**How to Cite**:
Albogamy, S. A., Alnemer, Maram J., Alanazi, Ahmad A., Alsaadi, Mona M., Alzaher, Mohammed A., Aljawad, Hussain M., Al Aloula, Ali S., Alazmiy, Barakat S., Bahaidarah, Fahad A., Aljehani, M. R., & Alamri, F. H. (2019). Prostate cancer: Early detection, diagnosis, and advances in treatment- Review of updated data for healthcare providers. *International Journal of Health Sciences*, *3*(S1), 369–385.
https://sciencescholar.us/journal/index.php/ijhs/article/view/15235

# Prostate cancer: Early detection, diagnosis, and advances in treatment- Review of updated data for healthcare providers

**Sahar Adi Albogamy**
KSA, National Guard Health Affairs

**Maram Jaafar Alnemer**
KSA, National Guard Health Affairs

**Ahmad Alhelo Alanazi**
KSA, National Guard Health Affairs

**Mona Mudlah Alsaadi**
KSA, National Guard Health Affairs

**Mohammed Abdullah Alzaher**
KSA, National Guard Health Affairs

**Hussain Mahdi Aljawad**
KSA, National Guard Health Affairs

**Ali Suliman Al Aloula**
KSA, National Guard Health Affairs

**Barakat Shumailan Alazmiy**
KSA, National Guard Health Affairs

**Fahad Abdulaziz Bahaidarah**
KSA, National Guard Health Affairs

**Mohammad Raja Aljehani**
KSA, National Guard Health Affairs

**Fouad Hamed Alamri**
KSA, National Guard Health Affairs

International Journal of Health Sciences E-ISSN 2550-696X © 2019.
***Corresponding email:*** *akk29337@gmail.com*
*Manuscript submitted: 01 Jan 2019, Manuscript revised: 09 Jan 2019, Accepted for publication: 15 Jan 2019*

***Abstract*---Background:** Prostate cancer (PCa) is the most commonly diagnosed cancer among men in the U.S. and the second leading cause of cancer-related deaths. Standard treatment options include radical prostatectomy and radiation for localized PCa, while androgen ablation therapy is used for recurrent or advanced stages. However, almost all patients progress to metastatic castration-resistant prostate cancer (mCRPC), with limited treatment options that offer only modest survival improvements. Immunotherapy has shown promise in addressing this challenge. **Aim:** This review aims to discuss the current advancements in the early detection, diagnosis, and treatment of PCa, with a focus on immunotherapy and ongoing clinical trials. **Methods:** A comprehensive literature review was conducted to analyze data from recent clinical trials, focusing on the efficacy of current treatments such as vaccines, immune checkpoint inhibitors (ICIs), cell-based therapies, and DNA-based immunotherapy approaches. Various ongoing clinical trials in the field were also reviewed. **Results:** Current FDA-approved treatments for mCRPC, such as docetaxel, abiraterone, and Sipuleucel-T, have shown survival advantages of 2-4 months. Immunotherapeutic approaches, including Sipuleucel-T, have demonstrated improved overall survival in clinical trials. Numerous ongoing trials are investigating new combinations of immunotherapies, vaccines, and immune modulators to enhance treatment efficacy. **Conclusion:** Advancements in immunotherapy have provided new hope for patients with advanced PCa. However, survival improvements remain modest, and further research is necessary to refine therapeutic approaches, particularly through combination treatments. Early detection and novel diagnostic methods continue to play a critical role in improving patient outcomes.

***Keywords*---**Prostate cancer, metastatic castration-resistant prostate cancer, immunotherapy, early detection, clinical trials, vaccines, immune checkpoint inhibitors.

## Introduction

Prostate cancer (PCa) is recognized as the most frequently diagnosed cancer and stands as the second leading cause of cancer-related mortality among men in the United States (1). The primary treatments for patients with localized PCa typically involve radical prostatectomy and/or radiation therapy, while patients with recurrent or advanced-stage PCa primarily receive androgen ablation therapy (2), potentially supplemented by intensified treatment methods. Despite achieving initial effective responses through androgen suppression therapy (AST), nearly all patients eventually transition to metastatic castration-resistant prostate cancer (mCRPC) (3). The FDA has approved several treatments for mCRPC, including docetaxel, abiraterone, enzalutamide, cabazitaxel, and Sipuleucel-T (Sip-T) (4–9), yet these therapies offer only a modest survival advantage of 2–4 months on average. The median overall survival (OS) for patients with mCRPC varies between 13 and 32 months, with a 5-year survival rate of only 15% (10, 11). Thus, there is a critical need to investigate new therapeutic strategies for mCRPC.

Significant progress has been made in the realm of immunotherapy over the past decade. In 2010, the FDA authorized the first dendritic cell-based vaccine, Sip-T, for non-symptomatic metastatic prostate cancer (9). This was followed by the approval of the immune checkpoint CTLA-4 inhibitor ipilimumab for metastatic melanoma in 2011 (12). Subsequently, PD-1/PD-L1 immune checkpoint inhibitors were authorized, beginning in 2014, for multiple cancer types, including lung cancer, kidney cancer, urothelial cancer, Hodgkin's disease, and breast cancer (13), as well as for solid tumors characterized by microsatellite instability and deficient mismatch repair (14). Aside from Sip-T, no other immunotherapeutic options have been sanctioned for PCa; however, numerous clinical trials are currently underway to evaluate the immune and clinical efficacy of various immunotherapies. This review will address the progress made in preclinical trials, the methodologies employed in this research, and the findings from recent clinical studies.

**Ongoing Clinical Trials:**

Numerous clinical trials, both completed and ongoing, are exploring a variety of immunotherapeutic strategies for mCRPC patients. These strategies include vaccines, immune checkpoint inhibitors (ICI), immunomodulators, adoptive cell transfer (ACT), oncolytic virus-mediated immune responses, and combinatorial approaches involving radiation and chemotherapy. As of May 1, 2019, over 1,100 active (or recruiting) clinical trials for PCa have been identified, with 63% focusing on therapeutic interventions and 12% specifically targeting immunotherapy.

**Diagnosis of Prostate Cancer**

Prostate cancer diagnosis typically begins with an assessment of risk factors and symptoms, alongside a thorough medical history and physical examination. The most common initial screening method is the prostate-specific antigen (PSA) test, which measures the level of PSA in the blood. Elevated PSA levels can indicate the presence of prostate cancer, but they may also result from benign conditions, such as benign prostatic hyperplasia (BPH) or prostatitis. Consequently, a comprehensive evaluation is necessary to interpret PSA results accurately, often involving a discussion of family history, age, and any urinary symptoms experienced by the patient. If PSA levels are elevated or if abnormalities are detected during a digital rectal examination (DRE), further diagnostic steps are warranted. These may include imaging studies such as transrectal ultrasound (TRUS), which helps visualize the prostate and guide biopsies. Magnetic resonance imaging (MRI) has also become increasingly important in the diagnosis and staging of prostate cancer, providing detailed images that can help assess the extent of the disease and identify suspicious lesions. In cases where imaging suggests the possibility of malignancy, a prostate biopsy is performed, typically using a TRUS-guided approach. During this procedure, small tissue samples are extracted from the prostate for histological examination, allowing for the confirmation of cancer diagnosis and the determination of its grade and stage.

Pathological evaluation of biopsy specimens is crucial for diagnosing prostate cancer and understanding its aggressiveness. The Gleason grading system, which scores the cancer based on the architectural patterns of prostate cells, is widely

used to predict the tumor's behavior. A higher Gleason score correlates with a more aggressive cancer and a worse prognosis. Additionally, advanced diagnostic techniques such as genomic testing can be employed to assess the molecular characteristics of the tumor, providing insights into its potential responsiveness to specific treatments and aiding in risk stratification. In summary, the diagnosis of prostate cancer is a multifaceted process that integrates clinical evaluation, laboratory tests, imaging modalities, and histopathological analysis. Early and accurate diagnosis is essential for determining the appropriate treatment strategy and improving patient outcomes, highlighting the importance of ongoing research into novel diagnostic approaches and biomarkers for prostate cancer.

**Vaccine-Based Therapies**
**DNA-Based Vaccines**:

DNA vaccines generate an immune response by being taken up, transcribed, and translated by host cells, which then produce foreign antigens recognized by the immune system. These vaccines can be tailored to leverage tumor-associated antigens (TAAs), leading to a significant activation and proliferation of T cells specific to the tumor antigens (15–18). This approach is currently being researched in the context of prostate cancer (PCa), which presents several TAAs, including prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), prostatic acid phosphatase (PAP), prostate stem cell antigen (PSCA), prostein, T cell receptor gamma alternate reading frame protein (TARP), Trp-p8, Six-transmembrane epithelial antigen of the prostate 1 (STEAP1), and NY-ESO-1 (19, 20). Among the most thoroughly investigated DNA vaccines for prostate cancer is one that encodes PAP along with granulocyte-macrophage colony-stimulating factor (GM-CSF) (pTVG-HP), which has been assessed in a phase I trial involving men with biochemically recurrent PCa. In this study, patients received six treatments of pTVG-HP and GM-CSF every two weeks. Findings from the trial indicated that the vaccine was well tolerated, with 9 of 22 patients developing specific CD4+ and/or CD8+ immune responses to PAP. Additionally, the PSA doubling time improved from 6.5 months before treatment to 9.3 months one year post-treatment (21). A follow-up analysis of peripheral blood mononuclear cells (PBMCs) from this cohort revealed that multiple vaccinations were essential for strong immune responses, as most PAP-specific T cells were not detectable until after completing the six-vaccination regimen (22). Currently, pTVG-HP is being studied in phase II clinical trials in combination with Sipuleucel-T (Sip-T) (NCT01706458) and nivolumab (NCT03600350).

Neoantigen DNA vaccinations are being explored as a personalized treatment strategy to activate T cells against tumor cells presenting neoantigens. These vaccines are created by identifying tumor-specific antigens through whole exome sequencing of both tumor and germline DNA (23). Although neoantigen DNA vaccinations are still in early development stages, dendritic cell (24) and peptide-based (25, 26) neoantigen vaccines have shown promise in eliciting T cell responses in preliminary clinical trials for melanoma, primary glioblastoma, and lung cancer, suggesting their potential efficacy in PCa. An intensive phase I trial combining neoantigen DNA vaccination with nivolumab, ipilimumab, and PROSTVAC is underway for patients with metastatic hormone-sensitive prostate cancer (NCT03532217).

**Cell-Based Vaccines**:

Cell-based vaccination typically involves using autologous or allogeneic whole cells, which may include antigen-presenting cells (APCs) and prostate cancer cells modified to express TAAs and/or GM-CSF, promoting anti-tumor immune responses (27). GVAX, a cell-based vaccine under investigation, consists of allogenic prostate cancer cell lines (LNCaP and PC3) that are engineered to overexpress GM-CSF, thereby activating dendritic cells (DCs) and subsequently T cells to generate strong anti-tumor responses. In an initial phase I/II trial, patients receiving a low dose (100 million cell booster) exhibited a median survival of 24 months, while those in the high-dose cohort (300 million cell booster) had a survival of 36.9 months, compared to the predicted survival of 19.5 months (27). However, two subsequent phase III trials (VITAL-1 and VITAL-2) failed to demonstrate improved outcomes, leading to their early termination due to lack of clinical efficacy (28, 29). Another phase I trial involved resected patient tumors that underwent retroviral transduction to express GM-CSF, leading to the activation of novel T and B cell responses against prostate cancer antigens (30). While GM-CSF cellular vaccinations are not currently being tested in clinical settings for prostate cancer, its potential use in other vaccine modalities for prostate cancer remains under preclinical evaluation, such as in combination with norcantharidin (31).

Sip-T, an autologous dendritic cell vaccine produced by ex vivo priming of patient dendritic cells with PA2024 (a fusion protein combining PAP and GM-CSF), became the first FDA-approved therapeutic cancer vaccine in 2010. Three multicenter phase III trials evaluated its efficacy in asymptomatic or minimally symptomatic patients with metastatic castration-resistant prostate cancer (mCRPC). The initial trials indicated no difference in time to tumor progression (TTP), yet revealed a statistically significant overall survival (OS) advantage for patients treated with Sip-T [25.9 vs. 21.4 months (P = 0.01, HR, 1.7), and 19.0 vs. 15.7 months (P = 0.3, HR, 1.27)] (34, 35). The third phase III trial (IMPACT) randomized 512 patients in a 2:1 ratio to receive Sip-T or placebo, with results mirroring those of the earlier trials, where patients treated with Sip-T achieved a median OS benefit of 4.1 months compared to placebo [25.8 vs. 21.7 months (P = 0.02, HR, 0.77)], though there was no significant difference in TTP (14.6 vs. 14.4 weeks) (9). Safety assessments indicated that the treatment was generally well tolerated, with no severe adverse events reported (36). Despite its demonstrated efficacy and safety, Sip-T has faced challenges in widespread acceptance primarily due to its high cost relative to the observed benefits (37). Ongoing investigations are exploring combination therapies to enhance the efficacy of Sip-T, including treatments with Atezolizumab (Anti-PD-L1) (NCT03024216), Ipilimumab (Anti-CTLA-4) (NCT01804465), radiation (NCT02463799, NCT01818986, NCT01807065), and chemotherapy (NCT01420965).

Chimeric antigen receptor (CAR) T cells are engineered ex vivo to express a T cell receptor (TCR) signaling domain fused with antibody variable regions, enabling them to recognize tumor surface antigens in an MHC-independent manner (38). CAR T cells targeting CD19 have demonstrated complete responses in B-cell hematologic malignancies (39), suggesting that CAR T cell therapy may also be a promising approach for solid tumors. A preclinical study employing a CAR

containing 4-1BB showed potent anti-tumor activity in a LAPC-9 xenograft model (40). Current clinical trials are assessing CAR T cells targeting EpCAM (NCT03013712), PSCA (NCT02744287), PSMA (NCT01140373, NCT03089203), and NY-ESO-1 (NCT03159585).

**Peptide-Based Vaccines**

Personalized peptide vaccines (PPV) involve the immunization with tumor-specific peptides designed to induce an immune response by activating cytotoxic T lymphocytes (CTL), which subsequently trigger anti-tumor reactions. Typically, the process for identifying peptides for vaccination involves screening pre-vaccination patient peptides to evaluate their potential for stimulating CTL or humoral responses in vitro [41]. Several targets have been identified for HLA-A24+ prostate cancer (PCa) patients, including prostatic acid phosphatase (PAP) [42], prostate-specific antigen (PSA) [43], and prostate-specific membrane antigen (PSMA) [44]. A randomized phase II study evaluated the combination of PPV and estramustine phosphate (EMP) versus EMP alone, revealing an improved progression-free survival (PFS) of 8.5 months for the combination therapy compared to 2.8 months with EMP alone. The combination therapy was deemed tolerable and safe, supporting its potential for future clinical trials [45]. Another randomized phase II trial showed that patients with docetaxel-resistant castration-resistant prostate cancer (CRPC) had improved overall survival (OS) with PPV compared to those without PPV (17.8 months vs. 10.5 months) [46]. Based on these promising results, a phase III placebo-controlled trial is underway to assess PPV in docetaxel-refractory metastatic CRPC (mCRPC) patients (UMIN000011308). A phase I/IIa dose escalation trial with the peptide vaccine UV1, containing a fragment from telomerase reverse transcriptase (hTERT), was conducted in patients with metastatic hormone-naïve prostate cancer. Results indicated that a majority of patients responded to the therapy, with immune responses detected in 18 of 21 patients, PSA levels declining in 14 of 21, and 10 of 21 patients exhibiting no tumor evidence on MRI [47]. This trial (NCT01784913) is ongoing, though there are no current phase III trials for UV1 in PCa.

**Viral Vector-Based Vaccines**

Viral-based vaccines are an immunotherapeutic approach that utilizes recombinant viral vectors encoding tumor-associated antigens (TAAs) to induce specific immune responses by mimicking natural infection within host immune cells [48]. PROSTVAC (TRICOM) is a poxvirus-based vaccine regimen that includes recombinant vaccinia and fowlpox virus boosters engineered to encode PSA and three co-stimulatory molecules: B7-1 (CD80), lymphocyte function-associated antigen 3 (LFA-3) (CD58), and intercellular adhesion molecule-1 (ICAM-1) (CD54) [49]. In a phase II trial involving 125 patients with minimally symptomatic mCRPC, PROSTVAC demonstrated a significant OS benefit compared to placebo (25.1 vs. 16.6 months, P = 0.0061, HR, 0.56), though it did not affect progression-free survival (PFS) [50]. Another phase II trial incorporating PROSTVAC with GM-CSF in 32 men with mCRPC similarly showed an increased median OS of 26.6 months, exceeding the predicted 17.4 months [51]. These outcomes led to a randomized, placebo-controlled phase III trial, which found that PROSTVAC, either alone or combined with GM-CSF, did not significantly impact

OS or survival without events compared to placebo [52]. These findings suggest that PROSTVAC monotherapy is ineffective, potentially due to an immunosuppressive tumor environment. Ongoing research is investigating combination therapies with PROSTVAC to enhance immune responses, including trials with DNA vaccines (NCT03532217), immune checkpoint inhibitors (ICIs) (NCT02506114, NCT02933255), and chemotherapy (NCT02649855).

Adenovirus type 5 (Ad5) is another vector used to target TAAs. A phase I trial studying the immune responses to an Ad5-PSA vaccine in 32 patients with hormone-refractory metastatic PCa found that 34% of patients produced anti-PSA antibodies, 68% showed anti-PSA T cell responses, 48% experienced an increase in PSA doubling time, and 55% survived longer than predicted [53]. An ongoing phase II trial (NCT00583024) investigating adenovirus/PSA responses in men with hormone-refractory PCa demonstrated that anti-PSA T cell responses were present in 100% of patients with recurrent disease and 67% in those with hormone-refractory disease [54]. A newly recruiting phase I trial aims to examine the response of mCRPC patients to adenoviral vaccines targeting PSA (ETBX-071), MUC1 (ETBX-061), and brachyury (ETBX-051) (NCT03481816). Additionally, an active phase I trial is testing ETBX-051 and ETBX-061 alongside an adenoviral CEA vaccine (ETBX-011) (NCT03384316).

**Immune Checkpoint Inhibitors (ICIs)**

Immune checkpoint inhibitors (ICIs) work by targeting regulatory molecules, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1), which are involved in suppressing the immune response. By blocking these molecules, ICIs promote T-cell activation and subsequent anti-tumor activity. Although ICIs have shown significant efficacy across several malignancies, their impact on prostate cancer (PCa) has been limited. Only tumors with high microsatellite instability (MSI) have received approval for ICI treatment in PCa, and efforts are ongoing to improve their efficacy, particularly through combination therapies.

**CTLA-4 Blockade**

Ipilimumab, an anti-CTLA-4 monoclonal antibody, is FDA-approved for melanoma but has been evaluated in various PCa trials. A phase I/II trial combining ipilimumab with radiotherapy showed tolerability and some clinical benefits, such as PSA declines in 50% of patients and stable disease in others. However, in a phase III trial, comparing ipilimumab with placebo in docetaxel-refractory PCa patients after radiotherapy, no significant improvement in overall survival (OS) was observed, although there was a slight progression-free survival (PFS) benefit. Another phase III study confirmed no significant difference in OS, though some PSA responses were seen (23% vs. 8%). As monotherapy results were modest, ipilimumab is being investigated in combination therapies, such as with radiation, PD-1 inhibitors like nivolumab, chemotherapy, and androgen suppression therapy (AST).

**PD-1/PD-L1 Blockade**

PD-1/PD-L1 inhibitors block the interaction between PD-1 on T-cells and PD-L1 on tumor cells, thereby reviving T-cell-mediated anti-tumor responses. In PCa, PD-1 inhibitors like nivolumab and pembrolizumab have shown limited efficacy as monotherapy. For instance, in a phase I trial of nivolumab in mCRPC patients, no objective responses were reported. However, combination therapies have shown promise, such as a phase II trial where pembrolizumab was administered to patients resistant to enzalutamide, resulting in PSA declines and tumor size reductions in some patients. Similarly, a phase Ib trial of pembrolizumab in PD-L1-positive tumors demonstrated partial responses and stable disease. Atezolizumab, an anti-PD-L1 antibody, was well-tolerated in mCRPC patients, with promising survival outcomes. Current clinical trials are exploring combinations of PD-1/PD-L1 inhibitors with PROSTVAC, chemotherapy, radium-223, Sipuleucel-T, and CTLA-4 inhibitors.

**B7-H3 Blockade**

B7-H3 is a novel immune checkpoint target for immunotherapy. It is overexpressed in PCa cells and inhibits T-cell function, contributing to immune evasion. B7-H3 expression correlates with more aggressive PCa phenotypes, including higher Gleason scores and mCRPC. Several monoclonal antibodies targeting B7-H3 are in clinical development, with phase I and II trials currently investigating their efficacy. These antibodies are being tested as monotherapy for their potential to disrupt tumor-driven immune suppression.

**Oncolytic Vaccines:**

Oncolytic viruses represent a promising area in cancer immunotherapy, specifically designed to target, replicate within, and kill cancer cells while sparing normal cells. Though still in the early stages of prostate cancer (PCa), some viral-based immunotherapies have advanced to clinical trials, offering insights into their potential.

**Ad5-yCD/mutTKSR39rep-hIL12**: One such promising agent is Ad5-yCD/mutTKSR39rep-hIL12, an oncolytic virus currently undergoing clinical trials. This virus delivers two suicide genes—cytosine deaminase (CD) and herpes simplex virus 1 thymidine kinase (HSV-1 TK)—to tumor cells. These genes convert non-toxic prodrugs into lethal compounds within cancer cells. In a Phase I trial, an improved version of this virus showed enhanced patient response when combined with intensity-modulated radiotherapy. Patients with intermediate-risk PCa demonstrated no detectable adenocarcinoma at 24 months, highlighting the potential of Ad5-based therapies for PCa (75). **Pelareorep (Reolysin)**: Pelareorep, a reovirus that targets Ras signaling pathways, has been another oncolytic virus tested in prostate cancer. In addition to direct oncolytic activity, pelareorep enhances immune responses by increasing pro-inflammatory cytokines, CD8+ T cells, and NK cell activity. Despite these effects, clinical trials testing pelareorep with chemotherapy agents like docetaxel and prednisone did not show a significant survival benefit in patients with metastatic castration-resistant

prostate cancer (mCRPC) (82). Currently, no further trials for pelareorep in PCa are ongoing, though trials in other cancer types are still being explored.

**Combination Immunotherapies**: Monotherapy using immunotherapeutics has often resulted in modest clinical benefits. Thus, combination therapies are being explored. Pairing vaccines with immune checkpoint inhibitors, androgen suppression therapy (AST), and other treatment modalities may enhance outcomes.

- **Vaccines and Immune Checkpoint Inhibitors**: Combining vaccines such as GVAX or PROSTVAC with immune checkpoint inhibitors like ipilimumab or pembrolizumab has shown increased anti-tumor T cell responses and PSA declines in patients with mCRPC. For example, in a phase I trial involving ipilimumab and PROSTVAC, 14 of 24 patients experienced PSA reductions (49).
- **AST and Immunotherapy**: Androgen suppression therapy, a common frontline treatment for mCRPC, has been shown to modulate the immune environment. Trials combining AST with immunotherapies like Sipuleucel-T and immune checkpoint inhibitors are underway, with early results suggesting enhanced CD8+ T cell responses (86).

In summary, while oncolytic viruses and combination immunotherapies hold significant promise in PCa treatment, ongoing research and clinical trials are essential to optimize these strategies and maximize patient outcomes.

**Conclusion**

Prostate cancer remains a significant health challenge, particularly in its advanced stages, where treatment options are limited, and survival rates remain low. The transition to metastatic castration-resistant prostate cancer (mCRPC) marks a critical point in disease progression, where traditional androgen ablation therapies become less effective. Despite the availability of treatments such as docetaxel, abiraterone, enzalutamide, and Sipuleucel-T, the overall survival benefit for patients with mCRPC remains modest, highlighting the urgent need for more effective therapeutic strategies. Immunotherapy has emerged as a promising avenue for treating prostate cancer, particularly with the FDA approval of Sipuleucel-T, the first therapeutic cancer vaccine. Although Sip-T has demonstrated improved overall survival in clinical trials, challenges such as high cost and limited widespread adoption have restricted its impact. Other immunotherapeutic approaches, such as immune checkpoint inhibitors, DNA-based vaccines, and chimeric antigen receptor (CAR) T cell therapies, are currently under investigation and offer potential for future advancements in prostate cancer treatment. Early-phase trials with DNA-based vaccines, including pTVG-HP, and cell-based vaccines like GVAX, have shown promise, although larger studies are required to confirm their clinical efficacy. The combination of immunotherapies with conventional treatments such as radiation and chemotherapy is an area of ongoing research, with hopes of achieving synergistic effects that could further extend patient survival. Additionally, personalized treatment strategies, including neoantigen DNA vaccinations and CAR T cell therapies targeting specific prostate cancer antigens, offer potential for highly tailored and effective therapies. Early detection remains crucial for improving

outcomes, and advancements in diagnostic techniques, such as genomic testing and advanced imaging methods like MRI, have enhanced the ability to identify prostate cancer at earlier stages and stratify risk more accurately. Continued research into novel biomarkers and diagnostic tools will be essential for guiding treatment decisions and improving long-term survival for patients. In conclusion, while significant progress has been made in the treatment of advanced prostate cancer, particularly through immunotherapy, further research and innovation are required to develop more effective, accessible, and personalized therapies that offer greater survival benefits.

**References**


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. (2018) 68:7–30. doi: 10.3322/caac.21442
2. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. (2014) 65:467–79. doi: 10.1016/j.eururo.2013.11.002
3. Shelley M, Harrison C, Coles B, Staffurth J, Wilt TJ, Mason MD. Chemotherapy for hormone-refractory prostate cancer. *Cochrane database Syst Rev*. (2006) 8:CD005247. doi: 10.1002/14651858.CD005247.pub2
4. Petrylak DP, Tangen CM, Hussain MHA, Lara PNJ, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. (2004) 351:1513–20. doi: 10.1056/NEJMoa041318
5. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. (2011) 364:1995–2005. doi: 10.1056/NEJMoa1014618
6. Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. (2012) 367:1187–97. doi: 10.1056/NEJMoa1207506
7. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. (2013) 369:213–23. doi: 10.1056/NEJMoa1213755
8. Patel SA, Hoffman-Censits J. Cabazitaxel in the treatment of metastatic castration-resistant prostate cancer: patient selection and special considerations. *Onco Targets Ther*. (2017) 10:4089–98. doi: 10.2147/OTT.S103532
9. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. (2010) 363:411–22. doi: 10.1056/NEJMoa1001294
10. Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, et al. Predicting time from metastasis to overall survival in castration-resistant prostate cancer: results from SEARCH. *Clin Genitourin Cancer* (2017) 15:60–6.e2. doi: 10.1016/j.clgc.2016.08.018
11. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. (2014) 371:424–33. doi: 10.1056/NEJMoa1405095

12. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. (2010) 363:711–23. doi: 10.1056/NEJMoa1003466
13. Tang J, Yu JX, Hubbard-Lucey VM, Neftelinov ST, Hodge JP, Lin Y. The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. *Nat Rev Drug Discov*. (2018) 17:854. doi: 10.1038/nrd.2018.210
14. Zhang, J., Quadri, S., Wolfgang, C. L., & Zheng, L. (2018). New development of biomarkers for gastrointestinal cancers: From neoplastic cells to tumor microenvironment. *Biomedicines*, *6*(3), 87.
15. Cole G, McCaffrey J, Ali AA, McCarthy HO. DNA vaccination for prostate cancer: key concepts and considerations. *Cancer Nanotechnol*. (2015) 6:2. doi: 10.1186/s12645-015-0010-5
16. Yang B, Jeang J, Yang A, Wu TC, Hung C-F. DNA vaccine for cancer immunotherapy. *Hum Vaccin Immunother*. (2014) 10:3153–64. doi: 10.4161/21645515.2014.980686
17. Zahm CD, Colluru VT, McNeel DG. DNA vaccines for prostate cancer. *Pharmacol Ther*. (2017) 174:27–42. doi: 10.1016/j.pharmthera.2017.02.016
18. Alam S, McNeel DG. DNA vaccines for the treatment of prostate cancer. *Exp Rev Vaccines*. (2010) 9:731–45. doi: 10.1586/erv.10.64
19. Kiessling A, Wehner R, Fussel S, Bachmann M, Wirth MP, Schmitz M. Tumor-associated antigens for specific immunotherapy of prostate cancer. *Cancers*. (2012) 4:193–217. doi: 10.3390/cancers4010193
20. Gati A, Lajmi N, Derouiche A, Marrakchi R, Chebil M, Benammar-Elgaaied A. NY-ESO-1 expression and immunogenicity in prostate cancer patients. *Tunis Med*. (2011) 89:779–83.
21. McNeel DG, Dunphy EJ, Davies JG, Frye TP, Johnson LE, Staab MJ, 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) 27:4047–54. doi: 10.1200/JCO.2008.19.9968
22. Becker JT, Olson BM, Johnson LE, Davies JG, Dunphy EJ, McNeel DG. DNA vaccine encoding prostatic acid phosphatase. (PAP) elicits long-term T-cell responses in patients with recurrent prostate cancer. *J Immunother*. (2010) 33:639–47. doi: 10.1097/CJI.0b013e3181dda23e
23. Guo Y, Lei K, Tang L. Neoantigen Vaccine delivery for personalized anticancer immunotherapy. *Front Immunol*. (2018) 9:1499. doi: 10.3389/fimmu.2018.01499
24. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science*. (2015) 348:803–8. doi: 10.1126/science.aaa3828
25. Sahin U, Derhovanessian E, Miller M, Kloke B-P, Simon P, Lower M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature*. (2017) 547:222–6.
26. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature*. (2017) 547:217–21. doi: 10.1038/nature22991
27. Small EJ, Sacks N, Nemunaitis J, Urba WJ, Dula E, Centeno AS, et al. Granulocyte macrophage colony-stimulating factor–secreting allogeneic

cellular immunotherapy for hormone-refractory prostate cancer. *Clin Cancer Res*. (2007) 13:3883–91. doi: 10.1158/1078-0432.CCR-06-2937
28. Demkow EST, Gerritsen W. 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). In *Proc 2009 Genitourin Cancer Symp*. Orlando, FL (2009).
29. Higano CS, Corman JM, Smith DC, Centeno AS, Steidle CP, Gittleman M, 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. doi: 10.1002/cncr.23669
30. Simons JW, Mikhak B, Chang JF, DeMarzo AM, Carducci MA, Lim M, et al. Induction of immunity to prostate cancer antigens: results of a clinical trial of vaccination with irradiated autologous prostate tumor cells engineered to secrete granulocyte-macrophage colony-stimulating factor using ex vivo gene transfer. *Cancer Res*. (1999) 59:5160–8.
31. Mo L, Zhang X, Shi X, Wei L, Zheng D, Li H, et al. Norcantharidin enhances antitumor immunity of GM-CSF prostate cancer cells vaccine by inducing apoptosis of regulatory T cells. *Cancer Sci*. (2018) 109:2109–18. doi: 10.1111/cas.13639
32. Burch PA, Breen JK, Buckner JC, Gastineau DA, Kaur JA, Laus RL, et al. Priming tissue-specific cellular immunity in a phase I trial of autologous dendritic cells for prostate cancer. *Clin Cancer Res*. (2000) 6:2175–82.
33. Anassi E, Ndefo UA. Sipuleucel-T. (provenge) injection: the first immunotherapy agent. (vaccine) for hormone-refractory prostate cancer. *P T*. (2011) 36:197–202.
34. Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T. (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol*. (2006) 24:3089–94. doi: 10.1200/JCO.2005.04.5252
35. Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, 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. doi: 10.1002/cncr.24429
36. Hall SJ, Klotz L, Pantuck AJ, George DJ, Whitmore JB, Frohlich MW, et al. Integrated safety data from 4 randomized, double-blind, controlled trials of autologous cellular immunotherapy with sipuleucel-T in patients with prostate cancer. *J Urol*. (2011) 186:877–81. doi: 10.1016/j.juro.2011.04.070
37. Holko P, Kawalec P. Economic evaluation of sipuleucel-T immunotherapy in castration-resistant prostate cancer. *Expert Rev Anticancer Ther*. (2014) 14:63–73. doi: 10.1586/14737140.2014.856270
38. Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. *Cancer Discov*. (2013) 3:388–98. doi: 10.1158/2159-8290.CD-12-0548
39. Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood*. (2015) 125:4017–23. doi: 10.1182/blood-2014-12-580068
40. Priceman SJ, Gerdts EA, Tilakawardane D, Kennewick KT, Murad JP, Park AK, et al. Co-stimulatory signaling determines tumor antigen sensitivity and persistence of CAR T cells targeting PSCA+ metastatic prostate

cancer. *Oncoimmunology*. (2018) 7:e1380764. doi: 10.1080/2162402X.2017.1380764

41. Noguchi M, Sasada T, Itoh K. Personalized peptide vaccination: a new approach for advanced cancer as therapeutic cancer vaccine. *Cancer Immunol Immunother*. (2013) 62:919–29. doi: 10.1007/s00262-012-1379-1
42. Inoue Y, Takaue Y, Takei M, Kato K, Kanai S, Harada Y, et al. Induction of tumor specific cytotoxic t lymphocytes in prostate cancer using prostatic acid phosphatase derived hla-a2402 binding peptide. *J Urol*. (2001) 166:1508–13. doi: 10.1016/S0022-5347(05)65821-1
43. Harada M, Kobayashi K, Matsueda S, Nakagawa M, Noguchi M, Itoh K. Prostate-specific antigen-derived epitopes capable of inducing cellular and humoral responses in HLA-A24+ prostate cancer patients. *Prostate*. (2003) 57:152–9. doi: 10.1002/pros.10280
44. Kobayashi K, Noguchi M, Itoh K, Harada M. Identification of a prostate-specific membrane antigen-derived peptide capable of eliciting both cellular and humoral immune responses in HLA-A24+ prostate cancer patients. *Cancer Sci*. (2003) 94:622–7. doi: 10.1111/j.1349-7006.2003.tb01493.x
45. Noguchi M, Kakuma T, Uemura H, Nasu Y, Kumon H, Hirao Y, 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. doi: 10.1007/s00262-010-0822-4
46. Noguchi M, Moriya F, Suekane S, Matsuoka K, Arai G, Matsueda S, et al. Phase II study of personalized peptide vaccination for castration-resistant prostate cancer patients who failed in docetaxel-based chemotherapy. *Prostate*. (2012) 72:834–45. doi: 10.1002/pros.21485
47. Lilleby W, Gaudernack G, Brunsvig PF, Vlatkovic L, Schulz M, Mills K, 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. doi: 10.1007/s00262-017-1994-y
48. Sultan H, Fesenkova VI, Addis D, Fan AE, Kumai T, Wu J, et al. Designing therapeutic cancer vaccines by mimicking viral infections. *Cancer Immunol Immunother*. (2017) 66:203–13. doi: 10.1007/s00262-016-1834-5
49. Madan RA, Bilusic M, Heery C, Schlom J, Gulley JL. Clinical evaluation of TRICOM vector therapeutic cancer vaccines. *Semin Oncol*. (2012) 39:296–304. doi: 10.1053/j.seminoncol.2012.02.010
50. Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, 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. doi: 10.1200/JCO.2009.25.0597
51. Gulley JL, Arlen PM, Madan RA, Tsang K-Y, Pazdur MP, Skarupa L, 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) 59:663–74. doi: 10.1007/s00262-009-0782-8
52. Hossain, M. K., Nahar, K., Donkor, O., & Apostolopoulos, V. (2018). Immune-based therapies for metastatic prostate cancer: an update. *Immunotherapy*, *10*(4), 283-298.

53. Lubaroff DM, Konety BR, Link B, Gerstbrein J, Madsen T, Shannon M, et al. Phase I clinical trial of an adenovirus/prostate-specific antigen vaccine for prostate cancer: safety and immunologic results. *Clin Cancer Res*. (2009) 15:7375–80. doi: 10.1158/1078-0432.CCR-09-1910
54. Lubaroff DM, Williams RD, Vaena D, Joudi F, Brown J, Smith M, et al. An ongoing phase II trial of an adenovirus/PSA vaccine for prostate cancer. In: *103rd Annu Meet Am Assoc Cancer Res*. Chicago, IL (2012).
55. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov*. (2018) 8:1069–86. doi: 10.1158/2159-8290.CD-18-0367
56. Slovin SF, Higano CS, Hamid O, Tejwani S, Harzstark A, Alumkal JJ, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol Off J Eur Soc Med Oncol*. (2013) 24:1813–21. doi: 10.1093/annonc/mdt107
57. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, 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. doi: 10.1016/S1470-2045(14)70189-5
58. Beer TM, Kwon ED, Drake CG, Fizazi K, Logothetis C, Gravis G, et al. Randomized, double-blind, phase III Trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. *J Clin Oncol*. (2017) 35:40–7. doi: 10.1200/JCO.2016.69.1584
59. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother cancer*. (2018) 6:8. doi: 10.1186/s40425-018-0316-z
60. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. (2012) 366:2443–54. doi: 10.1056/NEJMoa1200690
61. Graff JN, Alumkal JJ, Drake CG, Thomas GV, Redmond WL, Farhad M, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. *Oncotarget*. (2016) 7:52810–7. doi: 10.18632/oncotarget.10547
62. Hansen AR, Massard C, Ott PA, Haas NB, Lopez JS, Ejadi S, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Ann Oncol Off J Eur Soc Med Oncol*. (2018) 29:1807–13. doi: 10.1093/annonc/mdy232
63. Kim JW, Shaffer DR, Massard C, Powles T, Harshman LC, Braiteh FS, et al. A phase Ia study of safety and clinical activity of atezolizumab. (atezo) in patients. (pts) with metastatic castration-resistant prostate cancer. (mCRPC). *J Clin Oncol*. (2018) 36:187. doi: 10.1200/JCO.2018.36.6_suppl.187
64. Chapoval AI, Ni J, Lau JS, Wilcox RA, Flies DB, Liu D, et al. B7-H3: A costimulatory molecule for T cell activation and IFN-γ production. *Nat Immunol*. (2001) 2:269–74. doi: 10.1038/85339

65. Castellanos JR, Purvis IJ, Labak CM, Guda MR, Tsung AJ, Velpula KK, et al. B7-H3 role in the immune landscape of cancer. *Am J Clin Exp Immunol*. (2017) 6:66–75.
66. Picarda E, Ohaegbulam KC, Zang X. Molecular pathways: targeting B7-H3. (CD276) for human cancer immunotherapy. *Clin Cancer Res*. (2016) 22:3425–31. doi: 10.1158/1078-0432.CCR-15-2428
67. Benzon B, Zhao SG, Haffner MC, Takhar M, Erho N, Yousefi K, et al. Correlation of B7-H3 with androgen receptor, immune pathways and poor outcome in prostate cancer: an expression-based analysis. *Prostate Cancer Prostatic Dis*. (2017) 20:28–35. doi: 10.1038/pcan.2016.49
68. Shenderov E, Demarzo A, Boudadi K, Allaf M, Wang H, Chapman C, et al. Phase II neoadjuvant and immunologic study of B7-H3 targeting with enoblituzumab in localized intermediate- and high-risk prostate cancer. *J Clin Oncol*. (2018) 36:TPS5099. doi: 10.1200/JCO.2018.36.15_suppl.TPS5099
69. Lee P, Gujar S. Potentiating prostate cancer immunotherapy with oncolytic viruses. *Nat Rev Urol*. (2018) 15:235–50. doi: 10.1038/nrurol.2018.10
70. Bartlett DL, Liu Z, Sathaiah M, Ravindranathan R, Guo Z, He Y, et al. Oncolytic viruses as therapeutic cancer vaccines. *Mol Cancer*. (2013) 12:103. doi: 10.1186/1476-4598-12-103
71. Russell SJ, Barber GN. Oncolytic viruses as antigen-agnostic cancer vaccines. *Cancer Cell*. (2018) 33:599–605. doi: 10.1016/j.ccell.2018.03.011
72. Taguchi S, Fukuhara H, Homma Y, Todo T. Current status of clinical trials assessing oncolytic virus therapy for urological cancers. *Int J Urol*. (2017) 24:342–51. doi: 10.1111/iju.13325
73. Rogulski KR, Wing MS, Paielli DL, Gilbert JD, Kim JH, Freytag SO. Double suicide gene therapy augments the antitumor activity of a replication-competent lytic adenovirus through enhanced cytotoxicity and radiosensitization. *Hum Gene Ther*. (2000) 11:67–76. doi: 10.1089/10430340050016166
74. Freytag SO, Khil M, Stricker H, Peabody J, Menon M, DePeralta-Venturina M, et al. Phase I study of replication-competent adenovirus-mediated double suicide gene therapy for the treatment of locally recurrent prostate cancer. *Cancer Res*. (2002) 62:4968–76.
75. Freytag SO, Movsas B, Aref I, Stricker H, Peabody J, Pegg J, et al. Phase I trial of replication-competent adenovirus-mediated suicide gene therapy combined with IMRT for prostate cancer. *Mol Ther*. (2007) 15:1016–23. doi: 10.1038/mt.sj.6300120
76. Freytag SO, Barton KN, Zhang Y. Efficacy of oncolytic adenovirus expressing suicide genes and interleukin-12 in preclinical model of prostate cancer. *Gene Ther*. (2013) 20:1131–9. doi: 10.1038/gt.2013.40
77. Coffey MC, Strong JE, Forsyth PA, Lee PW. Reovirus therapy of tumors with activated Ras pathway. *Science*. (1998) 282:1332–4. doi: 10.1126/science.282.5392.1332
78. Phillips MB, Stuart JD, Rodríguez Stewart RM, Berry JT, Mainou BA, Boehme KW. Current understanding of reovirus oncolysis mechanisms. *Oncolyt Virother*. (2018) 7:53–63. doi: 10.2147/OV.S143808
79. Gujar SA, Pan DA, Marcato P, Garant KA, Lee PWK. Oncolytic virus-initiated protective immunity against prostate cancer. *Mol Ther*. (2011) 19:797–804. doi: 10.1038/mt.2010.297

80. Thirukkumaran CM, Nodwell MJ, Hirasawa K, Shi Z-Q, Diaz R, Luider J, et al. Oncolytic viral therapy for prostate cancer: efficacy of reovirus as a biological therapeutic. *Cancer Res*. (2010) 70:2435–44. doi: 10.1158/0008-5472.CAN-09-2408
81. Vidal L, Pandha HS, Yap TA, White CL, Twigger K, Vile RG, et al. A phase I study of intravenous oncolytic reovirus type 3 Dearing in patients with advanced cancer. *Clin Cancer Res*. (2008) 14:7127–37. doi: 10.1158/1078-0432.CCR-08-0524
82. Williams ES, Rodriguez-Bravo V, Chippada-Venkata U, De Ia Iglesia-Vicente J, Gong Y, Galsky M, et al. Generation of prostate cancer patient derived xenograft models from circulating tumor cells. *J Vis Exp*. (2015) 20:53182. doi: 10.3791/53182
83. van den Eertwegh AJM, Versluis J, van den Berg HP, Santegoets SJAM, van Moorselaar RJA, van der Sluis TM, 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) 13:509–17. doi: 10.1016/S1470-2045(12)70007-4
84. McNeel DG, Eickhoff JC, Wargowski E, Zahm C, Staab MJ, Straus J, et al. Concurrent, but not sequential, PD-1 blockade with a DNA vaccine elicits anti-tumor responses in patients with metastatic, castration-resistant prostate cancer. *Oncotarget*. (2018) 9:25586–96. doi: 10.18632/oncotarget.25387
85. Mercader M, Bodner BK, Moser MT, Kwon PS, Park ES, Manecke RG, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. *Proc Natl Acad Sci USA*. (2001) 98:14565–70. doi: 10.1073/pnas.251140998
86. Antonarakis ES, Kibel AS, Yu EY, Karsh LI, Elfiky A, Shore ND, et al. Sequencing of sipuleucel-T and androgen deprivation therapy in men with hormone-sensitive biochemically recurrent prostate cancer: a phase II randomized trial. *Clin Cancer Res*. (2017) 23:2451–9. doi: 10.1158/1078-0432.CCR-16-1780

**سرطان البروستاتا: الكشف المبكر، التشخيص، والتطورات في العلاج - مراجعة للبيانات المحدثة لمقدمي الرعاية الصحية.**

**الملخص:**

**الخلفية :**يُعتبر سرطان البروستاتا (PCa) أكثر أنواع السرطان تشخيصًا بين الرجال في الولايات المتحدة، وثاني سبب رئيسي للوفيات المرتبطة بالسرطان. تشمل خيارات العلاج القياسية استئصال البروستاتا الجذري والعلاج الإشعاعي لسرطان البروستاتا الموضعي، بينما يُستخدم علاج الإخصاء الهرموني للحالات المتكررة أو المتقدمة. ومع ذلك، يتطور معظم المرضى إلى سرطان البروستاتا النقيلي المقاوم للإخصاء(mCRPC) ، مع وجود خيارات علاجية محدودة تقدم تحسينات طفيفة في البقاء على قيد الحياة. وقد أظهرت العلاجات المناعية وعدًا في التصدي لهذا التحدي.

**الهدف :**تهدف هذه المراجعة إلى مناقشة التطورات الحالية في الكشف المبكر، التشخيص، وعلاج سرطان البروستاتا، مع التركيز على العلاج المناعي والتجارب السريرية الجارية.

**الطرق :**تم إجراء مراجعة شاملة للأدبيات لتحليل البيانات من التجارب السريرية الحديثة، مع التركيز على فعالية العلاجات الحالية مثل اللقاحات، ومثبطات نقاط التفتيش المناعية(ICIs) ، والعلاجات القائمة على الخلايا، والنُهج المناعية القائمة على الحمض النووي. كما تم استعراض التجارب السريرية الجارية في هذا المجال.

**النتائج :**أظهرت العلاجات المعتمدة من قِبل إدارة الغذاء والدواء الأمريكية (FDA) لعلاجmCRPC ، مثل الدوسيتاكسيل، والأبيراتيرون، وSipuleucel-T، فوائد في البقاء على قيد الحياة تتراوح بين 2-4 أشهر. كما أثبتت الأساليب العلاجية المناعية، بما في ذلك Sipuleucel-T، تحسين البقاء على قيد الحياة في التجارب السريرية. وهناك العديد من التجارب الجارية التي تحقق في توليفات جديدة من العلاجات المناعية، واللقاحات، والمُعدّلات المناعية لتعزيز فعالية العلاج.

**الخلاصة :**وفرت التطورات في العلاج المناعي أملًا جديدًا للمرضى المصابين بسرطان البروستاتا المتقدم. ومع ذلك، لا تزال تحسينات البقاء على قيد الحياة محدودة، وهناك حاجة إلى مزيد من الأبحاث لتحسين النهج العلاجية، لا سيما من خلال العلاجات التوليفية. كما يظل الكشف المبكر والأساليب التشخيصية الجديدة عاملين حاسمين في تحسين نتائج المرضى.

**الكلمات المفتاحية :**سرطان البروستاتا، سرطان البروستاتا النقيلي المقاوم للإخصاء، العلاج المناعي، الكشف المبكر، التجارب السريرية، اللقاحات، مثبطات نقاط التفتيش المناعية.