Metastatic castration-resistant prostate cancer: new therapies, novel combination strategies and implications for immunotherapy

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Abstract

For the past decade, docetaxel has remained the global standard of care for frontline treatment of metastatic castration-resistant prostate cancer (mCRPC). Until recently, there were limited options for patients with mCRPC following docetaxel failure or resistance, but now the approved treatment choices for these patients have expanded to include abiraterone acetate, cabazitaxel and enzalutamide. Additionally, the radioactive therapeutic agent radium-223 dichloride has been recently approved in patients with CRPC with bone metastases. Although each of these agents has been shown to convey significant survival benefit as a monotherapy, preclinical findings suggest that combining such innovative strategies with traditional treatments may achieve additive or synergistic effects, further augmenting patient benefit. This review will discuss the transformation of the post-docetaxel space in mCRPC, highlighting the spectrum of newly approved agents in this setting in the USA and the European Union, as well as summarizing treatments with non-chemotherapeutic mechanisms of action that have demonstrated promising results in recent phase 3 trials. Lastly, this review will address the potential of combinatorial regimens in mCRPC, including the pairing of novel immunotherapeutic approaches with chemotherapy, radiotherapy or androgen ablation.

Keywords

androgen ablation; chemotherapy; immunotherapy; post-docetaxel; prostate cancer; radiotherapy

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Note Added in Proof: Overall survival data on this trial were recently reported at ECCO; the trial did not meet its primary endpoint of an increase in overall survival.

Conflict of Interest: CG Drake has served as a consultant for Amplimmune, BMS, CoStim, Dendreon and Pfizer, and has patents/potential royalties licensed by Amplimmune. P Sharma has served as a paid consultant for BMS, Dendreon, Helsinn, Jounce and MedImmune, serves on the board of directors for Society for Immunotherapy of Cancer and has stock in Jounce. W Gerritsen serves on advisory boards for Aglaia Biomedical Ventures, Amgen, Bayer, BMS, Ipsen, Janssen, Merck and Sanofi, and has received speaker's honoraria from Astellas, BMS and Janssen.

Introduction

Prostate cancer is the most common non-skin cancer afflicting men in the Western world and represents the sixth leading cause of male cancer-related deaths worldwide.[1] As such, an imperative goal of therapy for prostate cancer is prolonging overall survival (OS).

Until 2010, docetaxel chemotherapy in combination with prednisone remained the established standard of care for patients with metastatic disease,[2,3] with limited options for patients following docetaxel failure. However, studies are revealing new ways to treat metastatic castration-resistant prostate cancer (mCRPC), including disease that has progressed on docetaxel therapy. These alternatives not only include novel approaches with traditional modalities such as chemotherapy and radiotherapy (RT) but also encompass further suppression of androgen signaling through alternative pathways and leveraging the immune system to promote an antitumor immune response.

As a result, the treatment paradigm for mCRPC is rapidly evolving in the USA and the European Union, and the nature of this evolution is transforming the timing of docetaxel therapy, the population that receives docetaxel, and the treatment choices for patients who progress after docetaxel therapy. This review will discuss the transformation of the treatment space for mCRPC from both US and EU perspectives, highlighting the spectrum of newly approved and investigational agents in both regions. It will also address the potential of combinatorial regimens in mCRPC, including pairings of novel immunotherapeutic strategies with traditional approaches such as chemotherapy, RT or androgen ablation.

Background: disease state and treatment paradigm

RT and prostatectomy are potentially curative for early-stage prostate cancer.[4] However, for patients with later-stage disease and those who progress following definitive therapy, androgen-deprivation therapy (ADT) is used for disease control.[2,5] The majority of patients are initially sensitive to ADT, but most tumors eventually become resistant to primary hormone therapy within a median time of 14–30 months.[6] The efficacy of ADT is affected by several disease characteristics, including lower biopsy Gleason score, the absence of metastases and lower serum prostate-specific antigen (PSA) at initiation of ADT.[7]

Patients with prostate cancer that has progressed despite castrate levels of testosterone (<50 ng/ml), that is, CRPC,[8] may expect a survival timeframe of 12–22 months from the time of progression.[9,10] Initially, many patients with mCRPC may be asymptomatic or have mild symptoms. Commonly, prostate cancer metastasizes to bone, which is associated with symptoms of pain and skeletal-related events, including fracture or spinal compression.[5] Palliation of bone metastases, along with prolongation of survival, remain key goals in the treatment of mCRPC.[5]

Historically, mCRPC was thought to be 'hormone-insensitive,' and chemotherapy with docetaxel and prednisone was the gold standard for more than a decade.[2,3] When compared with mitoxantrone-based regimens, docetaxel-based regimens increased median OS to ~16.5–19 months in patients with mCRPC.[11–13] Although ~50% of all men with mCRPC respond to docetaxel with reductions in PSA levels, the majority of responders ultimately

develop resistance to this treatment.[14] In fact, it has been reported that ~70% of patients have progressive disease, as measured by rising PSA levels or by Response Evaluation Criteria in Solid Tumors (RECIST), either during or within 3 months of completing docetaxel treatment.[15] The clinical challenge is when to start chemotherapy. For example, a patient with asymptomatic or mild symptomatic disease who would rather delay treatment until significant symptoms arise may risk less efficacious treatment outcomes due to more advanced disease. Docetaxel is associated with significant toxicity, which limits its use in mCRPC to instances in which the clinical benefit outweighs the adverse event (AE) profile (for example, rapidly progressing or symptomatic disease).[11,12,14] Furthermore, in some patients, treatment is contraindicated due to the presence of comorbidities. In practice, <50% of those with progressive mCRPC receive docetaxel; therefore, there is a need for improved first-line therapies and more options after docetaxel failure.

Recently, randomized phase 3 trials have reported statistically significant improvements in OS in mCRPC (Table 1).[11,13,15–19] These results have led to regulatory approvals of agents including sipuleucel-T (Provenge, Dendreon, Seattle, WA, USA),[20] abiraterone acetate (Zytiga, Jannsen Biotech, Horsham, PA, USA),[21,22] cabazitaxel (Jevtana, Sanofi-Aventis, Bridgewater, NJ, USA, and Sanofi-Aventis Groupe, Paris, France),[23,24] enzalutamide (Xtandi, Astellas Pharma US, Inc., Northbrook, IL, USA),[25] and radium-223 dichloride (Xofigo; Bayer Healthcare Pharmaceuticals; Wayne, NJ, USA)[26] in the USA and/or the European Union.

Harnessing the immune system to fight cancer

The immune system has an important role in the development of tumors, as evidenced, in part, by preclinical research showing that tumors are more aggressive when immune function is impaired. Tumors grow more rapidly in immunodeficient mice relative to controls, especially in those with deficiencies in the development or function of CD8+ cytotoxic T cells, CD4+ helper T cells or natural killer (NK) cells.[27] Furthermore, tumor infiltration by T cells and NK cells has been shown to improve the prognosis of patients across tumor types.[28]

Through a process known as 'immunosurveillance,' the immune system can recognize and eradicate precursors of cancer before they become clinically apparent.[29] The tumor can be completely eradicated or a state of equilibrium may be achieved between tumor immunity and tumor growth, whereby tumor growth is controlled. Unfortunately, for some, the presence of tumor cells that can avoid, resist or suppress the natural immune response may shift the equilibrium toward tumor growth.[30] Tumors escape the immune system by a number of mechanisms, including the secretion of immunosuppressive factors such as transforming growth factor β (TGF-β), which inhibits an antitumor immune response, or the recruitment of regulatory T cells (T_{regs}) or myeloid-derived suppressor cells to the tumor microenvironment, either of which can suppress the activity of cytotoxic T cells.[27]

Treatments that target the immune system to enhance antitumor immunity may provide clinical benefit in cancer patients and allow the long-term suppression of tumor growth. Key approaches include vaccine therapy using peptide-based or dendritic cell-based strategies, or adoptive cell transfer therapy. Additionally, an understanding of the pathways that regulate

antitumor immune responses has led to the development of immune checkpoint inhibitors as an alternative approach to treatment.[30] The approval of sipuleucel-T for mCRPC provided proof of concept that immunotherapeutic approaches are a viable treatment option in this setting, with encouraging results from clinical trials of Prostvac (Bavarian Nordic, Kvistgård, Denmark), a cancer vaccine, and ipilimumab (Yervoy, Bristol-Myers Squibb, Princeton, NJ, USA, and Bristol-Myers Squibb S.r.l., Anagni, Italy),[31,32] an immune checkpoint inhibitor, providing further supporting evidence.

Newly Approved Agents for mCRPC

First-line treatment

Approvals of sipuleucel-T, an autologous cellular immunotherapy product, and abiraterone acetate, an oral prodrug that blocks CYP17, provide oncologists in the USA with alternative options to first-line docetaxel.[20,21] More recently, abiraterone acetate was also approved by the European Medicines Agency (EMA) in the chemotherapy-naive population.[22]

Sipuleucel-T is generated from a patient's own peripheral blood mononuclear cells, which are then activated *ex vivo* with a recombinant fusion protein comprising granulocyte/macrophage colony-stimulating factor and prostatic acid phosphatase.[10] This active cellular immunotherapy was approved by the US Food and Drug Administration (FDA) in 2010 as a first-line treatment option in men with asymptomatic or minimally symptomatic mCRPC,[2,20] making it the first immunotherapy to receive regulatory approval for this tumor type. The approval was based on results of the phase 3 IMPACT trial, which randomized patients to either sipuleucel-T ($n = 341$) or placebo ($n = 171$) administered intravenously every 2 weeks, for a total of three infusions.[10] A significant survival benefit was demonstrated in the patients treated with sipuleucel-T relative to those in the placebo group (25.8 months vs 21.7 months, respectively; hazard ratio (HR) = 0.78, 95% confidence interval (CI) 0.61–0.98; $P = 0.03$); furthermore, a greater improvement in the 36-month survival rate (31 vs 23%, respectively) was evident in the sipuleucel-T arm compared with the placebo group.[10] AEs occurring more frequently with sipuleucel-T than placebo included chills (54.1 vs 12.5%, respectively), pyrexia (29.3 vs 13.7%, respectively) and headache (16 vs 4.8%, respectively).[10]

The IMPACT trial reported an OS benefit that was observed despite no significant differences in measurements of disease progression.[10] The authors surmised that this was attributable to delayed tumor responses, as observed with this and other immunotherapies in various tumor types, possibly due to the time required to activate the immune system against the tumor.[10,30] Recent immunological data showed a correlation between peripheral blood immune responses to the fusion protein and OS that is consistent with the proposed immunological mechanism of action.[33]

Abiraterone acetate blocks CYP17, a critical enzyme in testosterone synthesis.[17] Although initially approved in the post-chemotherapy setting, approval of abiraterone acetate in chemotherapy-naive disease came following positive results from the phase 3 COU-AA-302 trial, in which men with mCRPC who had not received docetaxel ($n = 1088$) and were treated with abiraterone acetate/prednisone trended toward improved OS relative to those

who received placebo/prednisone (median not reached vs 27.2 months, respectively; HR = 0.75, 95% CI = 0.61–0.93; P = 0.01); however, the difference in OS was not statistically significant because, at the time of analysis, the median OS end point had not yet been reached.[34] Furthermore, abiraterone acetate improved radiographic progression-free survival (rPFS) relative to placebo (16.5 months vs 8.3 months, respectively; HR = 0.53, 95% CI = 0.45–0.62; P < 0.001).[34] Fatigue, arthralgia and peripheral edema were more commonly reported in the abiraterone acetate treatment group than in the control group; grade 3–4 mineralocorticoid-related AEs, including fluid retention (28 vs 24%), hypokalemia (17 vs 13%) and hypertension (22 vs 13%), were more frequent in patients treated with abiraterone acetate/prednisone.[34] Of note, this study differed from previous chemotherapy studies in that progressive disease was predominantly defined as radiological progression rather than PSA progression.[11,12,34] A *post hoc* follow-up analysis suggested that continued treatment (24 months) with abiraterone acetate/prednisone may further delay disease progression and prolong survival, with acceptable safety and tolerability.[35]

Post-chemotherapy treatment

In addition to the approval of sipuleucel-T and abiraterone acetate in the first-line setting, abiraterone acetate and cabazitaxel have been approved as post-chemotherapy treatment options by both the FDA and EMA,[21–24] and enzalutamide was approved in the USA.[25] Each of these agents addresses the unmet need of mCRPC following docetaxel failure, which further expands available treatment options for this malignancy.

Approval of abiraterone acetate in the post-chemotherapy setting in mCRPC came following results from the phase 3 COU-AA-301 trial[17] that showed abiraterone acetate/prednisone demonstrated a statistically significant improvement in OS (15.8 months vs 11.2 months; HR = 0.74, 95% CI = 0.64–0.86; P < 0.0001) relative to placebo/prednisone in docetaxel-pretreated patients with mCRPC (n = 1195; randomized 2:1, experimental to control).[16] Median time to PSA progression (8.5 months vs 6.6 months, respectively; P < 0.0001), median rPFS (5.6 months vs 3.6 months, respectively; P < 0.0001) and the proportion of patients who had a PSA response (29.5 vs 5.5%; P = 0.0001) were all superior in the abiraterone group relative to the placebo group.[16] As observed in COU-AA-302, mineralocorticoid-related AEs were more frequent in the abiraterone acetate group than in the placebo group in this study.[17]

Cabazitaxel, a chemotherapeutic agent belonging to the taxane class of microtubule inhibitors, was approved by US and EU regulatory agencies[23,24] in the post-chemotherapy setting following the phase 3 TROPIC study in which 755 men were randomized to receive mitoxantrone/prednisone or cabazitaxel/prednisone.[15] Cabazitaxel treatment led to a statistically significantly longer OS in patients (15.1 months vs 12.7 months, respectively; HR = 0.70, 95% CI = 0.59–0.83; P < 0.0001) compared with those in the mitoxantrone group.[15] Additionally, median progression-free survival (PFS) was greater in the cabazitaxel arm relative to the mitoxantrone arm (2.8 months vs 1.4 months, respectively; HR = 0.74, 95% CI = 0.64–0.86; P < 0.0001).[15] The clinically significant grade 3 AEs that were more common in the cabazitaxel than mitoxantrone arm were neutropenia (82 vs 58%, respectively) and diarrhea (6 vs <1%, respectively).[15]

Enzalutamide (formerly known as MDV3100), an oral androgen receptor signaling inhibitor, was approved by the FDA for use in docetaxel-pretreated mCRPC in August 2012,[25] following positive results from the phase 3 AFFIRM trial.[18] Use of enzalutamide resulted in a 4.8-month improvement in OS relative to treatment with placebo (18.4 months vs 13.6 months, respectively; HR = 0.63, 95% CI = 0.53–0.75; $P < 0.001$) in men with mCRPC previously treated with docetaxel ($n = 1199$, randomized 2:1, respectively).[18] Enzalutamide also demonstrated superiority for key secondary end points relative to placebo, including the proportion of patients with reduced PSA levels by 50% (54 vs 2%, respectively; $P < 0.001$), soft-tissue response rate (29 vs 4%, respectively; $P < 0.001$), quality-of-life response rate (43 vs 18%, respectively; $P < 0.001$), time to PSA progression (8.3 months vs 3.0 months, respectively; HR = 0.25; $P < 0.001$), rPFS (8.3 months vs 2.9 months, respectively; HR = 0.40; $P < 0.001$) and time to first skeletal-related event (16.7 months vs 13.3 months, respectively; HR = 0.69; $P < 0.001$).[18] AEs that were reported more frequently in the enzalutamide group included fatigue, diarrhea and hot flashes. Additionally, seizures were reported in five patients (0.6%) receiving enzalutamide.[18] As steroids have been shown to activate androgen receptor signaling in preclinical models, a *post hoc* analysis of the AFFIRM study investigated the effects of concomitant corticosteroid use on the efficacy of enzalutamide. Interestingly, their use resulted in reduced OS and higher rates of grade 3–4 AEs in patients treated with either enzalutamide or placebo.[36]

Bone-targeting RT

As discussed previously, bone is a common metastatic site in mCRPC, and bone metastases are major contributors to morbidity and disease progression. Following the FDA's approval of denosumab (Xgeva, Amgen, Inc., Thousand Oaks, CA, USA), a human monoclonal antibody against receptor activator of nuclear factor-kappa B ligand, for the prevention of skeletal-related events in patients with bone metastases from solid tumors, including mCRPC,[37] additional therapeutic agents have been evaluated for their potential to positively impact both OS and the effects of bone metastases. The alpha particle-emitting radioactive therapeutic agent radium-223 dichloride has recently been approved by the FDA in patients with CRPC without visceral metastatic disease and with bone metastases.[26]

Radium-223 dichloride was evaluated in the phase 3 ALSYMPCA trial in 921 patients with bone metastases; half of them were chemotherapy-naive, whereas the other half had been pretreated with chemotherapy.[19,38] Patients were randomized 2:1 to radium-223 or placebo and stratified by pretreatment status. Treatment with radium-223 dichloride demonstrated statistically significant improvement in OS (14.9 months vs 11.3 months, respectively; HR = 0.695, 95% CI = 0.581–0.832; $P = 0.00007$) compared with placebo in patients.[19] Safety with radium-223 dichloride was reported as favorable, regardless of whether patients had previous docetaxel treatment, with a low incidence of myelosuppression (grade 3–4 neutropenia in 2.2 and 0.7% and grade 3–4 thrombocytopenia in 6.3 and 2% of the radium-223 dichloride and placebo groups, respectively).[19,38] Notably, men treated with radium-223 dichloride experienced significantly longer time to first skeletal-related event (15.6 months vs 9.8 months, respectively; HR = 0.658, 95% CI = 0.522–0.830; $P = 0.00037$) relative to placebo-treated patients.[19] In addition, this trial reported that radium-233 dichloride reduced pain (50 vs 62% reported pain as an AE; radium-223 dichloride vs

placebo, respectively) and opioid use (36 vs 50%; radium-223 dichloride vs placebo, respectively) in patients with CRPC with bone metastases.[39]

The introduction of each of these new agents is likely to affect the context in which docetaxel is used. Increased use of newer therapies in the first-line setting (to the extent that they are available in a given region) is widening the interval between progression to mCRPC and initiation of chemotherapy or, in some cases, precludes docetaxel therapy entirely.[40]

Phase 3 Studies in The Post-Docetaxel Setting: Ipilimumab

Ipilimumab is being evaluated in two phase 3 studies in CRPC,[41,42] one of which is in patients with docetaxel-pretreated mCRPC (discussed in the next section).[41] The evolving treatment landscape for patients in this setting has implications for clinical trial design in the near term, as well as for patient selection in the long run. If granted marketing authorization following phase 3 evaluation, ipilimumab is expected to further diversify the armamentarium of agents used in docetaxel-pretreated mCRPC beyond abiraterone acetate, cabazitaxel and enzalutamide.

Targeting immune checkpoints, such as with ipilimumab, is an immunotherapy approach that differs from vaccines like sipuleucel-T. Rather than targeting a tumor-specific antigen to modulate the immune system against the tumor, ipilimumab, a fully human IgG1 monoclonal antibody, binds cytotoxic T-lymphocyte antigen-4 (CTLA-4) to augment antitumor immune responses, thus targeting the immune system itself. Ipilimumab was approved in 2011 at a dose of 3 mg/kg for the treatment of unresectable or metastatic melanoma by regulatory agencies in >40 countries.[31,32] Notably, ipilimumab has demonstrated OS benefit in two phase 3 trials for advanced melanoma, with 19–36% of patients experiencing long-term (4-year) survival.[43–45] In advanced melanoma, ipilimumab has side effects that are reflective of its immune mechanism of action, which are manageable using product-specific treatment guidelines.[46,47] Furthermore, ipilimumab has shown clinical activity in a number of early clinical trials in prostate cancer.[48–50] As discussed in a later section, ipilimumab is currently being investigated in a phase 3 study (CA184-043) in patients with mCRPC post-docetaxel (NCT00861614) (Table 2).[41,51–63] In this study, patients receive a single dose of bone-directed RT (8 Gy), followed by either 10 mg/kg ipilimumab or placebo every 3 weeks for up to four doses, and either ipilimumab or placebo every 12 weeks as maintenance therapy. The primary end point of this trial is OS, while secondary end points include PFS, pain response and safety in both arms. Accrual was completed in 2012; this study is currently continuing to follow patients for survival.[41,63] Ipilimumab is also being evaluated in patients who have not yet received docetaxel (NCT01057810).[42]

Combinatorial Approaches to Treating Prostate Cancer

An improved understanding of the prostate cancer microenvironment is leading to more efficacious therapies, both through the improved use of existing treatments and the development of new agents. It is postulated that the most effective approaches against mCRPC may be the combination of innovative strategies with traditional treatments, or with

each other, to achieve additive or synergistic effects.[64] Such combinatorial strategies have been the subject of clinical investigation in mCRPC both before and after the administration of docetaxel/prednisone. Preclinical evidence has provided insight into the various mechanisms that lead to the development of prostate cancer; these pathways are not confined to the cancer epithelial cell but also involve the tumor microenvironment.[65] Multiple signaling pathways provide crosstalk between epithelial cells and stromal cells to promote tumor growth and metastases, including androgen receptor signaling and immune surveillance.[66]

Evaluation of the molecular mechanisms of action for taxane chemotherapies and androgen ablation therapy has revealed the potential for interplay that could lead to clinical synergy between these two classes of agents. Docetaxel, for example, down-regulates androgen receptor expression in a dose-dependent manner, suggesting that the combination of docetaxel and androgen ablation could be synergistic.[67] However, androgen ablation therapy has also been shown to augment class III β-tubulin expression, which is thought to impair taxane therapy.[68] Maturation of data from studies evaluating the combination of taxanes and androgen ablation will clarify the situation further.

Likewise, mechanistic evaluation suggests that it may be possible to increase the effects of immunotherapies by using them concurrently with other anticancer agents. Data suggest that combining agents that modulate immunosuppression with approaches that favor antigen-specific immune responses may be beneficial in patients with cancer. For instance, of 144 patients with metastatic melanoma who received ipilimumab, those with antibody responses to the cancer antigen NY-ESO-1 at baseline were more likely to experience clinical benefit than those without an antibody response.[69]

As shown in Figure 1, anticancer treatments can inhibit suppressive mechanisms of tumor-induced immune tolerance, boost T- and/or B-cell responses, or stress tumor cells to increase their immunogenicity or sensitivity to lysis.[28] As such, there is great interest in exploring potentially additive or synergistic regimens such as immunotherapy plus chemotherapy, RT or androgen ablation, in the clinic.

Immunotherapy in combination with chemotherapy

The overexpression of numerous distinctive antigens on prostate cancer cells and cell lines makes prostate cancer well suited for active immunotherapy.[70] Additionally, although chemotherapy is viewed as immunosuppressive because of its ablation of leukocytes, recent work indicates it may also have immunomodulatory effects.[28,71] Prostate tumors may promote immune tolerance early in the disease course; as such, chemotherapy may help overcome this hurdle of tumor-induced immune tolerance by reducing the amount of suppressive cytokines, such as TGF-β and interleukin 6, secreted by tumor cells.[28,70] Chemotherapy may also deplete T_{regs} and stimulate tumor-specific effector T-cell proliferation.[70,72] Furthermore, following chemotherapy-induced depletion, functional cancer-specific lymphocytes may repopulate the tumor microenvironment via homeostatic proliferation. In addition, preclinical data published by Brown *et al.*[73] suggest that a key mechanism by which homeostatic proliferation supports tumor rejection is by maintaining and/or re-establishing T-cell responsiveness.

Preclinical studies have reported that some chemotherapeutic agents, such as docetaxel and paclitaxel, promote specific immune cell types. For instance, docetaxel administration in 4T1-Neu mammary tumor-bearing mice selectively decreased myeloid-derived suppressor cell, while increasing cytotoxic T-lymphocyte (CTL) responses.[74] Similar preclinical studies reported that paclitaxel enhanced the antitumor effects of a toll-like receptor 9 agonist, while also diminishing T_{regs}.[75] Further research with murine tumor models suggests that sequencing of chemotherapy and immunotherapy may be critical. A study by Garnett *et al.*[76] found that administration of a standard dose of docetaxel following poxvirus immunizations improved vaccine-specific immune responses in tumor-bearing mice; however, administration of docetaxel prior to immunizations did not result in benefit.

Preclinical data suggest that CTLA-4 blockade may have synergistic antitumor activity with chemotherapy,[77–79] possibly because the cytotoxic effects of chemotherapeutic agents may provide a source of tumor antigens that are then presented to T cells by antigen-presenting cells. CTLA-4 blockade then promotes expansion and infiltration of tumor-primed CTLs. Additionally, chemotherapy may induce changes in tumor architecture to facilitate penetration of immunotherapeutic agents.[28,80] Interestingly, Jure-Kunkel *et al.*[78,79] reported that following treatment with CTLA-4 blockade and chemotherapy, some animals rejected a subsequent tumor rechallenge, suggesting the development of a protective immune response in certain tumor models.

Preclinical findings with immunotherapy paired with chemotherapy have translated to early clinical trials in prostate cancer (Table 3).[48,81–86] Ongoing phase 2 clinical trials in prostate cancer in which immunotherapies are being combined with chemotherapy are shown in Table 2.

Immunotherapy in combination with RT

Combining immunotherapy with RT treatment regimens for prostate cancer may also result in synergy, and preliminary observations have suggested that irradiation of cancer cells can prime an antitumor immune response.[87,88] This response may occur through the uptake of the damaged cancerous cells by antigen-presenting cells[89] and subsequently the presentation of tumor antigens to immune cells, or possibly through the induction of a more proinflammatory microenvironment.[87,90]

Preclinical data also suggest that there may be synergistic antitumor activity between RT and vaccine therapy[91] or CTLA-4 blockade.[92–94] For example, murine experiments by Chakraborty *et al.*[91] demonstrated synergy between local radiation of tumor and active vaccine therapy. The studies used mice transgenic for carcinoembryonic antigen (CEA) and a murine carcinoma cell line transfected with CEA. The vaccine regimen included a prime and boost strategy using CEA-TRICOM. A single dose of 8-Gy radiation to tumors induced upregulation of the death receptor Fas *in situ* for a number of days. Neither radiation at this dose nor vaccine therapy alone was capable of inhibiting growth of 8-day established tumors, but combining the two strategies led to a significant cure rate, and tumors exhibited a massive infiltration of T cells. Mice cured of tumors demonstrated CD4+ and CD8+ T-cell responses specific for CEA and also revealed the induction of high levels of T-cell responses

to two other antigens (gp70 and p53) overexpressed in tumors, suggesting the presence of a consequential antigen cascade.[91]

Demaria *et al.*[94] tested the hypothesis that the combination of RT to the primary tumor and CTLA-4 blockade can elicit antitumor immunity and thereby inhibit metastases. Using the poorly immunogenic metastatic mouse mammary carcinoma 4T1 as a model, they reported that blockade of CTLA-4 alone or use of RT alone resulted in similar survival rates to those of control mice. However, the combination of RT and CTLA-4 blockade in malignant mice led to synergistic effects, resulting in a statistically significant survival advantage.[94]

In an important mechanistic study, Pilones *et al.*[93] found that invariant natural killer T (iNKT) cells, a subset with unique regulatory functions, have a critical role in regulating the response to treatment with local RT and CTLA-4 blockade. The growth of poorly immunogenic and vastly metastatic 4T1 mammary carcinoma primary tumors and lung metastases was compared in wild-type and iNKT cell-deficient (iNKT –/–) mice after they received RT and/or a monoclonal antibody against CTLA-4. The response to RT in combination with CTLA-4 blockade was substantially increased in the absence of iNKT cells, with 50% of iNKT –/– mice (vs none of wild-type animals) exhibiting complete tumor regression, long-term survival or resistance to a challenge with 4T1 cells. Additionally, tumor-infiltrating iNKT cells were greatly reduced in wild-type mice that were administered RT plus CTLA-4 blockade.[93]

Most recently, Dewan *et al.*[92] reported that fractionated RT induced an abscopal effect, defined as tumor regression seen outside the field of RT, when used in combination with anti-CTLA-4 antibody in two independent carcinoma mouse models. Importantly, another study in an autochronous model of prostate cancer suggested that the timing of immunotherapy following RT may be quite restricted, which could have implications for future clinical development of combinatorial strategies.[95]

The concept of immunotherapy paired with RT has also been evaluated in clinical studies (Table 3) and is the subject of ongoing research (Table 2). Based on the preclinical evidence in mCRPC noted previously and antitumor responses in patients with advanced melanoma,[46,47] a phase 1/2, dose-escalation trial was conducted to evaluate the use of ipilimumab alone or in combination with RT in patients with mCRPC, with or without prior chemotherapy (Table 3).[48] Of 50 PSA-evaluable patients in the 10 mg/kg ± RT cohort of this trial, eight had PSA response lasting between 3 and > 13 months; furthermore, of the 28 tumor-evaluable patients receiving 10 mg/kg ± RT, 1 displayed complete response whereas 6 had stable disease.[48] Encouraging results from this phase 1/2 study of ipilimumab ± RT with or without prior docetaxel treatment, which included no dose-limiting toxicities within the dose-limiting toxicities period, has led to phase 3 evaluation of this agent. As mentioned previously, in the CA184-043 trial, ipilimumab is given following a single dose of RT in an effort to prime for an initial antitumor immune response (Table 2).[41,63] The results of this trial were recently reported (ECCO 2014); the study did not meet its primary endpoint of an increase in overall survival, but did meet a secondary endpoint of improved progression free survival (PFS).

As shown in Table 2, a phase 3 study is investigating the use of ProstAtak (AdV-tk + valacyclovir), an investigational agent that kills tumor cells and elicits an antitumor vaccine effect, in combination with standard external beam RT with or without ADT for intermediate–high-risk localized prostate cancer (NCT01436968).[61] This study has an estimated enrollment of 700 patients and has a primary end point of disease-free survival.[61]

Immunotherapy in combination with androgen ablation

Evidence suggests that in aged mice, androgen ablation can result in regeneration of the thymus and the appearance of naive T cells in the peripheral blood.[96,97] In humans, androgen ablation correlates with increased infiltration of CD4+ T cells into the prostate gland.[96,98]

Early clinical trials in prostate cancer have evaluated the use of androgen ablation with immunotherapy agents such as Prostvac and ipilimumab (Table 3), while a number of current phase 2 trials are examining the clinical benefit of pairing androgen ablation with agents such as ipilimumab and sipuleucel-T, amongst others (Table 2). Of note, intriguing preliminary data from an ongoing phase 2 trial investigating the regimen of ipilimumab with the hormonal agent leuprolide acetate in pre-surgery prostate cancer patients found that this combination affects T-cell responses, including a measurable increase in the frequency of T cells expressing inducible costimulator molecules (NCT01194271).[55,99] Recent results reporting early data regarding an ongoing phase 2 trial suggest that the combination of ipilimumab and ADT in castration-sensitive prostate cancer patients significantly increases the frequency of T cells expressing inducible costimulator (ICOS), as well as the levels of memory T-cell markers (NCT01377389).[56,100] Additionally, preliminary results from a phase 2 sequencing trial with sipuleucel-T and ADT in men with biochemically recurrent prostate cancer suggest that tumor-specific T-cell responses and immune responses are augmented when sipuleucel-T is given after rather than prior to ADT (NCT01431391).[57,101] Follow-up analyses will determine whether improved immune responses correlate with clinical parameters.[101]

A phase 2 study investigating the use of sipuleucel-T with concurrent or sequential abiraterone acetate plus prednisone (NCT01487863)[58] recently reported interim results, which suggest that sipuleucel-T can be successfully manufactured during concurrent abiraterone acetate/prednisone administration.[102] The potency and prime boost effect were similar to sipuleucel-T monotherapy. However, pending the release of mature data, it is not yet known how concurrent or sequential abiraterone acetate/prednisone administration impacts the efficacy of sipuleucel-T.[102]

Combining Agents with Novel Mechanisms of Action

Preclinical and early clinical studies of immunotherapy in combination with therapeutic modalities such as chemotherapy, RT or androgen ablation have revealed enhancement of endogenous or induced antitumor immune responses, providing support for future clinical evaluation of such pairings.[64] There is much interest in determining whether other modalities such as cryoablation would result in additive or synergistic effects when paired with immunotherapy, as cryotherapy has shown promising systemic antitumor effects when

combined with other anticancer agents such as chemotherapy.[103] Of note, with the emergence of checkpoint blockade strategies, the ability to combine multiple immunotherapy agents with divergent mechanisms of action has become an intriguing area of scientific research. The aim is to optimize immunotherapy by targeting different aspects of the immune response.[104] Given the recent phase 1 safety and activity findings regarding use of an antibody to block programmed death-1, an inhibitory receptor expressed by T cells, in various tumor types,[105] there is interest in combining cancer vaccines with such immune checkpoint blockade antibodies to induce synergistic antitumor responses.[104] Another approach involves the use of histone deacetylase inhibitors that can prime tumor cells for eradication by the immune system. This is achieved through multiple mechanisms, including the upregulation of surface molecules such as major histocompatibility complex class I/II as well as costimulatory (CD80, CD86) and adhesion molecules.[106] This upregulation may reduce the ability of tumor cells to evade immune detection. Furthermore, histone deacetylase inhibitors have been shown to downregulate T_{reg} cells and augment immunotherapy in animal models of renal and prostate cancers.[107]

Challenges in The mcrpc Treatment Landscape

Although advances in the biology of prostate cancer have vastly enhanced knowledge and expanded the pool of agents with demonstrated efficacy, medical oncologists face key challenges in defining the optimal treatment paradigm for this malignancy. First-line administration of non-chemotherapy agents such as sipuleucel-T and abiraterone acetate, rather than docetaxel, has dramatically altered the idea of the 'typical' patient with mCRPC. With the variety of newly approved agents in mCRPC, administration of docetaxel is expected to be delayed or even omitted, when possible, in favor of agents with a more desirable risk:benefit profile.[40] It is possible that in the coming years the use of docetaxel as a therapeutic 'landmark' may erode away, with treatment decisions relying even more heavily on an individual patient's prior responses to hormonal treatment and immunotherapy.

Additionally, there is a lack of head-to-head trials comparing existing standards of care and new or emerging treatments. Direct comparison of treatments will offer greater insight into the clinical activity of each agent. Furthermore, with the approval of abiraterone acetate, cabazitaxel and enzalutamide in the post-chemotherapy setting, there are at least three effective agents in this arena; therefore, choosing a comparator for future trials remains a huge hurdle.

Given the diverse mechanisms of action for each of the agents approved for mCRPC since 2010, determining optimal sequence and combinations of agents will be essential to the management of prostate cancer. For any two therapeutic approaches with non-overlapping mechanisms of action, there exists the potential for cultivating synergistic improvements in outcome, but there is also the potential for compounded toxicity profiles when the agents are used in combination. In some cases, there is a specific preclinically or clinically supported rationale for evaluating two agents or classes concurrently or sequentially with one another. For example, as enzalutamide does not need to be given with corticosteroids,[25] it may be a more suitable partner for immunotherapy than docetaxel. Likewise, the low rate of myelosuppression observed with radium-223 dichloride in the ALSYMPCA study,[19] as

previously discussed, suggests that it may be a better pairing with immunotherapy than standard RT. Additionally, in the European Union, abiraterone acetate is commonly administered with the mineralocorticoid receptor antagonist eprenolone rather than with prednisone, which may be important in terms of optimal combinations with immunotherapy, as practitioners seek to avoid the immunosuppressive effects of steroids so that patients can achieve maximal clinical benefit.

Of note, it is not clear whether sequencing of agents will result in superior survival of patients with mCRPC. Recent data in docetaxel-pretreated patients with mCRPC suggest that therapy with either enzalutamide or abiraterone acetate post-cabazitaxel results in prolonged OS compared with those who received enzalutamide or abiraterone acetate pre-cabazitaxel treatment (65 months vs 39 months (from first dose of docetaxel), respectively); prospective trials are required to confirm these results.[108] In certain cases, administration of agents simultaneously rather than sequentially may be more efficacious. Given that preliminary results from a trial in which enzalutamide was given after abiraterone acetate and docetaxel suggested possible reduced efficacy in mCRPC patients,[109] it is hypothesized that simultaneous administration of these agents may lead to improved benefit, a combination that is currently being evaluated clinically in mCRPC (NCT01650194).[110]

To this end, a long-term goal in the field is to distinguish clinical biomarkers that will aid in the selection of patients who will benefit from specific therapies, which is critical in tailoring individualized treatment regimens. It was previously shown that circulating tumor cells are prognostic biomarkers, both before and after treatment, in patients treated with taxanes,[111] and evaluation of circulating tumor cells as predictive biomarkers is now underway for newly approved agents. As immunotherapy continues to emerge as a treatment modality in mCRPC, it is likely that immunoprofiling will have a greater role in diagnosis, prognostic assessment and therapeutic strategy.[112] Although immunotherapy in mCRPC is effective in patients whose disease is chemotherapy-naive and in those pretreated with chemotherapy, in the sipuleucel-T and ipilimumab trials, only a subset of patients in each of these settings experienced therapeutic benefit.[10,48] We do not yet have a biomarker to determine which of these patients will exhibit the greatest benefit. Earlier use of secondary androgen ablation in the pre-chemotherapy space begs the question of whether patients who have received abiraterone acetate prior to chemotherapy would benefit from re-treatment with abiraterone acetate following failure of docetaxel. Again, data are sparse and biomarkers for androgen sensitivity are lacking, although it is possible that testosterone levels may indicate receptiveness to androgen ablation following docetaxel.

Conclusions

Worldwide, one of the most significant challenges posed in prostate cancer management has been establishing treatment for a patient who no longer responds to primary androgen ablation therapy and has further progressed on docetaxel-based chemotherapy. Our improved understanding of the complex biology that underscores the malignancy of prostate cancer has led to clinical investigation of innovative approaches such as hormonal therapy, radiopharmaceuticals, immunotherapy and newer chemotherapy, which offer clinicians more options to manage metastatic disease. Ipilimumab is currently being evaluated for efficacy in

the post-docetaxel setting in a phase 3 trial. If approved, ipilimumab is expected to further transform the treatment landscape for mCRPC.

The expanding arsenal of treatments for mCRPC has shifted the paradigm for late-line prostate cancer therapy, which has substantial implications for the trial design of future therapies seeking approval in this setting. There has also been a shift in the profile of the typical mCRPC patient, as a result of increased choices for first-line therapy. The potential of combinatorial regimens in mCRPC, including the pairing of novel immunotherapeutic approaches with chemotherapy, RT or androgen ablation, will continue this cycle of evolution, which will help to alleviate the current clinical challenge of navigating the most appropriate use of the newer available agents.

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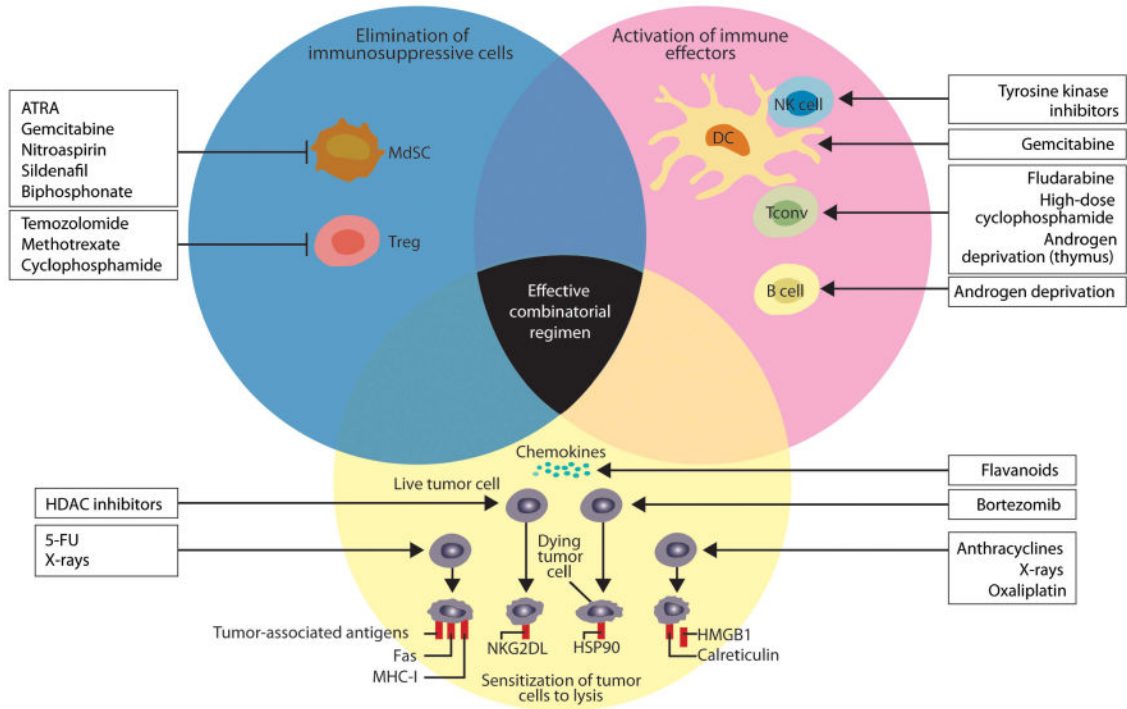
Figure 1.
Immune potentiating mechanisms of action of chemotherapies, RT and androgen deprivation. This figure shows how anticancer drugs can activate the immune system. Agents can inhibit immunosuppressive mechanisms of tumor-induced immune tolerance, boost T- and/or B-cell responses or stress tumor cells so they become immunogenic and sensitive to lysis. It is important to note that the anticancer therapies shown apply generally to the field, and some of the agents shown are not indicated for the treatment of mCRPC. Reproduced with permission from the *Journal of Clinical Investigation*.[28] 5-FU, 5-fluorouracil; ATRA, all-trans-retinoic acid; DC, dendritic cell; HDAC, histone deacetylases; HSP90, heat shock protein 90; mCRPC, metastatic castrate-resistant prostate cancer; MdSC, myeloid-derived suppressor cell; MHC-I, major histocompatibility complex class I; HMGB1, high mobility group box 1 protein; NK, natural killer cell; NKG2DL, NK cell group 2D ligands; Tconv, conventional effectors; Treg, regulatory T cell.

Table 1

Completed phase 3 trials in CRPC post-docetaxel with a survival advantage

Investigational vs control arm	Study	Patient population	Overall survival (mo)	Mean change (mo)	Tolerability	Reference
Docetaxel/prednisone vs mitoxantrone/prednisone[a]	TAX327	Advanced CRPC (N = 1006)	19.2 vs 16.3 (HR = 0.79; P = 0.004)	2.9	AEs were more common in the docetaxel arm	Berthold;[13] Tannock[11]
Cabazitaxel/prednisone vs mitoxantrone/prednisone	TROPIC	Docetaxel-pretreated mCRPC (N = 755)	15.1 vs 12.7 (HR = 0.70; P < 0.0001)	2.4	Grade ⩾3 neutropenia (82 vs 58%) and diarrhea (6 vs 1%) were more frequent in the cabazitaxel vs control arm	de Bono[15]
Abiraterone acetate/prednisone vs placebo/prednisone	COU-AA-301	Docetaxel-pretreated mCRPC (N = 1195)	15.8 vs 11.2 (HR = 0.74; P < 0.0001)	4.6	Most common grade 3–4 AEs amongst pts in the abiraterone acetate and placebo groups, respectively, were fatigue (9 vs 10%), anemia (8 vs 8%), back pain (7 vs 10%) and bone pain (6 vs 8%)	Fizazi;[16] de Bono[17]
Enzalutamide vs placebo	AFFIRM	Docetaxel-pretreated mCRPC (N = 1199)	18.4 vs 13.6 (HR = 0.63; P < 0.001)	4.8	AEs more frequently reported in the enzalutamide group included fatigue, diarrhea and hot flashes; seizures were reported in 5 pts (0.6%) receiving enzalutamide	Scher[18]
Radium-223 dichloride + BSC vs placebo/BSC	ALSYMPCA	Symptomatic CRPC with bone metastases, of whom 50% were chemotherapy-naive and 50% were post-docetaxel (N = 921)	14.9 vs 11.3 (HR = 0.70; P = 0.00007)	3.6	Grade 3–4 neutropenia in 2.2 vs 0.7%, and grade 3–4 thrombocytopenia in 6.3 vs 2% in radium-223 dichloride and placebo groups, respectively	Parker[19]

Abbreviations: AE, adverse event; BSC, best supportive care; CRPC, castration-resistant prostate cancer; HR, hazard ratio; mCRPC, metastatic CRPC; mo, month; pt, patient.

[a]Phase 3 TAX327 trial that led to docetaxel approval in advanced CRPC shown in table for comparison.

Table 2

Recruiting/ongoing phase 2 and 3 trials in prostate cancer with immunotherapy-combination regimens

	Clinicaltrials.gov identifier	Phase	Treatment arm(s)	Patient population	Primary outcome measure	Status	Sponsor
Immunotherapy combined with chemotherapy	NCT01145508[51]	2	Vaccinia-PSA (L155)-TRICOM vaccine + docetaxel/ prednisone vs Docetaxel/	Metastatic hormone-resistant PC	OS	Ongoing	National Cancer Institute (NCI)
	NCT01420965[52]	2	Sipuleucel-T vs Sipuleucel-T +CT-011 vs Sipuleucel-T + CT-011 + cyclophosphamide	Advanced CRPC	Determine feasibility and immune efficacy of combinations	Recruiting	Georgia Regents University
Immunotherapy combined with RT	NCT00861614[41]	3	Ipilimumab vs placebo, each following single dose of RT	CRPC	OS	Ongoing	Bristol-Myers Squibb
Immunotherapy combined with androgen ablation	NCT00450463[53]	2	Prostvac/TRICOM + flutamide vs Flutamide alone	Androgen insensitive, non-metastatic PC	Time to treatment failure	Recruiting	National Cancer Institute (NCI)
	NCT00583752[54]	2	3 rounds of adenovirus/PSA vaccine vs ADT 14 days prior to beginning adenovirus/PSA vaccinations	Recurrent PC after local therapy	PSA doubling-time response	Recruiting	University of Iowa
	NCT01194271[55]	2	Leuprolide acetate + ipilimumab + radical prostatectomy	PC	Longitudinal peripheral blood values	Recruiting	M.D. Anderson Cancer Center
	NCT01377389[56]	2	Ipilimumab + ADT	Castrate-sensitive PC	Proportion of pts achieving a PSA 0.2 ng/ml at month 7	Recruiting	M.D. Anderson Cancer Center
	NCT01431391[57]	2	ADT initiated 2 wks after the last sipuleucel-T infusion vs ADT initiated 12 wks prior to the first sipuleucel-T infusion	Non-metastatic PC and a rising serum PSA after primary therapy	Change in immune response to PA2024; to determine whether ADT started before or after sipuleucel-T leads to superior augmentation of immune response to sipuleucel-T	Ongoing	Dendreon
	NCT01487863[58]	2	Concurrent arm: Sipuleucel-T concurrent with	Metastatic CRPC	Evaluate cumulative sipuleucel-T CD54 upregulation	Ongoing	Dendreon

Clinicaltrials.gov identifier	Phase	Treatment arm(s)	Patient population	Primary outcome measure	Status	Sponsor
		abiraterone acetate/prednisone for 26 wks vs Sequential arm: Sipuleucel-T therapy followed by abiraterone acetate/prednisone. Abiraterone acetate/prednisone will start 6 wks after the last infusion of sipuleucel-T and continue for				
NCT01498978[59]	2	Ipilimumab + AST	Metastatic hormone-resistant PC	Fraction of pts who achieve an undetectable PSA (0.2 ng/ml)	Recruiting	OHSU Knight Cancer Institute
NCT01688492[60]	1/2	Ipilimumab + abiraterone acetate + prednisone	Chemotherapy and immunotherapy-naive metastatic CRPC	Safety; PFS	Recruiting	Memorial Sloan-Kettering Cancer Center
NCT01436968[61]	3	ProstAtak vaccine + valacyclovir + RT +/-ADT vs Placebo + valacyclovir + RT +/- ADT	Localized PC	DFS	Recruiting	Advantagene, Inc.
NCT01696877[62]	1/2	Degarelix acetate vs Cyclophosphamide + GVAX, followed by degarelix acetate	High-risk localized PC undergoing radical prostatectomy	Intraprostatic CD8+ T-cell infiltration; Number of pts with AEs	Recruiting	Sidney Kimmel Comprehensive Cancer Center

Immunotherapy–based triplet regimens

Abbreviations: ADT, androgen-deprivation therapy; AE, adverse event; AST, androgen suppression therapy; CRPC, castration-resistant prostate cancer; DFS, disease-free survival; OS, overall survival; PC, prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen; pt, patient; RT, radiotherapy; wk, week.

Table 3

Completed clinical trials in prostate cancer with immunotherapy-combination regimens

	Phase	Patient population (N)	Treatment arm(s)	Primary end point	Results	Reference
Immunotherapy combined with chemotherapy	2	Metastatic, androgen-independent PC (28)	Poxvirus-PSA vaccine + docetaxel/dexamethasone vs Poxvirus-PSA vaccine	Determine whether docetaxel/dexamethasone has an effect on generating an immune response to the vaccine	3.2 mo vs 1.8 mo median time to progression in the combination arm vs vaccine alone arm, respectively	Arlen[81]
	2	Hormone-resistant PC, docetaxel eligible (43)	Ipilimumab + docetaxel vs Ipilimumab	Safety and activity between arms	Two pts who received ipilimumab monotherapy vs 1pt who received ipilimumab + docetaxel had confirmed PSA responses; 18 pts experienced 52 serious AEs, 10 of which were attributed to ipilimumab	Small[82]
Immunotherapy combined with RT	2	CRPC (30)	Combination immunotherapy + RT vs RT	Determine whether a PSA-specific T-cell response to the vaccine regimen could be mounted in the presence of RT	13/17 pts who received combination immunotherapy + RT had >3-fold increase in the number of PSA-specific T cells relative to pts in the RT-alone arm, who failed to show a detectable increase in the number of PSA-specific T cells	Gulley[83]
	1/2	Metastatic CRPC, pre- and post-docetaxel (71)	Ipilimumab + RT vs Ipilimumab	Safety	No DLTs; treatment-related AEs and immune-related AEs were common in pts treated with or without RT	Slovin[48]
Immunotherapy combined with androgen ablation	1	Pts with post-prostatectomy recurrence of prostate cancer (6)	Vaccinia-PSA (Prostvac), after radical prostatectomy	Toxicity; serum PSA rise related to serum testosterone restoration, and immunologic effects	No DLTs, and toxicity was minimal; noteworthy variability in time required for testosterone restoration, 1 pt showed continued undetectable serum PSA (<0.2 ng/ml) for >8 mo after testosterone restoration	Sanda[84]
	2	Non-metastatic CRPC (42)	Prostvac-VF vs Nilutamide, with potential to crossover after PSA rise to receive combined therapies	Time to progression	Median survival exhibited a trend toward improvement for pts initially randomized to the vaccine arm (median 5.1 vs 3.4 y; $P = 0.13$); subset of 12 pts who initially received vaccine and then later received nilutamide suggested improved survival compared with the 8 pts who began with nilutamide and then were treated with vaccine (median 6.2 y vs 3.7 y, $P = 0.045$)	Madan[85]
	2	Advanced chemotherapy-naive CRPC (108)	Ipilimumab + androgen ablation vs Androgen ablation	Percentage without progression at 18 mo	55 vs 38% undetectable PSA by 3 mo in the combination arm vs androgen ablation alone arm, respectively	Tollefson[86]

Abbreviations: AE, adverse event; CRPC, castrate-resistant prostate cancer; DLT, dose-limiting toxicity; mo, month; PC, prostate cancer; PSA, prostate-specific antigen; pt, patient; RT, radiotherapy; y, year.