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Review Article

Prostate cancer immunotherapy: a review of recent advancements with novel treatment methods and efficacy

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Abstract: Immunotherapy remains to be an appealing treatment option for prostate cancer with some documented promise. Prostate cancer is traditionally considered as an immunologically "cold" tumor with low tumor mutation burden, low expression of PD-L1, sparse T-cell infiltration, and a immunosuppressive tumor microenvironment (TME). Sipuleucel-T (Provenge) is the first FDA approved immunotherapeutic agent for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (mCRPC); demonstrating a benefit in overall survival. However various clinical trials by immune checkpoint inhibitors (ICIs) and their combinations with other drugs have shown limited responses in mCRPC. Up to now, only a small subset of patients with mismatch repair deficiency/microsatellite instability high and CDK12 mutations can clinically benefit from ICIs and/or their combinations with other agents, such as DNA damage agents. The existence of a large heterogeneity in genomic alterations and a complex TME in prostate cancer suggests the need for identifying new immunotherapeutic targets. As well as designing personalized immunotherapy strategies based on patient-specific molecular signatures. There is also a need to adjust strategies to overcome histologic barriers such as tissue hypoxia and dense stroma. The racial differences of immunological responses between men of diverse ethnicities also merit further investigation to improve the efficacy of immunotherapy and better patient selection in prostate cancer.

Keywords: Prostate cancer, immunotherapy, immune checkpoint inhibitors, tumor microenvironment, African American, Race, European American

Introduction

Prostate cancer is the most commonly diagnosed cancer in men, and the second most diagnosed disease for men in the U.S. As of 2022, the estimated new cases of prostate cancer in the U.S is said to be 268,490 [1]. This makes up nearly 21% of all cancer cases in men. Alongside an estimated 34,500 deaths that year has made it the second most common form of cancer related death in the United States after lung and bronchus cancer [1]. With the advancement of detection methods such as the prostate health index, urine prostate cancer antigen 3 (PCA3) test, and magnetic resonance imaging (MRI) fusion prostate biopsy [2-4], diagnosis of this disease has greatly improved over the past few decades. However, the mortality rate of the disease remains very high despite modern day treatments.

A few forms of immunotherapy have become part of standard care over the past few years. Novel immunotherapy approaches utilize a wide variety of immune response mechanisms to target malignant cells. This treatment method has shown promising results in patients with aggressive cancers. Some of these agents have been able to produce deep and long-term remission in malignancies with otherwise limited treatment options. Advancements in immunology as well as the approval of drugs such as sipuleucel-T and ICIs provide a viable alternative treatment modality for castration-resistant prostate cancer (CRPC) to prevalent methods such as androgen suppression therapy and

chemotherapy [5, 6]. The goal of immunotherapy is to target cancer cells through the recognition by T-cells or antibodies; essentially encouraging an immune response to cancer, but it has been shown to be less effective against prostate cancer when compared to results from other cancers including non-small-cell lung cancer (NSCLC) [7], renal cell carcinoma (RCC) [8, 9], urothelial cancer [10, 11], head and neck cancer [12], and melanoma [13, 14]. The strong immunosuppressive tumor microenvironment (TME), lower infiltration of T-cells, and lower mutation burden in prostate cancer have resulted in lowered efficacy of treatment through immunotherapy [15]. Nevertheless, a subset of prostate cancer exhibits immunogenic phenotype. A special subgroup of patients with high PD-L1 tumor expression, CDK12 mutations, high tumor mutational burden, or tumors with high microsatellite instability (MSI) and mismatch repair-deficient (dMMR) have recently demonstrated excellent responses to immune checkpoint inhibitors (ICIs) and/or their combinations with other agents [15, 16]. Therefore, immunotherapy remains to be an appealing treatment option for prostate cancer to optimize the management of this disease. This review will summarize the current state of immunotherapy usage, including immune checkpoint blockade therapy, vaccine-based treatments, adoptive cell therapy and bispecific T cell engager (BiTE) therapy in prostate cancer treatment. In addition, we will discuss current mechanisms of resistance or responses to ICIs, and the immunological differences between African American (AA) and European American (EA) men with prostate cancer.

ICIs based therapy

Ipilimumab is the first FDA approved immune check point inhibitor. Ipilimumab is a monoclonal antibody that works to upregulate immune response by targeting the immune downregulating receptor, CTLA-4 [17]. Activated T cells induce CTLA-4 expression to send out inhibitory signal to T cells [18]. In addition, CTLA-4 is constitutively expressed in regulatory T cells to control cytotoxic T-cell activation [18]. When administered as a monotherapy, ipilimumab was shown to noticeably increase the ratio of regulator effector T lymphocytes present in the TME [17]. In a phase I trial, two out of fourteen patients with mCRPC who received a single intra-venous dose of Ipilimumab exhibited prostate specific antigen (PSA) decreases of > or =50% and treatment was well tolerated [19]. In another Phase I trial of tremelimumab (a humanized anti-CTLA-4 antibody) in combination with androgen deprivation using bicalutamide in PSA recurrent prostate cancer patients without radiographic evidence of metastatic disease, three out of eleven patients experienced an extension in PSA doubling time [20]. Phase I trial combining ipilimumab with a vaccine containing transgenes for PSA and for a triad of costimulatory molecules (PROSTVAC) in patients with mCRPC showed a PSA decline in 14 out of 24 (58%) chemotherapy-naïve patients [21]. A combination of evofosfamide, a prodrug that alleviates hypoxia, with ipilimumab resulted in 3 (16.7%) partial response and 12 (66.7%) stable disease in 18 patients with measurable disease at baseline [22]. These responsive patients had improved peripheral T-cell proliferation and increased intra-tumoral T-cell infiltration [22]. In a phase I trial of ipilimumab at escalating doses in combination with a fixed dose of GM-CSF, 24 patients with mCRPC were treated and three of six patients treated at the highest dose level had PSA declines of >50% [23]. The combined therapy induced the expansion of activated effector CD8 T cells and tumor-associated antigens specific T cells [23]. In phase I/II study in patients with metastatic CRPC (mCRPC), 50 patients received ipilimumab alone or as in combination with radiotherapy. Eight had PSA declines of ≥50%, one had complete response, and six had stable disease [24].

In a double-blind, phase 3 trial, 799 mCRPC patients were randomly assigned to palliative radiotherapy followed by ipilimumab or placebo [6]. There was a statistically significant improvement in progression-free survival but no statistically significant difference in overall survival (OS) between ipilimumab vs. placebo groups. However in long term follow-up study, OS rates in the ipilimumab versus placebo arms are 25.2% vs. 16.6% at 2 years, 15.3% vs. 7.9% at 3 years, 10.1% vs. 3.3% at 4 years, and 7.9% vs. 2.7% at 5 years. Approximately two to three times higher survival benefit after three years was identified in the ipilimumab arm [25]. Beer reported an increase in median progression-free survival in the ipilimumab arm (5.6 months) versus placebo arm (3.8 months) and a higher

PSA response rate (23% in the ipilimumab arm vs. 8% in the placebo arm) in a trial of ipilimumab versus placebo as monotherapy in asymptomatic/oligo-symptomatic chemo-naïve mCRPC [26].

Nivolumab is a human IgG4 monoclonal antibody for blocking PD-1. PD-1 interaction with its ligand prevents activation of T cells from attacking the cancer [27-29]. In the phase II clinical trial CheckMate 650, which investigated combined effects of ipilimumab and nivolumab in patients with mCRPC who had developed resistance to androgen receptor (AR)-targeted therapies, the combination resulted in 25% of objective response rate and was associated with considerable side effects leading to discontinuation of the therapy in the population [29]. In another phase II trial of nivolumab and ipilimumab combination, patients with ARV7 positive mCRPC were treated with or without enzalutamide. In the arm without enzalutamide, there was 13% (2/15) PSA response, and the objective response rate (ORR) was shown to be 25% (2/8). In the arm with enzalutamide, PSA response rate and ORR were shown to be 0% (0/15) and 0% (0/9) in those with measurable disease. 20% (3/15) patients without enzalutamide and 26.7% (4/15) patients with enzalutamide reached a durable progression-free survival more than two years. The results did not justify further studies in unselected patients [30].

Pembrolizumab is an anti-PD1 antibody. In a multiple cohort phase II trial (the KEYNOTE-199), a pembrolizumab monotherapy was utilized in 258 patients with Response Evaluation Criteria in Solid Tumours (RECIST)-measurable and bone-predominant mCRPC who were previously treated with docetaxel and targeted endocrine therapy. This study showed an ORR of 5% in PD-L1-positive RECIST-measurable patients and 3% in PD-L1-negative RECIST-measurable. Median OS was 9.5 months in PD-L1-positive RECIST-measurable patients, 7.9 months in PD-L1-negative RECIST-measurable patients, and 14.1 months in patients with bone-predominant disease regardless of PD-L1 expression [31]. Another nonrandomized phase Ib KEYNOTE-028 trial of pembrolizumab in PD-L1-positive, mCRPC patients who received at least two prior therapies showed an ORR of 17.4%, median progression-free survival (PFS) and OS of 3.5 and 7.9 months, respectively [32].

In the Phase 1b/2 KEYNOTE-365 study (NCT-02861573), pembrolizumab plus docetaxel and prednisone demonstrated a 34% PSA response rate, 23% ORR, 8.5 months of median radiographic PFS (rPFS), and 20.2 months of OS in chemotherapy-naïve mCRPC patients who were treated with abiraterone or enzalutamide before [33]. The multicenter, randomized, double-blind Phase III study, KEYNOTE-921, is now ongoing for further evaluating the therapeutic efficacies of pembrolizumab plus docetaxel and prednisone or prednisolone versus a placebo plus docetaxel in this patient population with primary endpoints of OS and rPFS [34].

A single-arm phase II trial of pembrolizumab in combination with enzalutamide was carried out in 28 men with mCRPC progressing on enzalutamide alone. The trial achieved a PSA response rate of 18% (5/28), ORR of 25% (3/12), median PSA PFS of 3.8 months, OS of 21.9 months in all patients and OS of 41.7 months in the responders [35]. Among the three responders, one is MSI high, and none had detectable PD-L1 expression in their baseline biopsy tissues [35]. A multicenter, randomized, double-blind, Phase III KEYNOTE-641 study is now ongoing to further evaluate the efficacy and safety of pembrolizumab plus enzalutamide versus enzalutamide plus placebo in estimated 1200 patients with mCRPC (NCT03834493) [36]. Similar studies have been performed with other ICIs and some of the phase III trials are being completed [37].

Phase I and II trials of pembrolizumab in combination with ADXS31-142 [a cancer vaccine containing a live-attenuated strain of the Gram-positive bacterium Listeria monocytogenes encoding a fusion protein consisting of PSA and a fragment of the immunostimulant listeriolysin O (LLO) protein], MVI-816 (a DNA vaccine encoding prostatic acid phosphatase) or cryotherapy were carried out in patients with progressive mCPRC or newly diagnosed oligometastatic hormone-sensitive prostate cancer [38-41]. These trials observed durable responses of the combined therapies in a subset of prostate cancer patients [38-41]. However future randomized clinical trials are needed to validate these findings.

The usage of atezolizumab, avelumab, and durvalumab to target PD-L1 and to block the inter-

action of PD-L1 with the PD-1 has also been explored as an option in treatment of advanced prostate cancer [42-49]. In the randomized phase III trial IMbassador 250 (no. NCT03016312), atezolizumab in combination with enzalutamide was compared to enzalutamide alone in 759 patients with mCRPC or locally advanced CRPC patients who had progressed on abiraterone, and docetaxel did not reach the primary endpoint for a better OS in the combination arm [43]. The results also suggested that atezolizumab plus enzalutamide might be useful in selected patients with pre-existing immunity, such as high PDL1 expression and high levels of CD8+ T cells [43]. A phase II study of avelumab with stereotactic ablative body radiotherapy in 31 men with progressive mCRPC treated previously with anti-androgen agents exhibited an ORR of 31%, rPFS of 8.4 months and median OS of 14.1 months [44]. In another phase II trial of avelumab in 15 men with progressive neuroendocrine or aggressive-variant metastatic prostate cancer (NEPC/AVPC) one man (6.7%) with MSH2 somatic mutation and MSI-high NEPC achieved complete remission for 2 years [48]. Seventeen patients with previously treated mCRPC with or without alterations in DDR genes who received durvalumab and olaparib combination were reported to have median rPFS of 16.1 months and a radiographic and/or PSA response of 53% [49].

Other trials for testing PD-1 blockade in combination with anti-IL6, TGF-β blockage, and IDO1 inhibitor, as well as other immune checkpoint targets, such as B7-H3 inhibitors enoblituzumab, LAG-3, OX40, and 4-1BBL are in various stages of clinical development for phase I and II trials in mCRPC [50-55] (NCT03821246, NCT02628535, NCT02923180, NCT01391143). Clinical trials of a variety of prostate cancer immune therapies were summarized as **Table 1**.

Current mechanisms underly ICIs responses in prostate cancer

A small subset (3-5%) of mCRPC patients with a microsatellite instability (MSI) and dMMR phenotype exhibit high-tumoral mutation burden and higher levels of tumor infiltrating lymphocytes (TILs). It has been reported that some cancer patients with dMMR, including mCRPC, colorectal, and endometrial cancers display exceptional responses to the anti-PD-1 pembrolizumab [56-58]. These results led to the approval of pembrolizumab by FDA for the treatment of all MMR-deficient metastatic tumors, which was based on a predictive biomarker alone, but not on tumor histology.

Biallelic loss of CDK12 represents another novel subtype of prostate cancer, which holds significant promise for immunotherapy and is genetically, transcriptionally, and phenotypically distinct from tumors with homologous recombination repair defects (HRD) and dMMR [59, 60]. CDK12 mutations occur in 2%-4% of primary prostate cancers and in 4.7%-11% of mCRPCs and associated with a high rate of metastases and short overall survival [61-67]. CDK12-mutated prostate cancer is characterized with focal tandem duplications (FTDs) leading to increased gene fusions and genomic rearrangements, the formation of fusion-related immunogenic neoantigens, and increased tumor-infiltrating lymphocytes and/or clonal expansion [59, 60, 68]. Wu [67] reported that 2 of 4 patients with biallelic CDK12 mutation exhibited an exceptional PSA response to anti-PD1 antibody. Other studies also found exceptional responses of two mCRPC patients to DNA-damaging therapies (bipolar androgen therapy that consist of periodical oscillation between castration levels and supraphysiological levels of testosterone and radium-223) after or in combination with immunotherapy (nivolumab and sipuleucel-T) [69, 70]. The anecdotal evidence suggests that a subset of prostate cancer patients with CDK12 mutations may favorably respond to PD-1 immunotherapy. However, recent studies using immunohistochemistry analysis of TIL landscape revealed that human prostate tumors with biallelic CDK12 aberrations were predominantly enriched for immunosuppressive $CD4^{+}FOXP3^{-}$ T lymphocytes but not for $CD4^{+}FOXP3^{+}$ or $CD8^{+}$TILs [71, 72]. This result suggests that immunotherapeutic strategies for better address the immunosuppressive tumor microenvironment are needed.

Other molecular alterations in prostate cancer may also affect the immune responses, which are clinically relevant. Calagua [73] reported that prostate tumors in a subset of aggressive localized prostate cancer cases express PD-L1 along with a high density of tumor infiltrating lymphocytes but without high microsatellite instability or CDK12 alterations. Exhausted progenitor CD8+ T cells and differentiated effector T cells as indicated by positive PD-1 and transcription factor TCF1 (encoded by

Table 1. Clinical Trials of varying treatment plans for mCRPC and other forms of carcinoma

Treatment	N	Target	Dosing Interval	Data Collection method	Results	Article
Ipilimumab	399 to 400	mCRPC that has progressed post docetaxel chemo therapy	10 mg/kg every 3 weeks	Intention-to-treat analysis	No significant difference	[6]
Nivolumab	854	Non-small-lung cancer	3 mg/kg every 2 weeks	Kaplan-Meier method	9%-15% increase in overall survival rates compared to docetaxel	[7]
Nivolumab	821	Advanced clear cell renal-cell carcinoma	3 mg/kg every 2 weeks	Kaplan-Meier method	Roughly 5 month increase in survival	[8]
Nivolumab plus Ipilimumab	1096	Advanced clear cell renal-cell carcinoma	1 mg/kg every 3 weeks	RECIST evaluation	15% increased survival rate	[9]
Pembrolizumab alone or with chemotherapy	1010	Advanced urothelial carcinoma	200 mg every 3 weeks	Comparisons of non-inferiority and superiority	No significant difference	[10]
Ramucirumab	530	Advanced or metastatic urothelial carcinoma	10 mg/kg every 3 weeks	Intention-to-treat analysis	Average 1.5 month increased survival	[11]
Avelumab	697	Advanced squamous cell carcinoma of head and neck	10 mg/kg every 2 weeks	Response Evaluation Criteria in Solid Tumors	No significant difference	[12]
Ipilimumab and Nivolumab	14	Melanoma	3 dose per kg every 3 weeks	ECOG	8.9 month OS vs. 2.9 months	[13]
Tremelimumab	11	PSA recurrent prostate cancer	150 mg of bicalutamide for 28 days followed by temelimumab on 29th day	Flow cytometric analysis	No significant adverse effects reported	[20]
Ipilimumab with PSA transgene vaccine	30	mCRPC	Varying doses of ipilimumab every 2 weeks with monthly vaccination booster	Flow cytometry And Kaplan-Meier method	Trending towards associations of longer overall survival with no conclusive data	[21]
Evofosfamide with Ipilimumab	22	Patients with mCRPC, pancreatic cancer, and/or head and neck cancer	400-640 mg/m^2 evofosfamide and 3 mg/kg ipilumumab every 3 weeks	RECIST Evaluation ECOG evaluation	No significant observations	[22]
CTLA4 blockade with GM-CSF combination	24	mCRPC	Escalating doses of ipilumumab with fixed dose of GM-CSF given every 4 weeks	Flow cytometry	>50% PSA decline in 3 patients with no significant observations in the rest	[23]
Ipilimumab	50	mCRPC	Varying doses of ipilimumab from 3-10 mg/kg every 3 weeks	RECIST	>50% PSA declines amongst some patients receiving 10 mg/kg doses	[24]
Ipilimumab	799	mCRPC	One dose of radiotherapy followed by 10 mg/kg ipilumumab every 3 weeks	Two sided log-rank test stratified by ECOG	Overall increased survival rates for patients given ipilumumab	[25]
Ipilimumab	598	Asymptomatic mCRPC	10 mg/kg every 3 weeks	Two sided log-rank test stratified by ECOG	No significant difference in overall survival rates	[26]
Nivolumab plus Ipilimumab	78	mCRPC	1 mg/kg nivolumab + 3 mg/kg ipilimumab followed by 480 mg nivolumab every 4 weeks	ECOG	Reported consistent safety	[28]
Nivolumab plus Ipilimumab	15	AR-V7 expressing mCRPC	1 mg/kg ipilimumab + 3 mg/kg nivolumab every 3 weeks	ECOG	No significant observations	[30]
Pembrolizumab	258	mCRPC	200 mg every 3 weeks	RECIST ECOG	Median overall survival rate of 14.1 months with acceptable safety	[31]
Pembrolizumab	23	Advanced prostate adenocarcinoma	10 mg/kg every 2 weeks	RECIST	Overall survival of 7.9 months	[32]
Pembrolizumab plus Docetaxel and Prednisone	104	mCRPC	200 mg pembrolizumab and 75 mg/m^2 docetaxel every 3 weeks, 5 mg prednisone BID	RECIST	Overall survival of 29.2 months, reported acceptable safety	[33]

Pembrolizumab plus Docetaxel	~1000	mCRPC	Every 3 weeks	RECIST TFST	Ongoing phase 3 trial	[34]
Pembrolizumab plus Enzalutamide	28	mCRPC	200 mg pembrolizumab every 3 weeks with 4 doses with enzalutamide	RECIST	Overall survival of 41.7 months	[35]
Pembrolizumab plus Enzalutamide	~1200	mCRPC	200 mg pembrolizumab every 3 weeks 160 mg/day enzalutamide	PCWG3 modified RECIST	Ongoing phase 3 trial	[36]
Pembrolizumab plus MV1-816	25	mCRPC	Every 3 weeks	RECIST	Overall survival of 22.9 months	[38]
pTVG-HP (MVI-816) Vaccine	99	mCRPC	200 μg 6 times every 2 weeks, then quarterly for 2 years	PCWG3 modified RECIST	No significant change	[39]
Pembrolizumab plus ADXS31-142	37	mCRPC	200 mg with monotherapy every 3 weeks	RECIST	Overall survival of 16.0 months	[40]
Pembrolizumab with Cryotherapy	12	mCRPC	200 mg every 3 weeks with eight months cryotherapy	Kaplan Meier	Overall survival of 17.5 months	[41]
Atezolizumab	35	mCRPC	Every 3 weeks	Kaplan Meier	Overall survival of 14.7 months with acceptable safety profile	[42]
Atezolizumab with Ezalutamide	759	mCRPC	Every 3 weeks	-	Ongoing study	[43]
Atezolizumab with Radium-223	45	mCRPC	840 mg every 2 weeks, Radium-223 every 4 weeks	RECIST	Overall survival of 16.3 months	[44]
Atezolizumab with Sipuleucel-T	37	mCRPC	1200 mg azetolizumab every 3 weeks, sipuleucel-T every 2 weeks	RECIST	Overall survival of 23.6 months	[45]
Atezolizumab with Cabozantinib	580	mCRPC	1200 mg atezoliumab followed by 40 mg cabozantinib PO QD	RECIST	Ongoing study	[46]
Avelumab with Stereotactive Ablative Body Radiotherapy	31	mCRPC	10 mg/kg every 2 weeks for 24 weeks	Clopper-Pearson	Overall survival of 14.1 months	[47]
Avelumab	15	mCRPC	10 mg/kg every 2 weeks	RECIST	Overall survival of 7.4 months	[48]
Durvalumab with Olaparib	17	mCRPC	1500 mg durvalumab every 4 weeks, 300 mg olaparib PO BID	RECIST	Overall survival of 16.1 months	[49]
Ieramilimab plus spartalizumab	255	Advanced or metastatic tumors	1 mg/kg every 2 weeks	RECIST	Acceptable safety profile	[53]
RhoC Vacccine	22	Prostate cancer	9.1 mg every 2 weeks for 6 cycles followed by every 4 weeks for 5 cycles	Flow cytometry	CD4 T-Cell response lasting 10 months and generally well tolerated	[54]
Nivolumab plus Ipilimumab	90	mCRPC	1 mg/kg nivolumab and 3 mg/kg ipilimumab IV followed by 480 mg nivolumab every 4 weeks	RECIST	Overall survival of 19.0 months	[80]

TCF7) staining were founded in the tumor infiltrating lymphocytes, which are expandable by ICIs [74, 75]. Areas within tumor tissue with MHC-II+ cells and CD8+TCF1+ T cells were also identified to be comparable with prostate cancer cases with dMMR, suggesting the existence of sufficient antigen-presenting cells (APC) niches. In addition, genomic losses of RB1, BRCA2, and CHD1 are common features of this subset of prostate cancer cases with potential immunogenicity.

Speckle-type pox virus and zinc finger protein (SPOP) are mutated in about 6-15% of localized and metastatic prostate cancer [76, 77]. Evolution from SPOP-mutated to CHD1-deleted prostate cancer is considered a unique molecular subtype of prostate cancer [78]. SPOP is a component of a cullin-RING-based BCR (BTB-CUL3-RBX1) E3 ubiquitin-protein ligase complex that promotes the ubiquitination and degradation of PD-L1 [79]. Expression of Mutated SPOP would stabilize PD-L1. Prostate tumors with SPOP mutation exhibited increased PD-L1 expression and fewer tumor TILs [79]. Kaur also reported that homologous recombination deficiency scores but not pathogenic germline BRCA2- and ATM-mutations were associated with higher numbers of TIL, including both cytotoxic and regulatory T-cells. It is also interesting to test novel immunotherapeutic strategies in SPOP mutant prostate cancer.

Potentially underlying mechanisms for resistance to ICIs in prostate cancer

Most prostate cancer patients are resistant to immunotherapies, especially to immune checkpoint inhibitors. It has been estimated that about 5%-17% of unselected mCRPC patients respond to pembrolizumab monotherapy [29]. An ORR of 10% and 26% was only observed in mCRPC patients with and without previous taxane-based chemotherapy, respectively, after nivolumab plus ipilimumab treatment in a mCRPC phase II trial (CHECK MATE-650) [79]. A lower infiltration of T-cells, Low tumor mutational burden (TMB), low PD-L1 expression, and immunosuppressive TME have been considered as major hindrances of successful immunotherapy in prostate cancer.

TMB is the number of non-synonymous mutations present per megabase (mut/Mb) and has been used as biomarker for predicting response to ICIs. Although prostate cancer is characterized with a high rate of genomic instability and chromosomal rearrangements, TMBs in both localized and metastatic prostate cancer were estimated to be about 0.7~1.0 and 2.3~4.4 per Mb, respectively, which are significantly lower compared to other ICIs responsive cancers, such as bladder (7.1 per Mb) and melanoma (12.1 per Mb) [80-83]. Only 3-8.3% of metastatic prostate cancer tumors have a high TMB [84-86]. A low TMB in prostate cancer was associated with fewer mutated peptides (35 mutated peptides in prostate cancer versus 197 and 276 mutated proteins in lung adenocarcinoma and melanoma) [87, 88], suggesting a poor collection of neoepitopes in prostate tumor may lead to less immune cell attraction to the tumor sites, epitope-MHC interactions and activation of TILs by APC. Therefore, a low TMB represents a significant hurdle for improving the efficacy of ICIs based immunotherapies in prostate cancer.

Compared to high-responsive tumors, such as melanoma and non-small cell lung carcinoma, for immunotherapies, the tumor immune microenvironment (TIME) in prostate cancer is generally featured with low frequency of TILs and high frequency of tumor-associated macrophages (TAMs). A unique and highly complex TIME in prostate cancer consists in different types of immune cells, working together to resist T-cell infiltration, even under treatment of ICIs [89]. Immune cell types estimated by deconvolution of RNA sequencing data from The Cancer Genome Atlas (TCGA) using by CIBERSORT algorithm revealed that total infiltrating T cells and mast cells were relatively less and infiltrating B cells, nature killer (NK) cells, macrophages and neutrophils are more compared with benign tissues [90]. Fewer infiltrating CD8+ T cells were consistently identified in prostate tumor tissues in several studies [90-92].

Local infiltration of CD8+ T cells in several types of tumors was shown to be associated with clinical benefits of ICIs with improved survival of cancer patients [93-97]. However a role of intratumoral CD8+ T cell density for predicting the clinical outcomes of prostate cancer patients remains debatable [98]. Previous studies have shown that a higher intratumoral CD8+ T cell density was associated with a poor

prognosis of prostate cancer patients [99, 100]. However most recent studies indicated that high levels of CD8+ T cell infiltration in radical prostatectomy specimens predicted a better survival and lower risks of biochemical recurrence and metastasis of prostate cancer patients [101, 102].

In addition, increased number of immunosuppressive cells including TAMs, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSC) affect the antitumor response of CD8+ T cells [103-110]. Macrophages consist of 30 to 50% of infiltrating immune cells in tumor microenvironment. A subset of macrophages, such as M2-tumor associated macrophages (M2-TAMs) have shown to promote resistances to immunotherapy, chemotherapy, and radiotherapy through secretion of soluble factors and remodeling of cell matrix for promoting proliferation, angiogenesis, immunosuppression and tumor cell migration and invasion [103-110]. Several studies have shown that increased M2-TAM infiltration in prostate cancer TME was associated with worst clinicopathological features and prognosis or with more aggressive diseases with an estimated odds ratio of 1.93 (95% confidence interval: 1.23-3.03) [103-110]. Inhibition of androgen receptor (AR) signaling induces major changes in the immune landscape of prostate tumors, including increased infiltration of TAMs [111-116]. The increased numbers of TAMs in AR signaling inhibitors treated tumors predicted tumor recurrence and treatment resistance [111-116]. TAMs express PD-L1 and PD-1 leading to a decreased phagocytosis activity [118, 119]. The decreased phagocytosis activity can be rescued by PD-1/PD-L1 blockade. M1 macrophages that are often stimulated by LPS or IFN-γ, etc. produce pro-inflammatory cytokines. Anti-PD-1/PD-L1 blockade induced an M1 macrophage polarization to reduce tumor burden [120, 121]. MMR-deficient prostate cancer has been shown to have higher densities of TILs compared to MMR-proficient tumors [122]. Sena [123] reported that MMR-deficient prostate cancer with parenchymal brain metastases exhibited very few CD8+ tumor-infiltrating lymphocytes but highly enriched macrophages. Studies also showed that reduction of Tregs by anti-CTLA-4 antibodies in tumors was associated with tumor regression and dependent on FcγRIV-expressing macrophage-mediated cell depletion [124-128]. Taken together, these studies suggest that macrophages may also significantly contribute to the efficacies of ICIs based immunotherapies.

In addition, prostate tumors expressed high levels of chemokines, CCL2, CCL22, and CXCL12, to attract MDSCs, Tregs, and low levels of CTL/NK/Th1 cells-recruiting chemokines (CCL5, CXCL9, CXCL10). MDSCs also emerge in the context of castration resistance (129). MDSCs could be additional mechanism of resistance to ICIs in advanced CRPC.

The blockade of PD-1 and PD-L1 between CD8+ T cells and tumor cells is expected to restore antitumor responses induced by tumor-infiltrating CD8+ T cells [130]. Therefore, low level of PD-L1 expression in prostate cancer could also significantly limit efficacy of anti-PD1 based immunotherapy [131]. Due to tumor heterogeneity and different antibody clone selection, immunohistochemistry protocols, and scoring system, there is a large variability of PD-L1 expression in prostate tumor tissues. One study reported that 29% of acinar prostate cancer, 7% ductal prostate carcinoma and 46% of neuroendocrine carcinomas were PD-L1-positive [132-148]. While different cut-off values for positivity were used, 1369/4708 (29%) prostate cancer cases were overall positive. 687/2676 (26%) cases were PD-L1-positive if at least ≥1% of tumor cells were counted as positive, 93/1062 (9%) were positive for ≥5% of stained tumor cells, and 9/523 (2%) cases expressed PD-L1 on >50% of tumor cells [132-148]. In contrast to lower levels of PD-L1, the levels of PD-L2 expression were significantly higher across all 9393 radical prostatectomy samples. [149]. In addition, other immune checkpoints or targets may be clinically relevant in prostate cancer such as v-domain Ig suppressor of T-cell activation (VISTA), Poly (ADP-ribose) polymerase (PARP), MSH2 and MSH6 mutations, etc. [150-155]. To improve the immunogenicity of the "cold" prostate tumor cells, multiple targeting and combination approaches may be needed.

Racial difference in immune response in prostate cancer

Although prostate cancer is diagnosed at an earlier age and more aggressive in AA men [156-158], accumulating evidence suggest

that AA prostate cancer respond favorably to immunotherapies, and specifically to cancer vaccines [159, 160]. In the PROCEED trial/registry, AA men with mCRPC who were treated with the cancer vaccine, Sipuleucel-T, had a median nine-month of overall survival advantage over EA men [159, 160]. Hawley [161] compared levels of circulating immune markers in AA and EA men with mCRPC who received sipuleucel-T. The results showed that AA men had statistically significantly higher levels of Th2-type (IL-4, IL-10, and IL-13) and inflammatory cytokines (IL-2, IL-12, and IL-6) compared with prostate-specific antigen-matched EA men both at baseline and 52 weeks after sipuleucel-T and that there are no differences in the antigen-specific T-cell response and the humoral responses to the immunizing antigen PA2024 and select secondary antigens.

A study performed by Calagua [73] showed a significant association between AA and PD-L1 overexpression in prostate cancer (26% in AA vs. 12% in EA), suggesting that AA men with prostate cancer may respond more favorably to anti-PD1 based immunotherapies. AA men were also shown to have lower DNA damage repair (DDR) activity compared to EA men [162-165]. Defective DNA damage responses are associated with improved radiation response and tumor immunogenicity [46, 166], which may implicate a combined approach of radiotherapy and immune therapy in AA men.

Prominent differences in tumor immunobiology between AA vs. EA men have been reported in several independent gene expression profiling studies [167-169]. For example, the gene expression study by Wallace revealed significantly different profiles of immune-related genes when comparing 69 tumors from AA and EA patients; autoimmune disease modulators, such as PTPN22 and components of the HLA complex, and key genes in antigen presentation were expressed at higher levels in AA tumors [168]. Kinseth [169] examined the differences in gene expression between AA and EA PCa by matching for age and pathological stage or Gleason scores as well as tumor-cell content and stroma-cell content. Striking differences in gene expression were observed in the stroma of AA patients relative to EA; 1016 genes with significant differences between the expression of EA and AA patients were observed. The vast majority (82%) of significant differences were downregulated. The down-regulated genes included many immune cell modulators compared to EA stroma such as interleukins (IL) -2, -4, -5, -6, -7, -10, -13, -15 and -22. Emerging data also have shown that levels of cytokines, IFNα, IFNγ, and TNFα signaling, ILs, and epithelial to mesenchymal (EMT) transition signaling, as well as tumor infiltrating lymphocytes were elevated in AA men, which suggest uniquely inflammatory phenotype in AA prostate cancer [163]. Weiner identified an enrichment of plasma cells in primary prostate tumors of AA men or men of African ancestry and elevated expression of NK cell activity markers and IgG [170], suggesting role of plasma cells in immune responses of AA men. Awasthi and his colleagues [163] have analyzed whole transcriptome data from the Decipher GRID registry and found that differentially expressed genes in major immune pathways were significantly enriched in AA compared to EA prostate cancer. In addition, IFN-induced transmembrane protein 3 (IFITM3) was validated in TCGA data base as a biomarker that was significantly associated with increased risk of prostate cancer recurrence for AA men. Tang [171] reported that AA prostate cancer patients with IFNL4 rs368234815-DG and IFNL4 rs12979860-T germline variants have poorer overall survival after prostatectomy surgery and that IFNL4 rs368234815-DG germline variant was associated with IFN-related DNA damage resistance signature.

Although many clinical trials of ICIs or in combination with other therapeutic approaches are ongoing, AA men are currently underrepresented in most of the clinical trials [172, 173]. There is a need for enhancing accrual of more AA men to clinical trials via prespecified enrolling clinical sites and by overcoming socioeconomic and cultural barriers [172, 173]. Clinical trials that specifically focused on the treatment response of AA men with metastatic prostate cancer will greatly facilitate our understanding of racial differences in the immune response. There are ongoing NCI efforts with sponsoring trials for enrollment of minority groups of patients.

Vaccine based treatments

The majority of immunotherapy vaccinations available for prostate cancer can be considered to be experimental. Sipuleucel-T currently the only FDA approved vaccine designated for

usage towards prostate cancer and be said the most effective in clinical usage [174, 175]. Sipuleucel-T is an autologous active cellular immunotherapy vaccine that primarily consists of autologous peripheral-blood mononuclear cells with APCs which are activated when exposed to PA2024, a recombinant fusion protein of PAP and costimulatory GM-CSF. A phase III trial (IMPACT: NCT00065442) in mCRPC patients demonstrated an improved OS by 4.1 months and a 22% reduction of relative mortality risk. However, only minimal antitumor responses were observed [175].

DNA vaccines have been examined largely in animals as a potential treatment for cancer. Their use in human remains controversial given the risk vs. benefit [176]. They offer a new approach over other anti-tumor vaccinations in terms of ease of use and the absence of infectious agents. Presently various phase 1 clinic trials are underway for prostate cancer DNA, namely NCT02411786 by Madison Vaccines Inc which encodes androgen receptors pTVG-AR, MVI-118 [177]. INO-5150 by Inovio Pharmceuticals is a dual-antigen DNA vaccine that utilizes parts of prostate-specific membrane antigen and the prostate specific antigen, which underwent phase I/II trial in biochemically relapsed prostate cancer patients [178].

PROSTVAC is an off the shelf vaccine that uses a recombinant strain of *vaccinia* paired with foxpowl vector boosts, transgenes, and costimulatory molecules to elicit an immune response from the body [179]. Patients that were treated with PROSTVAC have shown an increase in PSA-specific T-cell levels [179]. Two phase II studies of PROSTVAC have demonstrated its potential efficacy in treating mCRPC patients. One hundred twenty-five patients with mCRPC and a Gleason score of ≤7 were randomly given either PROSTVAC, or a placebo [180]. Patients treated with PROSTVAC demonstrated a median survival rate of 24.4 months; while patients treated with the placebo had a survival rate of 16.3 months [180]. A recent phase III study of PROSTVAC was conducted to follow up on this hypothesis but did not show any significant clinical benefit [181, 182]. The vaccine was reported to be well tolerated and eliciting an immune response, however there was minimal survival benefit [182].

GVAX uses the whole prostate cancer cell genetically modified to secrete the immune stimulatory cytokine granulocyte-macrophage colony-stimulating factor and allows the tumor cells themselves to be used as the antigen source for immunotherapy [183]. GVAX has shown to be a safe and potent cytokine and has elicited a high immune response dependent on the dosage. Patients only exhibited flu-like symptoms and a fever when treated. However, considering several failed phase 3 trials of this vaccination, further experimentation on it has largely been abandoned [184, 185].

Adoptive cell therapy

Adoptive Cell Therapy (ACT) has been shown to be effective in treating metastatic melanoma [186, 187]. This treatment involves the usage of T-lymphocytes specifically engineered to target specific viruses or tumors. Through the isolation and modification of patient T-lymphocytes with specific antigen receptors, followed by subsequent reinfusion, it is possible for patients produce an immunization-like response towards specific cancer antigens. Chimeric antigen receptors (CAR) allow for the production of artificial T-cell receptors for the purposes of ACT [188].

Epithelial cell adhesion molecule (EpCAM) targeting T-cells modified with CAR have shown to be effective in a wide range of cancer immunotherapies involving this stem cell antigen [189]. Studies performed on human prostate cancer cells with low expression levels of EpCAM have shown significant effectiveness in inhibiting tumor growth both *in vitro* and *in vito* [189]. The Natural Killer Group 2D (NKG2D) receptor has also been shown to a promising target for CAR T-cell therapy. When paired with the IL-7 gene it is shown to be effective in prostate cancer treatment [190]. To target prostate cancer more specifically, CAR-T cells were commonly generated against prostate-specific membrane antigen (PSMA). In a first in-human phase 1 trial of PSMA targeting CAR T cells armored with a dominant-negative TGF-β receptor (NCT0308-9203) in CRPC patients, 5 of 13 patients developed cytokine-release (CRS) at grade 2 or higher and 4 had decreases of ≥30% in PSA. One patient reached a >98% reduction in PSA with evidence of substantial clonal CAR T cell expansion. However, this one patient developed enterococcal sepsis 30 days after infusion, leading to multi-organ dysfunction and death [191]. Another ongoing clinical trial of PSMA-targeting CAR in mCRPC patients, 3 of 9

patients reached decreases of >50% in PSA and improvements in PSMA positron-emission-tomography imaging [192]. Three patients had CRS of grades 1-2 [192]. One patient experienced a complete clearance of measurable disease for over 5 months [192]. The results from these studies are promising, but CAR-T cell therapy still face many challenges or difficulties. Overcoming the immunosuppressive TME that are enriched with immunosuppressive cytokines and growth factors, TAMs, Treg, and MDSC and potential toxicities are some of the major limitations in CAR-T therapy.

Another method of ACT can be seen in TIL therapy, which involves the examination of specific lymphocytes located around the tumor. T-cells that best identify malignant tumor cells are treated and encouraged to proliferate around the tumor. Due to the T-cell exclusive nature of prostate cancer, it is often challenging to effectively incorporate TILs based immunotherapy into prostate cancer treatments [193]. This can be attributed to a lack of genomic complexity within prostate cancer cells compared to other cancers [194, 195]. Recent experiments on TILs in prostate cancer have indicated the potential for the viable extraction of functional and tumor reactive TIL within prostate cancer. In a study, twenty-eight prostate-TIL cultures were successfully extracted and expanded in a laboratory setting. The extracted TIL displayed an expansion frequency of roughly 50% across all samples. Analysis revealed a clear expression of chemokine receptors after expansion. Further studies into this form of therapy can potentially open more modalities in patient treatment [196].

A major challenge in CAR T-cell and TILs therapy is proliferating for long periods of time in immunosuppressive environments. As such, there is a push towards research that increases survival rates of CAR T-cells; notably through the incorporation of the TILs 4-1BB and CD137 receptor respectively [197, 198]. The inclusion of such therapies into patient care provides an efficient treatment method that suffers from fewer side effects associated with other methods of cancer treatment.

Bispecific T cell engager

Bispecific T cell engager (BiTE) antibodies can target PSMA on prostate cancer cells and engage T cell via CD3 receptor leading to T cell activation. AMG 212 (pasotuxizumab) demonstrated encouraging results in a phase I trial with dose-dependent PSA reductions and measurable tumor responses in approximately one-third of the 68 patients who were enrolled after progression on androgen deprivation therapy with abiraterone or enzalutamide and at least one taxane chemotherapy [199]. Limitation of this study included development of drug-neutralizing antibodies with subcutaneous injection and short serum half-life of the molecule. In order to overcome these limitations, AMG212 has been modified to AMG 160 with ongoing studies using IV formulation (NCT04631601) and half-life extended BiTE molecule [200].

Other target candidates on prostate cancer cells for BiTE therapy are being evaluated including the six-transmembrane epithelial antigen of prostate (STEAP), human carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5, also known as CEA) and delta-like protein 3 (DLL3), which are upregulated in different subtypes of prostate cancer [201, 202].

Conclusion

Prostate cancer exhibits many immunosuppressive characteristics associated with TME, low TMB, low expression of PD-L1 and sparse T-cell infiltration and therefore, prostate cancer has been considered as an immunologically “cold” tumor. Nevertheless, immunotherapy remains to be a promising treatment at least in a subset of prostate cancer patients. Prostate cancer tumors with high MSI/dMMR or CDK12 mutations can be more responsive to ICIs in clinics. Clinical data suggests higher degree of benefit in AA patients with prostate cancer treated with Sipuleucel-T. CAR-T therapy and BiTEs have shown some early encouraging clinical results with ongoing clinical trials evaluating the role of these treatments. Understanding resistant mechanisms to ICIs related to prostate TME and identification of new immune targets, could bring a new promising immune therapeutic approach for advanced prostate cancer and lead to extension of patent’s lifespan.

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Disclosure of conflict of interest

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