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Immunotherapy Landscape in Prostate Cancer: Successes, Failures and Promises

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Abstract As research focus in oncology has recently shifted to immunomodulation, the era of introduction of immunotherapeutic agents in the management of prostate cancer has just begun. With the success of checkpoint blockade drugs in certain advanced tumours, ongoing efforts are aimed at identification and validation of new actionable immune targets to consolidate and expand the initial success in other tumour types. In this paper, we review the immunotherapy research in the management of prostate cancer to date, as well as the various emerging immunotherapeutic agents and their possible use. Although monotherapy has thus far had disappointing results in prostate cancer, promising combination strategies are under evaluation.

Key words prostate cancer; immunotherapy; immunomodulation; combination therapy

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Introduction

Prostate cancer is the second commonest malignancy in men globally [1]. Despite advances in screening and treatment, in 2018, prostate cancer was a leading cause of cancer death among men at 6.7% of all deaths globally (approximately 360,000 deaths) with age-standardized incidence and mortality rates of 37.5 and 8.0 per 100,000 males, respectively, in high/very high human development index regions [1]. At present, the overall 5-year survival rate for prostate cancer in the United States of America (USA) is >99% for the localised and locoregional stages, but at only 30% for the distant metastatic stage [1]. While the use of prostate-specific antigen (PSA) screening has increased early disease detection and hence influenced cure rates, a subgroup of patients inexorably develops metastatic disease, which is deemed incurable. The introduction of drugs like abiraterone acetate, enzalutamide, apalutamide and darolutamide in the last few years has changed the treatment spectrum significantly, initially in the context of metastatic castration-resistant prostate cancer (mCRPC) [2-5] complemented by newer chemotherapy drugs, such as cabazitaxel [6], and bone targeting agents, such as alpharadin [7] and denosumab [8]. This progress has more recently expanded in the metastatic hormone-sensitive prostate cancer (mHSPC) setting [9-12] and non-metastatic (M0) CRPC [13-15]. Nevertheless, there is a lot of progress yet to be made towards the long-term control of mCRPC.

Immunotherapy has rapidly shifted the treatment paradigm for many cancers in the recent past including melanoma, renal cancer, and lung cancer [16-18]. Preclinical data suggest that prostate cancer is moderately immunogenic [19]. However, programmed cell death-ligand 1 (PD-L1), a biomarker for immune checkpoint inhibition in many cancer types, albeit non-uniformly, does not appear to be highly expressed in prostate cancer [20]. Furthermore, immune cells such as myeloid-derived suppressor cells and tumour-associated macrophages within the prostate tumour microenvironment (TME) restrict accumulation of T-cells and promote immune suppression [21]. In addition, a relative paucity of T-cells resulting from low non-synonymous mutation rate (0.3-2 mut/Mb) [22], correlating with lower number of tumour-associated antigens, leads to a restricted anti-tumour response [23]. On the other hand, resistance to second-generation hormonal therapy with enzalutamide in mCRPC seems to be associated with the expression of PD-1 and PD-L1/2 on antigen presenting cells [24].

In contrast to the marked success of checkpoint inhibition monotherapy in certain types of tumours, this strategy has thus far has limited success in prostate cancer. In this paper, we will review the role of current immunotherapeutic agents available for the treatment of prostate cancer and discuss various novel immunotherapy agents that are currently in development phase, as well as combination therapy strategies, designed to overcome the limited success immune checkpoint inhibition has thus far shown in prostate cancer.

Immune Checkpoint Inhibitors

The development of immune checkpoint inhibitors has revolutionised the field of immuno-oncology. These agents generate anti-tumour response by blocking co-inhibitory signalling pathways and promote immune-mediated killing of tumour cells by preventing tumour cells evading immunosurveillance.

Ipilimumab, a monoclonal antibody directed against cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), prevents T-cell inhibition and promotes the activation and proliferation of effector T-cells, was the first approved checkpoint inhibitor for patients with advanced melanoma [25-27]. The approval of ipilimumab, paved way for other immune checkpoint inhibitors to be evaluated. Pembrolizumab and nivolumab, programmed cell death-1 (PD-1) inhibitors, showed promising objective response rate (ORR) of 40–45% in melanoma and non-small cell lung cancer (NSCLC) [28-30] and 24% in urothelial cancer patients [31] while in triple-negative breast cancer (TNBC) patients, the response to PD-1 inhibitors was relatively moderate (19%) [32]. In contrast, an ORR of 87% with 17% complete response (CR), was observed in relapsed or refractory Hodgkin's lymphoma [23]. Subsequently, checkpoint inhibitors were approved by US Food and Drug Administration (FDA) for various further cancers and hence form an integral part of treatment algorithm (**Table 1**).

Only a subgroup of patients benefits from checkpoint inhibitors despite the success of CTLA-4 inhibitors and PD-1/PD-L1 inhibitors. Anti-tumour activity is regulated through complex factors in the TME, which is of three types based on the immune-cells infiltration: immune desert, immune excluded and immune inflamed [34]. These phenotypes exhibits specific mechanisms for preventing anti-tumour immune response [34]. Immune deserts are deprived of T-cells in the TME and lack T-cell priming and activation. The immune excluded TME signifies the presence of multiple chemokines and growth factors; however, accrued T-cells are unable to infiltrate the TME. Immune inflamed tumours exhibit infiltration of multiple immune cell subtypes [34].

Some cancer patients on checkpoint inhibitors develop severe immune-related adverse events (irAEs) [35] which are due to the inhibition of immune checkpoints that protect against autoimmunity, leading to various local and systemic immune-mediated autoimmune-like responses (Table 1). Recently long-term follow up of patients who received checkpoint inhibitors also reported cardiac toxicity and death [36].

With checkpoint inhibitors use becoming more common in treatment of different cancers, it has become imperative to understand the complex mechanism of resistance processes both primary and acquired, affecting the efficacy of these drugs. The interaction of tumour immunogenicity in TME plays an important role [37]. Poorly immunogenic tumours with low tumour mutational burden (TMB), such as prostate cancer, are primarily more resistant to treatment with checkpoint inhibition. Similarly, constant interactions between the immune system and cancer cells can result in varying heterogeneity intratumourally which in return may lead to poorly immunogenic tumour subclones within the tumour that lack expression of neoantigens, and hence develop acquired resistance to immunotherapy. Various factors within TME such as T*regs*, myeloid-derived suppressor cells, tumour-associated macrophages and various chemokines can affect the response to immunotherapy by stimulating tumour-cell motility, angiogenesis and immune-evasion. Other factors that play a role in developing immune-resistance are deficiencies in antigen presentation, compensatory upregulation of alternative immune checkpoints and concomitant aberrant activation of traditional oncologic pathways [37]. More recently changes in gut-biome has been linked to development of immune-resistance as well [37].

Keeping above in mind, it is crucial to develop predictive biomarkers to differentiate between responders and non-responders (both primary and acquired), and to determine the outcome of a proposed therapy in a patient before its initiation. To date, PD-L1 expression remains the most studied potential biomarker of checkpoint inhibitor response. Immunohistochemical detection of tumour cell PD-L1 expression has been associated with clinical response in clinical trials [38-40].

Ipilimumab

A phase-1/2 study of ipilimumab in 71 chemotherapy-naive patients with mCRPC showed durable PSA responses independent of prior chemotherapy, warranting further studies [41]. A

randomised phase-3 trial reported no survival benefit in 598 men with asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC without visceral metastasis who received ipilimumab (10mg/kg) or placebo, every three weeks, up to four doses, and then maintenance ipilimumab or placebo every three months until progression [42]. Although median progression free survival (PFS) was 5.6 months in the ipilimumab arm as compared to 3.8 months in the placebo arm, the median overall survival (OS) was 28.7 months and 29.7 months, respectively. Grade-3/4 treatment-related AEs occurred in 40% (ipilimumab arm) versus 6% (placebo arm), with diarrhoea being the most common AE (43%). A phase-3 trial that randomised 799 men with mCRPC with at least one bone metastasis and had progressed after docetaxel chemotherapy, to receive bone-directed radiotherapy (8Gy in one fraction) followed by either ipilimumab or placebo. Median PFS and median OS were 4 months and 11.2 months versus 3.1 months and 10 months for ipilimumab and placebo respectively. Post-hoc analysis showed a median OS of 22.7 months versus 15.8 months in patients with favourable prognostic features such as alkaline phosphatase concentration of less than 1.5 times of upper limit of normal (ULN), a haemoglobin concentration of 110 g/L or higher, and no visceral metastases [43].

Ipilimumab was also studied in the neoadjuvant setting in a phase-2 study of 16 men with high-risk prostate cancer who pre-surgically received a single 3-month depot of androgen-deprivation therapy (ADT) plus ipilimumab 10mg/kg two doses three months apart, to identify potential immune-inhibitory mechanisms to immunotherapy [44]. Although an increase recruitment of T-cells and macrophages were observed into the prostate tumour, a higher expression of inhibitory molecules such as PDL-1 and V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA) on macrophages was present, which in turn inhibited T-cell response accounting for the acquired resistance to ipilimumab.

Given the modest PFS responses along with the lack of a meaningful survival benefit, and the fact that multiple immunosuppressive mechanisms act in unison to affect anti-tumour response, the next step would be combination strategies to expand the immunotherapeutic effect. Such trials in prostate cancer include combination with chemotherapy (NCT03098160, NCT02423928), sipuleucel-T (NCT01804465) and PROSTVAC vaccine (NCT02506114, NCT00113984).

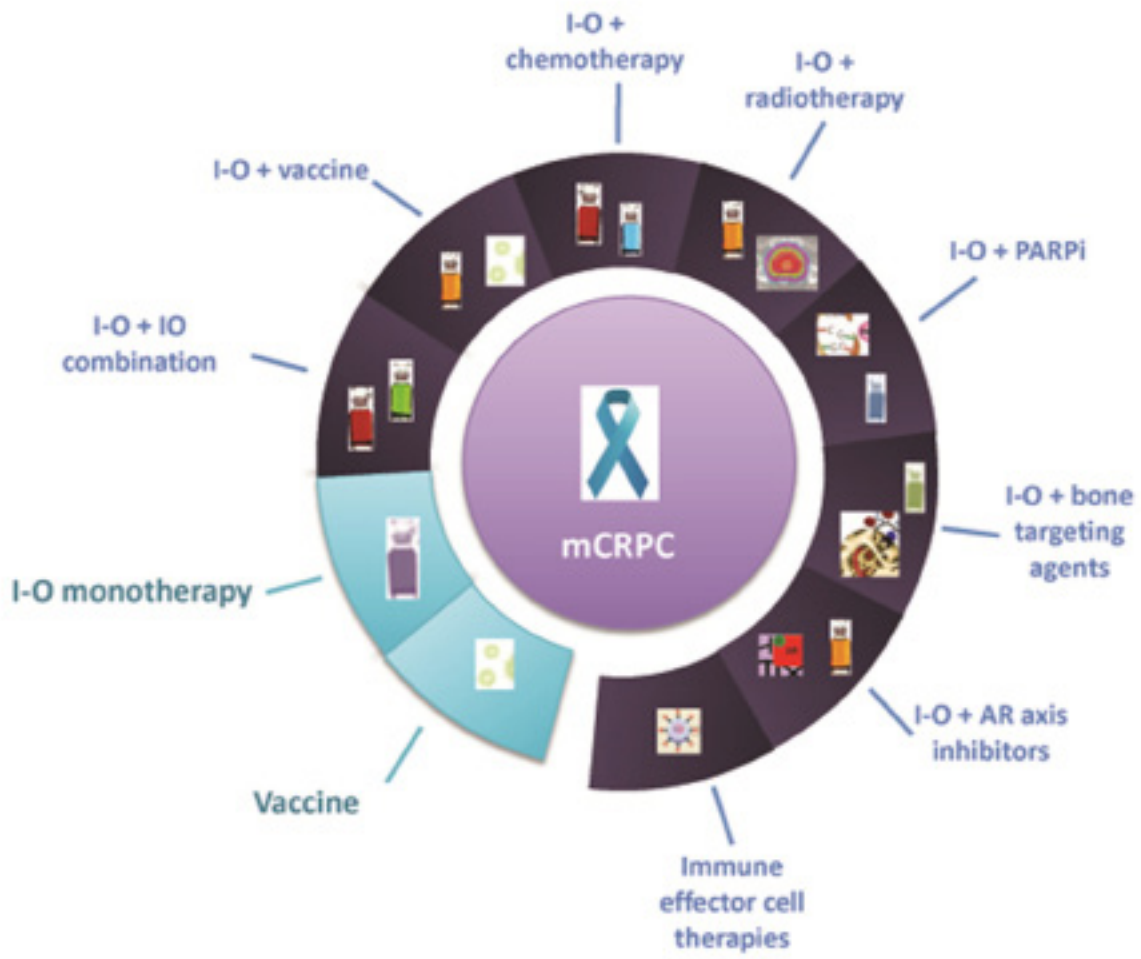

Figure 1. Treatment spectrum of immunotherapeutic agents in prostate cancer management. I-O: Checkpoint inhibitors; PARPi: poly-ADP ribose polymerase; AR: Androgen receptor; mCRPC: metastatic castration-resistant prostate cancer.

Nivolumab

In the phase-1 trial of nivolumab in 17 patients with various solid tumours, maximum tolerated dose (MTD) was not reached as no dose-limiting toxicity was observed at any dose up to 20 mg/kg [45]. Preliminary anti-tumour activity was seen in three patients who had a partial response (PR). Further development of nivolumab continued in melanoma, NSCLC, renal cancer, bladder cancer, and various other malignancies. In two phase-1 trials, nivolumab did not show encouraging ORRs in 25 heavily pretreated mCRPC patients [38, 39]. However, results of a phase-2 trial of combination immunotherapy with ipilimumab reported earlier this year were promising [46]. 78 patients with mCRPC were divided into two cohorts: asymptomatic or minimally symptomatic, who had progressed after at least one second-generation hormone therapy with no prior chemotherapy (cohort-1), and patients progressing after chemotherapy (cohort-2). ORRs were 26% and 10% in cohort-1 and-2 respectively, with four patients experiencing a CR, two in each cohort. PSA-response rate (>50% decline) was 21% in cohort-1 and 13% in cohort-2. ORR were higher in biomarker-enriched population, notably in patients with high TMB, PD-L1 expression >1%, DNA damage repair (DDR) defects and homologous recombination deficiency. These results were encouraging and several biomarker-driven clinical trials are now investigating nivolumab either alone or in combination in prostate cancer (NCT03040791, NCT03061539, NCT02601014, NCT03570619) while some trials are investigating combination of nivolumab with chemotherapy (NCT03338790), radiotherapy (NCT03543189), poly-ADP ribose polymerase inhibitors (PARPi) (NCT03572478, NCT03338790) and with peroxisome proliferator-activated receptor (PPAR)-alpha (NCT03829436). Nivolumab is also being investigated in combination with other immunomodulators such as vaccines (NCT02933255, NCT03815942, NCT03532217) and interleukin-8 inhibitor (NCT03689699).

Pembrolizumab

In the phase-1b KEYNOTE-028 study, patients with mCRPC and PD-L1 expression >1%, had a 13% (3/23) ORR and a median OS of eight months [47]. KEYNOTE-199, a phase-2 trial, investigated 258 patients with docetaxel-refractory mCRPC receiving pembrolizumab 200mg q3 weeks, dividing them in PD-L1 positive (>1%) and measurable disease (cohort-1), PD-L1 negative (<1%) and measurable disease (cohort-2), and non-measurable disease (cohort-3) patients [48]. PSA and radiologic response were noted in all three cohorts; 11% of all patients in three cohorts had a >50% PSA decline. Disease-control rate (DCR) were 27%, 42% and 57% respectively. Encouragingly, two patients in cohort-1 achieved CR. PD-L1 status did not accurately predicted response, however a higher response rate was noted in patients with BRCA1/2 or ATM mutations. These results, consistent with reports in other mismatch-repair deficient tumours [49], supported further research of pembrolizumab in mCRPC either alone or in combination, to look for predictive biomarker especially those with deleterious mutations.

Graff et al reported activity of the addition of pembrolizumab to enzalutamide in 28 patients with mCRPC who progressed on enzalutamide and had not received chemotherapy previously [50]. Pembrolizumab seemed to be able to partially reverse enzalutamide resistance. PSA-response was observed in five patients (18%), while radiologic response was at 25%. Median PSA-PFS, radiographic-PFS and median OS were 3.8, 10.8 and 22.2 months respectively. Neither microsatellite instability nor DDR accurately predicted for response to treatment.

Preliminary results of the phase-1b/2 umbrella KEYNOTE-365 study were presented earlier this year [51]. In the cohort-A, 41 mCRPC patients with post-docetaxel (and <2 lines of second-generation hormonal therapy) received pembrolizumab for up to two years plus olaparib 400mg twice daily until progression. Interestingly, 27% patients were PD-L1 positive, while none of them had DDR. PSA-response rate was 13% while radiologic-response rate was 7%. Overall DCR was 29%, while median OS was 14 months. Grade-3/4/5 AEs were seen in 51% of cases, higher than seen with pembrolizumab monotherapy in the past. Cohort-B of the KEYNOTE-365 investigated the combination of pembrolizumab with docetaxel in mCRPC patients progressing after second-generation hormonal therapy (72 patients, PD-L1 positive 29%). DCR was 57%, while median OS was not reached for a median follow-up of 10 months. Grade-3/4/5 AEs occurred in 27 (38%) patients.

Three phase-3 trials are investigating pembrolizumab against enzalutamide (docetaxel-naïve), docetaxel and olaparib (docetaxel-refractory) (NCT03834493, NCT03834506, NCT03834519) to consolidate its position within the mCRPC treatment landscape. Another trial is investigating pembrolizumab in mCRPC with or without DDR defects (NCT03248570). Moreover, further early phase trials are being conducted using pembrolizumab in combination with various therapeutic agents such as Radium-223 (NCT03093428), 177Lu-prostate specific membrane antigen (PSMA) (NCT03658447, NCT03805594) and various novel immunomodulating agents (NCT03406858, NCT03473925, NCT03454451, NCT03910660, NCT03007732, NCT03695835) including vaccines (NCT02325557, NCT02499835).

Atezolizumab

Kim et al reported results of 15 patients in a phase-1a trial investigating atezolizumab in patients with mCRPC previously progressed on enzalutamide +/- sipuleucel-T (pre-Docetaxel) [52]. It was very well tolerated with grade-3 irAEs of 7%, while no grade-4/5 events were noted. It also demonstrated median PFS of 3.4 months and 12-month OS rate of 55.6%. Median OS was not reached. 9% had a PR while 13% had a ≥50% decrease in PSA.

IMbassador250 is a phase-3 randomised clinical trial comparing atezolizumab 1200mg q3 weeks plus enzalutamide 160mg daily with enzalutamide alone in patients with mCRPC who have previously progressed on abiraterone acetate and a taxane chemotherapy [53]. The results of this trial are awaited. Further trials are being carried out to maximise the potential of atezolizumab in combination with various therapeutic strategies such as Sipuleucel-T (NCT03024216), Rad-223 (NCT02814669), cabozanitinib (NCT03170960), ipatasertib; a PIK3CA/AKT-inhibitor (NCT03673787) and different novel immunomodulators (NCT02655822, NCT03138889, NCT02410512).

Durvalumab

A phase-1 study of combination of durvaluma band olaparib in patients with mCRPC who had previously progressed on second-generation hormonal therapy showed 47% ORR in all comers [54]. 65% of these patients also had received chemotherapy previously. Overall 12-month PFS was 51.5%, however it was 83.3% for patients with DDR defects compared with 36.4% for those without DDR defects ($p = 0.031$). The combination was well tolerated with common grade-3/4 AEs of anaemia (35%), lymphopenia (24%), nausea (18%), fatigue (18%) and diarrhoea (18%). Further trials are being carried out investigating durvalumab in combination with different treatment modalities in different settings of prostate cancer i.e. with olaparib in patients with biochemically recurrent M0 prostate cancer harbouring DDR

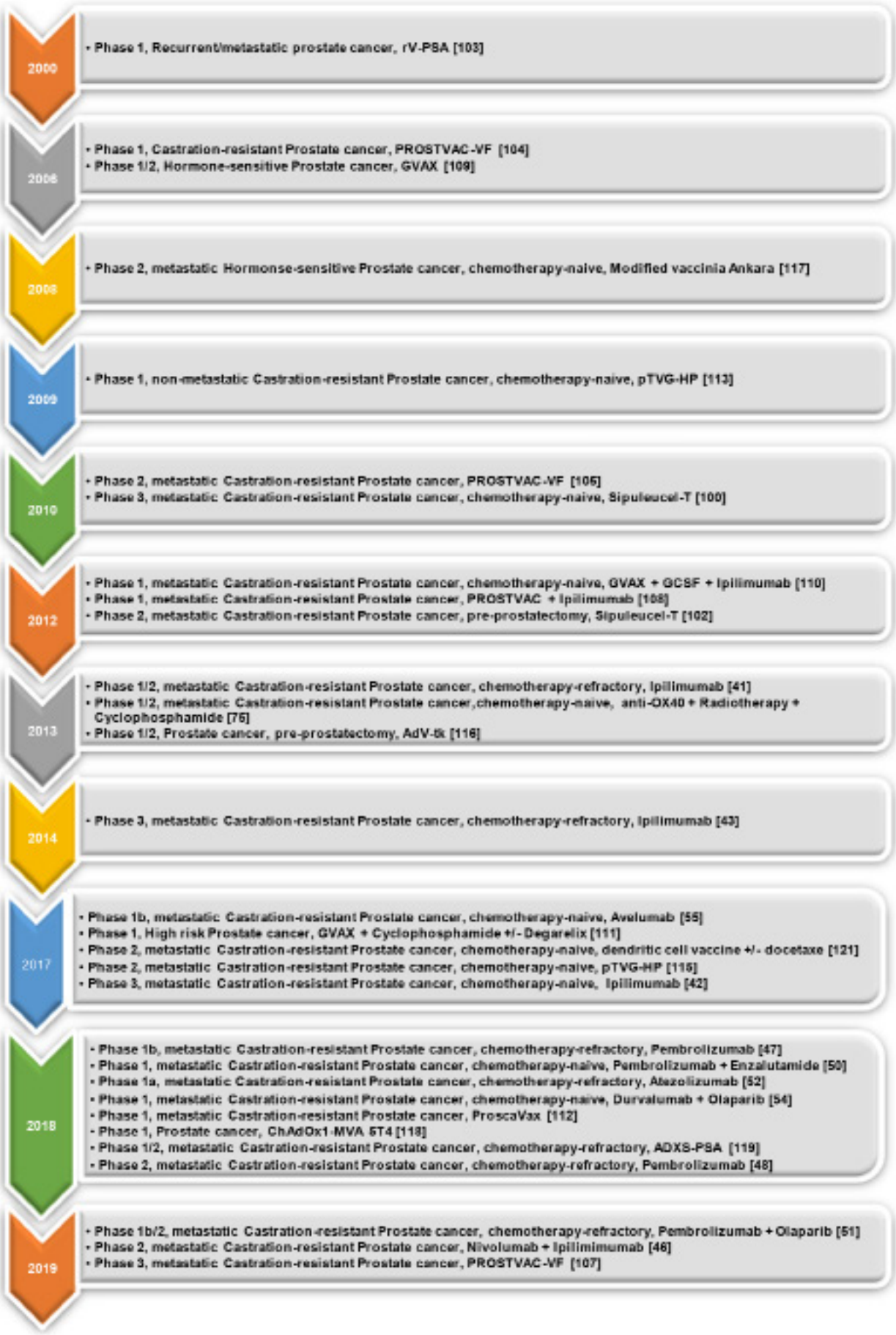

Figure 2. Reported clinical trials of immunotherapeutic agents in prostate cancer over the years.

(NCT03810105, NCT02484404); with anti-CTLA (tremelimumab) in mCRPC (NCT02788773); with stereotactic ablative radiation in oligometastatic recurrent HSPC (NCT03795207); with chemotherapy along with dual immunotherapy in mCRPC (NCT03518606); and with novel immunomodulating agents such as adenosine-A2 receptor antagonist (NCT02740985) and toll-like 3 receptor agonist (NCT02643303).

Avelumab

In a phase-1 avelumab monotherapy trial in 18 patients with heavily pretreated mCRPC, 41.1% patients had stable disease (SD) at 24 weeks of treatment, while 35.2% had disease progression at 6 weeks, radiologically reconfirmed at 12 weeks. PSA-response was assessed as PSA doubling time (PSADT) at three months. 17.6% patients had a prolonged PSADT, 41.1% patients had stable PSADT and 41.1% had decreased PSADT. Only 11% patients had grade-3/4 AEs (asymptomatic amylase and lipase elevations) [55]. Further trials with avelumab are investigating their use in neuroendocrine prostate cancer (NCT03179410), and combinations with enzalutamide or abiraterone in mCRPC (NCT03770455); with PARPi (NCT03330405); with chemotherapy (NCT03409458); and a novel immunomodulator (NCT03861403).

Novel immunotherapeutic agents and combinations of potential interest for prostate cancer

Drugs targeting checkpoint proteins

Lymphocyte activation Gene-3 (LAG-3)

LAG-3 is expressed on cell surface of lymphocytes and has been recently recognised as an important new target in cancer immunology [56]. Preclinical studies have revealed widespread co-expression of PD-1 and LAG-3 on tumour-infiltrating T-cells in several cancers and dual (anti-LAG-3/anti-PD-1) blockade has shown good synergistic results in animal tumour models [57]. Several such drugs, such as BMS986016, REGN3767, TSR033 and LAG525, are currently under evaluation (as monotherapy or in combination) in solid organ malignancies including prostate cancer, such as the phase-1b/2 MAGIC-8 (nivolumab +/-BMS-986016 in mHSPC, NCT03689699).

Killer-cell Ig-like receptors (KIR)

KIRs are expressed on mature natural-killer (NK) cells whose ligands are HLA molecules. Binding of HLA molecules to KIR results in inhibitory signalling that decreases NK cell-mediated tumour destruction. Highly effective NK cells are associated with good prognosis in patients with metastatic prostate cancer [58].

Lirilumab (anti-KIR) was tested in a dose-escalation study and was deemed well tolerated [59]. A phase-1/2 trial recently reported good safety profile [60] and significant clinical activity of lirilumab (in combination with nivolumab) in patients with advanced platinum-refractory squamous cell cancer of head and neck [61]. Further data from other expansion cohorts of this trial will provide important information on future development of these agents in other malignancies, including prostate cancer. The triple combination of lirilumab, nivolumab and ipilimumab is also being evaluated (NCT03203876).

Drugs targeting CD47 and CEACAM (Carcinoembryonic antigen cell adhesion molecules)

CD47

CD47 is an inhibitory signal protein present on tumour cells to avoid phagocytosis [62]. Preliminary data also suggest that CD47 is upregulated in various cancers, including prostate cancer [63]. Several molecules including CC-90002 (NCT02367196), Hu5F9-G4 (NCT02216409) and SRF-231 (NCT03512340), as well as bispecific antibodies such as TG-1801 (anti-CD47/CD19 bispecific MAb NI-0701) are being evaluated in haematological malignancies at present (NCT03804996).

CEACAM5

CEACAMs are the members of the CEA family of immunoglobulin glycoprotein cell adhesion molecules and being increasingly recognised as playing a key role in modulation of human malignancies [65].

CEACAM5 is a tumour-associated surface antigen expressed in over 60% of small cell neuroendocrine prostate cancers. Engineered chimeric antigen receptor T-cells targeting CEACAM5 induced antigen-specific cytotoxicity in neuroendocrine prostate cancer cell lines [64].

Drugs targeting co-stimulatory receptors

CD137

CD137 is a co-stimulatory receptor present on cytotoxic and regulatory T-cells (T*regs*) as well as NK cells. Its functions include activation of cytotoxic T-cells, inhibition of suppressive functions of T*regs* and enhancement of antibody-dependent cytotoxicity. A phase-1 dose finding study of urelumab, a monoclonal antibody agonist of CD-137, showed transaminitis as dose-limited toxicity and determined 0.1 mg/kg (q3 weeks) recommended phase-2 dose [65]. A phase-1/2 study combining urelumab with nivolumab showed ORR of 50% in melanoma (regardless of PD-L1 status), and lung, head, and neck cancer patients [66]. This combination was well tolerated with common treatment-related AEs being fatigue, transaminitis, and anaemia.

Another similar drug, PF-05082566, was evaluated in a phase-1 study in combination with rituximab in patients with relapsed or refractory non-Hodgkin lymphoma with good response rates [67]. It is being evaluated in solid organ malignancies (NCT01307267). In haematological malignancies, CD137-Chimeric Antigen Receptor (CAR) T-cell therapy and bispecific antibodies have emerged. This latter concept has also been tested in prostate cancer models, with an anti-CD137/PSMA bispecific antibody showing promising results [68].

CD27

CD27 is a co-stimulatory receptor that belongs to the tumour necrosis factor receptor superfamily and is expressed on T-cells, B-cells, and NK cells. Varlilumab, a CD27-agonist antibody, has shown to be well-tolerated and of promising anti-tumour activity in a phase-1 trial in patients with solid tumours, including prostate cancer [69]. Varlilumab is also being investigated in various combinations in several other malignancies (NCT02543645, NCT02413827, NCT02335918, and NCT02270372). A varlilumab/stereotactic body radiation therapy in a phase-1 combination trial for prostate cancer has been terminated because of low accruals (NCT02284971).

CD40

CD40 is largely expressed on antigen presenting cells (APCs) and is associated with APC maturation and immune enhancement, resulting in tumour-specific T-cell activation [70]. CP-870893,

Table 1. FDA approved checkpoint inhibitors, their indications and important adverse events [124-129].

Checkpoint inhibitor	Drugs	Tumour types	Adverse Events
CTLA4 antagonist	Ipilimumab	Melanoma Renal Cell Cancer MSI-H/dMMR colorectal cancer	Colitis (8%) Dermatologic Toxicities (29-50%) Hypophysiitis (10-17%) Hypothyroidism(<1%) Hyperthyroidism (<1%) Pneumonitis (<1%) Hepatitis (11%) Encephalitis (<1%) Nephritis (<1%) Pancreatitis (1.3%) Cardiac toxicities including myocarditis (<1%)
PD-1 inhibitors	Nivolumab Pembrolizumab	Melanoma Squamous Cell Cancer of Head & Neck Urothelial Cancer Non-small Cell Lung Cancer Small Cell Lung Cancer MSI-H/dMMR cancers, including colorectal cancer Hodgkin's lymphoma Renal Cell Cancer Hepatocellular Cancer Cervical cancer Primary mediastinal large B-cell lymphoma Merkel cell carcinoma	Colitis (1.5%) Dermatologic Toxicities (9-11%) Hypophysiitis (<1%) Hypothyroidism (5-9%) Hyperthyroidism (1-5%) Pneumonitis (1-4%) Hepatitis (1-2%) Encephalitis (<1%) Nephritis (1%) Pancreatitis (<1) Cardiac toxicities including myocarditis (1-5%)
PD-L1 inhibitors	Atezolizumab Durvalumab Avelumab	Non-small Cell Lung Cancer Urothelial Cancer Merkel cell carcinoma Urothelial Cancer	

CTLA-4: cytotoxic T-lymphocyte antigen-4; dMMR: mismatch repair deficient; MSI-H: microsatellite instability-high; PD-1: programmed death-1; PD-L1: programmed death ligand 1

an anti-CD40, in two separate phase-1 studies in patients with advanced solid tumours showed encouraging activity with grade-1/2 cytokine release-syndrome being the most common AE [71,72]. Lucatumumab (HCD122), ADC-1013, SEA-CD40, and APX005M are other anti-CD40 agents that are currently being investigated.

Glucocorticoid-induced tumour necrosis factor receptor (GITR) agonists and OX-40 agonists

GITR is expressed on T*regs* and induce activation of CD4+ and CD8+ cells. Preclinical studies of GITR-agonistic antibodies (including combinations with checkpoint inhibitors) showed preliminary signal of activity [73]. Phase-1 studies of TRX518 (NCT01239134) and MK-4166 (NCT02132754) in solid tumours are currently underway.

OX-40 (CD134) is expressed on CD4+, CD8+, and NK cells, and potentiates T-cell receptor (TCR) signalling on the surface of T-lymphocytes, leading to their activation and enhancement of T*regs* activity. In a phase-1 trial of OX40 agonist, 9B12/MEDI0562 showed limited anti-tumour activity with acceptable safety profile in patients with metastatic solid malignancies refractory to the conventional therapy [74]. A humanised version of the same drug (MEDI0562) is being tested in patients with solid organ malignancies in a phase-1 study (NCT02318394). Another trial using RG7888/MOXR0916 in combination with atezolizumab with or without bevacizumab is recruiting patients with metastatic carcinomas (NCT02410512). A combination of an anti-OX40, radiation and cyclophosphamide were studied in a phase-1/2 clinical trial in prostate cancer, achieving synergy in stimulating immune responses via tumour antigen release [75].

Drug-targeting tryptophan catabolism

Indoleamine 2,3-dioxygenase-1 (IDO1) is a tryptophan-catabolising enzyme expressed in many cancers that induces immune-tolerance by suppressing T-cell activity. IDO1 has been linked to the progression of prostate cancer with some prognostic significance [76]. The IDO1-inhibitor epacadostat, after encouraging early phase results [77], failed to reach its primary endpoint of improved PFS in a phase-3 combination study in melanoma [78], which led to halting of other phase-3 trials using IDO1-inhibitors. In another early phase study [79], epacadostat administered with ipilimumab inpatients with metastatic melanoma yielded an ORR of 30%. Combinational studies of epacadostat with nivolumab are currently in progress (NCT02327078).

A phase-1 study of single-agent indoximod involving 48 advanced cancer patients concluded this agent to be safe up to 2000mg taken twice daily [80]. Although there were no objective responses, durable SD (>6 months) was observed in five patients. Indoximod has been evaluated in combination with docetaxel in a dose-escalation study in 27 patients with metastatic cancer [81]. Investigators reported a PR rate of 18%, SD lasting less than 6 months in 36%, and SD lasting over 6 months in 4% of patients. In a phase-1b study, indoximod was combined with ipilimumab in metastatic melanoma with good tolerability [82]. A phase-2 combination study of indoximod with clinician choice of either ipilimumab, pembrolizumab, or nivolumab is ongoing (NCT02073123).

GDC-0919 is yet another experimental agent employing the same pathway. In a phase-1a study of 19 patients with recurrent/advanced solid tumours, MTD was not reached; however, 800 mg twice a day on a 21-/28-day cycle was well tolerated [83]. 44% had SD at the time of interim analysis with acceptable toxicity with an exception of one grade-4 lower gastrointestinal haemorrhage. A phase-1b study is currently recruiting patients with locally advanced or metastatic solid tumours for GDC-0919 and atezolizumab combination (NCT02471846).

Drugs targeting adenosine2A receptors (A2AR)

A2AR is activated in TME by accumulation of extracellular adenosine resulting in anti-tumour immunity suppression [84].

CPI-444, an oral selective A2AR-antagonist was investigated alone and in combination with atezolizumab in 47 patients with advanced cancers [85]. Overall DCR was 45% (mostly SD) in multiple histologies, including one patient with prostate cancer, and was equal for single agent cohort and for combination cohort. Further trials are being carried out in combination with atezolizumab (NCT02655822) and pembrolizumab (NCT03454451).

AZD4635, another A2AR-antagonist, is being investigated in advanced solid malignancies, including prostate cancer, as monotherapy and in combination with enzalutamide/abiraterone, olaparib or durvalumab (NCT02740985).

Drug-targeting chemokine signalling

The presence of immune cells in TME largely depends on chemokine ligands on these cells and their receptors on tumour cells [86]. Chemokines are structurally divided into four subgroups, namely, CXC, CC, CX3C, and C. Targeting the chemokine pathway could prove an important breakthrough in cancer treatment.

CXCR1/2

CXCR1/2-CXCL8 axis activates multiple intracellular signalling pathways that regulate proliferation and differentiation of immune cells. This axis also mediates progression of multiple cancers and hence is associated with early relapse and poor prognosis [87].

Reparixin, an inhibitor of CXCR1/2, has already shown activity in combination with paclitaxel both in hormone receptor positive and triple receptor negative breast cancer [88]. However, its impact on the prostate cancer TME remains to be studied.

AZD5069, a CXCR2 inhibitor, is being evaluated in combination with durvalumab for solid cancers including prostate cancer in an early phase study [89]. Interim results have suggested clinical benefit with manageable safety profile. The final results of this study are expected next year (NCT02499328).

CXCR4

Activation of CXCR4-CXCL12 axis activates intracellular pathways associated with cancer growth, metastasis and immune response. Recent evidence suggests that prostate cancer cells express CXCR4 and its upregulated in metastatic disease [90]. BL8040, LY2510924, and PTX9908 are currently undergoing evaluation in various solid and haematological malignancies.

Toll-like receptor (TLR) agonists

TLRs enhance immunity through recognition of microbial pathogen-associated molecular patterns and endogenous danger signals released from dying cells. It has been reported that TLR expression is reduced in prostate cancers. Disappointingly, TLR agonists as a single agent have shown poor efficacy in earlier trials, thus, necessitating further evaluation in combination with other agents to enhance their immunostimulatory effects. VTX-2337 is a TLR8 agonist that in combination with cetuximab in patients with head and neck cancer in a phase-1b clinical trial showed good

Table 2. Summary of reported clinical trials of immunotherapeutic agents involving patients with prostate cancer.

Drug	Phase	Population	Treatment	T-cell response	PSA response	ORR	Median PFS	Median OS
Ipilimumab [41-43]	1/2	mCRPC, chemo-pretreated, N = 71	Ipi /- RT	-	18.3%	21.41%	-	17.4 mo
	3	mCRPC, chemo-naïve, N = 598 (Arm A = 399, Arm B = 199)	Arm A:Ipi Arm B:placebo	-	Not reported	-	Arm A = 5.6 mo Arm B = 3.8 mo	Arm A = 28.7 mo Arm B = 29.7 mo
	3	mCRPC, chemo-pretreated, N = 799 (Arm A = 300 Arm B = 400)	Arm A:RT + Ipi Arm B:RT + placebo	-	Arm A = 13% Arm B = 5.2%	-	Arm A = 4.0 mo Arm B = 3.1 mo	Arm A = 11·2 mo Arm B = 10.0 mo
Nivolumab [38,39,46]	1	mCRPC, chemo-pretreated, N = 25	Nivo	-	-	36% in PD-L1 +ve tumours	-	-
	2	mCRPC, N =7 8 Cohort 1: chemo-naïve Cohort 2: chemo-pretreated	Ipi+ Nivo	-	Cohort 1 = 21% Cohort 2 = 13%	Cohort 1:26% Cohort 2:10%	-	-
Pembrolizumab [47,48,50,51]	1b	mCRPC, chemo-pretreated, N = 23	Pembro	-	-	17.4%	3.5 mo	7.9 mo
	2	mCRPC, chemo-pretreated, N = 258 Cohort 1: MD, PD-L1 +ve Cohort 2: MD, PD-L1 -ve Cohort 3: NMD	Pembro	-	-	Cohort 1: 5% Cohort 2: 3% Cohort 3: Not applicable	-	-
	1	mCRPC, chemo-naïve, N = 28	Enza+Pembro	-	18%	25%	10.8 mo	22.2 mo
	1b/2	mCRPC, chemo-pretreated, N = 41	Olaparib+Pembro	-	13%	71%	5 mo	14 mo
Atezolizumab [52]	1a	mCRPC, chemo-pretreated, N = 15	Atezo	-	13%	-	3.4 mo	NR
Durvalumab [54]	1	mCRPC, chemo-naive, N = 17	Olaparib+Durva	-	53%	-	16.1 mo	-
Avelumab [55]	1b	mCRPC, chemo-naive, N = 18	Avel	-	17.6%	41.1%	-	-
Varlilumab [69]	1	mCRPC, N = 2	Varlilumab	-	-	-	PR, CR	-
anti-OX40 [75]	1/2	mCRPC, chemo-pretreated, N = 9	Anti-OX40 + CP + RT	Elicited	44.4%	-	-	-
CPI-444 [85]	1	mCRPC, N = 2	CPI-444	-	-	-	SD	-
poly-ICLC [94]	1	mCRPC, N = 1	poly-ICLC + RT	-	-	-	PR	-
ALT-801 [96]	1	mCRPC, N = 2	ALT-801	-	-	-	2.3 mo	19.9 mo

Table 2. Summary of reported clinical trials of immunotherapeutic agents involving patients with prostate cancer (Continued).

Drug	Phase	Population	Treatment	T-cell response	PSA response	ORR	Median PFS	Median OS
	2	Prostate cancer, pre-prostatectomy, N = 42	Sipuleucel-T	Elicited post-prostatectomy	-	-	-	-
Sipuleucel-T [102,100]	3	mCRPC, N = 512 (Arm A= 341, Arm 2 = 171)	Arm A = Sipuleucel-T Arm B = placebo	-	-	-	Arm A = 14.6 mo Arm B = 14.4 mo	Arm A = 25.8 mo Arm B = 21.7 mo
rV-PSA [103]	1	Recurrent/metastatic Prostate cancer, N = 33	rV-PSA	Elicited	PSA stabilised	-	-	-
	1	CRPC, N = 10	PROSTVAC VF	Zero	-	-	-	-
PROSTVAC [104,105,107]	2	mCRPC, N = 122 (Arm A = 82, Arm B = 40)	Arm A = PROSTVAC Arm B = placebo	-	-	-	Arm A = 3.8 mo Arm B = 3.7 mo	Arm A = 25.1 mo Arm B = 16.6 mo
	3	mCRPC, N = 1297 (Arm V = 432, Arm VG = 432, Arm P = 433),	Arm V = PROSTVAC Arm VG = PROSTVAC + GM-CSF Arm P = Placebo	-	-	-	Arm V = 18.7 mo Arm VG = 13.7 mo Arm P = 20.0 mo	Arm V = 34.4 mo Arm VG = 33.2 mo Arm P = 34.3 mo
GVAX [109-111]	1/2	Biochemically-relapsed prostate cancer, N = 21	GVAX + GM-CSF	-	76%	-	4.7%	-
	1	mCRPC, chemo-naïve, N = 28	GVAX + GM-CSF + Ipi	46%	25%	-	-	29.2 mo
	1	High-risk prostate cancer N = 28 (Cohort A = 15, Cohort B = 13)	Arm A = Degarelix Arm B=CP + GVAX + Degarelix	NS increase in CD8+ and Treg densities in Arm B vs. A	-	-	-	-
ProscaVax [112]	1	mCRPC, N = 20	ProscaVax	80%	64%	-	-	-
pTVG-HP [113,115]	1	M0 CRPC, chemo-pretreated, N = 22	pTVG-HP	41%	31.8%	-	-	-
	2	mCRPC, chemo-pretreated, N = 14	pTVG-HP+Pembro	Not reported	Several	-	-	-
AdV-tk [116]	1/2	HSPC pre-prostatectomy, N = 9	AdV-tk	Elicited post-prostatectomy tissue specimens	77.7%	-	-	-

Table 2. Summary of reported clinical trials of immunotherapeutic agents involving patients with prostate cancer (Continued).

Drug	Phase	Population	Treatment	T-cell response	PSA response	ORR	Median PFS	Median OS
Modified vaccinia Ankara [117]	2	mHSPC, chemo-naïve, N = 27 (Cohort A = 13, Cohort B = 14)	Cohort A = modified vaccinia Ankara Cohort B = modified vaccinia Ankara + GM-CSF	Elicited post treatment 100%	-	0%	5.6 mo	-
ChAdOx1-MVA 5T4 [118]	1	Prostate cancer (intermediate and low risk), N = 39	ChAdOx1-MVA 5T4	Elicited in blood and prostate tissue	-	-	-	-
ADXS-PSA [119]	1/2	mCRPC, chemo-pretreated, N = 51 Cohort A=14, Cohort B = 37	Cohort A = ADXS-PSA Cohort B = ADXS-PSA + Pembro	-	Cohort A = 14% Cohort B = 43%	Cohort A = 0% Cohort B = 8.6%	-	-
Dendritic cell vaccine [121]	2	mCRPC, chemo-pretreated N = 43	Cohort A = DC vaccine + Docetaxel Cohort B = Docetaxel	Elicited post treatment 78% in cohort A	Cohort A = 38% Cohort B = 58%	Not reported	Cohort A = 5.7mo Cohort B = 5.5mo	Not reported

ADT: androgen deprivation therapy; Atezo: Atezolizumab; Avel: Avelumab; Chemo: chemotherapy; CP: cyclophosphamide; Durva: Durvalumab; Enza: Enzalutamide; GM-CSF: Granulocyte macrophage-colony stimulating factor; HSPC: hormone-sensitive prostate cancer; Ipi: Ipilimumab; mCRPC: Metastatic castration-resistant prostate cancer; MD: measurable disease; mHSPC=metastatic hormone-sensitive prostate cancer; Nivo=Nivolumab;NMD: non-measurable disease; NS: non-significant; OS: Overall survival; ORR: Objective response rate; Pembro: Pembrolizumab;mo: month(s);PFS: Progression-free survival; PSA: Prostate specific antigen; RT: Radiotherapy; DC: dendritic cells

tolerability and treatment response [91]. Another trial of VTX-2337 in combination with pegylated-doxorubicin involving patients with metastatic ovarian cancer is currently underway (NCT02431559).

In a double-blinded phase-2 trial, MGN1703 (TLR9 agonist) has shown promising activity as a maintenance therapy in 59 patients with metastatic colorectal cancer who had normalised tumour markers after the first-line induction therapy [92]. In a subgroup of patients with high-activated NK cell counts at baseline, there was a significant improvement in PFS. These results are encouraging but need further validation due to small study sample and immature survival data.

SD-101 (TLR9 agonist), in combination with pembrolizumab in a phase-1 study has shown good activity in 22 patients with melanoma [93]. ORR was 78% in checkpoint inhibitor-naïve patients as compared to 15% in patients who received checkpoint inhibitors previously. The 12-month PFS was 88%, and the OS was 89%. A phase-2 study of SD-101 in combination with radiotherapy and pembrolizumab in prostate cancer is ongoing (NCT03007732). Poly-ICLC (TLR3 agonist), is an immunostimulant being investigated in mCRPC patients in multiple trials as a vaccine adjuvant. A phase-1 study of 15 patients with mCRPC studied poly-ICLC along with dendritic vaccine and stereotactic radiotherapy [94]. The treatment was well tolerated. One heavily pretreated mCRPC patient had a mixed response while nine patients experienced SD. Further studies are ongoing combining this therapy with various treatment modalities including tremelimumab and durvalumab (NCT02643303), pembrolizumab (NCT03007732) and MUC1 vaccine (NCT00374049).

Drugs targeting the interleukin pathway

NKTR-214

NKTR-214 recombinant human interleukin-2 (IL-2), has shown good activity in preclinical tumour models [95]. Trials are being conducted for various tumours, including prostate cancer, alone and in combination with other checkpoint inhibitors (NCT03138889).

ALT-801

Recombinant human IL-2 is known to be able to induce durable CR in a small number of patients with metastatic melanoma and kidney cancer; however, it is associated with significant toxicities such as hypotension, capillary leak syndrome, and oliguria. ALT-801 is an innovative immunotherapeutic fusion protein consisting of IL-2, linked to a single-chain T-cell receptor domain that recognises a peptide epitope (aa264-272) of the human p53 antigen displayed on cancer cells in the context of HLA-A*0201 (p53+/HLA-A*0201). A phase-1 study of ALT-801 for advanced cancers showed SD in 38% of all 26 patients including one patient with mCRPC as best response [96].

ALT-803

Interleukin-15 (IL-15) is a key factor for the development, proliferation, and activation of NK cells and CD8+ memory T-cells. ALT-803 is a novel IL-15 agonist (N72D) with enhanced IL-15 biological activity and has so far been studied in animal models only. It has demonstrated durable anti-tumour activity in breast and colon murine models [97]. It is being investigated in combination with checkpoint inhibitor for mCRPC. Further clinical studies in combination with other immunotherapeutic agents in prostate cancer are warranted.

BMS986253

Interleukin-8 (IL-8) is known to promote immune escape and tumour progression and high serum IL-8 levels correlate with poor prognosis in various tumours [98]. A phase-1 study investigated BMS986253, an anti-IL-8, in 15 patients with advanced cancer [99]. PFS at 24 weeks was 73% while no grade-3/4 AEs were observed. 13.3% experienced grade-2 fatigue, hypophosphataemia and hypersomnia. It is currently being investigated in combination with nivolumab in HSPC (NCT03689699).

Vaccines

Although there are ever increasing number of emerging therapeutic agents in oncology, cancer vaccines have now become the most exciting expanding area of immunotherapeautics.

Sipuleucel-T (Provenge) is an autologous cellular immunotherapeutic vaccine, consisting of antigen-presenting cells, which have been activated *ex-vivo* with a recombinant fusion protein (PA2024), which in turn stimulates T-cell immune response against prostatic acid phosphatase in prostate cancer cells. IMPACT trial was a double-blind, placebo-controlled, phase-3 trial of 512 patients with mCRPC to receive either three infusions of sipuleucel-T or placebo two weeks apart. A median OS of 25.8 months in the sipuleucel-T patients versus 21.7 months in the placebo group was observed [100]. It was well-tolerated with grade-1/2 chills, fever and headache in most patients. This study elicited significant criticism regarding the observed albeit modest OS benefit without correlation with a PFS benefit or a T-cell response, and the absence of alternative mechanisms to explain the survival benefit [101]. Nevertheless, sipuleucel was approved by US FDA in 2010 for mCRPC. In a phase-2 study, 42 men with localised prostate cancer received sipuleucel-T prior to radical prostatectomy [102]. Increased incidence of T-cells was observed in the post-operative prostate gland histology compared to pre-operative biopsies. Currently, clinical trials are investigating combination of sipuleucel-T with other approved drugs, such as abiraterone acetate, enzalutamide, radium-223 and ipilimumab (NCT01487863, NCT01981122, NCT02463799, NCT01832870, NCT01804465).

rV-PSA is a recombinant vaccinia virus encoding human PSA in a phase-1 study of 33 mCRPC patients, showed a PSA response in 57.5% patients [103].

PROSTVAC-VF is a poxvirus-based vaccine that acts through genetically modified vaccinia virus and fowlpox virus encoding PSA. In a phase-1 trial of 10 patients with mCRPC who received PROSTVAC-VF, 40% patients had PSA stabilisation [104]. In a phase-2 study, 82 patients with mCRPC achieved 30% 3-year OS as compared to 17% in the control group with a median OS benefit of 9.9 months (26.2 months vs 16.3 months) [105]. A second reported phase-2 trial on 32 patients reported a median OS of 26.6 months, with patients with greater PSA-specific T-cell responses showing a trend ($p = 0.055$) towards enhanced survival [106]. However, the recently reported phase-3 study on 1298 asymptomatic or minimally symptomatic mCRPC patients, although confirmed its safety profile, failed to substantiate an OS benefit [107]. After these disappointing results, more trials are being run in combination with other immunotherapeutic agents, such as anti-PD-1, ipilimumab and nivolumab (NCT2506114, NCT02933255, NCT03532217). One such reported trial tested the combination of PROSTVAC-VF with ipilimumab in mCRPC in a phase-1 clinical trial. 14 of the 24 chemotherapy-naïve patients had reduction in PSA, six of them with a reduction of more than 50%. The median OS was 31.3 months, which was longer than PROSTVAC alone [108].

The granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine (GVAX)

showed promising activity in a phase-1 trial [109]. A median OS of 26.2 months in patients with asymptomatic mCRPC was observed. Most common AE was grade-1/2 injection-site reaction (100%). GVAX was later studied in combination with ipilimumab in 28 mCRPC patients in a phase-1 trial [110]. 39% grade-3/4 irAEs were seen (most common: hypophysitis, alveolitis, and hepatitis). 25% had PSA < 50% decline while 53.5% had SD radiologically. Another phase-1 trial investigated the use of neoadjuvant degarelix alone or in combination with GVAX and cyclophosphamide in 28 high-risk prostate cancer patients undergoing radical prostatectomy, versus no neoadjuvant treatment. Intratumoural immune infiltrates were marginally augmented by cyclophosphamide/GVAX/degarelix versus degarelix alone, while CD8+ and T*reg* densities were significantly greater in both study arms versus the control group. Time-to-PSA-relapse was also improved although not statistically significant (Hazard ratio = 0.42) [111]. Further trials with immunotherapy are warranted.

Interim results of the phase-1 trial investigating the Proscavax vaccine [PSA/Interleukin-2(IL-2)/Granulocyte-macrophage colony-stimulating factor (GM-CSF)] in patients with M0 biochemical relapse (HSPC or CRPC) indicated a good safety profile with interesting activity in slowing PSADT and mounted immune responses to PSA [112]. A phase-2 trial of Proscavax versus active surveillance in localised prostate cancer is underway (NCT03579654).

A phase-1/2 clinical study evaluated 22 biochemically recurrent M0 prostate cancer patients, who received pTVG-HP/PAP DNA-based vaccine encoding prostate acid phosphatase [113]. No significant AEs were observed. 31.8% of the patient had a doubling of PSADT while 45.4% had T-lymphocyte responses correlating with increased number of vaccinations [114]. A phase-2 trial reported good efficacy and safety profile of pTVG-HP/PAP when used in combination with pembrolizumab [115]. Further trials are investigating pTVG-HP/PAP versus GM-CSF in patients with biochemically recurrent prostate cancer (NCT01341652), combination with sipuleucel-T in mCRPC (NCT01706458), and combination with nivolumab in patients with PSA-recurrent prostate cancer (NCT03600350).

AdV-tk is a new gene-mediated cytotoxic immunotherapy vaccine. Intratumoural delivery of a Herpes virus thymidine-kinase gene inserted in an adenoviral vector mediates the effect of vaccine. Based on the promising results in a phase-1/2 trial [116], a phase-3 trial is investigating vaccine immunotherapy in combination with radiation therapy for intermediate to high-risk prostate cancer patients (NCT01436968).

PAN-301-1 is a human aspartyl-asparaginyl-β-hydroxylase-directed nanoparticle vaccine. A phase-1 trial is evaluating its safety and efficacy inpatients with biochemically-relapsed prostate cancer (NCT03120832).

Modified vaccinia virus Ankara vaccine delivering the 5T4 tumour-associated antigen (Tro-Vax) has failed to show objective response in a phase-2 CRPC trial, despite 5T4-specific immune responses and delayed time to PSA-progression [117].

The novel ChAdOx1-MVA5T4 vaccine consists of two recombinant viruses designed to produce the 5T4 protein once injected into the body. It was investigated in a phase-1 study in with low and intermediate risk prostate cancer [118]. The vaccine was well tolerated. 5T4-specific CD4 and CD8 T-cells were extracted from patients' prostate biopsies. A clinical trial is investigating its combination with nivolumab in intermediate risk and advanced prostate cancer (NCT03815942).

ADXS-PSA, an attenuated Listeria monocytogenes-based immunotherapy targeting PSA, designed to create antigen-specific T-cell effectors that kill tumour cells. A trial evaluated 51 patients with heavily pretreated mCRPC in 2 groups: A- ADXS-PSA; and B- ADXS-PSA in combination with pembrolizumab [119]. Common AEs (any grade) were cytokine release symptoms. PSA-response was 14% versus 43% in group-A and group-B respectively while PSA-response >50% was 0% versus 22%. Of the evaluable patients, SD was noted for 20% and 43% respectively.

NEO-PV-01 is a unique vaccine employing the concept of neoantigens. Tumour cell surface neoantigens are the "unique to cancer DNA sequences", that once identified, are synthesized in the lab and mixed with an adjuvant immune enhancer. This concept is being tested in a phase-1 study along with nivolumab in advanced malignancies (NCT02897765).

Coxsackie virus A21 is a bio-selected oncolytic and immunotherapeutic strain of Coxsackie family given intratumourally to provoke an immune response. It is being tested alone in several tumours including CRPC (NCT02043665), and in combination with pembrolizumab and ipilimumab, intravenously or intratumourally.

Another phase-1b clinical trial combining oncolytic virus, Ad11/Ad3 chimeric group-B adenovirus with nivolumab is underway in metastatic cancers (NCT02636036).

Dendritic cells (DCs) are leukocytes that are spread throughout the body and have ability to present antigens to T-cells and play an important role in immunosurveillance. A DC-vaccine comprises isolated DCs loaded *ex-vivo* with tumour-specific antigen to activate antigen-specific T-cells and generate an immune response *in-vivo* against antigen-bearing cancer cells [120]. A randomised phase-2 study compared a DC vaccine plus docetaxel to docetaxel monotherapy in 43 patients with mCRPC. Although the PSA responses and PFS were comparable, a tumour-associated antigen immune-response was observed in 78% patients in the doublet arm [121].

Immune effector cell therapies

The concept of development of modified and activated T-cells with innate anti-tumour activity using CARs, TCR and tumour-infiltrating lymphocytes is still experimental in epithelial malignancies but has been successfully trialled in patients with relapsed acute lymphoblastic leukaemia resulting in a high remission rate [122]. This opens up a new immunotherapeutic possibility in prostate cancer research models. This includes prostate stem cell antigen (PSCA) targeted studies such the GEM3PSCA bispecific antibody engaging T-cells (NCT03927573), as well as PSCA-CAR T-cell studies in CRPC (NCT03873805, NCT024744287, NCT03089203). Other approaches such as PSMA CAR-T therapy are still in early phase of development showing moderate success [123].

Discussion

Immune checkpoint inhibition monotherapy has shown limited activity in prostate cancer. Nevertheless, certain immunotherapeutic agents have demonstrated good activity in specific cohorts and will likely play a major role in changing the future landscape of prostate cancer treatment (**Table 2, Figure 2**). One of the noteworthy features of the immuno-oncology trials landscape in prostate cancer thus far is the lack of extensive immunoprofiling data in regard to the type, intensity and duration of T-cell response, both centrally and peripherally. Such a translational component is increasingly becoming an essential feature of immuno-oncology trials in other tumour types such as melanoma and renal cancer but is still largely lacking in prostate cancer. This is an aim to aspire for, as we are in need of understanding the compromises and difficulties to be overcome in the interaction of prostate cancer with the host local

microenvironment and immune system.

Given the moderate immunogenicity of prostate cancer, significant progress is more likely to occur either with combinations or with newer immune effector therapy approaches, such CAR-T or TCR therapies (**Figure 1**). Several studies are ongoing to find the best tolerated dose of newer agents alone or in combination with other chemotherapeutic and established immunotherapeutic agents. The ultimate utility of these agents would depend on survival results from ongoing clinical trials along with finding an appropriate biomarker for efficacy.

The future successful development of immunotherapy in prostate cancer would involve overcoming many obstacles, including better understanding of tumour heterogeneity, elucidating mechanisms of primary and secondary treatment resistance, developing effective synergistic combinations (and regimens) without increased treatment-related toxicities, and tackling a high cost of new agents in the era of constrained resources. In the battle against these unique challenges, the incorporation of unparalleled genomic information, new biomarkers for efficacy in clinical trials and strong pharmacodynamic endpoints may lead the way forward.

The future of immuno-oncology in prostate cancer

Currently, a large number of immuno-oncology drugs directed against several distinct steps of a well-recognised immunologic cascade that is rendered dysfunctional by a growing tumour are being investigated in various solid organ malignancies. Paving the way forward, these agents, if they demonstrate a good response, may attain an important role as solitary or adjunctive treatment (either with chemotherapy or other immunotherapeutic agents) in the near future in various cancers, including prostate cancer. The aim, of course, would be to improve upon the recent advances in the field of prostate cancer by achieving durable responses with combination immunotherapy strategies, with the help of appropriate biomarkers optimally identifying candidate patients.

Future clinical trials in prostate immuno-oncology should be geared towards finding the right drug for the right patient at the right time by innovative designs that are enriched for patients who would obtain the greatest survival benefit. As the prostate oncology community is ambitiously aiming to transform advanced prostate cancer into a chronic disease, clear survival benefit in the context of improved or maintained quality of life at a sustainable cost, especially for long-term treatments, is *sine qua non*.

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Ethics approval and consent to participate

This study did not require prior ethics approval or consent from human participants.

Author contributions

SB wrote and prepared the manuscript. MSK prepared the figures. MRG , CM and HTA reviewed the manuscript. AP prepared the figures, and reviewed the manuscript.

Competing interests

The authors declare no conflict of interest with the work.

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