Published in final edited form as:

Curr Opin Oncol. 2016 May ; 28(3): 232–240. doi:10.1097/CCO.0000000000000281.

The Evolving Role of Immunotherapy in Prostate Cancer

Lisa M. Cordes, Pharm.D.[1], **Ravi A. Madan, M.D.**[2], **James L. Gulley, M.D., Ph.D.**[2]

[1]Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

[2]Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Keywords

prostate cancer; immunotherapy; therapeutic cancer vaccine; immunomodulating agents

INTRODUCTION

Recent years have seen the rapid development of immune-based therapies in the treatment of advanced solid tumors. Although much of the current focus is on immune checkpoint inhibitors (cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, anti-programmed death-1 (PD-1) inhibitors), this burst of immunotherapeutic development actually began with a therapeutic cancer vaccine in prostate cancer, sipuleucel-T in 2010. Since 2010, however, the role of immunotherapy in other cancers such as lung cancer and melanoma has become clear, while the benefits of immune stimulating therapies in prostate cancer remain somewhat enigmatic. Emerging data and ongoing studies will help define the ultimate role of immunotherapy in the management of prostate cancer.

THERAPEUTIC VACCINES [header]

Therapeutic cancer vaccines are an attractive strategy for cancer treatment given that they harness the patient's own immune system and are associated with less toxicity when compared to cytotoxic chemotherapy. These vaccines act by stimulating an immune response to specific tumor-associated antigens (TAA) and may be divided into two categories: *in vivo* or *ex vivo*. *In vivo* strategies, which include PROSTVAC and AdV-tk, are designed to present TAAs to dendritic cells (DC) or other antigen presenting cells thereby inducing *in vivo* immune stimulation. Alternatively, vaccines such as sipuleucel-T and DCVAC/PCa use an *ex vivo* approach in which autologous immune cells are collected via leukapheresis, processed *ex vivo* with the goal of immune activation, then reinfused into the same patient [1–4]. Following suitable activation, it is hypothesized that activated immune

Correspondence: Ravi A. Madan; telephone: 301-496-3493; madanr@nih.gov.

Conflicts of Interest
Lisa M. Cordes: none
Ravi A. Madan: none
James L. Gulley: none

Disclosures: Lisa M. Cordes: none; Ravi A. Madan: none; James L. Gulley: none

cells including DCs migrate to lymph nodes for antigen presentation and priming of cytotoxic T cells. An activated T cell may then recognize a cell bearing its TAA potentially resulting in malignant cell lysis [5, 6]. Sipuleucel-T is FDA-approved for the treatment of prostate cancer, while several other vaccines, including PROSTVAC, DCVAC/PCa and AdV-tk, have also demonstrated promise in early phase studies [2, 4, 7] and are currently being evaluated in phase 3 trials (NCT01322490, NCT02111577, NCT01436968). [Table 1]

Sipuleucel-T [sub-header]

The potential benefit of immunotherapy in prostate cancer was initially suggested with sipuleucel-T, which is an autologous cellular immunotherapy FDA-approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) [3]. Although the precise mechanism is enigmatic, sipuleucel-T is designed to induce an immune response against prostate acid phosphatase (PAP). Antigen-presenting cell (APC) precursors are isolated from the peripheral blood mononuclear cells (PBMC), activated *in vitro* with the fusion protein PAP-GM-CSF (also known as PA2024) and reinfused into the patient. IMPACT, a randomized, double-blind, placebo-controlled, multicenter trial in patients with asymptomatic or minimally symptomatic mCRPC led to the approval of sipuleucel-T [8]. In this phase 3 trial, 512 patients were randomized 2:1 to receive sipuleucel-T or placebo. Patients who received sipuleucel-T experienced a 4.1 month improvement in median overall survival (OS) (25.8 vs. 21.7 months; P=0.03). No improvement in median time to progression was observed (14.6 vs. 14.4 weeks). Overall, sipuleucel-T was well tolerated and reported adverse events included chills, fever, and headache. In this study, sipuleucel-T was also shown to induce T-cell responses and humoral antigen spread and these responses seen in the blood were associated with improved OS [18, 19]. Also CD54 upregulation, a surrogate for human APC activation, was FDA approved as a potency measure of sipuleucel-T [20].

The immune effects of sipuleucel-T on the prostate tumor microenvironment were evaluated by Fong and colleagues [21]. Sipuleucel-T was administered to 37 men with previously untreated localized prostate cancer prior to radical prostatectomy (RP). The primary endpoint was the change in the number of infiltrating $CD3^+$ T cells/μm^2 within the prostate tissue between paired biopsy and post-treatment RP specimens. This trial demonstrated an increased infiltration of $CD3^+$ T cells at the tumor interface in the sipuleucel-T treated RP tissue when compared with the pretreatment biopsy tissue ($P < 0.001$). This important data provided some of the first evidence that sipuleucel-T can mobilize immune cells to the tumor microenvironment, supporting its purported mechanism of action.

DCVAC/PCa [sub-header]

DCVAC/PCa combines autologous mature DCs pulsed with killed prostate specific antigen (PSA)-positive LNCaP cells. A phase 1/2 open-label, single-arm trial combined DCVAC/PCa with chemotherapy in 25 patients with mCRPC [4]. Patients received DCVAC/PCa at a dose of 1×10^7 DCs/dose injected subcutaneously at day 0, 14, 35 then every 6 weeks until toxicity, or until the maximum number of doses manufactured from one leukapheresis was reached (median 12 doses administered). In addition, patients received an initial 7 days metronomic oral cyclophosphamide 50mg daily, which was included based on

its potential to deplete regulatory T cells thus allowing for optimal T cell activation [4, 22]. On day 14, the standard regimen of docetaxel 75 mg/m^2 every 3 weeks with prednisone 5 mg twice daily was initiated following the second DCVAC/PCa dose. In an effort to increase local accumulation and activation of DCs *in vivo*, imiquimod cream was applied topically to the administration site 24 hours before and after each vaccine injection. Imiquimod is a toll-like receptor-7 agonist that induces cytokines and has been used as a vaccine adjunct in other clinical studies [23, 24]. The primary and secondary endpoints of the DCVAC/PCa trial [4] included safety and immune response. The most common adverse events reported were fatigue, back pain, and paresthesias. No grade 4 or 5 toxicities were reported. When compared with the predicted median OS using established nomograms (11.8 months with the Halabi nomogram and 13 months with the MSKCC nomogram), the OS observed with the administration of DCVAC/PCa was significantly longer at 19 months (HR 0.26, 95% CI 0.13–0.51). As a result of this promising data, a randomized, double-blind, placebo-controlled, parallel-group phase 3 trial was initiated and is currently accruing (VIABLE; NCT02111577). VIABLE will evaluate the safety and efficacy of first-line docetaxel in combination with DCVAC/PCa or placebo for the treatment of patients with mCRPC [25].

BDCA-1BDC-01 [sub-header]

In a similar approach, purified populations of autologous CD1c (BDCA-1$^+$) blood-derived dendritic cells (BDC) are loaded with HLA-A*0201-restricted peptides. To derive the BDCA-1BDC-01 vaccine, CD1c$^+$ BDC are immunomagnetically isolated following apheresis. The BDCs are then pulsed with HLA-A*0201-restricted peptides derived from PSA, PAP, control influenza matrix protein, and keyhole limpet hemocyanin. This open-label, dose-finding study included 12 HLA-A*0201$^+$ patients with asymptomatic mCRPC [9]. Two doses and two routes of administration were compared, with the primary objectives being safety and feasibility. Three injections at doses between 1 and 5 × 10^6 DCs were administered either intravenously or intradermally at monthly intervals. The most common adverse events observed included grade 1/2 fever and pain. Although not a primary objective, patient survival was assessed 5 years after completion of the study. The median survival of 18 months for 11 of the 12 patients was within the anticipated range of 12.2 – 21.7 months. One patient remained alive after 5 years, but it cannot be determined whether this outcome was solely due to vaccine administration. Future randomized trials will be required to further evaluate the clinical efficacy of this vaccine strategy.

PROSTVAC [sub-header]

Despite positive results of personalized vaccines for prostate cancer requiring *ex vivo* processing, including sipuleucel-T, feasibility remains a challenge in clinical practice. Comparatively, *in vivo* vaccines are logistically simple but promising results from early-phase trials need to be validated [7]. PROSTVAC is a poxviral-based peptide vaccine encoding the PSA gene as the target antigen with three costimulatory molecules (B7.1, ICAM-1, and LFA-3). The prime-boost regimen consists of subcutaneous administrations of a primer vaccine (modified vaccinia vector) on day 1 followed by 6 booster vaccines (modified fowlpox vector) on days 14, 28, 56, 84, 112 and 140. A phase 2 double-blind, randomized clinical trial with 125 mCRPC patients has shown a significant improvement in median OS by 8.5 months in the PROSTVAC treatment arm compared with placebo

(P=0.0061) [7]. Another study [26] evaluated the immune impact of PROSTVAC in 104 patients comparing pre-vaccine and 4 weeks post-vaccine T cell responses. Of these patients, 57% (59/104) demonstrated an increase in PSA-specific T cells and 68% (19/28) mounted an immune response to TAAs not present in the vaccine (antigen spreading). An additional analysis has suggested an association between improved OS and a decrease in regulatory T cell function [27]. A phase 3 trial to confirm immune responses and OS benefit has completed accrual and results are awaited (PROSPECT; NCT03122490) [28]. The PROSPECT trial included 1298 participants with asymptomatic or minimally symptomatic mCRPC randomized to one of three arms: PROSTVAC, PROSTVAC plus GM-CSF, or placebo. The primary outcome is OS.

IMMUNE CHECKPOINT INHIBITORS [header]

Although the clinical benefit of immune checkpoint inhibitors in other solid tumors has been established, PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have yet to demonstrate a survival benefit in prostate cancer [14]. CTLA-4 is an immunologic checkpoint involved with the downregulation of T cell function. This downregulation occurs, in part, when CTLA-4 prevents the autoregulatory interaction of CD28 (on a T cell) with its ligand, B7 (on a DC) [29, 30] which diminishes T-cell activity within 48 hours after stimulation via an antigen presenting cell. Ipilimumab is a monoclonal antibody that blocks CTLA-4, allowing for enhanced T cell activity and is currently FDA-approved for the treatment of melanoma. Unlike therapeutic cancer vaccines, immune checkpoint inhibitors do not provide the immune system with a specific target tumor antigen.

Kwon and colleagues conducted a double-blind phase 3 trial including 799 men with mCRPC following progression on docetaxel [14]. All patients received radiotherapy (low dose to metastatic disease as an immune adjuvant) and were randomized in a 1:1 ratio to ipilimumab or placebo. No statistically significant difference in median OS was observed between the ipilimumab and placebo arms (11.2 vs. 10.0 months; P=0.053). Although the primary endpoint was not met, a subgroup analysis in patients with good prognostic factors demonstrated an OS benefit. Additional trials are needed to confirm these results. A concurrent study in chemotherapy-naïve, mCRPC (without radiation) did not meet its primary endpoint, however full results have not yet been made public (NCT01057810).

Success with combination immunotherapy, such as ipilimumab and nivolumab in metastatic melanoma [31], have provided evidence to support the hypothesis that combination immunotherapy may be more effective than single agents alone. Ongoing studies will evaluate a potential synergistic effect between checkpoint inhibitors and other agents which may lead to improved outcomes. In the neoadjuvant sipuleucel-T study described above by Fong and colleagues [21], the majority of infiltrating T cells at the tumor interface following sipuleucel-T were PD-1^{+} which may provide rationale to sequence vaccine administration followed by an anti-PD-1 monoclonal antibody or another agent that can augment T cell immunity. Furthermore, Bishop and colleagues [32] have demonstrated that patients progressing on enzalutamide had significantly increased PD-L1/2^{+} DCs compared to patients naïve to enzalutamide or responding to treatment. Because PD-1 expression is thought to correlate with response to PD-1 inhibitors [33], understanding the PD-1

alterations induced by established prostate cancer therapies will be vital in determining optimal treatment sequencing.

COMBINATION APPROACHES [header]

Immunotherapies in prostate cancer such as sipuleucel-T and PROSTVAC have demonstrated benefits in OS but have not shown a significant improvement in progression free survival (PFS) [7, 8]. These agents may not significantly reduce tumor burden but provide a continuous anti-tumor effect over a period of time, potentially resulting in a slower tumor growth rate [34, 35]. Therefore, combining an immunotherapy with an anti-androgen or cytotoxic modality may be a logical approach [36]. Such a strategy could benefit from short term tumor reduction (anti-androgens or cytotoxic agents) and may slow tumor growth/progression (via immunologic impact) over the long term [37]. Additionally, understanding immune-related changes to the tumor microenvironment and the potential synergy among agents will provide the framework to combine immunotherapy with hormonal agents or chemotherapy. [Table 2]

Androgen deprivation therapy (ADT) and immunotherapy [sub-header]—The ability for androgen ablative therapy to induce T cell infiltration of prostate tissue was demonstrated in a study by Mercader and colleagues [38]. Patients in this trial received no treatment or treatment with flutamide (250 mg three times daily) with leuprolide acetate (7.5 mg intramuscular depot) for 7, 14, 21, or 28 days before RP. Analysis of RP tissue for all treatment durations (7–28 days) demonstrated T cell infiltration into both the normal prostate tissue and tumor sites that were comprised predominantly of CD4+ T cells. Further evidence to support ADT in conjunction with immunotherapeutic agents is provided by data demonstrating an increase in naïve T-cell production by the thymus after testosterone suppression therapy is initiated [39]. The STAND trial [40, 41] looked to capitalize on this biologic phenomenon by evaluating the optimal sequencing of sipuleucel-T and ADT in biochemically recurrent prostate cancer (rising PSA with no metastatic disease on conventional imaging) after local therapy failure. Patients (n=68) in this randomized phase II trial were assigned to either sipuleucel-T then ADT (2 weeks post infusion 3) or ADT (3 month lead-in) then sipuleucel-T. A greater PA2024-specific T cell proliferation was seen in the sipuleucel-T followed by ADT arm ($p < 0.001$) perhaps establishing the optimal sequence of ADT and immunotherapy for future trials.

Enzalutamide and immunotherapy [sub-header]—Enzalutamide is a modern anti-androgen therapy that is very well tolerated and has demonstrated the ability to extend survival in mCRPC [42, 43]. Preliminary murine data has suggested that enzalutamide can also enhance thymic production of naïve T cells [44]. These studies by Ardiani and colleagues also characterized the immunologic effects of enzalutamide and vaccine in mice models. C57BL/6 or transgenic adenocarcinoma of the mouse prostate (TRAMP) mice were exposed to enzalutamide with or without a therapeutic vaccine. This study demonstrated the immunogenic modulation property of enzalutamide and improved OS in mice treated with combination enzalutamide and vaccine compared to no treatment, vaccine alone, or enzalutamide alone ($P \leq 0.0001$, $P=0.0003$, $P=0.0009$, respectively). Immunogenic modulation describes the cascade of events that occurs when conventional therapies alter the

tumor phenotype rendering the tumor cells more susceptible to immune-mediated attack [45]. Ardiani and colleagues provided further evidence of immunomodulatory properties of both enzalutamide and abiraterone [46]. The results of this study showed that LNCaP cells were rendered more sensitive to T cell killing by enzalutamide and this immunogenic modulation was mediated via an androgen receptor dependent modulation of the apoptotic pathway. Importantly, this study also provided evidence that despite treatment-associated reduction in PSA levels, enzalutamide still improved the sensitivity of tumor cells to PSA-specific T cell killing. Another trial [47] included 34 patients with biochemically recurrent prostate cancer who were randomized to receive enzalutamide with or without a therapeutic vaccine. Preliminary immune analysis of patients treated with enzalutamide alone (n=12) indicated increased naïve T cells and natural killer cells. The impact of combination therapy (enzalutamide plus vaccine) has yet to be reported. Results of these studies provide rationale for combining enzalutamide and immunotherapy across multiple tumor types with enzalutamide effectively serving as an immune adjuvant.

The STRIDE trial (NCT01981122) is an ongoing, randomized, open-label phase II study evaluating peripheral T cell proliferation response in patients receiving enzalutamide starting 2 weeks before (concurrent) or 10 weeks after (sequential) sipuleucel-T initiation [48, 49]. The primary objective is peripheral T cell proliferation response to PA2024, the sipuleucel-T immunizing antigen. Cytokines including IFN-γ, interleukin-2, and TNF-α were also evaluated in both arms. In 52 patients with asymptomatic or minimally symptomatic mCRPC, PA2024-specific T cell proliferative response was similar between the two groups. The concurrent or sequential administration schedule of enzalutamide with sipuleucel-T therefore does not appear to impair sipuleucel-T immune response or bring to light additional safety concerns. Longer follow-up is required to evaluate the clinical impact of this combination. Similarly, an ongoing study at the National Cancer Institute is evaluating enzalutamide with or without PROSTVAC in mCRPC (NCT01867333) with the primary endpoint being time to progression.

Abiraterone plus prednisone and immunotherapy [sub-header]—As mentioned above, preclinical evidence suggests the occurrence of abiraterone-mediated immunogenic modulation [46]. However, uncertainty surrounds the coadministration of prednisone-containing treatment regimens with immunotherapeutic agents due to the potential immunosuppressive effects of corticosteroids. Small and colleagues [50] conducted a phase 2 clinical trial evaluating sipuleucel-T with concurrent versus sequential abiraterone plus prednisone (employing the standard abiraterone treatment regimen). This open-label study randomized 69 patients with mCRPC to receive sipuleucel-T followed by abiraterone plus prednisone 1 day (concurrent) or 10 weeks (sequential) after the first sipuleucel-T infusion. No statistically significant differences in peripheral immune responses were observed between the concurrent arm compared to the sequential arm. These results suggest that the administration sequence of abiraterone plus prednisone with sipuleucel-T does not significantly alter the immune responses of sipuleucel-T or the ability to make activated APC cells (CD54). Perhaps more importantly, this data provides support that prednisone at doses up to 5 mg twice daily may be administered concurrently with sipuleucel-T without limiting the ability of the immune system to mount an immune response as measured in this

study. Reported adverse effects in this trial were similar between the two arms and no new safety concerns were observed with the combination.

Docetaxel and immunotherapy [sub-header]—Preclinical evidence suggests that certain cytotoxic chemotherapy can be synergistic with immunotherapy through sensitizing prostate tumors to cytotoxic T cell killing [51, 52]. In these murine tumor model studies, the use of vaccines in combination with docetaxel or paclitaxel demonstrated an enhanced antitumor effect when used in combination. Garnett and colleagues [53] examined the *in vivo* effects of docetaxel on immune-cell subsets in response to antigen-specific vaccination. Results of this study showed that docetaxel in combination with a recombinant viral vaccine is superior to either agent alone at reducing tumor burden in tumor-bearing mice. Additionally, docetaxel in conjunction with vaccine demonstrated an increased antigen-specific T cell response to the vaccine antigen and additional antigens not primarily targeted by the vaccine (antigen spreading). Although pre-clinical data helps formulate the hypothesis of a synergistic effect between immunotherapy and chemotherapy, additional clinical trials are needed. Furthermore, dose and sequence may be key factors in determining whether a chemotherapy agent augments or suppresses the immune response of a concurrently administered immunotherapy agent. The results of an ongoing study may provide further guidance regarding the sequencing of chemotherapy and immunotherapy. In this phase 2 trial, (NCT02649855) patients with mCSPC are randomized to receive ADT followed by simultaneous treatment (docetaxel plus PROSTVAC) or sequential treatment (docetaxel then PROSTVAC). The primary objective is to determine which sequence induces the greatest breadth of immune response (as measured by antigen spreading).

IDEAL IMMUNOTHERAPY CANDIDATES [header]

The only FDA-approved immunotherapy in prostate cancer, sipuleucel-T, has demonstrated improved OS in asymptomatic or minimally symptomatic mCRPC [8]. Because the activity of sipuleucel-T and other immunotherapies rely on the activation of the immune system, clinicians must be selective when recommending immunotherapy for patients. Evidence suggests that patients with better baseline prognostic factors, such as lower PSA values and less aggressive disease, may derive the most benefit from immunotherapy [14, 54–56]. An exploratory analysis of the IMPACT trial suggested patients with better prognostic factors at baseline, particularly a low PSA value, experience the greatest benefit of sipuleucel-T therapy [55]. Additionally, as mentioned above, Kwon and colleagues [14] evaluated the efficacy of ipilimumab versus placebo after radiotherapy in patients with mCRPC. Although the primary endpoint was not met, a post-hoc subgroup analysis based on prognostic factors revealed a statistically significant OS benefit in patients with good prognostic features ($p=0.0038$) and no significant response in the group with poor prognostic features ($p=0.8456$). Although this analysis needs to be validated, there is growing evidence to support optimal outcomes for patients with minimal metastatic disease. It is still unknown whether patients with non-metastatic disease will derive even further benefit. Also unknown is whether combining cytotoxic chemotherapy with immunotherapy in patients with poor prognostic factors will overcome this perceived lack of benefit from immunotherapy alone. Nonetheless, these data suggesting better immunotherapy responses in patients with indolent

disease features may help inform clinicians which patients would most likely benefit from such treatments.

FUTURE STRATEGIES [header]

Future strategies may employ different targets or combinations than have been used in the past. It is reported that approximately 42–70% of prostate cancers overexpress HER2/*neu* as tested by immunohistochemistry [57, 58]. Overexpression of HER2 in prostate cancer has been associated with higher relapse rates [57] and shorter time to recurrence [59]. Thus far, efforts to target HER2 in mCRPC have failed to demonstrate benefit [60, 61]. An alternate approach to the anti-HER2 monoclonal antibody, trastuzumab, is anti-CD3 activated T cells (ATC) redirected by anti-HER2 bispecific antibodies (HER2Bi) [15]. HER2Bi-armed ATC was investigated in a phase 1 dose escalation trial that included a cohort of 8 mCRPC patients. HER2 staining was not performed and patients were eligible regardless of HER2 expression status. PBMCs were collected via leukapheresis, activated with anti-CD3 monoclonal antibody and armed with HER2Bi. HER2Bi-armed ATC (aATC) was administered twice weekly for four consecutive weeks. All patients received subcutaneous IL-2 (300,000 IU/m^2 daily) and GM-CSF (250 mcg/m^2 twice weekly) beginning 3 days before and ending 1 week after the aATC infusion. The most common reported grade 3 toxicity was chills. Among the 7 evaluable patients with prostate cancer, two minor and one partial response was reported in the highest dose levels, 40 and 80 billion aATC. Although this trial included a small sample size and multiple confounders, the results are intriguing and warrant further investigation.

Another strategy that will likely be explored in the future is the use of multiple immunologic platforms together to improve clinical outcomes. As has been previously discussed, such strategies are designed to take advantage of immunologic synergies seen in other immunotherapy trials in the past, including vaccine/checkpoint inhibitor studies in prostate cancer [62, 63]. A phase I trial (NCT02616185) will evaluate the safety and preliminary evidence of clinical efficacy of an immunotherapy combination consisting of an adenovirus-based vaccine, a DNA-based vaccine, locally injected anti-CTLA-4 and low-dose sunitinib (deployed as a means to suppress regulatory T-cells). While the ultimate clinical results are unknown, studies like this demonstrate how immunologic understanding has grown in recent years. As opposed to monotherapy in late stage patients where immunotherapy must overcome significant biological hurdles to achieve success, immunologic synergy will be evaluated in early stage disease to determine if such approaches can improve clinical outcomes.

CONCLUSION

Immunotherapy has moved from a niche focus within the pharmaceutical industry and academic circles to center-stage, however, at this time the focus is primarily on one type of actor, immune checkpoint inhibitors. In reviewing the development of immunotherapy in prostate cancer we are reminded that this is the rare tumor type where vaccines and not checkpoint inhibitors have shown the most clinical activity, including sipuleucel-T which is the one FDA-approved immunotherapy for this disease. With other vaccines in phase III

testing, there could soon be multiple vaccines approved for the treatment of prostate cancer, potentially allowing for increasing use of sequential and combination immunotherapies in the future. Future development strategies may also include rationally developed immunologic platforms, including vaccines, checkpoint inhibitors and other immune modulators. The lack of toxicity associated with many of these immunotherapies, especially vaccines, raises the hope that patients could initiate such treatments early in the course of their disease (including perhaps in the adjuvant setting) and enjoy a lasting and sustained therapeutic response, and thus substantially delaying more toxic treatments. As the appreciation of the immune system and the understanding of immunotherapies continue to progress, future ambitious clinical trials will be designed to evaluate the true potential of immunomodulation to meaningfully alter and extend the lives of men with prostate cancer.

Acknowledgements

Lisa M. Cordes: none

Ravi A. Madan: none

James L. Gulley: none

Financial Support or Sponsorship

Lisa M. Cordes: none

Ravi A. Madan: none

James L. Gulley: none

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Madan RA, Arlen PM, Mohebtash M, et al. Prostvac-VF: a vector-based vaccine targeting PSA in prostate cancer. Expert Opin Investig Drugs 2009; 18: 1001–1011.
2. Rojas-Martinez A, Manzanera AG, Sukin SW, et al. Intraprostatic distribution and long-term follow-up after AdV-tk immunotherapy as neoadjuvant to surgery in patients with prostate cancer. Cancer Gene Ther 2013; 20: 642–649. [PubMed: 24052127]
3. Wei XX, Fong L, Small EJ. Prostate cancer immunotherapy with sipuleucel-t: current standards and future directions. Expert Rev Vaccines 2015; 14: 1529–1541. [PubMed: 26488270]
4. Podrazil M, Horvath R, Becht E, et al. Phase I/II clinical trial of dendritic-cell based immunotherapy (DCVAC/PCa) combined with chemotherapy in patients with metastatic, castration-resistant prostate cancer. Oncotarget 2015; 6: 18192–18205.■■The promising OS data from this trial led to an ongoing phase 3 trial evaluating docetaxel plus DCVAC/PCa or placebo.
5. Mellman I, Coukos G, Dranoff. Cancer immunotherapy comes of age. Nature 2011; 480: 480–489. [PubMed: 22193102]
6. Melero I, Gaudernack G, Gerritsen W, et al. Therapeutic vaccines for cancer: an overview of clinical trials. Nat Rev Clin Oncol 2014; 11: 509–524. [PubMed: 25001465]

7. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol 2010; 28: 1099–1105. [PubMed: 20100959]
8. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411–422. [PubMed: 20818862]
9. Prue RL, Vari F, Radford K, et al. A phase I clinical trial of CD1c (BDCA-1)+ dendritic cells pulsed with HLA-A*0201 peptides for immunotherapy of metastatic hormone refractory prostate cancer. J Immunother 2015; 38: 71–76. [PubMed: 25658616]
10. McNeel DG, Dunphy EJ, Davies JG, et al. Safety and immunological efficacy of a DNA vaccine encoding prostatic acid phosphatase in patients with stage D0 prostate cancer. J Clin Oncol 2009; 27: 4047–4054. [PubMed: 19636017]
11. Kübler H, Scheel B, Gnad-Vogt U, et al. Self-adjuvanted mRNA vaccination in advanced prostate cancer patients: a first-in-man phase I/IIa study. J Immunother Cancer 2015: 3: 26. [PubMed: 26082837]
12. Noguchi M, Arai G, Matsumoto K, et al. Phase I trial of a cancer vaccine consisting of 20 mixed peptides in patients with castration-resistant prostate cancer: dose-related immune boosting and suppression. Cancer Immunol Immunother 2015; 64: 493–505. [PubMed: 25662406]
13. Higano C, Saad F, Somer B, et al. A phase III trial of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic castration-resistant prostate cancer (CRPC). J Clin Oncol 2009; (suppl): abstr LBA150.
14. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184–043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014; 15: 700–712. [PubMed: 24831977] ▪Although this trial did not meet its primary endpoint, it provided further support of the hypothesis that patients with positive prognostic features derive the most benefit from immunotherapy.
15. Vaishampayan U, Thakur A, Rathore R, et al. Phase I study of anti-CD3 x anti-Her2 bispecific antibody in metastatic castrate resistant prostate cancer patients. Prostate Cancer 2015; 2015: 285193. Doi: 10.1155/2015/285193.
16. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2015; 16: 417–425. [PubMed: 25743937]
17. Armstrong AJ, Haggman M, Stadler WM, et al. Long-term survival and biomarker correlates of tasquinimod efficacy in a multicenter randomized study of men with minimally symptomatic metastatic castration-resistant prostate cancer. Clin Cancer Res 2013; 19: 6891–6901. [PubMed: 24255071]
18. Guha Thakurta D, Sheikh NA, Fan LQ, et al. Humoral immune response against nontargeted tumor antigens after treatment with sipuleucel-T and its association with improved clinical outcome. Clin Cancer Res 2015; 21: 3619–3630. [PubMed: 25649018]
19. Sheikh NA, Petrylak D, Kantoff PW, et al. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer. Cancer Immunol Immunother 2013; 62: 137–147. [PubMed: 22865266]
20. Sheikh NA, Jones LA. CD54 is a surrogate marker of antigen presenting cell activation. Cancer Immunol Immunother 2008; 57: 1381–1390. [PubMed: 18297282]
21. Fong L, Carroll P, Weinberg V, et al. Activated lymphocyte recruitment into the tumor microenvironment following preoperative sipuleucel-T for localized prostate cancer. J Natl Cancer Inst 2014; 106: dju268.▪ This trial was the first to demonstrate the immune effects of sipuleucel-T on the prostate tumor microenvironment.
22. Le DT, Jaffee EM. Regulatory T-cell modulation using cyclophosphamide in vaccine approaches: a current perspective. Cancer Res 2012; 72: 3439–3444. [PubMed: 22761338]
23. Adams S, O'Neill D, Nonaka D, et al. Imiquimod: a TLR-7 agonist as adjuvant for a recombinant protein cancer vaccine. J Clin Oncol 2007; 25 (18S): abstr 8545.

24. Dang Y, Wagner WM, Gad E, et al. Dendritic cell-activating vaccine adjuvants differ in the ability to elicit antitumor immunity due to an adjuvant-specific induction of immunosuppressive cells. Clin Cancer Res 2012; 18: 3122–3131. [PubMed: 22510348]
25. Vogelzang NJ, Beer TM, Bartunkova J, et al. Autologous dendritic cell vaccination (DCVAC/PCa added to docetaxel chemotherapy in a double-blind, randomized phase III trial (VIABLE) in men with advanced (mCRPC) prostate cancer. J Clin Oncol 2015: 33 (suppl): abstr TPS5070.■■ The results of this phase 3 trial may help establish the future course of immunotherapy in prostate cancer.
26. Gulley JL, Madan RA, Tsang KY, et al. Immune impact induced by PROSTVAC (PSA-TRICOM), a therapeutic vaccine for prostate cancer. Cancer Immunol Res 2014; 2: 133–141. [PubMed: 24778277]
27. Vergati M, Cereda V, Madan RA, et al. Analysis of circulating regulatory T cells in patients with metastatic prostate cancer pre- versus post-vaccination. Cancer Immunol Immunother 2011; 60: 197–206. [PubMed: 20976449]
28. Gulley JL, Giacchino JL, Breitmeyer JB, et al. Prospect: a randomized double-blind phase 3 efficacy study of PROSTVAC-VF immunotherapy in men with asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer. J Clin Oncol 2015; 33 (15_suppl): abstr TPS5081.■■The results of this large phase 3 trial may help establish the future course of immunotherapy in prostate cancer.
29. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015; 33: 1974–1982. [PubMed: 25605845]
30. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443–2454. [PubMed: 22658127]
31. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373: 23–34. [PubMed: 26027431]
32. Bishop JL, Sio A, Angeles A, et al. PD-L1 is highly expressed in enzalutamide resistant prostate cancer. Oncotarget 2014; 6: 234–242.
33. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014; 20: 5064–5074. [PubMed: 24714771]
34. Madan RA, Gulley JL, Fojo T, Dahut WL. Therapeutic cancer vaccines in prostate cancer: the paradox of improved survival without changes in time to progression. Oncologist 2010; 15: 969–75. [PubMed: 20798195]
35. Gulley JL, Madan RA, Arlen PM. Enhancing efficacy of therapeutic vaccinations by combination with other modalities. Vaccine 2007; 25: B89–B96. [PubMed: 17573164]
36. Gulley JL, Drake CG. Immunotherapy for prostate cancer: recent advances, lessons learned, and areas for further research. Clin Cancer Res 2011; 17: 3884–3891. [PubMed: 21680544]
37. Stein WD, Gulley JL, Schlom J, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. Clin Cancer Res 2011; 17: 907–917. [PubMed: 21106727]
38. Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawl in patients with prostate cancer. Proc Natl Acad Sci 2001; 98: 14565–14570.
39. Williams KM, Lucas PJ, Bare CV, et al. CCL25 increases thymopoiesis after androgen withdrawl. Blood 2008; 112: 3255–3263. [PubMed: 18694999]
40. Antonarakis ES, Kibel AS, Adams GW, et al. Immune responses and clinical outcomes in STAND, a randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically-recurrent prostate cancer (BRPC) after local therapy failure. J Clin Oncol 2015: 33 (suppl): abstr 5030.■ Results of this trial provide additional guidance on the sequencing of ADT and immunotherapy.
41. Antonarakis ES, Kibel AS, Adams GW, et al. Antigen-specific immune responses through 24 months in the STAND trial: A randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically-recurrent prostate cancer (BRPC). J Clin Oncol 2015: 33 (suppl): abstr 171.

42. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433. [PubMed: 24881730]
43. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197. [PubMed: 22894553]
44. Ardiani A, Farsaci B, Rogers CJ, et al. Combination therapy with a second-genderation androgen receptor antagonist and a metastasis vaccine improves survival in a spontaneous prostate cancer model. Clin Cancer Res 2013; 19: 6205. [PubMed: 24048332]
45. Hodge JW, Garnett CT, Farsaci B, et al. Chemotherapy-induced immunogenic modulation of tumor cells enhances killing by cytotoxic T lymphocytes and is distinct from immunogenic cell death. Int J Cancer 2013; 133: 624–637. [PubMed: 23364915]
46. Ardiani A, Gameiro SR, Kwilas AR, et al. Androgen deprivation therapy sensitizes prostate cancer cells to T-cell killing through androgen receptor dependent modulation of the apoptotic pathway. Oncotarget 2014; 5: 9335–9348. [PubMed: 25344864]
47. Madan RA, Donahue RN, Singh H, et al. Clinical and immunologic impact of short course enzalutamide without androgen deprivation therapy for biochemically recurrent prostate cancer. J Clin Oncol 2016; 34 (2S): abstr 214.
48. Quinn DI, Petrylak DP, Pieczonka CM, et al. A randomized phase II, open-label study of sipuleucel-T with concurrent or sequential enzalutamide in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2014: 32 (suppl): abstr e16071.
49. Quinn DI, Drake CG, Dreicer R, et al. Immune response from STRIDE, a randomized, phase 2, open label study of sipuleucel-T (sip-T) with concurrent vs sequential enzalutamide (enz) administration in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2015; 33 (suppl): abstr 5040.■ An interim analysis suggested sequential versus concurrent enzalutamide with sipuleucel-T does not alter sipuleucel-T immune response.
50. Small EJ, Lance RS, Gardner TA, et al. A randomized phase II trial of sipuleucel-T with concurrent versus sequential abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer. Clin Cancer Res 2015; 21: 3862–3869. [PubMed: 25925891] ■ This trial suggested low dose prednisone may not affect the immunogenicity of sipuleucel-T.
51. Prell RA, Gearin L, Simmons A, Vanroey M, Jooss K. The anti-tumor efficacy of a GM-CSF-secreting tumor cell vaccine is not inhibited by docetaxel administration. Cancer Immunol Immunother 2006; 55: 1285–1293. [PubMed: 16408214]
52. Eralp Y, Wang X, Wang JP, et al. Doxorubicin and paclitaxel enhance the antitumor efficacy of vaccines directed against HER2/neu in a murine mammary carcinoma model. Breast Cancer Res 2004; 6: R275–283. [PubMed: 15217493]
53. Garnett CT, Schlom J, Hodge JW. Combination of docetaxel and recombinant vaccine enhances T-cell responses and antitumor activity: effects of docetaxel on immune enhancement. Clin Cancer Res 2008; 14: 3536–3544. [PubMed: 18519787]
54. Gulley JL, Arlen PM, Madan RA, et al. Immunologic and prognostic factors associated with overall survival employing a poxviral-based PSA vaccine in metastatic castrate-resistant prostate cancer. Cancer Immunol Immunother 2010; 59: 663–674. [PubMed: 19890632]
55. Schellhammer PF, Chodak G, Whitmore JB, et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the immunotherapy for prostate adenocarcinoma treatment (IMPACT) trial. Urology 2013; 81: 1297–1302. [PubMed: 23582482]
56. Gulley JL, Madan RA, Schlom J. Impact of tumour volume on the potential efficacy of therapeutic vaccines. Current Oncology 2011; 18: e150–e157. [PubMed: 21655153]
57. Nishio Y, Yamada Y, Kokubo H, et al. Prognostic significance of immunohistochemical expression of the HER-2/neu oncoprotein in bone metastatic prostate cancer. Urology 2006; 68: 110–115. [PubMed: 16806433]
58. Ricciardelli C, Jackson MW, Choong CS, et al. Elevated levels of HER-2/neu and androgen receptor in clinically localized prostate cancer identifies metastatic potential. Prostate 2008: 68: 830–838. [PubMed: 18324648]

59. Okegawa T, Ninjo M, Kutahara K, Higashihara E. Pre-treatment serum level of HER2/neu as a prognostic factor in metastatic prostate cancer patients about to undergo endocrine therapy. Int J Urol 2006; 19: 1197–1201.

60. Lara PN, Chee KG, Longmate J, et al. Trastuzumab plus docetaxel in HER-2/neu-positive prostate carcinoma. Cancer 2004; 100: 2125–2131. [PubMed: 15139054]

61. Morris MJ, Reuter VE, Kelly WK, et al. HER-2 profiling and targeting in prostate carcinoma. Cancer 2002; 94: 980–986. [PubMed: 11920466]

62. Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol 2012; 13: 501–508. [PubMed: 22326924]

63. van den Eertwegh AJ, Versluis J, van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol 2012; 13: 509–517. [PubMed: 22326922]

Key Points

- Following the FDA approval of sipuleucel-T in 2010, promising phase 2 results with PROSTVAC and DCVAC/PCa have paved the way for therapeutic cancer vaccines as an attractive treatment strategy for prostate cancer.
- Clinical trials are ongoing to determine how and when to integrate immunotherapy into current treatment strategies.
- Immunotherapy combined with cytotoxic chemotherapy or with other immunotherapy agents holds promise of a synergistic effect.
- Results of recent studies suggest ideal immunotherapy candidates have asymptomatic or minimally symptomatic disease but certain aspects of patient selection remain unclear.

Purpose of Review

- In recent clinical trials, immunotherapeutic agents have demonstrated promising results for the treatment of prostate cancer. This review discusses emerging immunotherapies for prostate cancer and their evolving role in sequencing and combination therapy.

Recent Findings

- Therapeutic vaccines including PROSTVAC and DCVAC/PCa have completed promising phase 2 trials for the treatment of prostate cancer and phase 3 trials are underway. Recent evidence supports a synergistic relationship between immunotherapy agents themselves, anti-androgens and with cytotoxic chemotherapy. Prostate cancer patients with good prognostic factors, such as minimal disease burden, appear to achieve the optimal benefit from immunotherapy.

Summary

- Therapeutic cancer vaccines and immunomodulating agents have demonstrated activity in the treatment of prostate cancer. Immunotherapies may alter the prostate tumor microenvironment and ongoing studies aim to provide guidance on effective sequencing and combination strategies.

Table 1:

Select Immunotherapy Agents for Prostate Cancer

Class	Agent	Description	Key References
Therapeutic Vaccines	AdV-tk	Adenoviral vector containing the Herpes virus thymidine-kinase gene	Rojas-Martinez et al. [2]
	DCVAC/PCa	Autologous DCs pulsed with killed PSA-positive LNCaP cells	Podrazil et al. [4]
	PROSTVAC	Poxviral-based peptide vaccine encoding the PSA gene + 3 T-cell costimulatory molecules (B7.1, ICAM-1 and LFA-3)	Kantoff et al. [7]
	Sipuleucel-T	Autologous PBMCs activated *ex vivo* with PA2024 (PAP + GM-CSF)	Kantoff et al. [8]
	BDCA-1BDC-01	Autologous CD1c (BDCA-1^{+}) blood derived DCs loaded with HLA-A*0201-restricted peptides	Prue et al. [9]
	pTVG-HP	Plasmid DNA vaccine encoding PAP cDNA	McNeel et al. [10]
	CV9103 (RNActive)	Self-adjuvanted mRNA vaccine targeting 4 antigens: PSA, PSMA, PSCA and STEAP1	Kübler et al. [11]
	PPV (personalized peptide vaccine)	Personalized vaccine made with up to 4 peptides (such as PSA, PAP, PSMA and MDRP)based on a patient's unique immunoreactivity profile	Noguchi et al. [12]
	GVAX-PCa	Vaccine comprised of cells from the LNCaP and PC3 cell lines and genetically modified to secrete GM-CSF	Higano et al. [13]
Checkpoint Inhibitors	Ipilimumab	Fully human monoclonal antibody against CTLA-4	Kwon et al. [14]
Misc. Immuno-modulating agents	HER2Bi-aATC	Anti-CD3 ATC armed with anti-HER2 bispecific antibodies (HER2Bi)	Vaishampayan et al. [15]
	Lenalidomide	Immunomodulatory and anti-angiogenic properties	Petrylak et al. [16]
	Tasquinimod	Immunomodulatory and anti-angiogenic properties	Armstrong et al. [17]

*PSMA= prostate-specific membrane antigen, PSCA=prostate stem cell antigen, STEAP1=six-transmembrane epithelial antigen of the prostate 1

Table 2:

Select Active Phase 2/3 Clinical Trials Evaluating Immunotherapy in Prostate Cancer

Intervention	Intervention	Population	Phase	Study Identifier
Vaccine	PROSTVAC	Localized PC (active surveillance)	II	NCT02326805
	PROSTVAC	Localized PC (neoadjuvant)	II	NCT02153918
	PROSTVAC	mCRPC	III	NCT01322490
	pTVG-HP +/− GM-CSF	BRPC	II	NCT01341652
Vaccine + Hormonal Therapy	Enzalutamide +/− PROSTVAC	mCRPC	II	NCT01867333
	Ipilimumab + degarelix	mCSPC	II	NCT02020070
	Ipilimumab + ADT	mCSPC	II	NCT01377389
	DC1 vaccine + ADT	BRPC	II	NCT00970203
Vaccine + Radiation	AdV-tk + valacyclovir	Localized PC	III	NCT01436968
	Sipuleucel-T +/− radiation	mCRPC	II	NCT01807065
	Sipuleucel + radiation	mCRPC	II	NCT02232230
	Sipuleucel-T + SABR	mCRPC	II	NCT01818986
	Sipuleucel-T +/− radium-223	mCRPC	II	NCT02463799
Vaccine + Chemotherapy	DCVAC/PCa + docetaxel/prednisone	mCRPC	III	NCT02111577
	PROSTVAC + docetaxel	mCSPC	II	NCT02649855
Combination Immunotherapy	Sipuleucel-T, CT-011 (anti-PD1), cyclophosphamide	mCRPC	II	NCT01420965
	Sipuleucel-T + ipilimumab	mCRPC	II	NCT01804465
	Sipuleucel-T + CYT107. (Interleukin-7)	mCRPC	II	NCT01881867
	PROSTVAC +/− ipilimumab	Localized PC (neoadjuvant)	II	NCT02506114
	pTVG-HP + pembrolizumab	mCRPC	I/II	NCT02499835
	pTVG-HP + sipuleucel-T	mCRPC	II	NCT01706458
	Nivolumab + ipilimumab	mCRPC	II	NCT02601014
	Adenovirus (AdC68), plasmid DNA, tremelimumab, sunitinib	BRPC, mCRPC	I	NCT02616185

*PC=prostate cancer; BRPC=biochemically recurrent prostate cancer; mCSPC=metastatic castration-sensitive prostate cancer