Published in final edited form as:

Clin Cancer Res. 2017 November 15; 23(22): 6764–6770. doi:10.1158/1078-0432.CCR-17-0019.

Immunotherapy of Prostate Cancer: Facts and Hopes

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Abstract

In the last few years immunotherapy has become an important cancer treatment modality and while the principles of immunotherapy evolved over many decades, the FDA approvals of sipuleucel-T and ipilimumab began a new wave in immuno-oncology. Despite the current enthusiasm, it is unlikely that any of the immunotherapeutics alone can dramatically change prostate cancer outcomes, but combination strategies are more promising and provide a reason for optimism. Several completed and ongoing studies have shown that the combination of cancer vaccines or checkpoint inhibitors with different immunotherapeutic agents, hormonal therapy (enzalutamide), radiation therapy (radium 223), DNA-damaging agents (olaparib), or chemotherapy (docetaxel) can enhance immune responses and induce more dramatic, long-lasting clinical responses without significant toxicity. The goal of prostate cancer immunotherapy does not have to be complete eradication of advanced disease, but rather the return to an immunologic equilibrium with an indolent disease state. In addition to determining the optimal combination of treatment regimens, efforts are also ongoing to discover biomarkers of immune response. With such concerted efforts, the future of immunotherapy in prostate cancer looks brighter than ever.

Keywords

Prostate cancer; cancer vaccine; checkpoint inhibitor; combination strategies

Introduction

Prostate cancer is an ideal model for therapeutic cancer vaccines, since the prostate is a nonessential organ with multiple tumor-associated antigens as potential targets. In addition, prostate cancer is generally an indolent disease that provides sufficient time for the generation of an antitumor immune response. Although prostate cancer is a known immunogenic disease (1), it can escape the immune system by downregulating human leukocyte antigen class I and thereby render antigen presentation ineffective, by inducing T-cell apoptosis through expression of Fas ligand, by secreting immunosuppressive cytokines such as TGF-β, or by increasing regulatory T cells (Tregs) (2). As in many other cancers, the exact etiology of prostate cancer is still unknown; however, some studies have indicated that

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

inflammation may play a role in its pathogenesis (3). Available treatment options have significantly improved survival for metastatic castration-resistant prostate cancer (mCRPC) patients in the last decade, with 6 new drugs approved since 2010. Along with modern antiandrogen therapies, immunotherapy has the potential to dramatically impact this disease.

Here we review the status of prostate cancer immunotherapy, including cancer vaccines and checkpoint inhibitors, and discuss novel immunotherapy combinations that have progressed furthest in clinical development.

Rationale for the use of immunotherapy in prostate cancer

Sipuleucel-T (Dendreon Corp.), an autologous cellular immunotherapy, was approved by the U.S. Food and Drug Administration in 2010 for treatment of patients with asymptomatic or minimally symptomatic mCRPC. A pivotal phase III clinical trial (IMPACT) randomized 512 mCRPC patients 2:1 to receive sipuleucel-T or placebo. This positive study had a median overall survival (OS) of 25.8 vs. 21.7 months (hazard ratio [HR] = 0.77; $P = 0.02$), and no significant difference in time to progression (3.7 vs. 3.6 months; HR = 0.95; $P = 0.63$). The toxicity profile was good, with transient flu-like symptoms and fever as being the most common side effects (4).

To receive this therapeutic cancer vaccine, patients first undergo leukapheresis to obtain autologous peripheral blood mononuclear cells (PBMCs). The PBMCs are activated with a recombinant protein consisting of prostatic acid phosphatase and GM-CSF, then reinfused after 3 days. This process is repeated every 2 weeks for 3 doses. Although the exact mechanism of action of sipuleucel-T is not known, this treatment does not decrease prostate-specific antigen (PSA) levels or tumor size but does prolong OS, likely by affecting tumor growth (5). Interestingly, sipuleucel-T treatment resulted in humoral antigen spread, including development of antibodies to *ERAS*, *KLK2*, and *KRAS*, that was associated with improved OS (6). The Society for Immunotherapy of Cancer Consensus Recommendations indicate that sipuleucel-T vaccine should be considered early in the treatment of mCRPC, since doing so appears to have a greater OS benefit (7).

The immunotherapy revolution gained even greater momentum after several immune checkpoint inhibitors demonstrated durable responses and improved OS in up to 25% of unselected patients with solid tumors (8). Tumors such as melanoma, bladder cancer, and non-small cell lung cancer, among others, are considered “hot” due to their inflamed microenvironment with significant T-cell infiltration, increased programmed death ligand-1(PD-L1) expression, and high neoantigen load (9). Studies have demonstrated that cancers with multiple point mutations, that can serve as neoantigens such as colorectal cancer with high level of microsatellite instability (MSI-H), tend to respond better to immunotherapy (10).However, this is not the case with all tumor types (e.g., kidney cancer) (11) and thus may not fully explain the immune sensitivity of tumors.

Prostate cancer is at the other end of the spectrum: it is a “cold” tumor with minimal T cell infiltrates and very limited response to single-agent checkpoint inhibition, as demonstrated in recent studies (Table 1). The efficacy of ipilimumab (Bristol-Myers Squibb), an anti-CTLA-4 monoclonal antibody, in mCRPC was evaluated in 2 large, placebo-controlled,

randomized phase III clinical trials which administered ipilimumab before (12) or after docetaxel chemotherapy (13). In these studies, ipilimumab prolonged progression-free survival (PFS) and PSA responses in a subset of mCRPC patients. However, ipilimumab has no defined role in the management of mCRPC since both studies failed to meet their primary endpoint of improved OS.

A phase I study of nivolumab (Bristol-Myers Squibb), an anti-PD-1 monoclonal antibody, enrolled, among others, 17 mCRPC patients. No objective responses were observed, although one patient had a sustained PSA decline > 50% (14). KEYNOTE-028, a multicohort phase Ib study of pembrolizumab (Merck), another anti-PD-1 monoclonal antibody, in patients with advanced solid tumors, enrolled 23 patients with mCRPC. Of these, 3 (13%) had a confirmed partial response (PR) and 9 (39%) had stable disease (15). The lack of responses in both studies were possibly due to the fact that responses may correlate with PD-L1 expression, which is minimal in prostate cancer (16).

Pritchard *et al.* recently reported that 12% of mCRPC patients have MSI and mismatch repair gene mutations (*MSH2* or *MSH6*) (17), while other case series have reported a somewhat lower incidence of MSI in prostate cancer (2%–12%) (18). It is possible that mCRPC patients with MSI may respond better to single-agent checkpoint inhibition, and that is currently being prospectively evaluated (NCT02966587).

Experimental prostate cancer vaccines

PROSTVAC® (rilimogene galvacirepvac)

PROSTVAC (Bavarian Nordic A/S) is an off-the-shelf prostate cancer vaccine that consists of a recombinant vaccinia vector prime followed by multiple boosts with a recombinant fowlpox vector, plus transgenes for PSA and 3 costimulatory molecules (B7.1, ICAM-1, and LFA-3, known as TRICOM) (19). A phase II trial that randomized 122 mCRPC patients to receive PROSTVAC vs. placebo (2:1) demonstrated an improvement in median OS of 8.5 months and a 44% reduction in death rate (20). Revised data confirmed a survival advantage of 26.2 vs. 16.3 months (HR = 0.499; $P = 0.0019$) (21). The majority of patients (59/104) had increased PSA-specific T-cell responses, and within a subset of patients, 68% demonstrated evidence of antigen spreading 4 weeks after treatment (19). PROSTVAC is currently being evaluated in a phase III clinical trial targeting asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC patients (PROSPECT; NCT01322490). This study randomized 1297 patients to 3 arms: PROSTVAC plus GM-CSF, PROSTVAC plus GM-CSF placebo, and double placebo. Enrollment is completed and results are anticipated as early as the end of 2017. PROSTVAC is also being evaluated in multiple phase II trials as a single agent (Table 1) or as part of combination therapy.

DCVAC/PCa

DCVAC/PCa (SOTIO a.s.) is therapeutic cancer vaccine made of mature dendritic cells (DCs) exposed to killed human prostate cancer cells (LNCaP). In a phase I/II clinical trial in mCRPC, patients ($n = 25$) were given DCVAC/PCa concurrently with docetaxel chemotherapy. The vaccine was well-tolerated, with no serious vaccine-related adverse

events (AEs) reported. The median OS was 19.0 months, which was better than predicted survival using the Halabi nomogram (11.8 months). None of the immunologic parameters, such as decreased Tregs and increased $CD8^+$ T cells and PSA-specific $CD8^+$ cells, significantly correlated with OS (22). Based on the results of this study, a randomized phase III clinical trial is currently evaluating DCVAC/PCa in combination with concurrent docetaxel (VIABLE; NCT02111577). The study was initiated in May 2014 and will enroll 1200 patients. Results are pending.

ProstAtak® (aglatimagene besadenovec)

ProstAtak (Advantagene Inc.), an adenoviral vector encoding thymidine kinase (oncolytic virus), can cause cancer cell death when activated by oral valacyclovir. A phase I study of ProstAtak enrolled 10 patients with newly diagnosed prostate cancer: 7 with high-risk, 1 with intermediate-risk, and 2 with low-risk disease. Nine patients were treated surgically 7.3 to 15.7 weeks after vector injection. After a median follow-up of 11.3 years, 3 patients developed biochemical recurrence and none of them developed metastases. Treatment was safe and well-tolerated (23).

ProstAtak is currently being tested in a randomized (2:1), placebo-controlled phase III trial in patients with localized disease who are candidates for curative external beam radiation therapy (EBRT) (NCT01436968). Another ongoing phase II/III trial is testing ProstAtak in patients undergoing active surveillance (NCT02768363).

The success of the first cancer vaccine has intensified efforts to develop novel vaccines for prostate cancer, and several are currently in clinical development. Main categories include DNA vaccines, antigen-loaded DCs, and viral vectors targeting several tumor-associated antigens such as prostate stem cell antigen, PSA, and prostate-specific membrane antigen (PSMA), among others. Vaccines currently being evaluated in phase II and III studies are listed in Table 2. The most promising future immunotherapy strategies for prostate cancer are combinations of cancer vaccines with other treatment modalities.

Adoptive cell therapy

Adoptive cell therapy, that isolates and expands autologous or allogeneic tumor-reactive lymphocytes. It has demonstrated activity in melanoma using tumor-infiltrating lymphocytes (TILs) and in hematologic malignancies, melanoma, and synovial sarcoma using chimeric antigen receptor (CAR) T cells (24). An ongoing study is testing CAR-T cells that target PSMA (NCT01140373). Preliminary results show that 2 of the first 3 patients enrolled had stable disease for > 6 months with no reported AEs (25).

Combination therapies

The ideal immunotherapy should: 1) activate effector cytotoxic T cells against specific antigens within the tumor and expand additional T-cell clones that can migrate to the tumor and kill targeted cells, and 2) assist effector cells by neutralizing local immunosuppressive mechanisms responsible for immune escape (PD-1/PD-L1, indoleamine 2,3-dioxygenase, Tregs, etc.) (Figure 1) (26). Observed responses to single-agent checkpoint inhibitors or

therapeutic vaccines in prostate cancer have been minimal to modest, and those agents may not be optimal if used as monotherapy.

A promising new approach to prostate cancer immunotherapy involves efforts to make prostate cancer more T cell inflamed, since the majority of prostate cancer are not. There are several ways to cause inflammation within prostate tumors and recruiting more effector T cells into the tumor : 1) hormone therapy (can increase inflammatory infiltrates and PD-L1 expression), 2) chemotherapy (killing of cancer cells and releasing cancer antigens), 3) radiation therapy (increasing inflammation and immunomodulatory cytokines), 4) PARP inhibitors (damaging DNA), 5) adoptive cell transfer (generating new T-cells) or 6) combining two checkpoint inhibitors or combinations of a cancer vaccine and an checkpoint inhibitor (immunogenic intensification) (27). These treatment modalities could enhance immune cell response and with concurrent blockade of inhibitory pathways within the tumor microenvironment, could achieve optimal antitumor effects (9).

The timing of treatment is another crucial factor in optimizing immunotherapies for prostate cancer. The ideal timing for prostate cancer immunotherapy is in the neoadjuvant or adjuvant setting or after biochemical recurrence (PSA-only disease) when tumor burden is minimal and immunosuppressive cells and cytokines are at their lowest levels (2). On the other end of the spectrum, mCRPC patients have large tumor volume, multiple immunosuppressive cytokines, and limited time to wait for an immune response to become clinically effective. Studies evaluating immunotherapeutic agents or combinations in the neoadjuvant setting would allow for detailed exploration of the impact of these agents on the tumor microenvironment.

Identifying the the optimal timing and sequence of combination strategies is crucial and have the potential to significantly change outcomes in prostate cancer. Combination of different treatment modalities and immunotherapy is safe and many are currently being studied, with preliminary evidence showing promising activity (Table 3).

Hormone therapy and immunotherapy (vaccine or checkpoint inhibitor)

Androgen-deprivation therapy affects the immune system by inducing thymic regeneration leading to increased production of naive T cells (28), decreasing $CD4^+$ T-cell tolerance (29), and increasing $CD4^+$ effector T cells (30). The synergistic effect of castration and immunotherapy has been evaluated in multiple clinical trials (31).

Antiandrogens such as enzalutamide (Astellas Pharma/Medivation) also induce immunogenic modulation (32). Enzalutamide is currently being tested in combination with PROSTVAC in mCRPC (NCT01867333) and in biochemical recurrence (NCT01875250). Interestingly, mCRPC patients who progressed on enzalutamide were shown to have increased expression of PD-1 in circulating immune cells (33). Graff *et al.* reported a case series of 10 mCRPC patients enrolled in a phase II trial of pembrolizumab after progression on enzalutamide. Three out of 10 patients had rapid PSA declines and 2 had PRs, including one patient with MSI (34). KEYNOTE-365 is currently investigating pembrolizumab combination therapies in mCRPC, including pembrolizumab + olaparib, pembrolizumab + docetaxel + prednisone, and pembrolizumab + enzalutamide (NCT02861573).

Chemotherapy and immunotherapy (vaccine)

Many chemotherapies, such as docetaxel and gemcitabine, have a positive impact on the immune system. Preclinical studies have shown that docetaxel can increase antigen presentation and Fas expression, activate an antigen cascade (35), modulate the tumor microenvironment, and improve vaccine efficacy (36). Several ongoing studies are evaluating the combination of docetaxel and vaccine, including PROSTVAC + docetaxel in castration-sensitive prostate cancer (NCT02649855) and docetaxel + DCVAC/PCa (VIABLE; NCT02111577) in mCRPC.

Radiation (EBRT or radiopharmaceuticals) and immunotherapy (vaccine or checkpoint inhibitors)

Radiation can impact the immune system by damaging DNA, increasing expression of MHC class I, Fas, and ICAM-1, and by increasing cytokines such as TNF-α and IL-6. The goal is to modify the phenotype of cancer cells, making it easier for immune cells to recognize and kill them (37).

A phase II study of ^{153}samarium-EDTMP (Lantheus Holding), a radiopharmaceutical, plus PROSTVAC randomized 21 post-docetaxel mCRPC patients to receive the combination and 18 to receive ^{153}samarium-EDTMP alone. The median PFS was 3.7 months for the combination vs. 1.7 months for ^{153}samarium-EDTMP alone (HR = 0.51; $P = 0.041$), with no difference in median OS. No patients in the ^{153}samarium-EDTMP-alone arm had a PSA decline, while 4/21 (19%) patients in the combination arm had a PSA decline ≥ 30% (38).

Radium-223 (Bayer Pharma), a novel radiopharmaceutical, has demonstrated improved OS in mCRPC (39). Preclinical data indicate that it also has immunomodulatory effects (40). An ongoing phase I study is evaluating the combination of radium-223 and atezolizumab (Genentech) in mCRPC (NCT02814669), while another is evaluating the combination of radium-223 and sipuleucel-T (NCT02463799).

PARP inhibitors and checkpoint inhibitors

A recent report suggested that 11.8% of mCRPC patients have germline mutations in genes mediating DNA-repair processes, a rate higher than previously anticipated (41). Preclinical studies using a *BRCA-1*-deficient ovarian cancer model demonstrated that combining a CTLA-4 antibody with a PARP inhibitor had a synergistic effect, resulting in immune-mediated tumor killing and improved survival (42). In the TOPARP-A trial, 50 mCRPC patients previously treated with docetaxel were given olaparib, a PARP inhibitor. Sixteen patients (33%) showed a response, and 12 of them had response lasting > 6 months. Interestingly, 16 patients were also found to have mutations in DNA-repair genes, and 14 of these 16 patients (88%) showed a response (43).

Preliminary results of a phase II study of durvalumab (AstraZeneca), a PD-L1 antibody, plus olaparib (AstraZeneca) were recently reported (44). Overall, 8/10 patients showed declines in PSA, 5 of which were > 50%. The combination was well-tolerated and showed activity in an unselected population, with a median PFS of 7.8 months. Responses were observed in all patient subgroups, regardless of the number of prior lines of therapy, including those without

mutations in DNA-repair pathways. This ongoing trial has an accrual goal of 25 patients (NCT02484404). Preclinical studies have shown that PARP1 inhibitors can suppress androgen receptor activity and tumor growth even in the absence of *BRCA* mutations or DNA-damaging agents (45). While we don't know the mechanism of the activity seen, the double-strand DNA breaks caused by PARP inhibitors could lead to *STING* pathway upregulation. Immunogenic modulation or neoantigen formation may also explain observed activity in mCRPC.

Vaccines and checkpoint inhibitors (immunogenic intensification)

Preclinical studies have suggested that different therapeutic cancer vaccine platforms can activate different T-cell populations, even if they target the same antigens (46), and that the combination of cancer vaccines and checkpoint inhibitors has synergistic effects (47, 48). Ideally, cancer vaccines should activate immune cells and direct them to the tumor (49), where they can increase lymphocyte infiltration and drive increased PD-L1 expression within the tumor microenvironment. One of the major concerns with this approach has been the possibility of increased toxicity; however, preliminary data suggest that this combination is no more toxic than a single-agent checkpoint inhibitor (50). Consequently, a vaccine plus a PD-1 inhibitor may be less toxic than a vaccine plus a CTLA-4 inhibitor.

A phase I trial evaluated the combination of GVAX (Aduro Biotech), a whole tumor-cell vaccine, and ipilimumab in mCRPC. Seven of 28 patients had > 50% PSA declines, while one patient had a complete response (51). Another study treated 30 patients, 24 of whom were chemotherapy-naïve, with PROSTVAC and ipilimumab. Six of the 30 patients had PSA declines > 50%. The median OS was 34.4 months, and 2-year OS was 73%, which was better than historical controls (52).

A phase I/II study of a *Listeria*-vector vaccine (Advaxis, Inc.) plus pembrolizumab is currently accruing patients with mCRPC (NCT02325557). Another phase II study will evaluate the combination of PROSTVAC, ipilimumab, and nivolumab in prostate cancer patients prior to curative surgery (NCT02933255).

The most interesting combination strategies combine cancer vaccines and checkpoint inhibitors or 2 different checkpoint inhibitors plus vaccines. Our group recently reported a phase I trial of ipilimumab in combination with PROSTVAC in 30 mCRPC patients. Among chemotherapy-naïve patients, 14 (58%) did have PSA declines. Median OS was 34.4 months, with a median Halabi-predicted survival of 17.2 months (53), suggesting a treatment effect with a favorable safety profile. An ongoing phase I study of PROSTVAC in combination with nivolumab and/or ipilimumab in men with prostate cancer (NCT02933255) prior curative surgery will evaluate the impact of this immunologic combination on the tumor microenvironment, focusing on immune cell infiltration as the primary endpoint.

Conclusions

While prostate cancer appears to have been left out of the ongoing immunotherapeutic revolution currently underway in medical oncology, that perspective may be nearsighted. As

a phase III study with the therapeutic cancer vaccine sipuleucel-T has demonstrated, and early data from trials of checkpoint inhibitors suggest, prostate cancer can be amenable to immunotherapeutic strategies, which will likely involve multiple immune-based platforms. Combinations of therapies that can change the “cold” prostate cancer tumor microenvironment to immunologically “hot” by driving T cells to the tumor may be one way to optimize immunotherapy in prostate cancer. Existing conventional therapies such as chemotherapies, antiandrogens, and radiopharmaceuticals have demonstrated pro-immune effects and may become part of future immune-based platforms. Many clinical trials are evaluating immunotherapy combinations, some of them earlier on in the disease process. Results of these studies will shape the future of prostate cancer immunotherapy.

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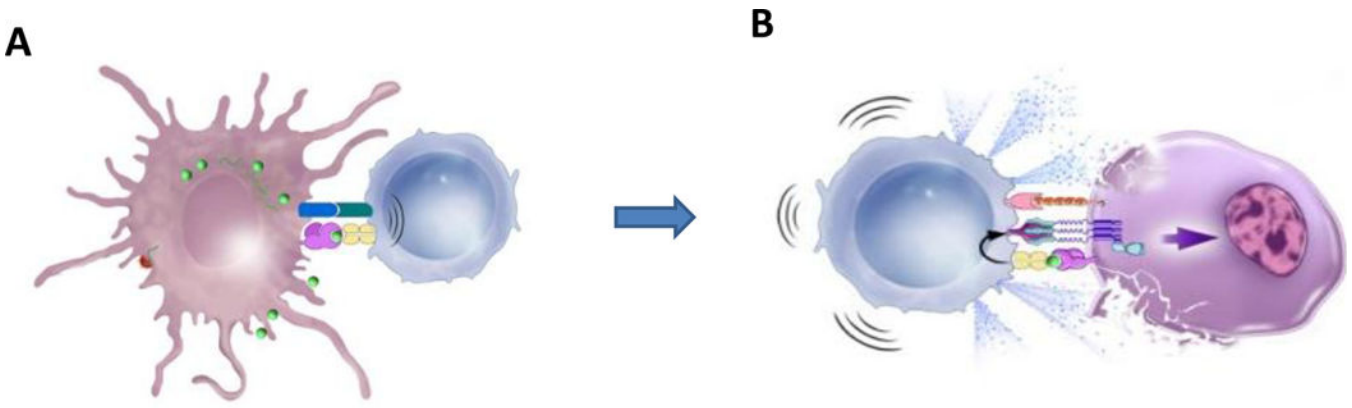

Figure 1. Requirements for effective immunotherapy

A) Generation of immune response.

Antigen-presenting cells process targeted antigens (green) and present them to T cells with major histocompatibility complexes (MHC) on their surface, along with costimulatory molecules. This complex stimulates T cells to become cytotoxic $CD8^+$ T cells.

B) Functional effector cells within the tumor.

Activated cytotoxic T cells recognize targeted antigens on the surface of cancer cells and release cytotoxins such as perforin and granzymes, triggering caspases and apoptosis. In addition, activated T cells also express Fas ligands that bind to Fas receptors on tumor cells, also inducing apoptosis.

Table 1

Clinical studies of checkpoint inhibitors in prostate cancer

Drug/reference	Phase/disease/(*n*)	Dose	Results
Ipilimumab (post-chemo) (13)	Phase III, mCRPC (799)	8 Gy EBRT to one bone lesion followed by ipilimumab 10 mg/kg or placebo for 4 doses, then maintenance every 3 months	Median OS 11.2 vs.10.0 months (HR = 0.85; *P* = 0.053)
Ipilimumab (chemo-naïve) (12)	Phase III, mCRPC (799)	Ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses, then maintenance every 3 months	Median OS 28.7 vs. 29.7 months (HR = 1.11; *P* = 0.3667)
Nivolumab (14)	Phase I, mCRPC (17)	Nivolumab 0.1–10 mg/kg i.v. every 2 weeks	No objective responses, one patient sustained > 50% PSA decline
Pembrolizumab (15)	Phase I, mCRPC (23)	Pembrolizumab 10 mg/kg every 2 weeks up to 24 months	3 patients with confirmed PR (ORR 13%) and 9 with SD (39%)
Tremelimumab (54)	Phase I, BCR (11)	Tremelimumab with high-dose bicalutamide	3 patients with prolonged PSA doubling time

EBRT: external beam radiation therapy; HR: hazard ratio; mCRPC: metastatic castration-resistant prostate cancer; ORR: overall response rate; OS: overall survival; PR: partial response; PSA: prostate-specific antigen; SD: stable disease; BCR: biochemical recurrence (PSA-only disease)

Table 2

Experimental therapeutic prostate cancer vaccines currently in phase II and III clinical trials

Vaccine	Type	Phase	Disease stage	NCT
DCVac	Dendritic-cell vaccine	III	mCRPC	NCT02111577
PROSTVAC	Poxvirus-based vaccine	III II II II	mCRPC Adjuvant therapy BCR Active surveillance	NCT01322490 NCT02772562 NCT02649439 NCT02326805
ProstAtack	Oncolytic virus	III	Curative EBRT Active surveillance	NCT01436968 NCT02768363
ME TARP	Autologous dendritic-cell vaccine targeting TARP	II	BCR	NCT02362451
DC1	Alpha-type-1-polarized dendritic cells with apoptotic allogeneic tumor (LNCap)	II	BCR	NCT00970203
GX301	4 human telomerase reverse transcriptase (hTERT) peptides and 2 adjuvants	II	mCRPC	NCT02293707
mDC/pDC	Tumor peptide-loaded dendritic cells (myeloid, plasmacytoid, and their combination)	II	mCRPC	NCT02692976
ADXS31-142	Live-attenuated strain of *Listeria monocytogenes* encoding PSA fused to a fragment of the immunostimulant listeriolysin O protein	I/II	mCRPC	NCT02325557
DC vaccine	Autologous dendritic cells with mRNA from primary prostate cancer tissue, hTERT, and survivin	I/II	Adjuvant, high risk of PSA relapse	NCT01197625
Ad5-SGE-REIC/Dkk-3	Recombinant adenovirus designed to increase intracellular production of REIC protein	I/II	Localized prostate cancer	NCT01931046

EBRT: external beam radiation therapy; mCRPC: metastatic castration-resistant prostate cancer; BCR: biochemical recurrence (PSA-only disease)

Table 3

Combination strategies for prostate cancer

Combination	Rationale	Clinical trials
Radiation + vaccine or checkpoint inhibitor	Cells death => antigen release. Increased inflammation and secretion of immunomodulatory cytokines.	Radium-223 + sipuleucel-T Radium-223 + pembrolizumab Radium-223 + atezolizumab
Chemotherapy + vaccine or checkpoint inhibitor	Reduced tumor burden. Increased Fas expression. Antigen cascade.	Docetaxel + PROSTVAC Docetaxel + DCVAC/PCa Docetaxel + pembrolizumab
Hormone therapy (antiandrogens) + cancer vaccine or checkpoint inhibitor	Reduced tumor burden. Increased production of naive T cells and $CD4^+$ effector T cells. Increased PD-L1 expression (enzalutamide).	Enzalutamide + PROSTVAC Enzalutamide + pembrolizumab
Checkpoint inhibitor + cancer vaccine or another checkpoint inhibitor	Activation of different T-cell population. Increased inflammation.	*Listeria*-based vaccine + pembrolizumab
PARP inhibitor + checkpoint inhibitor	DNA damage => antigen release. Increased inflammation.	Olaparib + pembrolizumab Olaparib + durvalumab