Immunotherapy for Prostate Cancer: Where Do We Go From Here?—PART 1: Prostate Cancer Vaccines:

http://www.cancernetwork.com/prostate-cancer/immunotherapy-prostate-cancer-where-do-we-go-herepart-1-prostate-cancer-vaccines/page/0/1

Abstract / Synopsis:

Immunotherapies have emerged as a revolutionary modality for cancer treatment, and a variety of immune-based approaches are currently being investigated in the field of prostate cancer. Despite the 2010 approval of sipuleucel-T, subsequent progress in prostate cancer immunotherapy development has been limited by disappointing results with novel vaccination approaches and by prostate cancer's general resistance to immune checkpoint blockade. Nevertheless, there remains strong preclinical and clinical evidence to suggest that prostate cancer is a susceptible target for immune therapies. Innovative strategies for vaccine development, adoptive cell transfer, alleviation of immunosuppression in the tumor microenvironment, and combinatorial approaches using existing drugs and novel immune agents hold great promise for improving the treatment of prostate cancer. The first article in this two-part series will provide an overview of both past and present therapeutic vaccination strategies for the promotion of antitumor immunity against prostate cancer. Later, in Part 2, we will discuss novel areas of clinical development and identify the trends that may define the future of prostate cancer immunotherapy.

Introduction

Prostate cancer is the most commonly diagnosed malignant tumor in American men and the second leading cause of cancer-related mortality.[1] Even with recent advances in multimodality therapy for localized disease, relapse occurs in 30% of patients,[2]while men with metastatic disease ultimately develop therapeutic resistance despite the advent of novel cytotoxic drugs, anti-androgen therapies, and radiopharmaceuticals. Immunologic approaches have long been of

interest in prostate cancer because the disease has several characteristics that theoretically make it a suitable immunotherapy target.[3] The prostate is a nonessential organ whose tissues produce multiple tumor-associated antigens (TAAs) for which specific T-cell populations targeting them have been identified. These T cells can potentially serve as the central effectors of adaptive antitumor immunity. Additionally, the relatively slow growth kinetics of prostate cancer may provide a longer window for the development of effective immune responses. Despite these potential advantages, prostate cancer is generally thought to be a “cold” tumor, with limited T-cell infiltration and minimal responses to date to single-agent immune checkpoint therapies. Prostate cancer has a relatively low tumor mutation burden,[4,5] which has frequently been considered an indicator of a tumor’s poor inherent responsiveness to checkpoint inhibition; in addition, emerging data are identifying the presence of specific genetic phenotypes that are associated with the development of less immunogenic intratumoral landscapes.[6] Furthermore, prostate cancer tumors have been known to downregulate human leukocyte antigen (HLA) class I expression, induce T-cell apoptosis, increase immunosuppressive cytokines, and increase suppressive regulatory T cell (Treg) populations in order to evade immune surveillance.[7,8] Consequently, there is a significant need to develop approaches that can circumvent the inherent immunosuppression of the prostate cancer tumor microenvironment. Clinical applications of immunotherapeutic approaches in prostate cancer have yielded mixed results, but spurred by the success of sipuleucel-T, the first therapeutic vaccine approved for use in human cancer, numerous novel vaccination approaches that enhance antitumor immunity are now being investigated (Table).

Sipuleucel-T

Sipuleucel-T consists of autologous peripheral blood–derived mononuclear cells cultured with a prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) fusion protein. Sipuleucel-T was approved for use in the setting of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer on the basis of three trials whose results demonstrated

clinical efficacy. An integrated analysis of two of the trials, D9901 and D9902A, demonstrated an improved median survival in those treated with sipuleucel-T of 23.2 months vs 18.9 months for placebo, which was equivalent to a 33% reduction in the risk of death (hazard ratio [HR], 1.5; 95% CI, 1.1–2.05; *P* = .011).[9] It should be noted, however, that overall survival (OS) was a secondary endpoint in these studies, and that the primary endpoint of improved progression-free survival (PFS) was not met. Concerns have also been raised over the pooling of data from two independent studies and over possible inequivalence of baseline disease characteristics among the compared subgroups.[10] The subsequent IMPACT trial randomized 512 patients with metastatic castration-resistant prostate cancer in a 2:1 ratio to sipuleucel-T or the control treatment and found a significant 4.1-month increase in OS for the therapy group, although with no difference in time to progression; there were no major differences in adverse effects between the two arms.[11]

Despite these results and the subsequent US Food and Drug Administration approval of sipuleucel-T, its widespread adoption has been hampered by the involved manufacturing process, concerns about detrimental effects of the leukapheresis procedures, the limited therapeutic window and magnitude of clinical benefit, and questions raised by the discordance between the PFS and OS outcomes. Of particular importance is the recognition of this phenomenon of improved survival without changes in PFS as a recurrent theme in immunotherapy trials. This has been noted in several other clinical contexts, including in pre-approval trials of checkpoint inhibitors in metastatic melanoma and renal cell carcinoma,[12,13] and it raises the important question of what are the most appropriate parameters for measuring efficacy in the age of novel immunotherapies.

Although the exact mechanism of action of sipuleucel-T is not known, correlative studies provide insight into clinical predictors of response and immunologic effects of the therapy. Retrospective analyses have suggested increased benefit in patients with more favorable prognostic features, such as lower baseline prostate-specific antigen (PSA) and lactate dehydrogenase (LDH) levels and better performance status.[14] Increased tumor burden is generally believed to correspond to greater

systemic immunosuppression, and the suggestion of a later onset of action of sipuleucel-T based on the delayed separation of Kaplan-Meier survival curves has led to recent recommendations to consider sipuleucel-T vaccination early in the treatment of metastatic castration-resistant prostate cancer.[15]

Mechanistically, sipuleucel-T has demonstrated robust activation of antigen-presenting cells (APCs), antigen-specific T-cell responses, and increases in cytokines associated with T-cell activation. The number of APCs and their activation, as measured by CD54 upregulation, have positively correlated with improved OS.[16] Interestingly, sipuleucel-T has also resulted in humoral antigen spread to a variety of targets beyond PAP, with immunoglobulin (Ig) G responses to PSA and LGALS3 that have correlated with improved OS.[17] A neoadjuvant trial of sipuleucel-T prior to radical prostatectomy found that treatment could increase the frequency of activated CD4+ and CD8+ T cells in the tumor microenvironment, particularly at the interface with adjacent benign tissue.[18] The broad stimulation of systemic immunity, along with the recruitment of possible effector T cells to tumor by sipuleucel-T, provides a further rationale for combining vaccination approaches with other activators of T-cell function. This robust immunologic response also suggests the need to consider further studies evaluating vaccination in the neoadjuvant and adjuvant settings for localized disease, when vaccination may enable the development of sustained antitumor immune surveillance.

Other Vaccine Approaches

Cell-based vaccines

Despite the approval of sipuleucel-T, a variety of alternate vaccine approaches have had much less success in the management of prostate cancer. GVAX is a cellular vaccine consisting of irradiated cells from PC-3 and LNCaP prostate cancer cell lines that are modified to constitutively express GM-CSF.[19,20] The theoretical advantages of this approach include the opportunity to induce immunologic responses to multiple TAAs and the possibility of mass-producing vaccines that can be

administered without the need for HLA matching.[21] Ultimately, two phase III trials to test the therapeutic efficacy of GVAX were undertaken. The VITAL-1 trial comparing GVAX to docetaxel plus prednisone in asymptomatic castration-resistant prostate cancer was terminated after a futility analysis demonstrated a less than 30% chance of meeting the improved survival endpoint. VITAL-2, which compared the combination of GVAX and docetaxel to docetaxel and prednisone was also stopped after an interim analysis showed an increased risk of death in the GVAX arm.[22] Clinical development of GVAX was ultimately halted.

Virus-based vaccines

PROSTVAC (PSA-TRICOM) is a cancer vaccine composed of a series of poxviral vectors (vaccinia during the initial priming vaccine and fowlpox for all boosts) engineered to express PSA and a triad of human T-cell costimulatory molecules (B7.1, intercellular adhesion molecule 1, and lymphocyte function-associated antigen 3).[23,24] A phase II study of 125 patients with minimally symptomatic metastatic castration-resistant prostate cancer randomized to placebo or PROSTVAC with adjuvant GM-CSF did not demonstrate improvement in the primary PFS endpoint but showed an increased median OS of 25.1 vs 16.6 months (HR, 0.56; P = .0061).[25] A similar trial by the National Cancer Institute that allowed for enrollment of patients with symptomatic or visceral metastatic castration-resistant prostate cancer demonstrated a median OS of 26.6 months, with 12/32 patients demonstrating PSA decline. Patients with lower-risk disease as defined by a Halabi model–predicted survival of > 18 months at the time of treatment had a particularly notable duration of survival (median OS, 37.3 months), suggesting the possibility that vaccination provides the greatest benefit for patients with lower tumor burden or a less aggressive phenotype.[23] In the setting of biochemical recurrence after definitive local therapy, 63% of patients treated with PROSTVAC in conjunction with GM-CSF were progression-free at 6 months, and there was a notable reduction in PSA doubling time following treatment.[26]

Based on the promising phase II data in patients with metastatic castration-resistant prostate cancer, PROSPECT (ClinicalTrials.gov

identifier: NCT01322490), a global phase III trial enrolling 1,297 patients with metastatic castration-resistant prostate cancer, was undertaken to evaluate the efficacy of PROSTVAC-VF ± GM-CSF. Unfortunately, this trial was stopped in September 2017 when a preplanned interim analysis found the therapy to be unlikely to meet its OS endpoint.

Despite the disappointing results of the PROSPECT trial, there are compelling data to demonstrate the immunogenicity of PSA-encoding poxviral vaccines. An aggregate evaluation of blood T-cell responses across seven early poxviral vaccine trials showed 57% of patients (59/104) with a twofold or greater increase in PSA-specific T cells following the vaccine. Interestingly, a majority of these patients also demonstrated the phenomenon of antigen-spreading, with documented T-cell response to non-PSA antigen targets.[27] A similar vaccination strategy incorporating only a single costimulatory molecule (B7.1) was administered in conjunction with radiotherapy for localized prostate cancer and was found to produce a significant increase in PSA-specific T cells compared with radiotherapy alone.[28] Consequently, PROSTVAC has been administered in combination with escalating doses of ipilimumab in a phase I trial in metastatic castration-resistant prostate cancer. This trial demonstrated no significant increase in adverse events with the combination compared with ipilimumab alone,[29] with 14/24 chemotherapy-naive patients (58%) experiencing PSA decline, and with 6/24 having declines of > 50%; moreover, the median OS in this trial was a robust 31.6 months.[30] Currently, the optimal clinical contexts and combination strategies for PROSTVAC remain questions of interest, with ongoing trials being conducted in the localized (NCT02326805, NCT03315871, NCT00096551), neoadjuvant (NCT02506114, NCT02153918), adjuvant (NCT02772562), biochemical recurrence (NCT00450463, NCT01875250), metastatic castration-sensitive prostate cancer (NCT02649855), and castration-resistant prostate cancer (NCT01867333, NCT02933255) settings.

DNA vaccines

DNA vaccines consist of closed circular DNA plasmids designed to encode an antigen of interest under a strong mammalian promoter. The first trial to evaluate a DNA vaccine encoding prostate-specific membrane antigen (PSMA) in combination with adjuvant GM-CSF was initiated nearly 2 decades ago and demonstrated the safety and feasibility of generating immune responses to self-antigens in prostate cancer patients.[31] A variation on this theme involved the use of PSMA fused to tetanus toxin in patients who had exhibited biochemical recurrence of prostate cancer. Here, all patients demonstrated an increase in CD4+ T cells targeting tetanus toxin fragment C and CD8+ T cells specific for the PSMA epitope; an increase in PSA doubling time was also seen.[32]

pTVG-HP is a DNA vaccine encoding human PAP (hPAP) that produced persistent hPAP-specific T-cell responses that correlated with favorable changes in PSA doubling time. These responses frequently occurred later in the course of DNA immunization, and the vaccine was able to augment responses when given as a booster, sustaining a persistent type 1 T helper cell–based T-cell response with an extended dosing schedule.[33]

KEY POINTS

- **To date, sipuleucel-T remains the only vaccination strategy approved for use in prostate cancer based on improvements in overall survival—although lack of PSA modulation, challenges of administration, and cost have limited its widespread utilization.**
- **Various vaccination approaches have so far failed to show significant clinical benefit in late-stage trials, but the consistent demonstration of antigen-specific immune responses and improvements in surrogate endpoints such as PSA doubling time with many vaccination strategies is reason for optimism about the future.**
- **Growing evidence suggests that implementation of vaccination strategies earlier in disease and/or in combination strategies may enhance clinical benefit. Future studies will have to investigate vaccination use in localized and low-tumor-burden states, in addition to use of vaccines in synergistic combinations with other immunostimulatory agents.**

Several prostate cancer DNA vaccine trials are now active, most notably trials utilizing pTVG-HP in combination with GM-CSF (NCT01341652), as a prime boost to sipuleucel-T therapy (NCT01706458), and with

programmed death 1 (PD-1) blockade via pembrolizumab (NCT02499835). The last of these strategies is based on preclinical models demonstrating upregulation of PD-1 in the T cells of mice treated with pTVG-HP DNA vaccinations, with preliminary data showing encouraging antitumor activity in a setting where single-agent PD-1 blockade has largely been ineffective.[34] Several novel vaccination strategies currently in early development include a DNA vaccine that encodes the androgen receptor ligand binding domain (NCT02411786), dual targeting with simultaneous use of partially humanized PSA and PSMA coding constructs (NCT02514213), and novel combinations with immunomodulatory agents and checkpoint inhibitors (NCT02616185).

Adenoviral vaccines

Another method for directly inducing immunogenic cell death of prostate tumor cells involves the use of a replication-deficient adenoviral vector expressing the herpes simplex virus thymidine-kinase gene (*HSV-TK*) delivered directly to localized prostate cancer (AdV-tk). Administration of the antiherpetic prodrug induces local cytotoxicity, and when combined with inflammation from standard debulking surgery or radiation, this therapy may theoretically activate both innate and adaptive antitumor immune responses. The HSV-TK protein also acts as a super-antigen–like molecule in this setting.[35] Following demonstration of safety in a phase I trial,[36,37] the combination of intraprostatic AdV-tk, androgen deprivation therapy, and radiation for high-risk localized disease achieved lower recurrence rates compared with historical controls.[38] There has also been suggestion of a prolonged time to recurrence when AdV-tk is utilized in the neoadjuvant setting.[39] These findings have led to a placebo-controlled phase III trial in patients with localized disease who are candidates for curative external beam radiation therapy (NCT01436968).

Dendritic cell vaccines

Dendritic cells (DCs), which capture, process, and present antigens to T cells,[40] have received considerable interest as a basis for cellular vaccines that can be manipulated to induce responses against TAAs.

Three main approaches have been evaluated in DC vaccination: ex vivo antigenic peptide loading followed by autologous infusion of the conditioned DCs, gene modification of DCs in vivo through the use of recombinant viruses, and ex vivo genetic engineering for antigen presentation with or without enhanced cosignaling.

DCVAC/PCa is a promising vaccination strategy that is now being evaluated in a global phase III clinical trial (VIABLE; NCT02111577). It is an autologous DC-based vaccine composed of Poly (I:C)–activated DCs pulsed with killed prostate cancer cells from the LNCaP cell line. Phase I and II trials showed that a regimen of DCVAC and metronomic cyclophosphamide co-administered with docetaxel increased OS by 7.2 months over historical controls with metastatic castration-resistant prostate cancer.[41] This regimen was well tolerated overall, with no serious anaphylactic reactions or adverse events attributed to immunotherapy. NCT02107430 is another active trial testing the efficacy of DCVAC/PCa in the adjuvant setting following definitive radiation for high-risk localized disease.

Different formulations of DC vaccines utilizing alternative sources of TAAs and other adjuvants are in early stages of development as well. These include DCs pulsed with recombinant human PSMA and recombinant survivin peptide,[42] with prostate cell line lysates,[43] with PSMA and inducible CD40,[44] and with the T-cell receptor γ chain alternate reading frame protein (TARP).[45] It remains to be seen how these vaccination approaches can be optimized and sequenced to enhance antitumor immunity and what modes of therapeutic utilization, likely in combinatorial approaches, will prove most effective.

Bacteria-based vaccines

Listeria monocytogenes is an intracellular pathogen that is actively phagocytosed by APCs and is able to subsequently replicate in the cytosol via escape from the phagosome. These pathogenic features enable the generation of both CD4 and CD8 responses, since Listeria antigens are processed through both the major histocompatibility complex (MHC) I and MHC II pathways.[46] The use of an attenuated

form of Listeria engineered to express TAAs leverages these immunogenic features to induce an antitumor immune response; vaccines with an attenuated Listeria vector are being investigated in a variety of disease contexts. Preclinical data have demonstrated the ability of Listeria vector vaccines to generate an antigen-specific tumor response and to induce tumor regression in murine prostate cancer models, both as a single agent[47] and when administered with radiation therapy.[48] Two commercial Listeria platforms are currently being evaluated in phase I clinical trials, for safety alone (ADU-741/JNJ-64041809; in NCT02625857) and in combination with PD-1 checkpoint blockade (ADXS31-142; in NCT02325557).

Peptide vaccines

Another approach to the stimulation of antitumor immune activity involves the use of personalized peptide vaccines (PPVs). These consist of multiple exogenously administered cancer-associated peptides that can be presented on HLA class I molecules for recognition by T cells. Adjuvants such as toll-like receptor ligands, Montanide ISA-51, or agonists of stimulator of interferon genes (STING) are used to stimulate polarized type 1 T helper cell or CD8+ T-cell responses.[49] Aided by rapid improvements in next-generation sequencing and the development of algorithms for epitope prediction, these peptides seek to induce robust and rapid cytotoxic T-lymphocyte activation without the costs and cell availability limitations of cell-based approaches.[50] The first randomized phase II trial of PPVs in prostate cancer, reported in 2010, was an open-label, multicenter, crossover study comparing a four-peptide vaccine plus a low dose of estramustine phosphate (EMP; 280 mg/d) with a standard EMP dose (560 mg/d) in patients with metastatic or nonmetastatic castration-resistant prostate cancer.[51] Median PFS was 8.5 months in the PPV-plus-EMP group and 2.8 months in the EMP-only group (P = .0012); the HR for OS was 0.3 (95% CI, 0.1–0.91) in favor of the PPV-plus-EMP group (log-rank P = .0328). The combination was tolerated without major adverse effects. Another study, which assessed PSA kinetics and immune responses associated with a PPV, found that peptide-specific IgG and T-cell responses strongly correlated with PSA doubling time, which in turn showed a correlation with OS.[52] These

markers may be important surrogates to monitor in light of the observation that PFS and OS often do not track together in the setting of prostate cancer immunotherapies. A recent trial of 72 patients with early-stage castration-resistant prostate cancer found that those treated with PPV plus low-dose dexamethasone vs dexamethasone alone showed marked improvements in PFS (22.0 vs 7.0 months; *P* = .0076) and OS (73.9 vs 34.9 months; *P* = .00084), a significant finding that needs to be validated in a phase III setting.[53] Combining PPV with low-dose cyclophosphamide in an attempt to abrogate immunosuppressive Treg populations did not affect clinical response; however, while Tregs were decreased with combination therapy, it is possible this immunostimulatory effect was compensated for by the increase in levels of myeloid-derived suppressor cells. Of note, a subset analysis revealed that patients who exhibited a humoral immune response to the peptide in the vaccine or increased peptide-specific cytotoxic T-lymphocyte activity in peripheral blood showed significantly longer survival.[54]

A novel vaccine approach involves use of peptides of the reverse transcriptase subunit of telomerase (hTERT), which is often overexpressed in cancer cells and which plays an important role in tumor proliferation. Earlier studies demonstrated extensive epitope spreading within hTERT following vaccination with a 16–amino acid hTERT peptide fragment,[55] and based on these data, a therapeutic hTERT vaccine consisting of the three highest-frequency hTERT peptides was tested in patients with prostate cancer. In this phase I study, hTERT vaccine and GM-CSF were administered to patients with metastatic hormone-naive prostate cancer who were beginning androgen deprivation therapy. Out of 22 patients, 21 also received radiotherapy to the prostate or adjacent bony lesions during the vaccination period. As expected, a majority of the patients experienced significant reduction in PSA levels, but in addition, 86% demonstrated an immune response to the administered peptides. Of note, 2 patients in the highest-dose (0.7 mg) peptide group experienced anaphylactic reactions; ultimately, intermediate peptide dosing at 0.3 mg was deemed safe and most immunogenic.[56] GX301 is a vaccine consisting of four telomerase peptides and the adjuvants Montanide ISA-51 and imiquimod; it was found to be safe and immunogenic in an early trial,[57] and a phase II

trial in patients with metastatic castration-resistant prostate cancer who have already been treated with docetaxel is now active (NCT02293707).

Conclusion

While later-phase trials of single-agent vaccination therapies beyond sipuleucel-T have not yielded significant clinical benefit to date, these studies have provided a valuable foundation that can guide the development of subsequent strategies for prostate cancer immunotherapy. It is clear from correlative clinical trial experiments that numerous vaccination approaches are able to induce immunologic responses to putative TAAs. Furthermore, patient subset analyses of clinical trials suggest that certain populations, particularly those with a lower tumor burden and those earlier in the course of disease progression, may ultimately be more likely to benefit from vaccination strategies. This argues for the need to carefully evaluate the patient populations being treated in vaccination trials and to consider utilization of vaccines in localized and oligometastatic settings.

Future vaccination approaches will undoubtedly seek to utilize vaccines in conjunction with the many agents now being developed to stimulate both the innate and adaptive immune system. Promising strategies may also look to incorporate vaccines in conjunction with existing modalities of treatment, such as radiation therapy, that are known to have immunomodulatory properties. We will discuss many of the alternative immunotherapeutic approaches currently under investigation in Part 2 of this series. As we continue to gain a deeper understanding of the immunogenic properties of prostate cancer vaccines and identify new ways to augment antitumor immunity, the full therapeutic promise of prostate cancer vaccination may yet be fulfilled.

Financial Disclosure: *Dr. Fong has received research funding from Bavarian Nordic, Bristol-Myers Squibb, Dendreon, Madison Vaccines, Merck, and Roche/Genentech. Dr. Patel has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article*.

Pages

- « first
- ‹ previous
- 1

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.

2. Kupelian PA, Mahadevan A, Reddy CA, et al. Use of different definitions of biochemical failure after external beam radiotherapy changes conclusions about relative treatment efficacy for localized prostate cancer. Urology. 2006;68:593-8.

3. Drake CG. Prostate cancer as a model for tumour immunotherapy. Nat Rev Immunol. 2010;10:580-93.

4. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500:415-21.

5. Salem ME, Xiu J, Lenz HJ, et al. Characterization of tumor mutation load (TML) in solid tumor. J Clin Oncol. 2017;35(15 suppl):abstr 11517.

6. Bezzi M, Seitzer N, Ishikawa T, et al. Diverse genetic-driven immune landscapes dictate tumor progression through distinct mechanisms. Nat Med. 2018 Jan 8. [Epub ahead of print]

7. Kitamura H, Torigoe T, Asanuma H, et al. Down-regulation of HLA class I antigens in prostate cancer tissues and up-regulation by histone deacetylase inhibition. J Urol. 2007;178:692-6.

8. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol. 2007;25:267-96.

9. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009;115:3670-9.

10. Graff JN, Chamberlain ED. Sipuleucel-T in the treatment of prostate cancer: an evidence-based review of its place in therapy. Core Evid. 2014;10:1-10.

11. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411-22.

12. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17:1558-68.

13. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803-13.

14. 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;81:1297-302.

15. McNeel DG, Bander NH, Beer TM, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma. J Immunother Cancer. 2016;4:92.

16. Sheikh N, Petrylak D, Kantoff P, 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;62:137-47.

17. GuhaThakurta 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;21:3619-30.

18. Fong L, Carroll P, Weinberg V, et al. Activated lymphocyte recruitment into the tumor microenvironment following preoperative sipuleucel-T for localized prostate cancer. J Nat Cancer Inst. 2014;106:dju268.

19. Small EJ, Sacks N, Nemunaitis J, et al. Granulocyte macrophage colony-stimulating factor–secreting allogeneic cellular immunotherapy for hormone-refractory prostate cancer. Clin Cancer Res. 2007;13:3883-91.

20. Higano CS, Corman JM, Smith DC, et al. Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. Cancer. 2008;113:975-84.

21. Simmons AD, Li B, Gonzalez-Edick M, et al. GM-CSF-secreting cancer immunotherapies: preclinical analysis of the mechanism of action. Cancer Immunol Immunother. 2007;56:1653-65.

22. Small TD, Gerritsen WR, Rolland F, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). 2009 ASCO Genitourinary Cancers Symposium; Orlando, FL; February 26–28, 2009. Abstr 7.

23. Madan RA, Arlen PM, Mohebtash M, et al. Prostvac-VF: a vector-based vaccine targeting PSA in prostate cancer. Expert Opin Investig Drugs. 2009;18:1001-11.

24. Hodge JW, Sabzevari H, Yafal AG, et al. A triad of costimulatory molecules synergize to amplify T-cell activation. Cancer Res. 1999;59:5800-7.

25. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010;28:1099-105.

26. DiPaola RS, Chen YH, Bubley GJ, et al. A national multicenter phase 2 study of prostate-specific antigen (PSA) pox virus vaccine with sequential androgen ablation therapy in patients with PSA progression: ECOG 9802. Eur Urol. 2015;68:365-71.

27. 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;2:133-41.

28. Gulley JL, Arlen PM, Bastian A, et al. Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. Clin Cancer Res. 2005;11:3353-62.

29. Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol. 2012;13:501-8.

30. Jochems C, Tucker JA, Tsang KY, et al. A combination trial of vaccine plus ipilimumab in metastatic castration-resistant prostate cancer patients: immune correlates. Cancer Immunol Immunother. 2014;63:407-18.

31. Mincheff M, Tchakarov S, Zoubak S, et al. Naked DNA and adenoviral immunizations for immunotherapy of prostate cancer: a phase I/II clinical trial. Eur Urol. 2000;38:208-17.

32. Chudley L, McCann K, Mander A, et al. DNA fusion-gene vaccination in patients with prostate cancer induces high-frequency CD8(+) T-cell responses and increases PSA doubling time. Cancer Immunol Immunother. 2012;61:2161-70.

33. McNeel DG, Becker JT, Eickhoff JC, et al. Real-time immune monitoring to guide plasmid DNA vaccination schedule targeting prostatic acid phosphatase in patients with castration-resistant prostate cancer. Clin Cancer Res. 2014;20:3692-704.

34. McNeel D, Eickhoff J, Jeraj R, et al. O11 DNA vaccine with PD-1 blockade elicits anti-tumor responses in patients with metastatic, castration-resistant prostate cancer (mCRPC). J Immunother Cancer. 2017;5(Suppl 2):abstr 011.

35. Aguilar LK, Guzik BW, Aguilar-Cordova E. Cytotoxic immunotherapy strategies for cancer: mechanisms and clinical development. J Cell Biochem. 2011;112:1969-77.

36. Herman JR, Adler HL, Aguilar-Cordova E, et al. In situ gene therapy for adenocarcinoma of the prostate: a phase I clinical trial. Hum Gene Ther. 1999;10:1239-49.

37. Miles BJ, Shalev M, Aguilar-Cordova E, et al. Prostate-specific antigen response and systemic T cell activation after in situ gene therapy in prostate cancer patients failing radiotherapy. Hum Gene Ther. 2001;12:1955-67.

38. Fujita T, Teh BS, Timme TL, et al. Sustained long-term immune responses after in situ gene therapy combined with radiotherapy and hormonal therapy in prostate cancer patients. Int J Radiat Oncol Biol Phys. 2006;65:84-90.

39. 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;20:642-9.

40. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998;392:245-52.

41. 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;6:18192-205.

42. Xi HB, Wang GX, Fu B, et al. Survivin and PSMA loaded dendritic cell vaccine for the treatment of prostate cancer. Biol Pharm Bull. 2015;38:827-35.

43. Reyes D, Salazar L, Espinoza E, et al. Tumour cell lysate-loaded dendritic cell vaccine induces biochemical and memory immune response in castration-resistant prostate cancer patients. Br J Cancer. 2013;109:1488-97.

44. Sonpavde G, McMannis JD, Bai Y, et al. Phase I trial of antigen-targeted autologous dendritic cell-based vaccine with in vivo activation of inducible CD40 for advanced prostate cancer. Cancer Immunol Immunother. 2017;66:1345-57.

45. Wood LV, Fojo A, Roberson BD, et al. TARP vaccination is associated with slowing in PSA velocity and decreasing tumor growth rates in patients with stage D0 prostate cancer. Oncoimmunology. 2016;5:e1197459.

46. Sinha G. Listeria vaccines join the checkpoint frenzy. Nature Biotechnol. 2014;32:1176-7.

47. Shahabi V, Reyes-Reyes M, Wallecha A, et al. Development of a Listeria monocytogenes based vaccine against prostate cancer. Cancer Immunol Immunother. 2008;57:1301-13.

48. Hannan R, Zhang H, Wallecha A, et al. Combined immunotherapy with Listeria monocytogenes-based PSA vaccine and radiation therapy leads to a therapeutic response in a murine model of prostate cancer. Cancer Immunol Immunother. 2012;61:2227-38.

49. Melief CJ, van Hall T, Arens R, et al. Therapeutic cancer vaccines. J Clin Invest. 2015;125:3401-12.

50. Itoh K, Yamada A. Personalized peptide vaccines: a new therapeutic modality for cancer. Cancer Science. 2006;97:970-6.

51. Noguchi M, Kakuma T, Uemura H, et al. A randomized phase II trial of personalized peptide vaccine plus low dose estramustine phosphate (EMP) versus standard dose EMP in patients with castration resistant prostate cancer. Cancer Immunol Immunother. 2010;59:1001-9.

52. Noguchi M, Moriya F, Suekane S, et al. A phase II trial of personalized peptide vaccination in castration-resistant prostate cancer patients: prolongation of prostate-specific antigen doubling time. BMC Cancer. 2013;13:613.

53. Yoshimura K, Minami T, Nozawa M, et al. A phase 2 randomized controlled trial of personalized peptide vaccine immunotherapy with low-dose dexamethasone versus dexamethasone alone in chemotherapy-naive castration-resistant prostate cancer. Eur Urol. 2016;70:35-41.

54. Noguchi M, Moriya F, Koga N, et al. A randomized phase II clinical trial of personalized peptide vaccination with metronomic low-dose cyclophosphamide in patients with metastatic castration-resistant prostate cancer. Cancer Immunol Immunother. 2016;65:151-60.

55. Inderberg-Suso E, Trachsel S, Lislerud K, et al. Widespread CD4+ T-cell reactivity to novel hTERT epitopes following vaccination of cancer patients with a single hTERT peptide GV1001. Oncoimmunology. 2012;1:670-86.

56. Lilleby W, Gaudernack G, Brunsvig PF, et al. Phase I/IIa clinical trial of a novel hTERT peptide vaccine in men with metastatic hormone-naive prostate cancer. Cancer Immunol Immunother. 2017;66:891-901.

57. Fenoglio D, Traverso P, Parodi A, et al. A multi-peptide, dual-adjuvant telomerase vaccine (GX301) is highly immunogenic in patients with prostate and renal cancer. Cancer Immunol Immunother. 2013;62:1041-52.