


Review

The Prostate Cancer Immune Microenvironment, Biomarkers and Therapeutic Intervention

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Simple Summary: Prostate cancer is the most commonly occurring internal malignancy in men. Immunotherapies are emerging as important cancer therapies, having been successfully applied to a range of solid tumour types. However, due to the highly immunosuppressive tumour microenvironment, these successes have not been replicated in prostate cancer. To aid in the selection of patients who would be responsive to immunotherapy, efforts are underway to identify biomarkers which may be indicative of a positive therapeutic response. This review provides an overview of the prostate tumour microenvironment, summarises the immunotherapy approaches being explored for use in prostate cancer, and examines the use of biomarkers for therapy selection.

Abstract: Advanced prostate cancers have a poor survival rate and a lack of effective treatment options. In order to broaden the available treatments, immunotherapies have been investigated. These include cancer vaccines, immune checkpoint inhibitors, chimeric antigen receptor T cells and bispecific antibodies. In addition, combinations of different immunotherapies and with standard therapy have been explored. Despite the success of the Sipuleucel-T vaccine in the metastatic, castrate-resistant prostate cancer setting, other immunotherapies have not shown the same efficacy in this population at large. Some individual patients, however, have shown remarkable responsiveness to these therapies. Therefore, work is underway to identify which populations will respond positively to therapy via the identification of predictive biomarkers. These include biomarkers of the immunologically active tumour microenvironment and biomarkers indicative of high neoantigen expression in the tumour. This review examines the constitution of the prostate tumour immune microenvironment, explores the effectiveness of immunotherapies, and finally investigates how therapy selection can be optimised by the use of biomarkers.

Keywords: prostate cancer; immunotherapy; predictive and prognostic biomarkers; tumour microenvironment; tumour immune microenvironment



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1. Introduction

Prostate cancer is the second most frequently diagnosed cancer, and the fifth leading cause of cancer death among men in 2020 [1]. For instance, in 2018 in the U.S there were 3,245,430 men living with prostate cancer. In the U.S in 2021 there will be an estimated

248,530 new diagnoses of prostate cancer, and 34,130 deaths [2]. Due to this high prevalence, prostate cancer screening, consisting of prostate specific antigen (PSA) detection and digital rectal exam, generally commences in men in their 50s. Prostate cancer is a biologically heterogeneous disease that produces variable clinical outcomes. Low- and intermediate-risk localised prostate cancer is generally treated with curative attempts with ablative therapies such as surgery and radiotherapy. Of those patients treated for primary disease, up to 30–40% will eventually fail, and the disease will manifest through biochemical recurrence (BCR) [3,4]. Of these BCR patients who are treated with hormonal therapies approximately 10–20% will develop castrate-resistant cancer within 5 years [5]. Metastatic, castrate-resistant prostate cancer (mCRPC) is a highly aggressive stage of the disease, and has a prognosis of 9–13 months' survival [5]. Due to this poor survival rate of mCRPC, alternate avenues of treatment are being investigated.

Prostate cancer tissue is composed of tumour cells and host components such as immune cells, stromal matrix and soluble factors (e.g., cytokines) with the host components referred to as the Tumour Immune Microenvironment (TIME). Within the TIME, crosstalk occurs between the immune cells, stromal cells, the non-cellular components and the tumour cells, resulting not only in the evolution of the TIME, but also playing a role in tumour progression, tumour clearance or treatment response. The TIME interacts with soluble factors secreted by the cancer cells, and in turn, also interacts with the tumour cells. Importantly, whilst providing structural support and contact with prostate cancer cells, the TIME also produces soluble factors, all of which combined can drive prostate cancer progression [6]. Traditionally, it is believed that tumour-intrinsic signalling pathways are oncogenic pathways, however, emerging evidence is showing that this signalling can also regulate the TIME and subsequently tumour immune escape [7,8]. In prostate cancer, this can include PI3K/PTEN/AKT signalling [9,10], TLR9 [11] and p53 loss of function [12], which drives the accumulation, expansion, infiltration and activation of MDSCs. However, immune cells within the prostate cancer TIME act as a double-edged sword, because across the various stages of the disease, the immune cells can also mediate their invasive capacity.

Immunotherapies have shown substantial benefit in other cancers, however, there have been challenges in overcoming the immunosuppressive tumour microenvironment of prostate cancer.

2. The Prostate Tumour Immune Microenvironment

Immune evasion is a hallmark of cancer and dysregulation of the immune microenvironment contributes to malignant progression in prostate cancer [13]. The prostate tumour microenvironment consists of three main compartments: the stroma, the tumour and the immune cells (Figure 1). Together, cellular populations, nutrients and signalling molecules generate a highly immunosuppressive tumour microenvironment.

2.1. The Stromal Compartment

The stromal compartment is inherently plastic and can rapidly respond to damage sustained by the adjacent epithelium. When responding to such damage, stromal cells are phenotypically and genotypically altered, and there is increased matrix remodelling and altered expression of repair-associated growth factors and cytokines. This state is known as reactive stroma [14,15]. In prostate cancer development, reactive stroma initiates during pre-malignant prostatic intraepithelial neoplasia, and co-evolves as the cancer develops [16]. Carcinoma-associated fibroblasts (CAFs) are the main type of cells present in reactive stroma and are central in mediating pro-survival signalling in cancer cells. In terms of the immune microenvironment, CAF proliferation has been shown to lead to the development of a fibrous stroma, which induces localized vasculature remodelling and a state of hypoxia and chronic inflammation [17]. Chronic inflammation is akin to a pre-cancerous state inducing re-modelling of the normal tissue environment, where NF- κ B signalling pathways play a defining role. Here, NF- κ B-controlled signalling networks modulate the expression of cascades of pro-inflammatory genes, particularly cytokines and

chemokines, and also regulate inflammasome formation. In response, immunosuppressive cell populations are recruited to the microenvironment, while cytotoxic T-cell function and dendritic cell maturation are inhibited [18–21]. The transcription factor (HIF-1) which is regulated by oxygen, is also overexpressed in prostate cancer, and is correlated to the clinical stage of the disease [22,23]. Importantly, hypoxia can mediate prostatic adenocarcinoma cell plasticity with the acquisition of a mesenchymal phenotype in a process known as epithelial–mesenchymal transition (EMT). This process can also contribute to immune escape via a loss of cell–cell recognition, as observed with decreased e-cadherin modulating the T-cell synapse which is required for an efficient immune response [24]. In addition, mesenchymal cells exhibit decreased MHC1 expression levels which promotes differentiation/recruitment of T-regulatory lymphocytes (Tregs), immature DCs and ultimately tumour immunosuppression [24].

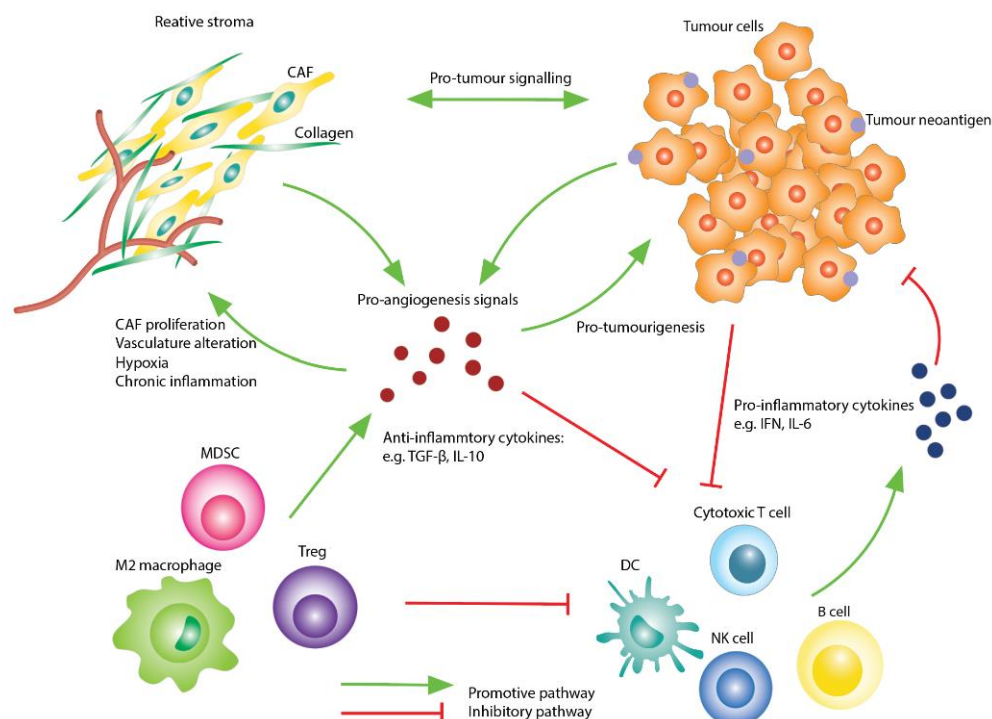


Figure 1. The tumour immune microenvironment of prostate cancer. The tumour microenvironment is composed of stroma, tumour cells and a variety of immune cells. The stromal components and tumour cells interact and promote a hypoxic and pro-tumour environment through cytokine production and pro-inflammatory signalling. As the immune cells infiltrate into the tumour microenvironment, immunosuppressive cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and M2 macrophages, suppress the anti-tumour activity of dendritic cells (DCs), cytotoxic T cells, natural killer (NK) and B cells, which together promote an immunosuppressive environment.

2.2. The Immune Cell Compartment

The prostate tumour microenvironment has altered levels of the various classes of immune cells compared to healthy prostate tissue. This includes tumour-associated macrophages (TAMs), T cells and neutrophils [25]. Interestingly, increased levels of inactive immune cells such as resting natural killer cells, naive B cells and resting dendritic cells are present, which may suggest that the prostate cancer microenvironment inhibits the activation of these cells [25].

The prostate cancer TIME is traditionally regarded as immunologically ‘cold’ due to its relatively low levels of infiltrating T lymphocytes [26]. This is in part due to the low tumour mutational burden observed in prostate tumours compared to tumours such as melanoma and renal cell carcinoma, thus reducing the presence of tumour neoantigens [25,27]. This, paired with the frequent loss or reduction in major histocompatibility complex (MHC)

class I and II expression in antigen-presenting cells, means that the number of anti-tumour T cells being attracted to the tumour is minimal [28–31]. Further contributing to the immunosuppressive microenvironment is the lack of afferent lymphatics to the prostate and the immunosuppressive properties of seminal fluid [32].

In prostate cancer, T cells are the major class of tumour-infiltrating lymphocytes. Higher numbers of infiltrating T cells have been correlated with better clinical outcomes in a variety of solid tumours, including bladder cancer, colorectal cancer, ovarian cancer and melanoma [33–36]. In contrast, the prognostic value of tumour T-cell infiltration is controversial, with both very low and high levels being associated with worse clinical outcomes in prostatectomy specimens [37–40]. This suggests that in cases with low levels of T cells infiltrating, the immune system has failed to mount an effective anti-tumour response. On the other hand, cases with high levels of T-cell infiltration may suggest that the T cells being recruited are able to function effectively. Alternatively, there may be a defect in recruiting the appropriate T-cell subpopulations. For example, these patients might have high infiltration of Tregs. Tregs play an important role in downregulating the cytotoxic T-cell response, and high levels of FOXP3+ Treg infiltration is a negative predictor of overall survival in a range of cancers [41]. High levels of FOXP3+ Tregs have been identified in prostate cancer tumour samples and peripheral blood samples, and may in part explain the dysfunction observed in the cytotoxic CD8+ T cells [42,43].

CD8+ T cells have potent cytotoxic activity and play a key role in anti-tumour immunity. The prognostic value of CD8+ T-cell infiltration in prostate cancer is inconclusive. Several studies have suggested that high CD8+ T-cell infiltration in the tumour epithelium has been reported to be associated with improved overall survival or lower risk of disease relapse and progression in prostatectomy specimens [44,45]. Another study concluded that higher CD8+ and lower programmed death ligand 1 (PD-L1) expression was associated with lower risk of biochemical recurrence and metastasis development [46]. However, others have shown that high levels of CD8+ T cells are associated with worse prognosis [47,48]. One of these studies hypothesised that the failure of high levels of CD8+ T cells to reduce disease recurrence may be due to T-cell exhaustion, and associated expression of PD-1. Interestingly, another study demonstrated that low levels of PD-L1, an immune-suppression marker and ligand of PD-1, combined with high levels of CD8+ T cells, was associated with improved prognosis [46]. This suggests that T-cell exhaustion may play a role in this finding, given the importance of the PD-1/PD-L1 axis in T-cell activation.

Myeloid-derived suppressor cells (MDSCs) and TAMs are key inflammatory cells which also contribute to the immunosuppressive prostate cancer TIME. MDSCs are activated by Tregs and exert their immunosuppressive functions by depletion of arginine and tryptophan in the surrounding tissue. Ultimately, this leads to T-cell cell-cycle arrest and decreased expression of T-cell receptors [49,50]. TAMs can be stratified into two distinct subpopulations, however, the majority of TAMs present in prostate cancer are M2-like, which are associated with an anti-inflammatory phenotype [51]. The presence of M2-like TAMs in both epithelial and stromal compartments is associated with tumour aggressiveness and poorer patient outcomes [52,53].

2.3. Cytokines and Signalling Molecules

A plethora of cytokines are present in the TIME and play an important role in promoting tumorigenesis and regulating the immunosuppressive environment. One example is transforming growth factor- β (TGF- β). In healthy systems, TGF- β acts as a tumour suppressor, where it inhibits proliferation and induces apoptosis. However, when overexpressed in cancers, such as prostate cancer, TGF- β becomes a potent promoter of tumour invasiveness and metastasis [54,55]. One way it mediates this is through promotion of tumour immune evasion through suppression of proliferation and differentiation of lymphocytes, natural killer cells and macrophages [56,57]. On the other hand, anti-tumour cytokines, such as type I interferon (IFN), and their respective signalling pathways, are often suppressed in prostate cancer, especially in the metastatic state [58]. As IFN is important to the coordina-

tion of the immune response, the reactivation of the pathway with therapy may promote long-term anti-tumour immunity.

3. Immunotherapy Strategies in Prostate Cancer

Immunotherapy aims to enhance the adaptive immune response, either through enhancing specificity or promoting stronger activation against the tumour. This approach has found success in a range of cancers. However, the immunologically ‘cold’ nature of prostate cancer has made the development of effective immunotherapies more challenging. Clinical trials currently investigating the use of immunotherapies in prostate cancer patients are summarized in Supplementary Table S1.

3.1. Cancer Vaccines

One class of immunotherapies is cancer vaccines. Cancer vaccines prime the patient’s immune system to recognise tumour-associated antigens (Figure 2A). Numerous types of cancer vaccines have been trialled in the prostate cancer setting, including autologous and allogeneic cellular vaccines to stimulate the function of antigen presenting cells, DNA and peptide vaccines which deliver engineered nucleic acids mimicking prostate tumour antigens, and oncolytic virus vaccines which cause direct lysis of tumour cells allowing for the release of a broad range of tumour antigens [59].

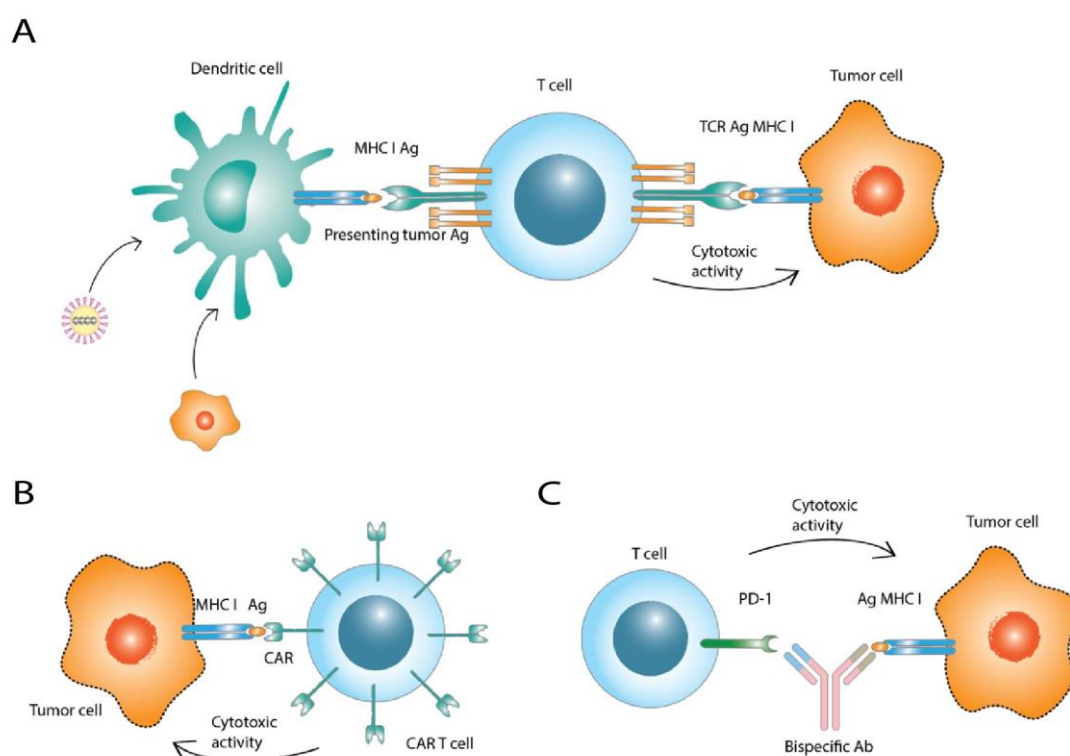


Figure 2. Immunotherapy Strategies in Prostate Cancer. Immunotherapy aims to enhance the adaptive immune response by enhancing specificity or promoting stronger activation against the tumour. **(A)** Cancer vaccines involve vaccination of the patient with tumour peptides, allogeneic whole tumour cells or autologous DCs as vehicles for delivery of the tumour antigen, priming the patient’s immune system to recognize the tumour-associated antigens. **(B)** Chimeric Antigen Receptor T Cells (CAR-T) are genetically modified T cells which express a patient antigen-specific chimeric receptor combining both antibody specificity and T-cell effector and regulatory functions. **(C)** Bispecific antibodies (BiTEs) are designed to target the CD3 protein through an effector arm and a tumour antigen via a target arm, which promotes the interaction between tumour cells and CD8⁺ T cells, resulting in tumour cell death.

Sipuleucel-T is the only FDA-approved immunotherapy for mCRPC. Sipuleucel-T is an autologous cellular cancer vaccine which targets the immune system against prostatic acid phosphatase [60]. Sipuleucel-T treatment significantly increased median overall survival in mCRPC patients [61,62]. Of note, the greatest survival benefits were observed in patients with lower PSA [63]. This highlights that treatment may be more beneficial in the early disease stages, as newly activated cytotoxic T cells have more time to function [64,65]. The importance of an activated immune response is further highlighted by the fact that patients treated with Sipuleucel-T exhibited a 3-fold increase in the presence of activated effector T cells in the tumour microenvironment [64].

Additional vaccines which exhibit signs of efficacy in prostate cancer include PROSTVAC, GVAX and DCVAC/PCa. PROSTVAC is a virus-based vaccine which targets PSA and employs a triad of co-stimulatory molecules (TRICOM; CD-80, ICAM-1, LFA-3) which aid T-cell function, ultimately eliciting a robust immune response [66]. Despite promising initial results in mCRPC, other trials have failed to demonstrate its associated benefits as a monotherapy [67,68]. Similarly, despite promising results of improved patient survival in phase I and II trials, phase III trials with the allogenic GVAX in mCRPC demonstrated poor results and were terminated early [69–71].

3.2. Immune Checkpoint Inhibitors

In order to prevent autoimmunity, healthy cells display proteins known as immune checkpoint molecules. When a T cell binds these, an ‘off’ signal is sent to prevent T-cell-mediated destruction of the healthy cell. In cancer, however, these immune checkpoints are often upregulated and enhance immune evasion by the tumour. Immune checkpoint inhibitor (ICIs) monoclonal antibodies work by stopping this ‘off’ signal, and therefore allow the tumour to be targeted by the T cells (Figure 3) [72,73].

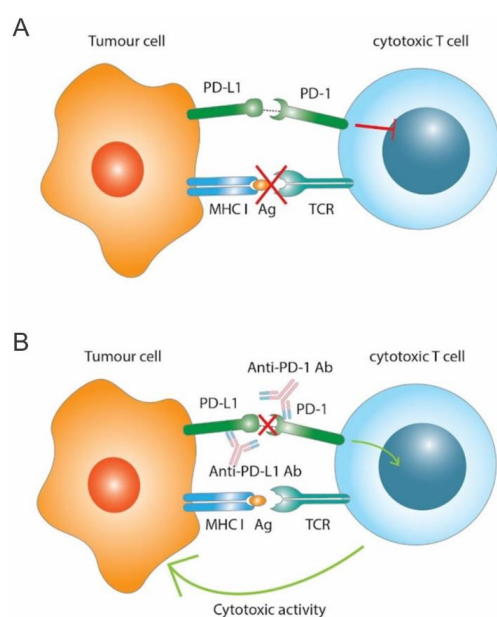


Figure 3. The PD-1 and PD-L1 interaction and its inhibition by immunotherapy. (A) PD-1 is expressed on cytotoxic T cells and PD-L1 is expressed on tumour cells. The T-cell receptor (TCR) binds to the tumour antigen (Ag) presented on the tumour cell surface by major histocompatibility complex class I (MHC I). When PD-L1 binds to PD-1, the activity of the cytotoxic T cell will be suppressed and the interaction between TCR and MHC I is blocked. The subsequent immune checkpoint activation can cause apoptosis of cytotoxic T cells. (B) Inhibition of PD-1 and PD-L1 activation by anti-PD-1/PD-L1 immunotherapy. Immune checkpoint inhibitors are antibodies that can specifically bind to the immune checkpoint molecules, such as PD-1 and its ligand PD-L1. This binding blocks the interaction between PD-1 and PD-L1 and promotes the anti-tumour activity of the cytotoxic T cell.

Ipilimumab is an ICI that targets CTLA-4, which has been trialled in mCRPC. In mCRPC patients who had failed docetaxel therapy, treatment with ipilimumab, alone or in combination with radiation therapy, resulted in increased median progression-free survival. However, no benefit to overall survival was observed [74]. The benefit was stronger in patients with favourable prognostic factors, especially the absence of visceral metastases. However, a follow-up study in asymptomatic or minimally symptomatic mCRPC patients without visceral metastases did not demonstrate any significant benefit to overall survival [75]. Similarly, anti-PD-1 and anti-PD-L1 agents, such as pembrolizumab, avelumab and nivolumab have been trialled in heavily pre-treated mCRPC. In a phase I trial of nivolumab, an objective response was not observed, while a phase 1 trial of avelumab reported that 39% of patients had stable disease at >24 weeks [76]. In the same clinical settings, pembrolizumab treatment demonstrated an objective response rate of 17% [77].

3.3. Chimeric Antigen Receptor T Cells

Chimeric Antigen Receptor T Cells (CAR-T) are genetically enhanced T cells modified to engage with specific patient tumour antigens [78], (Figure 2B). This approach has found success in haematological cancers but has shown limited efficacy in the treatment of solid tumours. CAR-T cells targeting PSMA have been developed for the treatment of prostate cancer. This approach has had limited success in clearing tumours, but has demonstrated tumouristatic effects in some preliminary studies [79,80]. Newer generations of CAR-T therapy are integrating elements to counteract the immunosuppressive environment. One study looking at PSMA-directed/TGF- β -insensitive CAR-T cells has reported promising initial results [81,82].

3.4. Bispecific Antibodies

Bispecific antibodies consist of two monoclonal antibodies known as bispecific T-cell engagers (BiTEs) attached by a flexible linker (Figure 2C). These antibodies conjugate simultaneously with tumour antigens and the T cell to promote cytotoxic 4T-cell trafficking and function [83]. A phase I study using the BiTE Pasotuxizumab, which engages CD3 on T cells and PSMA, in androgen deprivation therapy (ADT) and chemotherapy-refractory mCRPC reported positive results, with 88% of patients exhibiting a PSA response in a dose-dependent manner. Interestingly, this resulted in a long-term response in 12.5% of the patients [84]. Another PMSA targeting BiTE, AMG 160, has resulted in a greater than 50% decline in PSA in about one-third of patients, with two patients showing a partial response and eight patients a stable disease (NCT03792841). Trispecific approaches are also being investigated, as demonstrated by the phase I study investigating the safety profile of HPN24 in mCRPC patients who have progressed in systemic therapy (NCT03577028). This is a CD3-PSMA-targeting monoclonal antibody with an albumin-binding domain for extending the half-life of the compound.

3.5. Combination Therapy Strategies

Given the lack of success in finding a single-agent immunotherapy for prostate cancer, the focus has shifted to identifying combination therapies. This includes combining with standard therapies as well as identifying useful dual-immunotherapy approaches.

As chemotherapy is one of the main treatments for cancer, there is strong interest in combining it with immunotherapies, and this approach has yielded early promise. A study of nivolumab plus docetaxel in chemotherapy-native mCRPC patients with ongoing ADT therapy reported an objective response rate of 40% and a median overall survival of 18 months following treatment [85]. Interim analysis from a second study of pembrolizumab and docetaxel and prednisone in mCRPC previously treated with ADT reported an objective response rate of 23.1% [86]. It has been suggested that chemotherapy releases neoantigens from the tumour upon cell death and these neoantigens promote the activation of CD8⁺ cells, thus promoting the efficacy of immunotherapies.

Like chemotherapy, poly-ADP ribose polymerase (PARP) inhibitors promote the necrotic release of tumour neoantigens. Additionally, like chemotherapy, their effectiveness as part of a combination therapy with immunotherapies has also been investigated. Most promisingly, treatment with durvalumab and PARP inhibitor, oliparib, in mCRPC patients who had progressed with androgen deprivation therapy reported that 53% of patients had a radiographic and/or PSA response [87]. An interim analysis of a second study reports a PSA response in 9%, and a partial response in 8% of those with measurable disease in mCRPC patients previously treated with docetaxel, following treatment with pembrolizumab and oliparib [88].

Another combination of interest is treatment with androgen-deprivation therapy and immunotherapies. It has been shown that ADT results in increased trafficking of anti-tumour immune cells, and as such, ADT may enhance the effectiveness of immunotherapies [89]. Across multiple studies, treatment with pembrolizumab in patients with mCRPC who had previously been treated with ADT reported a disease control rate of between 35 and 51%, however, one study did not show any benefit of therapy [90–92].

The combination of anti-angiogenic therapies with those of immunotherapies has also recently attracted interest. Here, it has been shown that tumour angiogenesis-targeted agents such as Sunitinib can induce a pro-immunogenic state in the tumour by inducing miR-221 expression. This is then thought to cause an induction of an interferon-related gene signature in the prostate cancer cells supported by miR-221 upregulation [93]. These data would suggest that the treatment combination of tumour kinase inhibitors (TKIs) and immune-based approaches might be a promising avenue to explore with TKIs treatment, inducing an immune responsive environment due to boosting miR-221 expression levels.

One of the main immunotherapy combination strategies under investigation is co-treatment with anti-PD-1 and anti-CTLA-4 agents. A study on asymptomatic or minimally symptomatic mCRPC patients not previously treated with ipilimumab and nivolumab showed an objective response rate of 26% at interim reporting, while in those who had progressed with chemotherapy, the objective response rate was 10% [94,95]. Ipilimumab and nivolumab have also been trialled in a subgroup of mCRPC patients positive for AR-V7. Outcomes tended to be better in a subset of patients, specifically in those with DNA damage repair mutations, however this was only significantly different in terms of progression-free survival [96]. This highlights the importance of biomarkers to enable selection of patients who will respond to therapy.

4. Immune Therapy Biomarkers

Metastatic prostate cancer presents a range of challenges to treatment with immunotherapy. Early studies on the use of these agents in prostate cancer have been characterised by a lack of response in a high percentage of patients. However, there is evidence that some subpopulations are highly responsive to immunotherapy. Therefore, it will likely be pertinent to identify improved molecular biomarkers that will allow for the selection of those patients that are most likely to benefit.

4.1. Immune Checkpoint Molecules as Biomarkers

ICI directly targets the immune checkpoint molecules; therefore, it follows that the expression of such molecules may be an important determinant of therapy response. PD-L1 levels have been shown to have varying degrees of association with therapy, with expression correlated with ICI response in melanoma but not in squamous cell carcinoma and non-small-cell lung cancer [97–99]. The expression of PD-L1 and PD-1 is low in healthy prostate tissue, present in around 0.5% and 1.5% of cases, respectively, and is increased in prostate cancer cases, with one study reporting positive staining in 13.2% and 7.7%, respectively [100]. Although dynamic expression is observed, high PD-L1 expression is associated with prostate cancer aggressiveness, with 61.7% of aggressive primary prostate tumours and 50% of CRPC expressing PD-L1 [101,102]. Despite this, PD-L1 expression does not strongly predict response to ICI in prostate cancer. A study examining pembrolizumab

efficacy in PD-L1-positive versus PD-L1-negative cohorts of treatment-refractory mCRPC patients reported objective response rates of 5% and 3%, respectively [103]. This suggests that other factors contribute to the effectiveness of anti-PD-L1 therapy in these patients and that simple measurement of PD-L1 levels in tissue may not be an effective biomarker of treatment response.

4.2. Genetic Variations as Biomarkers

Genetic mutations present in a tumour can be a powerful predictor of therapy response. Prostate cancer has traditionally been difficult to target with immunotherapy due to its low number of mutations and therefore presence of fewer neoantigens, especially in relation to other highly mutated cancers such as melanoma and lung cancer [27].

Patients with high microsatellite instability (MSI-H) or mismatch-repair-deficient (MMRd) tumours have a high tumour mutational burden (TMB) and increased presence of tumour neoantigens, and are therefore strong candidates for immune checkpoint inhibitor immunotherapy [104,105]. The ICI pembrolizumab is FDA-approved for use in metastatic/unresectable MSI-H/MMRd tumours, however it is only effective in a subset of prostate cancer patients [106]. A retrospective study reported durable clinical benefit in 45.5% of MSI-H/MMRd prostate tumours treated with anti-PD1 or anti-PDL1 agents, either as monotherapy or combination therapy [107]. In addition, a second study observed increased overall survival in patients with higher-than-median TMB following ICI therapy [94].

Increased neoantigen expression and higher TMB is also associated with mutations in specific genes, particularly those involved in DNA damage repair such as BRCA1/2, ATM, MSH2, POLE and CDK12 [108–111]. A comprehensive analysis of POLE/POLD1 mutation in multiple cancer types reported that 1.8% of primary prostate tumours had mutations in one or both genes, correlating with a significantly higher TMB. Patients with POLE/POLD1 mutations have been shown to have longer overall survival following ICI treatment across all tumour types, with POLE/POLD1 reported as an independent risk factor for identifying prostate cancer patients who benefited from ICI [110].

CDK12 mutations are observed in 1.2% of primary prostate tumours, rising to 6.9% of mCRPC. A unique mutation signature was observed for CDK12-deficient tumours, differentiating it distinctly from MMRd prostate tumours [105]. PSA decline following ICI treatment has been observed in patients with CDK-12 mutations in a number of studies [105,111–113]. Interestingly, there was no difference observed between patients with mono- versus bi-allelic mutations in PSA decline, however, PSA-progression-free survival was marginally improved for those with biallelic mutations [113]. These retrospective studies indicate that prospective randomized trials incorporating genomic screening and selection of patients with MSI-H/MMRd prostate tumours with higher-than-median TMB or CDK12 mutations would be highly informative as to the usefulness of treating these patients with ICI-based therapies. At the present time, this combined strategy would appear to be the most promising of the genomic-based approaches to enhance ICI response rates in prostate cancer.

4.3. Peripheral Immune-Based Biomarkers

Traditionally, mutational status of tumours has been assessed via biopsy, however biopsy acquisition is an invasive procedure that is not always practical for cancer patients. In contrast, blood samples are relatively easy to obtain and are being investigated as a potentially rich source of biomarkers.

One such source of biomarkers is circulating tumour DNA (ctDNA). ctDNA-based assays are becoming increasingly popular as an alternative to biopsy for the detection of actionable genetic mutations. A case series reported the detection of MSI-H status in two prostate cancer patients via ctDNA samples. Importantly, they were able to monitor the response to treatment by using the frequency of variant alleles in blood samples as a readout, since it can be repeated for real-time monitoring of tumour clones [114]. This

demonstrates the utility of such technologies as biomarkers of potential treatment efficacy and in monitoring response.

Cytokines are key regulators of the immune response; therefore, several studies have explored cytokine levels at baseline and their correlation with response to immunotherapy treatment, in particular treatment with cancer vaccines. One study suggests that higher baseline circulating interleukin-10 (IL-10) levels in CRPC patients may be negatively associated with response to treatment with a DNA vaccine encoding prostatic acid phosphatase [115]. A second study demonstrated that higher baseline levels of interleukin-6 (IL-6) was associated with shorter survival in patients treated with the personalized peptide vaccine [116].

The presence of various immune cell populations, such as T cells and MDSCs, have also been investigated for their merit as predictive biomarkers for clinical response to immunotherapy. Lower baseline levels of PD-1⁺Tim-3^{NEG} CD4 effector memory cells and higher baseline PD-1^{NEG}Tim-3⁺ CD8 and CTLA-4^{NEG} Tregs in mCRPC predicted improved survival following treatment with PROSTVAC and ipilimumab [117]. Similarly, higher baseline levels of CD4⁺CTLA-4⁺ T cells predicted improved survival when treated with GVAX and ipilimumab. In contrast, CRPC patients with higher CD14⁺HLA-DR-monocytic MDSCs had worse survival following treatment [118]. There is also evidence that early changes in circulating immune cells can be used to monitor the response and adjust treatments accordingly, as a study reported that in mCRPC patients treated with DCVac and docetaxel an on-treatment decrease in MDSC independently predicted disease-specific survival [119].

5. Conclusions

As the second most commonly diagnosed cancer in males, prostate cancer is a major health concern. In particular, metastatic, castrate-resistant prostate cancer patients have poor survival rates. Immunotherapies have seen success in many other cancers; however, the treatment of prostate cancer through these methods suffers due to the immunosuppressive tumour microenvironment. Recent studies have helped elucidate many of the immune-suppressive mechanisms at play in prostate cancer. This knowledge, in combination with biomarkers, can help inform treatment selection and allow these mechanisms to be overcome through combination therapy strategies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/uro2020010/s1>, Table S1: Current immunotherapy clinical trials in prostate cancer [120–159].

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Abbreviations

ADT (Androgen-deprivation therapy); AKT (Akt strain transforming); ATM (ataxia telangiectasia mutated); BCR (biochemical recurrence); BRCA1 (Breast Cancer gene 1); BRAC2 (Breast Cancer Gene 2); CAF5 (carcinoma-associated fibroblasts); CAR-T (Chimeric antigen receptor T cells); CD3 (cluster of differentiation 3); CD38 (cluster of differentiation 38); CD39 (cluster of differentiation 39); CD73 (cluster of differentiation 73); CDK12 (cyclin-dependent kinase 12); CRPC (castrate-resistant prostate cancer); CtDNA (circulating tumour DNA); (CTLA-4 cytotoxic T-lymphocyte-associated protein 4); DCs (dendritic cells); DLL3 (delta-like ligand 3); FDA (Food and Drug Administration); FOXP3 (Forkhead box P3); DNA (deoxyribonucleic acid); ICAM-1 (intercellular adhesion molecule-1); ICI (immune checkpoint inhibitor); IFN (interferon); IL-6 (interleukin 6); IL-8 (interleukin 8); IL-10 (interleukin 10); LFA-3 (Lymphocyte Function-Associated Antigen 3); mCRPC (metastatic, castrate-resistant prostate cancer); MDSCs (myeloid-derived suppressor cells); MHC (major histocompatibility complex); MMRd (mismatch repair deficient); MSH-I (high microsatellite instability); NK (natural killer cells); MSH2 (MutS homolog 2); PAP (prostatic acid phosphatase); PARP (poly-ADP ribose polymerase); (PD-1 (Programmed cell death protein 1); PD-L1 (Programmed death-ligand 1); PI3K (phosphoinositide 3-kinases); POLD1 (DNA Polymerase Delta 1); POLE (DNA polymerase epsilon); PSA (prostate-specific antigen); PSMA (Prostate Specific Membrane Antigen); PTEN (phosphatase and tensin homolog); STEAP1 (six-transmembrane epithelial antigen of prostate); TAMS (tumour-associated macrophages); TCR (T-cell receptor); TGF- β (transforming growth factor- β); TGF- β RII (transforming growth factor- β receptor II); TIME (tumour immune microenvironment); TKI (tyrosine kinase inhibitor); Tregs (regulatory T cells); Tumour mutational burden (TMB)

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