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LEADING ARTICLE

Evolving Role of Immunotherapy in Metastatic Castration Refractory Prostate Cancer

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Abstract

Immunotherapies have shown remarkable success in the treatment of multiple cancer types; however, despite encouraging preclinical activity, registration trials of immunotherapy in prostate cancer have largely been unsuccessful. Sipuleucel-T remains the only approved immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer based on modest improvement in overall survival. This immune evasion in the case of prostate cancer has been attributed to tumor-intrinsic factors, an immunosuppressive tumor microenvironment, and host factors, which ultimately make it an inert 'cold' tumor. Recently, multiple approaches have been investigated to turn prostate cancer into a 'hot' tumor. Antibodies directed against programmed cell death protein 1 have a tumor agnostic approval for a small minority of patients with microsatellite instability-high or mismatch repair-deficient metastatic prostate cancer. Herein, we present an overview of the current immunotherapy landscape in metastatic castration-resistant prostate cancer with a focus on immune checkpoint inhibitors. We describe the results of clinical trials of immune checkpoint inhibitors in patients with metastatic castration-resistant prostate cancer; either as single agents or in combination with other checkpoint inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, tyrosine kinase inhibitors, novel hormonal therapies, chemotherapies, and radioligands. Finally, we review upcoming immunotherapies, including novel monoclonal antibodies, chimeric-antigen receptor (CAR) T cells, Bi-Specific T cell Engagers (BiTEs), therapies targeting the adenosine pathway, and other miscellaneous agents.

1 Introduction

Immunotherapies have changed the treatment landscape of cancer but have historically shown limited efficacy in prostate cancer, which is generally considered an immunologically cold tumor [1]. This immune unresponsiveness is attributed to a combination of intrinsic factors in prostate cancer, its immunosuppressive microenvironment, and host physiological factors such as age and hormonal influence [1]. Multiple tumor-intrinsic factors, such as loss of PTEN,

Key Points

The field of immunotherapy in prostate cancer has lagged behind other cancer types where multiple immunotherapeutic agents have been approved over the last decade.

Sipuleucel-T is the only immunotherapy approved in the setting of metastatic prostate cancer, and is associated with modest survival benefit.

Based on the results of early-phase trials of several novel immunotherapy-based regimens, it is likely that the treatment paradigm of metastatic castration refractory prostate cancer is going to be revolutionized in the near future. Some of the promising agents or regimens include the combination of immune check point inhibitors with cabozantinib or poly(ADP-ribose) polymerase (PARP) inhibitors, novel radioimmune agents, monoclonal antibodies, chimeric-antigen receptor (CAR) T cells, and Bi-Specific T-cell Engagers (BiTEs).

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altered interferon-1 signaling, decreased major histocompatibility complex (MHC) class I (MHC-1) expression, low tumor-associated antigen expression, low tumor mutational burden, and decreased incidence of DNA damage repair defects, make prostate cancer immunologically inert [1]. Therefore, a huge focus is being placed on the development of novel immunotherapy in the form of novel combinatorial regimens.

Herein, we review the role of immunotherapy in the treatment of metastatic castration-resistant prostate cancer (mCRPC). We begin with a discussion of vaccine-based approaches, followed by an examination of ongoing investigations of immune checkpoint inhibitors as monotherapies and in novel therapeutic combinations. We conclude with a summary of updates on novel agents, which will likely influence the future of immunotherapy in mCRPC. Selected ongoing clinical trials are summarized in Table 1, and Fig. 1 provides a synopsis of the mechanisms of action of various immune agents.

2 Early Immunotherapies: Cancer Vaccines

Previous immunotherapies for mCRPC consisted primarily of the cancer treatment vaccines PROSTVAC and Sipuleucel-T (Provenge®). Although not designed to be curative or preventative agents, these vaccine treatments are believed to engage the immune system and induce a cell-mediated response, driven primarily by T cells, against pre-existing prostate cancer.

2.1 PROSTVAC

PROSTVAC is a genetically engineered poxvirus that contains transgenes for prostate-specific antigen (PSA) and a synergistic triad of T-cell costimulatory molecules, collectively designated as TRICOM, which includes ICAM-1 (CD54), B7.1 (CD80), and LFA-3 (CD58) [2–4]. This unique approach induces T-cell activation with the PSA epitope [5, 6], followed by an enhancement of antitumor activity upon engagement of TRICOM [4].

In a phase I study of 42 mCRPC patients, PROSTVAC treatment led to an increase in the proportion of active PSA-specific T cells, and was associated with a low-toxicity profile of erythema, tenderness, and vesicle formation at the site of injection [7]. In a second phase I trial of 15 mCRPC patients, PSA-specific immune responses were observed in four of six HLA-A2 + patients, and a decrease in PSA velocity was seen in 9 of 15 patients [8]. A phase II trial randomized 125 minimally symptomatic mCRPC patients 2:1 to receive PROSTVAC or a control vector. The primary endpoint of progression-free survival (PFS) was similar in both groups (stratified log-rank p value = 0.6). However, a significant improvement in median overall survival was observed (OS; 25.1 months vs. 16.6 months; hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.37–0.85; $p = 0.0061$). Again, PROSTVAC was well-tolerated, with low-grade adverse events (AE) of fatigue, fever, and nausea [9].

This improvement in OS led to a phase III study to further investigate these findings [10]. A total of 1297 mCRPC patients were randomized to receive PROSTVAC (arm V, $n = 432$), PROSTVAC plus granulocyte–macrophage colony-stimulating factor (GM-CSF; arm VG, $n = 432$), or placebo (arm P, $n = 433$), with a primary endpoint of OS and secondary endpoints of patients alive without the following events at 6 months: radiographic progression, pain progression, chemotherapy initiation, or death [10]. The trial was terminated prematurely as no significant effect on median OS was identified (arm V: 34.4 months; arm VG: 33.2 months; arm P: 34.3 months). Compared with placebo, the HR for Arm V was 1.01 (95% CI 0.84–1.20; $p = 0.47$), and 1.02 (95% CI 0.86–1.22; $p = 0.59$) for Arm VG. There was also no significant difference in the percentage of patients alive without the above-mentioned events (arm V: 29.4%; arm VG: 28.0%; arm P: 30.3%) [10].

2.2 Sipuleucel-T

Sipuleucel-T (Provenge®) is an autologous cellular immunotherapy consisting of peripheral blood mononuclear cells enriched for dendritic cell fraction, which are activated ex vivo with PA2024 (prostatic acid phosphatase and granulocyte-stimulating factor fusion protein) and then reinfused into the patient to stimulate antigen-specific T cells [11].

Given the promising findings in early-phase studies, phase III trials were initiated. In the placebo-controlled D9901 trial, 127 patients with mCRPC were randomized in a 2:1 ratio to receive sipuleucel-T ($n = 82$) or placebo ($n = 45$). The results demonstrated an improved median OS with sipuleucel-T when compared with placebo (25.9 months vs. 21.4 months; HR 1.71, 95% CI 1.13–2.58; $p = 0.01$). Another identical trial, D9902A, was stopped before the availability of survival results based on initial disease progression results in D9901. In a pooled analysis of both D9901 and D9902A, sipuleucel-T showed an improved median OS compared with placebo (23.2 months vs. 18.9 months; HR 1.50, 95% CI 1.10–2.05; $p = 0.011$) [12]. However, these studies did not show a significant improvement in time to disease progression, which was the primary endpoint in both trials. Therefore, a placebo-controlled, phase III study, IMPACT, was conducted with OS as the primary endpoint [13]. Overall, 512 mCRPC patients were randomized in a 2:1 ratio to sipuleucel-T ($n = 341$) or placebo ($n = 171$) [13]. Sipuleucel-T demonstrated a significant improvement in median OS compared with placebo (25.8 months vs. 21.7 months; adjusted HR 0.78, 95% CI 0.61–0.98; $p = 0.03$). Again, no differences with objective or clinical disease progression were observed

Table 1 Selected ongoing immunotherapy clinical trials in patients with castration-resistant prostate cancer

NCT number (acronym)	Phase	*N*	Intervention/treatment	Randomized?	Notes	Expected end date
Vaccine						
NCT00583024 (APP22)	II	66	AdPSA	No	PSA AdV vaccine	July 2021
NCT03481816	I	18	ETBX-071 + ETBX-061 + ETBX-051	No	ETBX-071 is a PSA AdV vaccine. ETBX-061 is a MUC1 AdV vaccine. ETBX-051 is a brachyury AdV vaccine	January 2025
NCT01867333	II	57	PROSTVAC + enzalutamide Enzalutamide	Yes	PROSTVAC is a viral vector that expresses PSA and three co-stimulatory molecules	January 2021
Vaccine + immune checkpoint inhibitor						
NCT04382898 (PRO-MERIT)	I/II	80	W_pro1 W_pro1 + goserelin W_pro1 + cemiplimab (anti-PD-1) + goserelin	Yes	W_pro1 is an mRNA-liposome complex of five antigens Cemiplimab (anti-PD-1)	July 2023
NCT02933255	I/II	29	PROSTVAC + nivolumab	No		August 2022
NCT03493945	I/II	113[a]	BN-Brachyury + M7824 BN-Brachyury + ALT-803 BN-Brachyury + ALT-803 + epacadostat	Yes	M7824 is an anti-PD-L1/TGFβ mAb. ALT-803 is an IL-14 agonist	December 2022
NCT02616185	I	160	PF-06753512 (VBIR-1) + PF-06801591 + sunitinib	No	PF-06753512 is a combination of AdC68, plasmid DNA, tremelimumab (anti-CTLA-4 mAb). PF-06801591 is an anti-PD-1 mAb	February 2023
NCT03815942 (ADVANCE)	II	36	ChAdOx1-MVA 5T4 + nivolumab	No	The recombinant viruses ChAdOx1 and MVA, which express 5T4 fetal oncoprotein	May 2021
Radionuclide + immune checkpoint inhibitor						
NCT04071236	I/II	90	Radium-223 Radium-223 + nedisertib Radium-223 + nedisertib + avelumab	Yes	Nedisertib is a DNA-PK inhibitor that interferes with the non-homologous end-joining pathway	March 2021
NCT04109729 (Rad2Nivo)	I/II	36	Radium-223 + nivolumab	No		June 2024
NCT03658447 (PRINCE)	I/II	37	177Lu-PSMA + pembrolizumab	No	177Lu-PSMA is a conjugate of a PSMA ligand and a β-emitting radioisotope lutetium Lu 177	October 2021
NCT03805594	I	30	177Lu-PSMA + pembrolizumab	No		June 2021
Adenosine A_{2A} receptor agonist combination						
NCT02740985	I	307[a]	AZD4635 AZD4635 + durvalumab AZD4635 + enzalutamide AZD4635 + abiraterone AZD4635 + durvalumab + oleclumab AZD4635 + docetaxel	No	AZD4635 is an A2AR antagonist. Oleclumab is an anti-CD73 mAb, CD73 converts AMP to adenosine	March 2021
NCT03629756	I	44[a]	AB928 (anti-A2AR) + AB122 (anti-PD-1)	No	AB928 is an A2AR antagonist. AB122 is an anti-PD-1 mAb	September 2021
NCT03549000	I	344[a]	NZV930 NZV930 + PDR001 NZV930 + NIR178 NZV930 + PDR001 + NIR178	No	NZV930 is an anti-CD73 mAb. PDR001 is an anti-PD-1 mAb. NIR178 is an A2AR antagonist	February 2022

Table 1 (continued)

NCT number (acronym)	Phase	*N*	Intervention/treatment	Randomized?	Notes	Expected end date
NCT04306900	I	152[a]	TTX-030 + budigalimab + docetaxel	Yes	TTX-030 is an anit-CD39 mAb, CD39 converts ATP to ADP. Budigalimab is an anti-PD-1 mAb	December 2022
Single and combination immune checkpoint inhibitors						
NCT03570619 (IMPACT)	II	40[a]	Nivolumab + ipilimumab	No	For patients with CDK12 mutations	September 2021
NCT03204812	II	27	Durvalumab + tremelimumab	No	Anti-PD-1 and anti-CTLA-4	June 2020
NCT04104893 (CHOMP)	II	30	Pembrolizumab	No	For patients with CDK12, MLH1, MSH2, MLH3, PMS1, MSH6, and PMS2 mutations or MSI-H status	March 2023
NCT03040791 (ImmunoProst)	II	29[a]	Nivolumab	No	For patients with germline or somatic BRCA1, BRCA2, ATM, PTEN, CHEK2, RAD51C, RAD51D, PALB2, MLH1, MSH2, MSH6, PMS2 mutations	July 2020
NCT03385655	II	500	Durvalumab + tremelimumab Other non-immunotherapy arms: ipatasertib, CFI400945, darolutamide, savolitinib, carboplatin, adavosertib	No	Large trial with treatment selection based on liquid biopsy genomics. CFI400945 is a PLK4 inhibitor	December 2021
Other immune checkpoint inhibitor combinations						
NCT01688492	I/II	57	Ipilimumab + abiraterone	No		September 2020
NCT03338790 (CheckMate 9KD)	II	330	Nivolumab + rucaparib Nivolumab + docetaxel Nivolumab + enzalutamide	No		November 2021
NCT04159896	II	49	CEP-11981 + nivolumab	No	CEP-11981 is a pan-TKI with selectivity for VEGFR and TIE2.	March 2022
NCT04388852	I	80[a]	Valemetostat (DS3201) + ipilimumab	No	Valemetostat is an inhibitor of both EZH1 and EZH2	January 2022
NCT03835533 (PORTER)	I	45	NKTR-214 + nivolumab SBRT + CDX-301 + Poly-ICLC + nivolumab CDX-301 + INO-5151 + nivolumab	No	NKTR-214 is an IL-2 pathway agonist, CDX-301 is an FLT-3 ligand, Poly-ICLC is a TLR-3 agonist, INO-5151 is a DNA-based combination of PSA/PSMA and an IL-12 activator	March 2023
NCT03834519 (KEYLYNK-010)	III	780	Pembrolizumab + olaparib Abiraterone or enzalutamide	Yes	Preliminary results https://doi.org/10.1200/jco.2020.38.6_suppl.tps256	September 2022
NCT03834506 (KEYNOTE-921)	III	1000	Pembrolizumab + docetaxel Placebo + docetaxel	Yes		February 2023
NCT04100018	III	984	Nivolumab + docetaxel Docetaxel + placebo	Yes		May 2024
Adoptive cell transfer						
NCT01140373	I	13	PSMA CAR-T	No	Preliminary results: https://doi.org/10.1200/jco.2013.31.6_suppl.72 CAR-T cells persisted in blood for up to 2 weeks	June 2020

Table 1 (continued)

NCT number (acronym)	Phase	*N*	Intervention/treatment	Randomized?	Notes	Expected end date
NCT03089203	I	18	PSMA-TGFβRDN CAR-T	No	CAR-T cells that are insensitive to TGFβ and that target PSMA	September 2021
NCT03013712 (CARTEPC)	I/II	60[a]	EpCAM CAR-T	No	EpCAM is an epithelial surface antigen that is upregulated in many cancers	December 2020
NCT03970382	I	148[a]	NeoTCR-P1 NeoTCR-P1 + nivolumab	No	NeoTCR-P1 are patient-specific neoantigen specific CAR-T cells	Decembe3r 2023
NCT02463799	II	36	Sipuleucel-T + radium 223 Sipuleucel-T	Yes	Preliminary results: https://doi.org/10.1200/jco.2020.38.6_suppl.130 Addition of sipuleucel-T improved clinical outcomes, possible synergism	December 2020
NCT01804465	II	50	Sipuleucel-T + immediate ipilimumab Sipuleucel-T + delayed ipilimumab	Yes	Patients will receive ipilimumab on day 1 after final sipuleucel-T treatment (immediate) or 3 weeks later (delayed)	October 2021
NCT01818986	II	20	Sipuleucel-T + SABR	No		December 2024
Bispecific monoclonal antibodies						
NCT04077021	I	70	CCW702	Yes	mAb against CD3 and PSMA	December 2023
NCT03792841	I	120	AMG 160 AMG 160 + pembrolizumab	No	mAb against CD3 and PSMA, in vitro and ex vitro data https://doi.org/10.1200/jco.2020.38.6_suppl.155	April 2024
NCT04221542	I	70	AMG 509	No	mAb against CD3 and PSMA	October 2025

AdV adenovirus, *SABR* stereotactic ablative body radiation, *SBRT* stereotactic body radiation therapy, *PD-L1* programmed death ligand 1, *TGF* tumor growth factor, *CAR-T* chimeric antigen receptor T cell, *TKI* tyrosine kinase inhibitor, *MSI-H* microsatellite instability–high, *mAb* monoclonal antibody, *CRPC* castration-resistant prostate cancer, *IL* interleukin, *PSA* prostate-specific antigen, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *VEGFR* vascular endothelial growth factor receptor, *PSMA* prostate-specific membrane antigen, *EpCAM* epithelial cell adhesion molecule, *MHC-I* major histocompatibility complex class I, *ATP* adenosine triphosphate

[a]Includes cancers other than CRPC

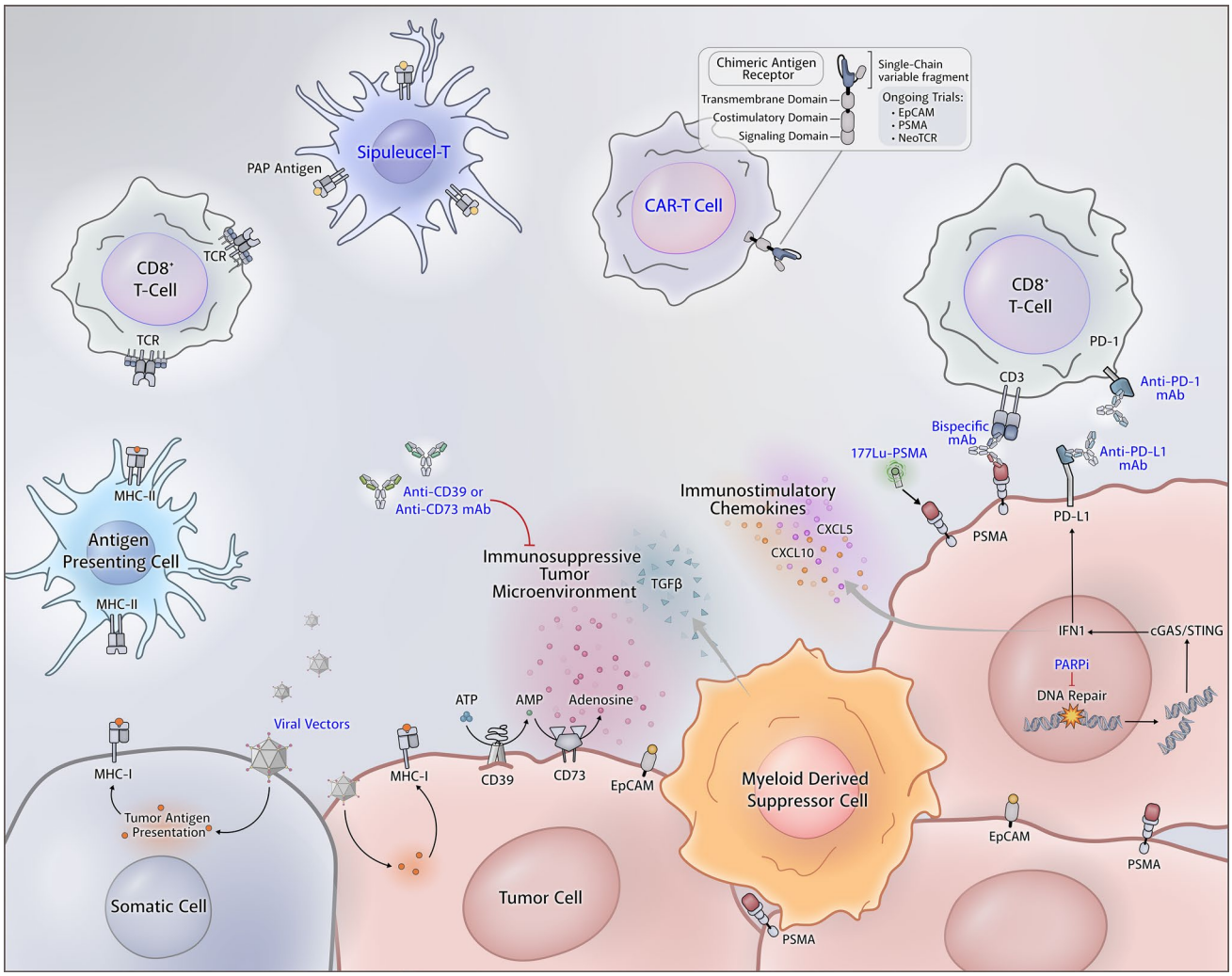

Fig. 1 An overview of immune system pathways and targets in prostate cancer. Tumor specific-antigens from viral vectors (e.g. PROSTVAC) are displayed on MHCs. Prostate cancer cells often express unique markers such as PSMA that are targetable with CAR-Ts. Patient-specific neoantigens are also potential targets with custom NeoTCRs. Other cell-mediated therapies, such as Sipuleucel-T, use prostate cancer-specific antigen-presenting cells displaying PAP to stimulate the immune system. Increased levels of extracellular adenosine, myeloid-derived suppressor cells, and immune checkpoints such as PD-1/PD-L1 prevent anti-tumor immunity but are also targetable with various monoclonal antibodies. Use of PARPi can cause the cells to not only increase chemokine production but also increase PD-L1 expression. *MHCs* major histocompatibility complexes, *PSMA* prostate-specific membrane antigen, *CAR-Ts* chimeric antigen receptor T cells, *NeoTCRs* neoantigen T-cell receptors, *PAP* prostatic acid phosphatase, *PD-1* programmed cell death protein 1, *PD-L1* programmed cell death ligand 1, *PARP* poly(ADP ribose) polymerase, *PARPi* PARP inhibitor, *mAb* monoclonal antibody, *TGF* tumor growth factor, *EpCAM* epithelial cell adhesion molecule, *MHC-I* major histocompatibility complex class I, *ATP* adenosine triphosphate, *AMP* adenosine monophosphate, *IFN 1* interferon 1, *cGAS/STING* cyclic GMP-AMP Synthase/Stimulator of Interferon Genes, *TGF-β* transforming growth factor beta

[13]. Based on these results, sipuleucel-T was approved by the US FDA for the treatment of men with mCRPC with asymptomatic or minimally symptomatic disease. Currently, the treatment is only available in the US. A study conducted under contract to the Agency for Healthcare Research and Quality was of the opinion that these phase III trial designs had an inherent potential for confounding due to differences in post-progression treatment, making estimates of the actual benefit with sipuleucel-T less certain [14].

In a post hoc subgroup analysis [15] of OS by age from these phase III trials, there was an 11-month OS difference in the placebo group between patients younger than 65 years of age and patients ≥ 65 years of age (28.2 vs. 17.2 months; $p < 0.01$). This was surprising as age is not prognostic for OS in mCRPC patients. In the IMPACT study, OS benefit by sipuleucel-T seemed to be derived entirely from the older patient cohort (< 65 years of age: HR 1.41, 95% CI 0.87–2.29 vs. ≥ 65 years: HR 0.58, 95% CI 0.43–0.76).

Patients < 65 years of age in whom sipuleucel-T did not appear to be effective, appeared to live longer, with a median OS of 29 months compared with patients ≥ 65 years of age in whom the intervention appeared to be effective (median OS of 23.4 months). There have been concerns regarding the apparent shorter OS of older patients in the placebo arm, along with speculation regarding the detrimental effect of placebo intervention [15]. At present, sipuleucel-T is recommended only for asymptomatic or minimally symptomatic mCRPC patients with no liver metastasis, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and life expectancy of more than 6 months. It is not recommended for patients with small-cell/neuroendocrine histology [16].

NCT03024216 is a phase Ib study that randomized asymptomatic or minimally symptomatic progressive mCRPC patients who met the standard criteria for sipuleucel-T to either atezolizumab (1200 mg intravenously every 3 weeks) for two doses followed by sipuleucel-T every 2 weeks for a total of three infusions (Arm 1), or sipuleucel-T every 2 weeks for three infusions followed by atezolizumab (1200 mg intravenously every 3 weeks) for two doses (Arm 2) [17]. The primary endpoint was safety. Available results from 37 enrolled patients showed a median PFS of 8.2 months in Arm 1 and 5.8 months in Arm 2 ($p = 0.054$). No grade 3/4 immune-related toxicities were observed [17].

3 Immune Checkpoint Inhibitors: Monotherapy

Immune checkpoints regulate immune pathways that maintain self-tolerance and limit immune-related collateral tissue damage with infections. These pathways are exploited by cancer cells to evade anti-tumor immunological responses by downregulating T-cell activity and creating an immunosuppressive environment [18]. Antibodies directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand (PD-L1) have received FDA approval for multiple tumor types and have been assessed in mCRPC as discussed below [18].

3.1 Ipilimumab

Ipilimumab is a fully human immunoglobulin (Ig) G1 monoclonal antibody that inhibits CTLA-4 [18]. In human tumor tissues, CTLA-4 blockade has been associated with an increased density of intratumoral CD4 + and CD8 + cells without depletion of regulatory T cells [19]. Early-phase clinical trials established ipilimumab as a safe and tolerable treatment in the mCRPC setting. A phase I study of 30 mCRPC patients, of whom 24 were chemotherapy-naïve, did not identify any dose-limiting toxic effects upon treatment with escalating doses of ipilimumab in combination with a fixed dose of PROSTVAC [20]. Additional phase I and I/II studies of mCRPC patients further confirmed the clinical potential of ipilimumab treatment, with common grade 3 or 4 immune-related AEs of diarrhea, colitis, rash, and hepatitis [20–22].

Based on these findings, the phase III CA184-043 trial was initiated to assess the efficacy of ipilimumab after radiotherapy in mCRPC patients who had progressed on docetaxel. Overall, 799 patients were randomized in a 1:1 ratio to receive ipilimumab ($n = 399$) or placebo ($n = 400$). The primary endpoint was OS in the intent-to-treat population [23]. The results did not show a significant difference in median OS between both treatment groups. The median OS with ipilimumab was 11.2 months, compared with 10.0 months with placebo (HR 0.85, 95% CI 0.72–1.00; $p = 0.053$). The rates of all-grade and grade 3/4 immune-related AEs with ipilimumab were 63% and 26%, respectively [23]. In a recently reported preplanned long-term analysis, OS was significantly improved with ipilimumab [24]. OS rates in the ipilimumab arm were higher at 3 years (15.3% vs. 7.9%), 4 years (10.1% vs. 3.3%), and 5 years (7.9% vs. 2.7%) compared with placebo [24]; however, these data were analyzed after the primary OS analysis and hence must be considered as hypothesis-generating and not definitive.

3.2 Pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1, leading to the counteraction of immune evasion by cancer cells [18]. In two independent cohorts with primary prostate cancer, moderate to high PD-L1 expression was observed in > 50% of the samples and was associated with shorter time to biochemical recurrence [25]. In the phase Ib KEYNOTE-028 trial, 23 mCRPC patients with measurable disease and PD-L1 expression in ≥ 1% of tumor or stromal cells were treated with pembrolizumab. The ORR was 17.4%, median PFS was 3.5 months, and the median OS was 7.9 months [26].

The phase II KEYNOTE-199 study enrolled mCRPC patients previously treated with docetaxel and one or more targeted endocrine therapies in five cohorts based on clinical and molecular disease characteristics. Patients in cohorts 1, 2, and 3 were treated with pembrolizumab. Cohort 1 ($n = 133$) included PD-L1 + (defined as combined positivity score [CPS] ≥ 1) patients with measurable disease, cohort 2 ($n = 66$) included PD-L1 − patients with measurable disease, and cohort 3 ($n = 59$) included patients with bone-predominant disease regardless of PD-L1 status [27]. The primary endpoint was ORR in cohorts 1 and 2, both separately and combined. Across all cohorts, pembrolizumab showed

acceptable safety but limited antitumor activity. The ORR was 5% in cohort 1 and 3% in cohort 2. The median duration of response (DOR) was not reached in cohort 1 and was 10.6 months in cohort 2. The disease control rate (DCR) and median OS were 10% and 9.5 months, respectively, in cohort 1, 9% and 7.9 months in cohort 2, and 22% and 14.1 months in cohort 3 [27]. ORR was 11% in patients with BRCA1/2 or ATM aberrations, compared with 3% in patients without any homologous recombination repair (HRR) defects [27]. Tumor mutational burden and PD-L1 status were associated with better PSA response [28].

4 Immune Checkpoint Inhibitors: Combination Therapies

4.1 Nivolumab + Ipilimumab

Nivolumab is a fully human IgG4 monoclonal antibody that inhibits the PD-1 receptor [18]. Preclinical and clinical studies have suggested a synergistic effect of anti-PD-1 and anti-CTLA-4 antibodies, which has led to the exploration of this combination in mCRPC [29–32]. CheckMate 650 is a phase II study of nivolumab plus ipilimumab in asymptomatic/minimally symptomatic mCRPC patients, with primary endpoints of ORR and radiographic PFS, and a secondary endpoint of safety [33]. Interim results showed an ORR of 26% in chemotherapy-naïve patients with measurable disease and 10% in patients with measurable disease who have progressed on taxane-based chemotherapy [33].

4.2 Immune Checkpoint Inhibitors with Poly(ADP ribose) Polymerase (PARP) Inhibitors

Poly(ADP ribose) polymerase (PARP) is recruited to sites of DNA damage and catalyzes ADP ribosylation reactions essential to DNA repair mechanisms, such as HRR and base excision repair, to avoid cell cycle arrest [34]. PARP inhibition results in unrepaired DNA breaks leading to genomic instability, thereby causing cell death. In tumors with BRCA1 and 2 deleterious alterations, PARP inhibitors lead to synthetic lethality. PARP inhibitors also trap PARP 1 and 2 enzymes at damaged DNA, and these trapped PARP-DNA complexes are much more cytotoxic than single-strand breaks due to PARP inactivation [35]. About 11.8% of patients with metastatic prostate cancer have germline mutations in DNA-repair genes, while 19.3% of mCRPC patients have an aberration in BRCA2, BRCA1, or ATM genes [36, 37]. In a prospective genomic analysis of 1033 patients, 3.1% of mCRPC patients demonstrated phenotypic evidence of microsatellite instability–high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors [38]. Additionally, among 11 MSI-H/dMMR mCRPC patients treated with immune checkpoint inhibitors, six (54.5%) had a > 50% decline in PSA levels, of whom four had radiographic responses [38].

Two PARP inhibitors, olaparib and rucaparib, have received FDA approval for mCRPC patients with deleterious or suspected deleterious germline or somatic HRR or BRCA 1 and 2 mutations, respectively [39]. PARP inhibitors were recently found to trigger antitumor immunity through stimulator of interferon genes (STING) activation, which is followed by the upregulation of chemokines that recruit T cells [40]. As PD-L1 is also upregulated, the antitumor response can be amplified with therapies targeting the PD-1 axis [41]. Several clinical trials are currently underway to assess the efficacy of immune checkpoints in combination with PARP inhibitors.

4.2.1 Pembrolizumab + Olaparib

Cohort A of KEYNOTE 365 is evaluating pembrolizumab in combination with olaparib in mCRPC patients previously treated with docetaxel and up to two novel hormonal therapies (NHTs) [42]. The primary endpoints of this phase Ib/II trial are safety and PSA response rate, and secondary endpoints are ORR, OS, PFS, and time to PSA progression. Available results from 84 treated patients showed a PSA response rate of 9%, ORR of 8.3%, a median time to PSA progression of 16 weeks, median radiographic PFS of 4 months, and median OS of 14 months [42]. In a subgroup analysis, the T-cell-inflamed gene expression profile was not associated with ORR or PSA response [43].

KEYLYNK-010 (NCT03834519) is a phase III study evaluating the efficacy and safety of pembrolizumab in combination with olaparib in molecularly unselected mCRPC patients who have progressed on an NHT (abiraterone or enzalutamide) and docetaxel [44]. Patients will be randomized in a 2:1 ratio to the experimental arm or alternate NHT. Primary endpoints are OS and radiological PFS, and secondary endpoints are the time to initiation of subsequent anticancer therapy, ORR, and DOR. The anticipated study completion date is 30 September 2022 [44].

4.2.2 Nivolumab + Rucaparib

Cohort A of the phase II CheckMate 9KD trial (NCT03338790) is evaluating the combination of nivolumab with rucaparib in patients with mCRPC [45]. Primary endpoints of the study include ORR and PSA response rate, and secondary endpoints are OS, PFS, response kinetics, and safety [45]. The study is projected to reach its completion in 2021.

4.2.3 Durvalumab + Olaparib

A phase II study evaluated durvalumab, a human IgG1-K monoclonal antibody, in combination with olaparib in patients with mCRPC who had prior treatment with at least one NHT. Of the 17 patients enrolled, median radiographic PFS was 16.1 months, and 53% (9 of 17) of patients had a radiological and/or PSA response (95% CI 4.5–16.1 months), with a 12-month radiographic PFS of 51.5% (95% CI 25.7–72.3%). The trial was enriched with patients with germline or somatic alterations in DNA damage repair genes, and the median radiographic PFS in these patients was 16.1 months [46].

4.3 Immune Checkpoint Inhibitors with Tyrosine Kinase Inhibitors

Proangiogenic factors, which are often produced in response to hypoxia or oncoproteins, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor, are known to modulate immunity by inducing regulatory T cells and inhibiting the maturation of dendritic cells [47–49]. These mechanisms decrease T-cell infiltration into the tumor milieu. Antiangiogenic agents that inhibit VEGF/VEGF receptors have shown to reverse the tumor-induced immune suppression by altering the tumor microenvironment [50, 51]. Cabozantinib is a multikinase inhibitor that targets MET, RET, AXL, and VEGF receptor 2, which are central to tumor cell proliferation and angiogenesis [52, 53]. In preclinical models, cabozantinib, alone or in combination with a cancer vaccine, sensitized tumor cells to immune-mediated killing by reducing the function of regulatory T cells and amplifying cytokine production from effector T cells [54]. These findings have led to the evaluation of cabozantinib with immunotherapy in patients with mCRPC.

4.3.1 Atezolizumab + Cabozantinib

In cohort six of the phase Ib COSMIC-021 trial, cabozantinib was evaluated in combination with atezolizumab, a PD-L1 inhibitor in patients with mCRPC [55]. As of October 2019, 44 mCRPC patients were enrolled to receive the combination regimen [55]. The combination demonstrated significant clinical activity, with an ORR of 32%, a DCR of 80%, and a median DOR of 8.3 months [55]. The combination was safe, with common AEs of fatigue, nausea, and decreased appetite [55]. Based on these encouraging results, the combination is being evaluated in a phase III trial (CONTACT-02, NCT04446117). The study will be randomizing 580 patients with mCRPC who have progressed on an NHT in a 1:1 ratio to the combination of cabozantinib with atezolizumab or alternate NHT (abiraterone or enzalutamide).

4.4 Immune Checkpoint Inhibitors with Novel Hormonal Therapies

The initiation and progression of prostate cancer are heavily dependent on the androgen receptor (AR) signaling pathway [56]. Enzalutamide is an AR antagonist that competitively inhibits the binding of androgens to AR, nuclear translocation of AR, and AR binding to chromosomal DNA [57]. Enzalutamide has demonstrated to improve OS in both docetaxel-naïve and pretreated mCRPC patients [58, 59]. In preclinical studies, enzalutamide has shown to not only inhibit the proliferation of prostate cancer cells, but also to increase their sensitivity to cytotoxic T-lymphocyte-mediated killing [60, 61], thus proving the rationale for its combination with immunotherapies in mCRPC.

4.4.1 Pembrolizumab + Enzalutamide

Cohorts 4 and 5 of KEYNOTE 199 evaluated pembrolizumab with enzalutamide in patients with chemotherapy-naïve and enzalutamide refractory mCRPC patients. Cohort 4 included patients with measurable disease, while cohort 5 included patients with bone-predominant disease. In cohort 4, the ORR (primary endpoint) was 12% and the DCR was 51%. In cohort 5, the DCR was 51% [62].

Cohort C of the phase Ib/II clinical trial KEYNOTE 365 is evaluating the combination of pembrolizumab with enzalutamide in patients with mCRPC who were intolerant to or had progression on abiraterone [63]. The primary endpoints were PSA response rate, ORR, and safety. Available results from 103 enrolled patients showed a PSA response rate of 22%. In patients with measurable disease and $\geq$ 27 weeks of follow-up, the ORR was 12%, and the DCR was 32%. Median DOR has not yet been reached, radiological PFS was 6.1 months, and median OS was 20.4 months [63]. A T-cell-inflamed gene expression profile was not significantly associated with ORR or PSA response [63]. The combination is being evaluated in the phase III KEYNOTE-641 (NCT03834493) study in patients with mCRPC [63].

4.4.2 Nivolumab + Enzalutamide

CheckMate 9KD (cohort C) is a phase II trial evaluating the nivolumab + enzalutamide combination in mCRPC patients [45]. Results are anticipated in 2021.

4.4.3 Atezolizumab + Enzalutamide

IMbassador 250 was a randomized, phase III study that compared the safety and efficacy of atezolizumab with enzalutamide in patients with mCRPC who previously progressed on abiraterone and docetaxel, or were ineligible to receive

taxane-based chemotherapy. The trial enrolled 759 patients who were randomized in a 1:1 ratio to atezolizumab with enzalutamide ($n = 379$) or enzalutamide alone ($n = 380$); however, the study was terminated early upon failure of the experimental arm to improve OS (15.2 months with combination vs. 16.6 months enzalutamide alone; HR 1.12, 95% CI 0.91–1.37; $p = 0.28$) [64].

4.5 Immune Checkpoint Inhibitors with Docetaxel

Docetaxel has been shown to improve OS in mCRPC patients [65]. It inhibits microtubular depolymerization, thereby arresting dividing cells in the G2-M phase, and induces BCL2 phosphorylation that ultimately leads to apoptosis [66]. Docetaxel has also demonstrated immunomodulatory effects, by rendering tumor cells more sensitive to immune-mediated killing by enhanced cytotoxic T lymphocyte lysis [67, 68]. Additionally, docetaxel has been found to augment MHC-I expression and loading, as well as to enhance the release of potent cancer antigens following the degradation of cancer cells [68, 69]. When administered following or in combination with cancer vaccines, docetaxel has shown to increase antitumor activity as a result of more robust antigen-specific T-cell responses, with significant decreases in tumor volume [70]. These findings generated considerable enthusiasm to combine docetaxel with immune checkpoints.

4.5.1 Pembrolizumab + Docetaxel

Cohort B of the phase Ib/II KEYNOTE 365 study evaluated the efficacy of the pembrolizumab with docetaxel combination in patients with mCRPC who had progression or were intolerant to NHT. The primary endpoints were safety, PSA response rate, and ORR [71]. Among the 104 treated patients, the PSA response rate was 28%, ORR was 18%, and DCR was 51%. The median radiographic PFS, time to PSA progression, and OS were 8.3 months, 6.2 months, and 20.4 months, respectively. The most common treatment-related AEs (≥ 30%) were alopecia, diarrhea, and fatigue. Again, T-cell-inflamed gene expression profile was not associated with ORR or PSA response [71]. The combination is currently being evaluated in the phase III KEYNOTE 921 (NCT03834506) trial, with a projected study completion in 2023 [71].

4.5.2 Nivolumab + Docetaxel

CheckMate 9KD (cohort B) is a phase II trial evaluating nivolumab in combination with docetaxel in patients with mCRPC [72]. Co-primary endpoints are ORR and PSA response rate. At an interim analysis of 41 patients, the combination showed an ORR of 36.8%, PSA response rate of 46.3%, and median radiographic PFS of 8.2 months. The safety profile was consistent with those of individual agents [72]. A phase III randomized trial, CheckMate 7DX (NCT04100018), is further evaluating the combination in patients with mCRPC, with primary endpoints of radiographic PFS and OS.

5 Immune Checkpoint Inhibitors with ^{177}Lu-PSMA-617 Radioligand Therapy

^{177}Lu-PSMA-617 is a radioligand composed of Lutetium-177, a therapeutic radionuclide that primarily emits β radiation, and PSMA-617, a high-affinity ligand of human prostate-specific membrane antigen (PSMA) [73, 74]. PSMA-617 binds to PSMA, an antigen that is overexpressed in prostate cancer, followed by its internalization into the cancer cell [75, 76]. Therefore, by utilizing a targeted approach, PSMA-617 directs the β radiation from ^{177}Lu to the tumor site, thereby attempting to avoid exposure to the rest of the body. Currently, a phase Ib trial of 30 patients (NCT03805594) and a phase Ib/II trial of 37 patients (PRINCE; NCT03658447) are investigating the potential safety and efficacy of ^{177}Lu-PSMA-617 in combination with pembrolizumab in patients with mCRPC. Both studies are anticipated to complete in 2021.

6 Promising Future Directions

6.1 Targeting Soluble MIC with Novel Monoclonal Antibodies

The expression of major histocompatibility I chain-related molecule (MIC) is upregulated on most epithelial cells during times of stress, including the early stages of prostate cancer [77]. Membrane-bound MIC interacts with NKG2D expressed on T and natural killer (NK) cells to trigger immune activation [78, 79]. Membrane-bound MIC is cleaved by proteases as cancer progresses, resulting in tumor-derived soluble MIC (sMIC), which binds to NKG2D and induces endocytosis and degradation of NKG2D, thereby suppressing the NK and tumor antigen-specific T-cell response [80, 81]. A significant increase in sMIC and a deficiency in NK cell function have been reported among advanced prostate cancer patients [82]. In preclinical studies, targeting sMIC with monoclonal antibodies has been found to invigorate antitumor immune responses, eliminate primary and metastatic tumors, and sensitize prostate tumors to CTLA-4 and PD-1/PD-L1 blockade therapy [83–86]. The potential clinical efficacy of a combination treatment including anti-sMIC and immune checkpoints still needs to be explored.

6.2 Prostate-Specific Membrane Antigen (PSMA)-Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy

Chimeric antigen receptor (CAR) T cells (CAR-Ts) are genetically engineered T cells consisting of a fusion protein that contains an extracellular component of a monoclonal antibody variable fragment, which improves affinity and specificity toward an antigen, and a T-cell receptor intracellular signaling domain(s), which relays costimulatory signals [87, 88]. CARs are thus able to simulate T-cell recognition and activity without the limitations of reduced MHC-associated antigen presentation and expression, which is one of the major mechanisms of immunoevasion by tumor cells [89]. CAR-Ts have transformed the treatment landscape for leukemia and are now gaining traction in solid tumors [90, 91]. In preclinical studies, the transfer of a CAR designed to target PSMA into tumor-bearing mice led to significant eradication of the neoplasia [88].

PSMA-targeted CAR-Ts in mCRPC have since been investigated in a phase I dose-escalating trial (NCT01140373). At interim analysis, of the four patients receiving an infusion of 1×10^7 CAR-Ts/kg, one patient had stable disease for > 6 months and a second patient had stable disease for > 16 months, while the third and fourth patients progressed [92]. Further results are awaited.

Transforming growth factor (TGF)-β causes immunosuppression in the tumor microenvironment by inhibiting T-cell proliferation, NK cell function, and antigen presentation, and thereby plays a role in the progression of prostate cancer [93, 94]. In mouse models, co-expression of a null TGFβ receptor enhanced the potency of PSMA-directed CAR-Ts, as evidenced by increased proliferation of T cells, enhanced cytokine secretion, long-term persistence of immune cells, and tumor eradication [95]. A phase I clinical trial (NCT03089203) is evaluating the safety and efficacy of PSMA-directed/TGFβ-insensitive CAR-Ts in patients with mCRPC [96].

Other notable CAR-Ts in clinical trials include P-PSMA-101 with or without rimiducid (NCT04249947), PSMA-specific CAR-T (NCT04053062), anti-PSCA-CAR-41BB/TCRzeta-CD19t expressing CAR-T (NCT03873805), BPX-601 anti-PSCA CAR-T with rimiducid (NCT02744287), and anti-EpCAM-CAR-CD3zeta-CD28 CAR-T (NCT03013712).

6.3 Bi-Specific T-cell Engagers (BiTEs)

Bi-Specific T-cell Engagers (BiTEs) are recombinant fusion proteins that have two linked, single-chain variable fragments (scFvs) from two different antibodies, one of which binds to T cells through a cell-surface receptor such as CD3, and the other that targets a tumor-specific antigen [97]. BiTEs are independent of MHC haplotype and therefore are 'off-the-shelf' therapy [97]. Pasotuxizumab is a PSMA-targeting BiTE that has been evaluated in a phase I dose-escalation study (NCT01723475). Of the 16 patients enrolled, three had a ≥ 50% PSA response and there were two long-term responders [98]. Other notable BiTEs in clinical trials include HPN424 (NCT03577028), JNJ-63898081 (NCT03926013), and AMG 160 (NCT03792841), which are PSMA-targeting BiTEs, and AMG 509 (NCT04221542), which is directed towards six transmembrane epithelial antigens of the prostate 1 (STEAP1) [99]. As of July 2020, the phase I trial of AMG 160 treatment in mCRPC was found to be tolerable and efficacious, with cytokine release syndrome (CRS) being the most common AE (all-grade, approximately 90%; grade 3, approximately 25%; and no grade 4 or 5 CRS) [100]. The confirmed PSA responses and objective responses were observed in 27% and 13% of patients, respectively [100].

6.4 Targeting the Adenosine Pathway

Elevated adenosine level is associated with an immunosuppressive tumor microenvironment and can be targeted by blocking adenosine A2A and A2B receptors or antibodies targeting ecto-nucleotidases CD73 and CD39 involved in adenosine formation [101]. In a phase I clinical trial, AZD4635, an adenosine A2A receptor antagonist, showed responses either as a single agent or in combination with durvalumab [102]. A phase I trial is evaluating ciforadenant, another adenosine A2A receptor antagonist, as a single agent and in combination with atezolizumab in patients with mCRPC. Available preliminary results showed one partial response with combination treatment among 14 evaluate patients, along with a clinical benefit rate of 57% [103]. Another combination regimen of NIR178 (an A2A receptor antagonist) and PDR001 (anti-PD-1 monoclonal antibody) is being examined in a phase II trial of immunotherapy-naïve mCRPC patients, with an estimated completion in 2021 (NCT03207867).

6.5 Miscellaneous Agents

TGFβ receptor inhibitors such as galunisertib (NCT02452008) and PF-06952229 (NCT03685591) are being evaluated in patients with mCRPC, and radium-223 is also being evaluated in combination with pembrolizumab (NCT03093428) and nivolumab (NCT04109729) in patients with mCRPC. Furthermore, NCT04116775 is evaluating fecal microbiota transplant with pembrolizumab in patients with mCRPC. Other agents that are being evaluated in combination with PD-1-directed therapies in the mCRPC setting include ipatasertib (AKT inhibitor; NCT03673787), isatuximab (anti-CD38 antibody; NCT03367819), naptumomab

(5T4-targeted immunotoxin; NCT03983954), GB1275 (CD11b agonist; NCT04060342), utomilumab (4-1BB antibody; NCT03217747), and PF-4518600 (OX40 receptor agonist; NCT03217747) [104].

7 Conclusions

At present, several clinical trials are evaluating immunotherapies either as a single agent or in combination treatment regimens. Increasing focus is being placed on immune checkpoint inhibitors in various combinations, adenosine receptor antagonists, adoptive cell transfer, and bispecific monoclonal antibodies in the hope of increasing the response in patients with prostate cancer, especially in the mCRPC setting. Despite evidence of immune checkpoint inhibitor activity in preclinical studies, clinical trials examining the efficacies of immunotherapies in the mCRPC setting have not yielded promising results. Potential reasons include PTEN loss leading to altered interferon-1 signaling, decreased MHC-1 expression, low tumor mutational burden, and minimal T-cell infiltration [1]. Such observations have led to the classification of prostate cancer as a 'cold' tumor. Current guidelines do recommend treatment with immune checkpoint inhibitors for patients with MSI-H/dMMR mCRPC, although these patients constitute a very small minority of patients in clinical practice [16]. The way forward includes exploring pathways to turn prostate cancer into a 'hot' tumor by altering the tumor microenvironment.

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