III, Perry-Lalley D, Dudley ME, et al. High avidity CTLs for two self-antigens demonstrate superior in vitro and in vivo antitumor efficacy. *J Immunol* 1999;162:989–94 [PubMed: 9916724]
32. Bullock TN, Mullins DW, Colella TA, Engelhard VH. Manipulation of avidity to improve effectiveness of adoptively transferred CD8(+) T cells for melanoma immunotherapy in human MHC class I-transgenic mice. *J Immunol* 2001;167:5824–31 [PubMed: 11698456]
33. Hodge JW, Chakraborty M, Kudo-Saito C, et al. Multiple costimulatory modalities enhance CTL avidity. *J Immunol* 2005;174:5994–6004 [PubMed: 15879092]
34. Kwon ED, Hurwitz AA, Foster BA, et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. *Proc Natl Acad Sci USA* 1997;94:8099–103 [PubMed: 9223321]
35. Pilon SA, Kelly C, Wei WZ. Broadening of epitope recognition during immune rejection of ErbB-2-positive tumor prevents growth of ErbB-2-negative tumor. *J Immunol* 2003;170:1202–8 [PubMed: 12538677]

36. Chakraborty M, Abrams SI, Coleman CN, et al. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. *Cancer Res* 2004;64:4328–37 [PubMed: 15205348]
37. Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* 2005;11:728–34 [PubMed: 15701862]
38. Waitz R, Solomon SB, Petre EN, et al. Potent induction of tumor immunity by combining tumor cryoablation with anti-CTLA-4 therapy. *Cancer Res* 2012;72:430–9 [PubMed: 22108823]
39. Hurwitz AA, Yu TF, Leach DR, Allison JP. CTLA-4 blockade synergizes with tumor-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma. *Proc Natl Acad Sci USA* 1998;95:10067–71 [PubMed: 9707601]
40. van Elsland A, Hurwitz AA, Allison JP. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. *J Exp Med* 1999;190:355–66 [PubMed: 10430624]
41. Hurwitz AA, Foster BA, Kwon ED, et al. Combination immunotherapy of primary prostate cancer in a transgenic mouse model using CTLA-4 blockade. *Cancer Res* 2000;60:2444–8 [PubMed: 10811122]
42. Garnett C, Farsaci B, Schlom J, Hodge JW. Docetaxel modulates phenotype of human carcinoma cells, including drug-resistant tumor cells, resulting in enhanced killing by CTLs [abstract 4790]. *Proceedings: 101st AACR Annual Meeting*; 2010
43. Hodge JW, Ardiani A, Farsaci B, et al. The tipping point for combination therapy: cancer vaccines with radiation, chemotherapy, or targeted small molecule inhibitors. *Semin Oncol* 2012;39:323–39 [PubMed: 22595055]
44. Aragon-Ching JB, Williams KM, Gulley JL. Impact of androgen-deprivation therapy on the immune system: implications for combination therapy of prostate cancer. *Front Biosci* 2007;12:4957–71 [PubMed: 17569623]
45. Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. *Proc Natl Acad Sci USA* 2001;98:14565–70 [PubMed: 11734652]
46. Gannon PO, Poisson AO, Delvoye N, et al. Characterization of the intra-prostatic immune cell infiltration in androgen-deprived prostate cancer patients. *J Immunol Methods* 2009;348:9–17 [PubMed: 19552894]
47. Drake CG, Doody AD, Mihalyo MA, et al. Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. *Cancer Cell* 2005;7:239–49 [PubMed: 15766662]
48. Sutherland JS, Goldberg GL, Hammett MV, et al. Activation of thymic regeneration in mice and humans following androgen blockade. *J Immunol* 2005;175:2741–53 [PubMed: 16081852]
49. Roden AC, Moser MT, Tri SD, et al. Augmentation of T cell levels and responses induced by androgen deprivation. *J Immunol* 2004;173:6098–108 [PubMed: 15528346]
50. Page ST, Plymate SR, Bremner WJ, et al. Effect of medical castration on CD4+ CD25+ T cells, CD8+ T cell IFN-gamma expression, and NK cells: a physiological role for testosterone and/or its metabolites. *Am J Physiol Endocrinol Metab* 2006;290:E856–63 [PubMed: 16352669]
51. Lechleider RJ, Arlen PM, Tsang KY, et al. Safety and immunologic response of a viral vaccine to prostate-specific antigen in combination with radiation therapy when metronomic-dose interleukin 2 is used as an adjuvant. *Clin Cancer Res* 2008;14:5284–91 [PubMed: 18698048]
52. Gulley JL, Arlen PM, Bastian A, et al. Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. *Clin Cancer Res* 2005;11:3353–62 [PubMed: 15867235]
53. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691–7 [PubMed: 22614989]
54. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 2011;480(7378):480–9 [PubMed: 22193102]

55. Small EJ, Tchekmedyian NS, Rini BI, et al. A pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. *Clin Cancer Res* 2007;13:1810–15 [PubMed: 17363537]
56. Study of Immunotherapy to Treat Advanced Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT00861614?term=NCT00861614&rank=1> [Cited September 2012]
57. Phase 3 Study of Immunotherapy to Treat Advanced Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01057810?term=NCT01057810&rank=1> [Cited September 2012]
58. Slovin S, Hamid O, Tejwani S, et al. Ipilimumab (IPI) in metastatic castrate-resistant prostate cancer (mCRPC): results from an open-label, multicenter phase I/II study. *J Clin Oncol* 2012;30(5S):abstract 25
59. Small EJ, Higano CS, Tchekmedyian NS, et al. Randomized phase II study comparing 4 monthly doses of ipilimumab (MDX-010) as a single agent or in combination with a single dose of docetaxel in patients with hormone-refractory prostate cancer. *J Clin Oncol* 2006;24(18S):abstract 4609
- 60. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23 [PubMed: 20525992] Phase III randomized control trial that showed ipilimumab with or without a gp100 peptide vaccine, as compared with gp100 vaccine alone, improved OS in previously treated metastatic melanoma.
61. Tollefson M, Kames R, Thompson R, et al. A randomized phase II study of ipilimumab with androgen ablation compared with androgen ablation alone in patients with advanced prostate cancer [poster] [abstract 168]. *ASCO Genitourinary Cancers Symposium*; 2010
62. McNeel DG, Smith HA, Eickhoff JC, et al. Phase I trial of tremelimumab in combination with short-term androgen deprivation in patients with PSA-recurrent prostate cancer. *Cancer Immunol Immunother* 2012;61:1137–47 [PubMed: 22210552]
63. Harzstark A, Fong L, Weinberg V, et al. Final results of a phase I study of CTLA-4 blockade in combination with GM-CSF for metastatic castration resistant prostate cancer (mCRPC). *J Clin Oncol* 2010;28(15S):abstract 4689
64. van den Eertwegh AJ, Versluis J, van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2012;13:509–17 [PubMed: 22326922]
65. Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2012;13:501–8 [PubMed: 22326924]
66. Madan RA, Gulley JL, Fojo T, Dahut WL. Therapeutic cancer vaccines in prostate cancer: the paradox of improved survival without changes in time to progression. *Oncologist* 2010;15(9):969–75 [PubMed: 20798195]
67. Gulley JL, Drake CG. Immunotherapy for prostate cancer: recent advances, lessons learned, and areas for further research. *Clin Cancer Res* 2011;17(12):3884–91 [PubMed: 21680544]
68. Di Lorenzo G, Buonerba C, Kantoff PW. Immunotherapy for the treatment of prostate cancer. *Nat Rev Clin Oncol* 2011;8(9):551–61 [PubMed: 21606971]
69. Schlom J, Arlen PM, Gulley JL. Cancer vaccines: moving beyond current paradigms. *Clin Cancer Res* 2007;13:3776–82 [PubMed: 17606707]
70. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26(7):1148–59 [PubMed: 18309951]
71. Steel JC, Waldmann TA, Morris JC. Interleukin-15 biology and its therapeutic implications in cancer. *Trends Pharmacol Sci* 2012;33:35–41 [PubMed: 22032984]
72. Fry TJ, Mackall CL. Interleukin-7: master regulator of peripheral T-cell homeostasis? *Trends Immunol* 2001;22:564–71 [PubMed: 11574281]
73. Sportes C, Babb RR, Krumlauf MC, et al. Phase I study of recombinant human interleukin-7 administration in subjects with refractory malignancy. *Clin Cancer Res* 2010;16:727–35 [PubMed: 20068111]

74. Burchill MA, Yang J, Vang KB, Farrar MA. Interleukin-2 receptor signaling in regulatory T cell development and homeostasis. *Immunol Lett* 2007;114:1–8 [PubMed: 17936914]
75. Borrello IM, Levitsky HI, Stock W, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting cellular immunotherapy in combination with autologous stem cell transplantation (ASCT) as postremission therapy for acute myeloid leukemia (AML). *Blood* 2009;114:1736–45 [PubMed: 19556425]
76. Greiner JW, Guadagni F, Noguchi P, et al. Recombinant interferon enhances monoclonal antibody-targeting of carcinoma lesions in vivo. *Science* 1987;235:895–8 [PubMed: 3580039]
77. Schlom J Therapeutic cancer vaccines: current status and moving forward. *J Natl Cancer Inst* 2012;104:599–613 [PubMed: 22395641]
78. Litzinger MT, Fernando R, Curiel TJ, et al. IL-2 immunotoxin denileukin difitox reduces regulatory T cells and enhances vaccine-mediated T-cell immunity. *Blood* 2007;110:3192–201 [PubMed: 17616639]
79. Morris J, Shapiro G, Tan A, et al. Phase I/II study of GC1008: a human anti-transforming growth factor-beta (TGFbeta) monoclonal antibody (MAb) in patients with advanced malignant melanoma (MM) or renal cell carcinoma (RCC). *J Clin Oncol* 2008;26(Suppl):abstract 9028
80. Schaer DA, Cohen AD, Wolchok JD. Anti-GITR antibodies–potential clinical applications for tumor immunotherapy. *Curr Opin Investig Drugs* 2010;11:1378–86
81. Weinberg AD, Morris NP, Kovacsics-Bankowski M, et al. Science gone translational: the OX40 agonist story. *Immunol Rev* 2011;244:218–31 [PubMed: 22017441]
82. Lynch DH. The promise of 4–1BB (CD137)-mediated immunomodulation and the immunotherapy of cancer. *Immunol Rev* 2008;222:277–86 [PubMed: 18364008]
83. Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 2006;314:126–9 [PubMed: 16946036]
84. Urba WJ, Longo DL. Redirecting T cells. *N Engl J Med* 2011;365:754–7 [PubMed: 21830939]
85. Ruggeri L, Mancusi A, Capanni M, et al. Exploitation of alloreactive NK cells in adoptive immunotherapy of cancer. *Curr Opin Immunol* 2005;17:211–17 [PubMed: 15766683]
86. Phase 1 Trial of Ipilimumab and GVAX in Patients With Metastatic Castration-resistant Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01510288> [Cited September 2012]
87. Phase I Trial of a PSA Based Vaccine and an Anti-CTLA-4 Antibody in Adults With Metastatic Androgen Independent Prostrate Cancer Available from: <http://clinicaltrials.gov/ct2/show/study/NCT00113984?term=NCT00113984&rank=1> [Cited September 2012]
88. Ipilimumab and Sargramostim in Treating Patients With Metastatic Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT00064129?term=NCT00064129&rank=1> [Cited September 2012]
89. Comparison Study of MDX-010 (CTLA-4) Alone and Combined With Docetaxel in the Treatment of Patients With Hormone Refractory Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT00050596?term=NCT00050596&rank=1> [Cited September 2012]
90. MDX-010 for Advanced Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT00170157?term=NCT00170157&rank=1> [Cited September 2012]
91. Ipilimumab + Androgen Deprivation Therapy in Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01377389?term=NCT01377389&rank=1> [Cited September 2012]
92. Neoadjuvant Ipilimumab in Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01194271?term=NCT01194271&rank=1> [Cited September 2012]
93. Ipilimumab and GMCSF Immunotherapy for Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01530984?term=NCT01530984&rank=1> [Cited September 2012]
94. Ipilimumab in Combination With Androgen Suppression Therapy in Treating Patients With Metastatic Hormone-Resistant Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01498978?term=NCT01498978&rank=1> [Cited September 2012]
95. Study of MDX-010 in Patients With Metastatic Hormone-Refractory Prostate Cancer (MDX010–21) Available from: <http://clinicaltrials.gov/ct2/show/NCT00323882?term=NCT00323882&rank=1> [Cited September 2012]

96. Combining Ipilimumab With Abiraterone Acetate Plus Prednisone in Chemotherapy and Immunotherapy-naïve Patients With Progressive Metastatic Castration-resistant Prostate Cancer Available from: <http://clinicaltrials.gov/ct2/show/NCT01688492?term=NCT01688492&rank=1> [Cited September 2012]
- 97. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364(26):2517–26 [PubMed: 21639810] This Phase III randomized control trial showed that ipilimumab and dacarbazine together improved OS in treatment-naïve metastatic melanoma compared to placebo and dacarbazine.

Box 1.**Drug summary**

Drug name	Ipilimumab
Phase	Phase III clinical trials
Indication	Prostate cancer
Pharmacology description	CTLA-4 inhibitor
Route of administration	Injectable, in solution
Chemical structure	Fully human mAb
	Fully human immunoglobulin (IgG1κ) consisting of four polypeptide chains; two identical heavy chains primarily consisting of 447 amino acids each with two identical kappa light chains consisting of 215 amino acids each linked through interchain disulfide bonds
Pivotal trial(s)	[60,97]
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Figure 1. Hypothesized pathways of CTLA-4-related immunosuppression.

CTLA-4 can act intrinsically on the T cell that expresses it. Proposed intrinsic pathways may involve downstream inhibitory pathways or competitive inhibition of the positive pathway mediated by CD28. Alternatively, CTLA-4 may act via involvement of other cells, such as APCs, or processes outside of the T cell that expresses it. Extrinsic pathways include inhibitory cytokine release by immune cells. There are multiple theories on how CTLA-4 aids in extrinsic sequestration of the B7 ligand, thereby preventing its positive function. Data presented at the AACR Tumor Immunology: Multidisciplinary Science Driving Basic and Clinical Advances meeting in Miami last week. Recent data (unpublished) from Allison's lab suggests that anti-CTLA4 antibodies may also deplete intratumoral T-regs by antibody dependant cellular cytotoxicity.

Figure 2. Simplified model of cross-presentation and CTL stimulation by multiple modalities. By killing and/or modifying tumor cells, ionizing radiation and cytotoxic chemotherapy may induce an antigen cascade that releases multiple MHC-1-restricted tumor-associated antigens. APCs such as dendritic cells, when exposed to these antigens and appropriate maturation signals, cross-present the antigens to CD4 T cells (not shown) and CD8 CTLs. The resulting cytotoxic immune response targets modulated and nonmodulated tumor cells not killed by the primary treatment modality, setting off a dynamic immune response late into therapy.

Table 1.

Immunotherapeutic antitumor strategies used alone or in combination.

Strategies	Example	Refs.
Immunostimulants	IL-2, IL-15, IL-7, GM-CSF, IFN	[71–76]
Therapeutic vaccines	Peptides/proteins, recombinant vectors, tumor cells, APCs	[77]
Immune checkpoint inhibitors	Anti-CTLA-4 antibodies, anti-PD-1 and anti-PD-L-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 and anti-B7-H4 antibodies	[8–11,77]
Miscellaneous immunomodulators and drug-immune conjugates	Costimulatory receptor agonists (CD134, glucocorticoid-induced TNF receptor-related protein), monoclonal anti-CD25-diphtheria toxin, monoclonal anti-TGF-β, IL-2 and diphtheria toxin conjugate, NHS-IL-12, hu14.18-IL-2, radiation, cytotoxic chemotherapy, small molecule inhibitors	[43,78–82]
Adoptive cellular therapy	Autologous TILs, allogeneic and autologous peripheral T cells, gene-modified T cells (chimeric TCR), NK cells	[83–85]

APC: Antigen-presenting cell; CTLA-4: Cytotoxic T lymphocyte-associated antibody 4; IL: Interleukin; PD-1: Programmed death 1; TCR: T-cell receptor; TIL: Tumor-infiltrating lymphocyte.

Table 2.

Summary of published trials employing ipilimumab in prostate cancer.

Study agent	Phase	Disease	(n)	Endpoints	Results	irAEs (grade 3)	Refs.
Ipilimumab	I	mCRPC	14	Safety, PSA response	50% PSA declines in 2/14 pts	1	[55]
Concurrent ipilimumab + GVAX	I	Chemo-naïve mCRPC	28	Primary: MTD and safety Secondary: PSA response, TTP, immune response, survival	50% greater decline in PSA in 7 (25%) pts	9	[64,86]
Concurrent ipilimumab + PSA-TRICOM + GM-CSF	I	mCRPC	30 (80% chemo-naïve)	Primary: safety Secondary: PSA response, OS, immune response	PSA decline in 14/24 (58%) chemo-naïve pts; 6 with > 50% PSA decline. Median Halabi-predicted OS: 18.5 months Actual median OS: 31.8 months with 74% survival probability at 24 months	12	[63,87]
Concurrent Ipilimumab + GM-CSF	I	mCRPC	36	Primary: safety Secondary: PSA response, radiographic response	50% PSA declines in 3/6 pts at 3 mg/kg and 1/6 pts at 10 mg/kg	10 (all grade 3)	[61,87]
Ipilimumab ± radiation	I/II	mCRPC	50	Safety, PSA response, radiographic response	Decline in baseline PSA of 50% in 8/50 evaluable pts in the ipilimumab 10 mg/kg ± radiation group	Colitis (16%), diarrhea (8%), hepatitis (10%)	[58]
Ipilimumab vs ipilimumab + docetaxel	II	mCRPC	43 chemo-naïve	Safety, PSA response	PSA declines of 50% in total of 3 pts in both arms	5/52 SAEs in 18 pts were irAEs (grade not reported)	[59,88]
Ipilimumab + ADT vs ipilimumab	II	Advanced CaP	108	Safety, PSA and clinical response	Ipilimumab + ADT group showed more undetectable PSA by 3 months (55 vs 38%)	Ipilimumab + ADT: colitis 4.5%; diarrhea 4.5%	[61,90]

ADT: Androgen-deprivation therapy; MTD: Maximum tolerated dose; OS: Overall survival; PSA: Prostate-specific antigen; pts: Patients; SAE: Severe adverse event; TTP: Time to progression.

Table 3.

Summary of unpublished clinical trials employing ipilimumab in prostate cancer.

Study drugs	Phase	Eligibility	Estimated enrollment	Primary outcome	Refs.
Ipilimumab + ADT	II	Metastatic castration-sensitive prostate cancer	48	PSA response	[91]
Neoadjuvant ipilimumab + ADT	II	High-risk prostate cancer; undergoing prostatectomy	20	Local and systemic immune variables	[92]
Ipilimumab alone vs ipilimumab + GM-CSF	II	mCRPC	54	PSA response	[93]
Ipilimumab + ADT	II	mCRPC	30	PSA response	[94]
Ipilimumab	I/II	mCRPC	66	Safety	[95]
Ipilimumab + abiraterone acetate	I/II	mCRPC	25	Safety	[96]
Ipilimumab vs placebo	III	Chemo-naïve mCRPC	600	OS	[57]
Ipilimumab vs placebo following radiation	III	Chemo-treated mCRPC	800	OS	[56]

ADT: Androgen-deprivation therapy; mCRPC: Metastatic castration-resistant prostate cancer; PSA: Prostate-specific antigen.