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Combining immunotherapies for the treatment of prostate cancer

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Abstract

Sipuleucel-T, a therapeutic dendritic-cell vaccine, was Food and Drug Administration-approved for prostate cancer in 2010. No new immunotherapies for prostate cancer have been approved since. However, novel agents and combination approaches offer great promise for improving outcomes for prostate cancer patients. Here we review the latest developments in immunotherapy for prostate cancer. Sipuleucel-T has demonstrated a survival advantage of 4.1 months in metastatic castration-resistant prostate cancer. PSA-TRICOM (PROSTVAC), a prostate-specific antigen-targeted vaccine platform, showed evidence of clinical and immunologic efficacy in early-phase clinical trials, and results from a phase III trial in advanced disease are pending. While immune checkpoint inhibitors appear to have modest activity as monotherapy, preclinical and clinical data suggest that they may synergize with vaccines, poly [ADP-ribose] polymerase inhibitors, and other agents. Several clinical studies that combine these therapies are underway.

Combining prostate cancer vaccines with immune checkpoint inhibitors has great potential for improving clinical outcomes in prostate cancer. Such combination approaches may create and then recruit tumor-specific T cells to tumor while also increasing their effector function. Other emerging agents may also enhance immune-mediated tumor destruction.

Keywords

Prostate cancer; Tumor vaccine; Immunotherapy; PARP inhibitor; Checkpoint inhibitor

Introduction

The past decade has delivered remarkable advances in immunotherapy for many types of cancer. With this progress, ‘immunotherapy’ has come to encompass many tactically distinct treatments, including vaccines, immunomodulating checkpoint inhibitors, enzyme inhibitors, and immunocyto- kines. Sipuleucel-T, generally categorized as a dendritic-cell (DC) vaccine, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic prostate cancer.

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Meanwhile, the treatment landscapes of melanoma, kidney cancer, nonsmall cell lung cancer, urothelial carcinoma, and Hodgkin's lymphoma have been transformed by checkpoint inhibitors [1–6]. These antagonist monoclonal antibodies act as immunomodulators, potentiating antitumor immunity by targeting regulatory molecules on cell surfaces. The most well studied checkpoint inhibitors target cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand-1 (PD-L1), and are predominantly involved in regulating T-cell activity [1–4,6]. The immune functions of these molecules have been reviewed elsewhere [7–11]. Briefly, blockade of these molecules affects interactions in several immune compartments, including the tumor microenvironment (TME). In some cases, these agents dampen the immune system's natural inhibitory functions, resulting in increased antitumor activity.

Much can be learned from clinical trial data and correlative studies of these agents in prostate cancer (Table 1). While checkpoint inhibitor monotherapies have not substantially improved clinical outcomes for patients with prostate cancer, approaches that combine immune checkpoint inhibitors, vaccines, and other agents are under investigation to manipulate the immune system leading to increased antitumor activity.

Clinical experience with therapeutic vaccines

Sipuleucel-T, a DC vaccine, is the only immunotherapy currently approved by the FDA for prostate cancer. Three other vaccine platforms, PROSTVAC (PSA-TRICOM), DCVAC/PCa, and ProstAtak are in phase III clinical trials in the metastatic (PROSTVAC and DCVAC/PCa) and localized neoadjuvant (ProstAtak) settings. Studies conducted on peripheral blood and prostate biopsy samples have contributed to the understanding of these drugs' mechanisms of action.

Sipuleucel-T—Sipuleucel-T is a cellular product derived from a patient's own harvested peripheral blood mononuclear cells. After incubation with a fusion protein (PA2024) incorporating the prostate tumor-associated antigen prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor, the immune cells are infused into the patient with the goal of generating an antitumor immune response.

Approval of sipuleucel-T in 2010 followed results from the phase III IMPACT trial in 512 patients with metastatic castrate-resistant prostate cancer (mCRPC). Patients who received sipuleucel-T had a median overall survival (OS) of 25.8 months, compared to 21.7 months with placebo [12]. Despite this survival advantage, no statistically significant differences in time to objective or clinical progression were observed between groups. Outcomes were similar in a smaller phase III study in men with minimally symptomatic mCRPC [13]. Median OS was 25.9 months with sipuleucel-T vs. 21.4 months with placebo.

Sipuleucel-T appears to enhance multiple immune functions following treatment [14–16]. However, antigen-specific responses appear to play the most important role in OS benefit. In 78.8% of monitored patients, PAP/PA2024-specific antibodies, PAP/PA2024-specific T-cell activation, and/or PAP/PA2024-specific T-cell proliferation were observed and correlated with OS ($P = 0.003$) [14]. Antigen spreading, i.e., the generation of immunoglobulin specific for tumor-associated antigens not included in the vaccine [17], has also been observed [16].

In a study of sipuleucel-T, Fong et al provided proof of concept for a possible T-cell-mediated mechanism of action. In 37 men with localized prostate cancer, neoadjuvant sipuleucel-T was associated with a 3-fold increase in activated T cells in 57% (95% CI: 39–79) of post-radical prostatectomy (RP) biopsies compared to pretreatment biopsies (binomial proportions: all $P < 0.001$). This increase was not observed in 12 control RP samples from men who did not receive sipuleucel-T [18], suggesting that sipuleucel-T mobilizes immune cells to the TME.

PROSTVAC—PROSTVAC (PSA-TRICOM) is a prostate-specific antigen (PSA)-targeted recombinant viral vaccine administered as a recombinant vaccinia priming dose followed by monthly recombinant fowlpox boosts. The TRICOM platform incorporates the costimulatory molecules B7.1, ICAM-1, and LFA-3. Presentation of these molecules to naïve T cells during antigen presentation favors type 1 helper T-cell responses, characterized by antigen-specific cytotoxic T-cell proliferation [19]. PROSTVAC increases T-cell avidity 100-fold over vaccines that do not incorporate TRICOM [20]. This is significant, since higher-avidity T cells require less antigen to induce T-cell-mediated tumor-cell lysis.

Immune responses following treatment with PROST- VAC have been well described. In one trial, 59/104 patients (57%) had a 2-fold increase in PSA-specific T cells as evidenced by IFN- γ ELISPOT assay following vaccine [21]. Antigen spreading was observed in 19/28 (68%) evaluated patients.

PROSTVAC is well tolerated [22,23]. In a randomized phase II study in which 82 patients received PROSTVAC and 42 received a control vector, PSA declines were rare, but median OS was 25.1 months for patients given PROSTVAC vs. 16.6 months for controls (HR = 0.56; 95% CI: 0.37–0.85; $P = 0.0061$) [24]. Results from a recently completed multicenter phase III trial of PROST- VAC with or without granulocyte-macrophage colony- stimulating factor vs. placebo in patients with mCRPC (n = 1,297) are pending (NCT01322490). Studies of PROST- VAC in the adjuvant and biochemically recurrent settings are recruiting patients (NCT02772562 and NCT02649439).

DCVAC/PCa—DCVAC/PCa is an autologous DC vaccine derived from peripheral blood mononuclear cells obtained by apheresis that are pulsed with killed prostate cancer cells. The mature DCs are then injected subcutaneously. In a phase I/II trial, 25 men with mCRPC received DCVAC/PCa plus docetaxel. Patients were also given low-dose oral cyclophosphamide to deplete regulatory T cells [25] and a topical Toll-like receptor agonist at the injection site to enhance immune activation. The vaccine was well tolerated and resulted in a median OS of 19 months. This compared favorably to both the Halabi nomogram-predicted OS of 11.8 months (HR = 0.26; 95% CI: 0.13–0.51) and the MSKCC nomogram-predicted OS of 13 months (HR = 0.33; 95% CI: 0.17–0.63) [26]. The global phase III VIBBLE trial of DCVAC/PCa plus first-line chemotherapy for mCRPC (NCT02111577) began recruiting patients in 2014 (target: 1,170 patients).

ProstAtak—ProstAtak® transfers a herpes simplex virus thymidine kinase to tumor cells via an adenoviral vector. Combining ProstAtak with a prodrug creates cytotoxic and immunostimulatory effects [27] that are well tolerated [28]. In a phase I/II trial, 9 men with

localized prostate cancer received ProstAtak prior to RP. At a median follow-up of 11.3 years, 6 patients were still alive and 3 had died of issues unrelated to prostate cancer [29]. A phase III trial of ProstAtak is currently enrolling patients with intermediate- to high-risk localized prostate cancer (NCT01436968). Beginning 15 days to 8 weeks after standard radiotherapy (RT), patients will receive 3 intraprostatic, transrectal ultrasound-guided injections of ProstAtak or placebo. The primary endpoint of this study is progression-free survival.

Clinical experience with immune checkpoint inhibitors

Two phase III trials of ipilimumab (anti-CTLA-4) monotherapy in mCRPC have been completed. In one study, men with mCRPC metastatic to bone who had progressed on docetaxel ($n = 799$) were randomized 1:1 to receive RT followed by ipilimumab or RT followed by placebo. Median OS was 11.2 months (95% CI: 9.5–12.7) and 10.0 months (95% CI: 8.3–11.0) (HR = 0.85; 95% CI: 0.72–1.00; $P = 0.053$), respectively [30]. In the second study, chemotherapy-naïve patients with mCRPC ($n = 602$) were randomized 2:1 to receive up to 4 doses of ipilimumab 10mg/kg or placebo every 3 weeks, followed by a maintenance dose every 3 months. As in the post-docetaxel study, no improvement in OS was observed. Median OS was 28.7 months in the ipilimumab arm (95% CI: 24.5–32.5) vs. 29.7 months in the placebo arm (95% CI: 26.1–34.2) (HR = 1.11; 95.87% CI: 0.88–1.39; $P = 0.3667$) [31]. Ongoing studies are evaluating ipilimumab in combination with several other agents including sipuleucel-T (NCT01832870), androgen deprivation (NCT1688492 and NCT01377389), and anti-PD-1 (NCT02985957).

A small cohort study in men with metastatic prostate cancer taking enzalutamide, an androgen receptor antagonist, linked increased numbers of circulating PD-L1⁺ DCs to enzalutamide resistance, suggesting that PD-L1 up-regulation on DCs is a method of immune escape employed by enzalutamide-resistant prostate cancer [32]. This may be mediated by PD-L1 expression on myeloid-derived suppressor cells, a type of immune cell that can localize to tumor and promote an immunosuppressive milieu [8]. Such effects may be overcome by PD-1/PD-L1 blockade.

Clinically, small data sets from studies of PD-1/PD-L1 inhibition in prostate cancer have revealed modest activity [33,34] and confirmed PD-L1 expression in some [32,34,35] but not all [36] tumor specimens. These data plus preliminary reports from ongoing trials suggest that anti-PD-1/PD-L1 treatments may have clinical benefit in select populations. At the 2016 Annual Meeting of the European Society of Medical Oncology, data were presented from an ongoing phase II trial of pembrolizumab in mCRPC patients who had progressed on enzalutamide (NCT02312557). Patients were given pembrolizumab 200 mg i.v. every 3 weeks for 4 doses while continuing enzalutamide. Of the first 20 patients to complete treatment, 20% (4/20) had a PSA reduction of $\geq 50\%$, durable for 16–61 weeks. Two patients with measurable disease in liver and lymph nodes had ongoing partial responses after 61 and 22 weeks of follow-up, respectively. Tumor biopsies from both of these patients were PD-L1⁺, and one showed microsatellite instability [37]. Despite an initial lack of enthusiasm for anti-PD-1/PD-L1 monotherapy, a potentially reproducible response rate of 20% approaches the response rates seen with FDA-approved agents in other

malignancies such as metastatic urothelial carcinoma (24%) [5] and nonsmall cell lung cancer (15%–20%) [3,38,39]. A currently recruiting phase II trial will stratify mCRPC patients by tumor PD-L1 status and presence of bone metastases before treating them with pembrolizumab (NCT02787005).

Enhancing vaccines with immune checkpoint inhibitors—As single agents, immune checkpoint inhibitors have failed to substantially improve clinical outcomes in prostate cancer [30–34,36,37]. Evidence suggests that immune checkpoint inhibitors may be more active in inflamed tumors characterized by immune infiltrate [40]. Thus, the antitumor immune responses seen with PROSTVAC and sipuleucel-T [18,22–24] may be a way to inflame the TME with lymphocytes [18], creating a setting in which immune checkpoint inhibitors can be useful.

This hypothesis was tested in a phase I study combining PROSTVAC with escalating doses of ipilimumab in patients with mCRPC. PSA declines were observed in 14/ 24 (58%) patients; 6 of those declines were 50% [41]. Median OS in chemotherapy-naïve patients ($n = 24$) was not reached and was 31.3 months (range: 4.8–41.4) in chemotherapy-treated patients ($n = 6$) [42]. While not set up for direct comparison, the median OS (not reached) with ipilimumab plus PROSTVAC in chemotherapy-naïve patients vs. the phase II median OS with PROSTVAC alone in that population (26.6 months) nonetheless suggests enhanced activity for the combination therapy [42]. Of note, the patient populations in each study had similar baseline characteristics and similar median Halabi nomogram-predicted survival (PROSTVAC alone = 17.2 months; PROSTVAC plus ipilimumab = 18.5 months).

An ongoing phase I trial is testing sipuleucel-T in combination with ipilimumab (NCT01832870) and a phase combination with ipilimumab II trial testing this combination with sequence variation is recruiting subjects (NCT01804465). A phase II study testing PROSTVAC with or without ipilimumab in the neoadjuvant setting is currently recruiting patients (NCT02506114).

As mentioned above, increased expression of PD-L1 on circulating DCs has been observed in patients with enzalutamide-resistant prostate cancer, suggesting a role for anti-PD-1/PD-L1 treatment in castration-resistant disease [32]. A phase I/II study currently underway combines a DNA vaccine encoding PAP plus pembrolizumab in sequence or concurrently in mCRPC patients (NCT02499835). Preliminary data showed decreased tumor volume at 12 weeks in 3/6 patients treated with the combination [43]. A phase I study of sipuleucel-T plus the PD-L1 inhibitor atezolizumab in mCRPC is planned (NCT03024216). Other clinical studies in mCRPC combining vaccines and anti-PD-1/PD-L1 agents are in various stages of development (NCT02325557, NCT02499835, and NCT03007732).

Anti-CTLA-4 and anti-PD-1 therapies affect the immune system in different ways, offering the potential for synergy when given in combination. Such synergy has been confirmed in advanced melanoma, where the combination of the anti-PD-1 agent nivolumab plus ipilimumab increased response rates compared to either therapy alone. However, approximately 55% of patients experienced grade 3 to 4 adverse events [44,45]. A phase I/II study currently recruiting combines PROSTVAC with ipilimumab, nivolumab, or the triple

combination (NCT02933255). Any improvements in immune response will need to be reconciled with the increased toxicity expected with this approach.

PARP inhibition in prostate cancer—Observational studies have shown that a significant proportion of mCRPC patients (19.3%) harbor somatic mutations in BRCA1/BRCA2 (DNA damage repair enzymes) or ATM (an enzyme promoting cell-cycle arrest during DNA damage repair) [46]. This suggests that targeting other DNA repair enzymes may throw mCRPC cells into fatal states of disrepair. PARP (poly [ADP-ribose] polymerase) is an enzyme that initiates single-strand DNA repair. Olaparib is an oral PARP inhibitor approved for treatment of BRCA $\frac{1}{2}$ -mutant ovarian cancer. PARP inhibition is active in patients with BRCA $\frac{1}{2}$ mutations, including prostate cancer patients [47]. Findings from a 2015 study that examined the mutational status of mCRPC patients treated with olaparib suggest the drug is highly active in patients with BRCA $\frac{1}{2}$ and ATM mutations [48]. BRCA $\frac{1}{2}$ mutations were found in 10% (50% germline) and ATM mutations in 12% (60% germline) of 49 patients analyzed. All patients with BRCA2 mutations ($n = 7$) and 4/5 patients with ATM mutations had clinical responses to olaparib. In early 2016, olaparib received breakthrough designation from the FDA for men with BRCA $\frac{1}{2}$ or ATM germline-mutated prostate cancer.

It has been hypothesized that increased cytosolic doublestranded tumor-associated DNA resulting from PARP inhibition may enhance the recently characterized stimulator of interferon genes immune response pathway [49], and perhaps tumor antigenicity, favoring an inflamed tumor phenotype. This may be a situation in which PD-1/PD-L1 inhibition is useful. These hypotheses provided rationale for an ongoing phase II study combining olaparib plus durvalumab (anti-PD-L1) in prostate cancer, unselected for DNA damage repair mutations or PD-L1 expression (NCT02484404). Preliminary data presented at the 2017 Annual Meeting of the American Society of Clinical Oncology showed PSA declines 50% in 7/16 prostate cancer patients on treatment for >2 months [50]. A planned phase I study with 3 cohorts will compare pembrolizumab plus olaparib, pembrolizumab plus docetaxel plus prednisone, and pembrolizumab plus enzalutamide (NCT02861573).

Other combination approaches for enhancing efficacy

The growing number of immunotherapeutic agents, each with a unique effect on the immune system, has created a growing number of potential combinations. While too extensive to review here, some additional immunomodulatory approaches deserve mention. Epacadostat, an indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor, decreases production of an immunosuppressive metabolite produced in the TME [51]. A recent study reported objective responses in 14/19 treatment-naïve patients with advanced melanoma (4 complete responses, 7 partial responses, and 3 stable disease) who received epacadostat plus pembrolizumab (anti-PD-1) [52]. Although these data are from early-phase trials, the improvement in response rate provides rationale for testing epacadostat in combination with PD-1/PD-L1 inhibitors or other immunotherapies in prostate cancer. For example, ALT-803 is a synthetic interleukin-15 superagonist that has demonstrated antitumor activity in murine tumor models. Specifically, this immunocytokine produced increases in T-cell and natural killer

cell (NK cell) numbers, and enhanced the function of NK cells [53]. Several phase I/II trials, including a phase I trial in solid tumors (NCT01946789) testing ALT-803 are underway.

Identifying new modes of tumor resistance will be key to designing combination approaches. For example, VISTA (V-domain Ig Suppressor of T-cell Activation) is a recently characterized immune checkpoint molecule expressed on T cells that is structurally homologous to PD-L1 [54]. Gene expression profiling on posttreatment prostate tumor samples from patients who received ipilimumab plus androgen deprivation therapy (NCT01194271) revealed an increase in PD-L1 and VISTA gene expression, as well as increased PD-1, PD-L1, and VISTA protein expression, compared to pretreatment samples [55]. These findings warrant further investigation of VISTA's role in tumor resistance following immunotherapy and its potential as a companion therapeutic target to the other agents discussed here.

Conclusion

Clinical trials of immunotherapies for prostate cancer have thus far produced mixed results. Sipuleucel-T has been shown to increase median OS by 4.1 months in men with mCRPC [12,13]. However, single-agent immune checkpoint inhibitors appear to have modest activity and potential utility only in select patients [30,31,33,34,37]. Early-phase trials of PROSTVAC are promising, and results from a phase III trial are pending [24].

The lack of success with immune checkpoint monotherapy may be due to the absence of effector T cells within the TME. Thus, immune checkpoint inhibitors may still be viable as therapeutics for prostate cancer when used in combination with other agents. Vaccines offer a means to generate tumor-specific T cells and mobilize them to the tumor, creating a situation in which immune checkpoint inhibitors may be helpful in prostate cancer. This hypothesis is supported by correlative studies that consistently show tumor vaccines can produce tumor-specific circulating T cells and induce T-cell trafficking to tumor [18,21].

While combining vaccines with anti-CTLA-4 and/or anti-PD-1/PD-L1 agents is a dominant strategy, other immunomodulatory agents are rapidly becoming available, including PARP inhibitors, which are active in select patients as monotherapy [48] but may also work synergistically with checkpoint inhibitors. IDO1 inhibition can dampen the inhibitory milieu of the TME, and has demonstrated promising early-phase results combined with anti-PD-1 therapy in advanced melanoma [51,52]. Immunomodulatory cytokines such as ALT-803 are another innovative modality that may prove useful in combination approaches.

As more immunotherapy modalities emerge, the number of potential combination approaches increases. Interpretation of preclinical and clinical data will drive rational planning of future clinical investigations aimed at identifying active multidrug regimens with acceptable safety profiles.

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Table 1

Selected immunotherapies for prostate cancer in advanced-stage development

Agent	Treatment type	Monotherapy	Combination therapy
Sipuleucel-T	Dendritic-cell vaccine	• FDA approved for mCRPC • Improved survival in mCRPC in 2 phase III trials: 25.8 vs. 21.7 months (NCT20818862) 25.9 vs. 21.4 months (NCT16809734)	• Ongoing phase I trial of sipuleucel-T plus ipilimumab in mCRPC (NCT01832870) • Phase II study evaluating sequence with ipilimumab (NCT01804465) • Planned phase I trial of sipuleucel-T plus atezolizumab (anti-PD-L1) in mCRPC (NCT03024216)
PROSTVAC (PSA-TRICOM)	PSA-targeted recombinant viral vaccine	• Improved survival in phase II trial; (25.1 vs. 16.6 months) • Randomized phase III trial completed; analysis pending (NCT01322490) • Phase II study as adjuvant following RP (NCT02772562) • Phase II trial in biochemical recurrence (NCT02649439)	• Phase I study of PROSTVAC plus ipilimumab in chemotherapy-naïve patients; PSA decline 50% in 6/24 (25%) patients; median OS: not reached (chemotherapy-naïve) and 31.1 months (chemotherapy pretreated) (NCT22326924) • Phase II study of PROSTVAC with or without ipilimumab in neoadjuvant setting; recruiting (NCT02506114) • Phase III study of PROSTVAC with ipilimumab, nivolumab, or both (NCT02933255)
DCVAC/PCa	Dendritic-cell vaccine	Several ongoing phase II studies; http://www.sotio.com/clinical-trials/prostate-cancer/phase-iii-viable	• Improved survival (19 months) compared to Halabi (11.8) and MSKCC (13) nomograms in phase II study of DCVAC/PCa plus docetaxel plus oral low-dose cyclophosphamide and topical imiquimod (Toll-like receptor agonist) in mCRPC • Global phase III trial in combination with taxol chemotherapy in mCRPC; currently recruiting (VIABLE/ NCT02111577)
ProstAtak	Locally injected adenoviral thymidine kinase vector plus prodrug	• Phase II trial recruiting patients with localized disease, randomizing to ProstAtak or placebo given concurrently with local RT (NCT01436968)	
Nivolumab	Anti-PD-1 IgG4 monoclonal antibody	• Zero objective responses in 17 prostate cancer patients treated in phase I trial (NCT22658127)	• Planned phase II study of ipilimumab plus nivolumab in mCRPC (NCT03061539) • Phase II study of ipilimumab plus nivolumab in mCRPC (NCT02985957)
Pembrolizumab	Anti-PD-1 IgG4 monoclonal antibody	• Ongoing phase Ib trial in advanced prostate cancer patients with 1% tumor PD-L1 positivity (NCT02054806) • Phase II trial currently recruiting mCRPC patients stratified by PD-L1 tumor status and presence of bone metastases (NCT02787005)	• Ongoing phase II trial of pembrolizumab plus enzalutamide in mCRPC progressing on enzalutamide (NCT02312557); preliminary reports show 4/20 patients with PSA reduction 50% [37] • Ongoing phase I/II trial of pembrolizumab plus PAP-targeted DNA vaccine in sequence or concurrently in mCRPC (NCT02499835) • Phase II study of pembrolizumab plus ADXS-PSA (PSA-targeted immunostimulant) in mCRPC; currently recruiting (NCT02325557) • Phase I/II trial of pembrolizumab concurrently or following pTVG-HP plasmid DNA vaccine in mCRPC; currently recruiting (NCT02499835) • Planned phase II trial of definitive RT plus adjuvant pembrolizumab with or without intratumoral SD-101 (Tolllike receptor-9 agonist) in newly diagnosed hormone-naïve oligometastatic prostate cancer (NCT03007732)
Ipilimumab	Anti-CTLA-4 IgG1 monoclonal antibody	Negative for survival benefit in 2 phase III trials: • 11.2 vs. 10 months in mCRPC patients who progressed on docetaxel (NCT24831977) • 28.7 vs. 29.7 months (NCT28034081)	• Ipilimumab plus ADT (NCT01832870, NCT01377389) • Ipilimumab plus PROSTVAC in neoadjuvant setting (NCT01194271) • Phase II study of ipilimumab plus nivolumab in mCRPC stratified by previous treatment with second-generation hormone therapy, chemotherapy, or no treatment; recruiting (NCT02985957)

Agent	Treatment type	Monotherapy	Combination therapy
Olaparib	PARP inhibitor	Active in patients with BRCA2 mutations and some patients with ATM mutations (NCT26510020)	• Ongoing phase I/II trial of pembrolizumab plus olaparib (NCT02484404); PSA responses of 50% observed in 5/7 patients who had been on treatment for more than 2 months [50]

ADT = androgen-deprivation therapy; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; mCRPC = metastatic castration-resistant prostate cancer; MSKCC = Memorial Sloan Kettering Cancer Center; PAP = prostatic acid phosphatase; PARP = poly (ADP-ribose) polymerase; PD-1 = programmed cell death protein-1; PD-L1 = programmed death ligand-1; RP = radical prostatectomy.