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Review

The new era of prostate-specific membrane antigen-directed immunotherapies and beyond in advanced prostate cancer: a review

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***Abstract*:** The lack of success in prostate cancer from immune checkpoint inhibitors, which is likely multifactorial, has led to the development and investigation of a number of other novel immunotherapeutic techniques, including antibody–drug conjugates, T-cell redirected bispecific therapies, cancer vaccines and chimeric antigen receptor T-cell therapies. Prostate-specific membrane antigen (PSMA) is a tumour-associated antigen (TAA) that is highly expressed in metastatic prostate cancer and has been validated as an effective target for radionuclide treatment. But while PSMA has thus far been the 'front runner' target for these novel immunotherapeutic techniques, it may not be the ideal target for immunotherapy and there are other potential targetable TAAs that will require further exploration. This review will focus on these various PSMA-directed therapies, as well as other potential targets for immunotherapy beyond PSMA.

Keywords: antibody–drug conjugates, bispecific antibodies, CAR-T-cell therapy, immunotherapy, prostate cancer

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Introduction

The landscape of cancer medicine has evolved significantly in recent decades with the incorporation of immunotherapy into standard practice. Immune checkpoint inhibitors have become pivotal treatments across many solid organ malignancies, including melanoma and lung cancer, and finding new opportunities in which to employ these therapies continues to be the focus of much clinical research. Thus far, in prostate cancer, immune checkpoint inhibitors have had limited efficacy, both as monotherapies and as immunotherapy-based combinations.

Several studies have investigated the use of these agents in a number of clinical settings, without any significant success. The anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), ipilimumab, was not found to improve survival compared to placebo in unselected populations of patients with metastatic castrate-resistant prostate cancer (mCRPC) in both the pre- and post-docetaxel setting, although a pre-planned long-term analysis of the post-docetaxel study did show two to three times higher survival rates at 3 years and beyond.[1,2]

In IMbassador250, Atezolizumab [anti-programmed cell death ligand 1 (PD-L1)] in combination with enzalutamide did not improve survival compared to enzalutamide alone in castrate-resistant disease progressed on abiraterone.[3] In KEYNOTE-199, pembrolizumab [anti-programmed cell death protein 1 (PD-1)] monotherapy showed minimal anti-tumour activity with objective response rates of 5% in PD-L1-positive and 3% in PD-L1-negative populations, respectively.[4] In CheckMate650, the combination of anti-CTLA-4 and anti-PD-1 did demonstrate anti-tumour activity in chemotherapy-naïve and chemotherapy-experienced patients with mCRPC, with objective response rates of 25%

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and 10%, respectively; however, rates of grade 3–4 adverse events were high (42–53% of patients).[5]

The lack of benefit of immune checkpoint inhibitors in prostate cancer is likely multifactorial, attributed at least partly to the 'cold' immune tumour microenvironment (TME), low levels of PD-L1 and low tumour mutational burdens.[6] Perhaps however, this lack of efficacy of immunotherapies directed towards non-specific immune checkpoints could be overcome by targeting tumour-associated antigens (TAAs) or tumour-specific antigens (TSAs). Sipuleucel-T is an autologous cellular immunotherapy agent aimed at stimulating T-cell immune response targeted against prostatic acid phosphatase, an antigen that is highly expressed in most prostate cancers and is considered a TAA.[7] Despite a modest survival advantage demonstrated among men with mCRPC, uptake has been poor due to cost, complexity of administration and lack of immediate PSA decline, with no significant reduction of prostate-specific antigen level ⩾50% (PSA50 response) or improvement in progression-free survival.[8]

There may be more effective means of targeting TAAs and TSAs, which could offer greater clinical benefit. Prostate-specific membrane antigen (PSMA) is a TAA that is highly expressed in mCRPC and has been validated as an effective target for treatment, with radionuclide therapy targeting PSMA shown to prolong progression-free survival and overall survival in the TheraP and VISION trials.[9,10] This had led to the development of a variety of immunotherapeutic approaches targeting PSMA, including antibody drug conjugates (ADCs), T-cell re-directed bispecific (TCB) therapies, cancer vaccines and chimeric antigen receptor (CAR)-T cell therapy. Heterogeneity of TAA expression may impact therapeutic response differentially with different approaches, such as radioligand *versus* immunotherapy agents. This review will focus on advantages and limitations of various PSMA-directed therapies, as well as other potential targets for immunotherapy beyond PSMA.

Antibody–drug conjugates

ADCs are highly potent therapeutic agents which combine chemotherapy and immunotherapy. ADCs consist of a monoclonal antibody directed towards a specific TAA expressed on the surface of tumour cells, conjugated to a cytotoxic 'payload' *via* a chemical linker. The first ADC to receive regulatory approval in solid tumours was trastuzumab emtansine for HER2-amplified advanced breast cancer in 2012, and more recently has been followed by the approval and incorporation into practice of sacituzumab govitecan and trastuzumab deruxtecan in advanced breast cancer, and enfortumab vedotin in urothelial cancer.[11–14]

Selection of the appropriate TAA, monoclonal antibody, cytotoxic agent and chemical linker are key requirements for a successful ADC.[15] PSMA meets the conditions for a suitable choice of TAA for an ADC: it has limited or no expression on healthy cells but is highly expressed on tumour cells, and promotes internalisation to facilitate transport of the ADC into the cell. Key requirements for the monoclonal antibody component of the ADC include high target-binding affinity and specificity, good retention, low immunogenicity and cross-reactivity, and appropriate linkage-binding properties. A stabilised linker is required to avoid releasing the cytotoxic drug as the ADC circulates, maintain cytotoxic agent in an inactive state while bound to the antibody, and release the drug upon internalisation.[15] Finally, the cytotoxic payload must be chosen carefully to ensure its stability during systemic circulation and have sufficient potency to destroy tumour cells, even at low doses.[15]

Several PSMA-targeted ADCs have reached clinical trial stage in humans. MLN2704 is an ADC targeting PSMA comprising MLN591, a de-immunised anti-PSMA monoclonal antibody, linked to a potent anti-microtubule chemotherapeutic agent maytansinoid-1 (DM1).[16,17] In a phase I/II clinical trial, 62 patients with mCRPC received MLN2704 in ascending doses. Five patients (8%) achieved the primary efficacy end point of a sustained ⩾50% decline in PSA. Neurotoxicity rates were high [44 patients (71%) developed peripheral neuropathy, six patients (10%) grade 3–4] and dose limiting. Another PSMA-ADC of immunoglobulin G1 anti-PSMA monoclonal antibody, conjugated to monomethylauristatin E was tested in a phase II trial of 119 mCRPC subjects (both chemotherapy experienced and chemotherapy naïve) who had progressed following abiraterone or enzalutamide.[18] Anti-tumour activity was demonstrated with respect to PSA declines (PSA50 response in 14% of all; 21% of chemotherapy-naïve patients),

circulating tumour cell conversions/reductions (declines ⩾ 50% in 78% of all treated and 89% of chemotherapy naïve), and radiological assessments (stable disease in 60.7% of patients). Treatment-related adverse events were common and often serious, including neutropenia (in 32% of patients) and neuropathy (8% had grade 3), and led to treatment cessation in 31% of subjects.[18] MEDI3726, an ADC targeting PSMA carrying a pyrrolobenzodiazepine payload, was evaluated in a phase I trial of patients with mCRPC progressed on abiraterone and/or enzalutamide and taxane-based chemotherapy.[19] The composite response rate was 4/33 (12.1%). Three patients (9%) had a PSA50 response. Grade 3/4 treatment-related toxicities, predominantly skin toxicities and effusions, occurred in 15 patients (45.5%), with 11 patients (33.3%) discontinuing the drug.[19]

The design and development of PSMA-targeted ADCs have been hampered by issues with toxicity and limited efficacy, perhaps related to the cross-targeting of non-cancer tissues resulting in a narrow therapeutic index, along with lability of the linkers and vulnerability to degradation and the unknown optimal concentrations to improve bioavailability and tissue penetration.

While ADC constructs have evolved significantly since these early studies, such as improved stability of linkers, TAA selection in prostate cancer has also evolved. Novel ADCs targeting TAAs other than PSMA have demonstrated impressive efficacy. One such target is B7-H3, which is overexpressed in various cancers. DS-7300 is an ADC targeting B7-H3, linked to an exatecan-derivative payload. A phase I study of DS-7300 in 29 heavily pre-treated mCRPC patients demonstrated encouraging efficacy, with 6 partial responses and 15 stable diseases, and preliminary data indicating PSA response and improvement in bone metastases.[20] The safety profile was acceptable, with no grade ⩾3 adverse events were reported. Another target, anti-six transmembrane epithelial antigen of the prostate 1 (STEAP-1), is a transmembrane channel for ion and protein transport, and is highly expressed in prostate cancer with limited expression in non-prostate tissues, making it an ideal ADC candidate for prostate cancer. DSTP30865 is an ADC targeting STEAP1 that demonstrated 18% PSA50 response rate in a phase I trial in mCRPC patients.[21] Sacituzumab govitecan (IMMU-132), already in use in metastatic triple-negative breast cancer and currently being investigated in phase III trials in urothelial cancer, is a Trop-2 targeting ADC composed of SN-38 (the active metabolite of irinotecan).[21] It has shown modest clinical activity in mCRPC and is being investigated in a phase II trial of mCRPC patients pre-treated with abiraterone or enzalutamide.[22,23] Finally in a phase Ia/Ib study of FOR46, an ADC targeting CD46, highly expressed in prostate cancer and enriched following androgen receptor blockade in mCRPC, tumour regression was demonstrated in 10/21 (48%) of patients, and the PSA50 response rate was 45%. Neutropenia, infusion reactions and neuropathy were the most common toxicities, though primary granulocyte colony-stimulating factor (G-CSF) prophylaxis helped mitigate transient neutropenia.[24]

While the early success of these newer non-PSMA-targeted ADCs may be explained by next-generation antibodies, linkers and payloads, there must be some reflection as to whether PSMA is the ideal TAA for ADCs. While there may be a perception that most prostate cancer patients will highly express PSMA, data from TheraP[10] and VISION[9] clinical trials have demonstrated that 13–28% of patients will not have sufficient uptake on PSMA positron emission tomography (PET) to be suitable for ^{177}LuPSMA-617, and of those who were eligible for treatment only 25–33% of patients would have sufficiently high PSMA expression (SUVmean > 10 on PSMA PET) to achieve greatest benefit from ^{177}LuPSMA-617.[25,26] While novel radionuclides using alpha emitters such as ^{225}Ac may increase the proportion of patients who gain substantial benefit, currently, for beta emitting radionuclides such as ^{177}LuPSMA-617, higher target expression correlates with greater benefit, and this may possibly also be extrapolated to ADCs. Despite a large proportion of patients gaining only modest benefit, the tolerability of ^{177}LuPSMA-617 has allowed it to be quickly adopted as a standard of care. For ADCs, where toxicity is greater, there may be a higher bar to clear when it comes to efficacy data, and subsequently, selecting a target with consistently high expression may be important.

Allowing for differences in technique and limitations of cross-study comparisons, studies examining immunohistochemistry expression in prostate cancer specimens showed consistently higher expression of CD46 and B7-H3 compared to PSMA. Roth *et al.*[27] demonstrated moderate to marked intensity of B7-H3 in 100% of Gleason

8-9 and 88% of Gleason 7 specimens. Su *et al.*[28] demonstrated strong staining of CD46 in 80% of prostate cancer specimens. Comparatively, Hupe *et al.*[29] demonstrated medium to high PSMA staining in 81% of Gleason Grade group 4 and 5, and 67% of Gleason Grade group 3. While we suggest that expression of target is an important factor for benefit from ADCs, recent data from the TROPICS-02 breast cancer trial have demonstrated that sacituzumab govitecan is effective across a wide range of Trop-2 expression levels, including activity in those with very low Trop-2 expression defined as H-score $\leqslant 10$.[30] This is due to bystander effect where the lipophilic payload leaks into surrounding cells after cleavage from antibody, thereby affecting non or low antigen expressing cells. Clearly, there is much more to understand when it comes to ADCs, and perhaps the key to further developing improving these agents is to continue to fine-tune antibodies, target affinity, linkers and payloads, as well as identifying the optimal tumour target. Simultaneously, it will be important to identify ways to identify and overcome known mechanisms of resistance, such as physical barriers to penetration into TME,[31] downregulation of target (TAA) expression, reduced activity of lysosomes and proteolytic cell machinery to reduce linker cleavage or upregulation of transmembrane drug efflux channels.[32,33]

TCB therapies

TCB therapies represent an evolving therapeutic field in prostate cancer. By activating T cells in the presence of cancer cells, they may help overcome the immunosuppressive TME in prostate cancer. TCB therapies are bispecific antibody constructs in which one epitope binds to T cells *via* the T-cell receptor/CD3 complex, and the other is targeted against a TAA, such as PSMA. By activating the patient's T cells, TCB therapies induce targeted tumour cell death independent of endogenous T-cell recognition or MHC restriction.[34]

Pasotuxizumab (AMG212) is a first-generation PSMA TCB therapy designed to engage T cells *via* CD3 and prostate cancer cells *via* PSMA.[35] In a phase I study of 47 patients with mCRPC, pasotuxizumab was initially delivered *via* a daily subcutaneous injection; however, after all patients developed antidrug antibodies, continuous infusion was employed. Early evidence of clinical activity was demonstrated; 9/31 (26%) and 3/16 (19%) in the subcutaneous and continuous infusion groups had a PSA50 response, including two long-term responders. AMG160 is a next-generation PSMA $\times$ CD3 TCB therapy with an extended half-life studied in progressive mCRPC refractory to at least one taxane-regimen and novel hormonal therapy.[36] During dose escalation, PSA responses occurred in 15/24 (63%) patients and PSA50 responses in 34% of patients. The most common adverse event was cytokine release syndrome (CRS; affecting 90.7% of patients, grade 3 25.6%) and was manageable with no grade 4/5 events or treatment discontinuations. Three reversible dose-limiting treatment toxicities occurred due to rash and gastrointestinal haemorrhage. Updated reports from this study are awaited. Other PSMA TCB therapies currently in phase I clinical trials in mCRPC include AMG340 and JANX007.[37,38] Notably, none of these trials selected for patients with PSMA expression, either by tissue staining or by PSMA PET scan. However, retrospective analyses of PSMA expression may shed light on whether level of TAA expression has an impact on efficacy of PSMA-targeted TCB therapy.

TCB therapies engaging CD28, complimentary to CD3 as the costimulatory T-cell signal, have also been investigated. REGN5678, a human IgG4-based, first-in-class costimulatory TCR therapies bridging PSMA-expressing cells with CD28.[39] Early clinical data (unpublished) from an ongoing phase I/II trial have shown promising dose-dependent anti-tumour activity in combination with cemiplimab (anti-PD-1).[40]

There are several TCB therapies being trialled in the prostate cancer that are directed towards other TAAs. Tarlatamab is a half-life extended TCB therapy targeting delta-like ligand 3 DLL3, an inhibitory Notch ligand which is a promising target in neuroendocrine prostate cancer, binding it to CD3 on T-cells.[41] It is currently being evaluated in a phase Ib study. Interim results from a first-in-human study of tarlatamab in patients with small-cell lung cancer, where DLL3 is also highly expressed, have shown efficacy and an acceptable safety profile.[42] Other CD3 engaging TCBs being developed for mCRPC are targeting human kallikrein 2 (KLK2) (JNJ-78278343), STEAP-1 (AMG509) and oncofetal antigen 5T4 (GEN1044).[43–45]

Common challenges with TCB therapies include the requirement for repeated dosing or continuous infusion, and immune-related toxicities

including CRS, which can be manageable with mitigation strategies such as steroid pre-medication for the initial doses or a step-dosing strategy. For PSMA-targeted TCB therapies, patients can also develop PSMA-specific toxicities including xerostomia, dry eyes, thrombocytopenia and leukopenia, nausea and vomiting. Furthermore, TCB therapies may generate anti-drug antibodies, limiting their efficacy.[46] Despite significant investment in developing TCB therapies in solid cancers, to date, there is only one TCB therapy that has gained FDA approval for a solid malignancy: Tebentafusp is a bispecific gp100 peptide-HLA-directed CD3 T-cell engager, FDA approved for HLA-A*02:01-positive metastatic uveal melanoma patients.

Given the success of ^{177}LuPSMA-617 in prostate cancer, multiple novel TCB therapies continue to target PSMA; however, next-generation TCBs have made adjustments to reduce the rates of CRS observed thus far, either through reduced CD3 affinity (AMG340), or masking the binding site for CD3 (JANX007).[37,38] The outcomes of these approaches are eagerly awaited. However, given the success seen targeting other TAAs in prostate cancer, the question is whether PSMA is the best target for this particular treatment modality, particularly given the rapid internalisation of PSMA upon binding. Rapid internalisation is a feature that should benefit both radionuclide and ADC approaches, however, for TCB therapies, where the CD3 engaging component must continue to be expressed on the cell surface to engage T cells, rapid internalisation may be counter-productive. Interestingly, one paper has postulated whether this is something that can be utilised when designing novel TCB therapies: in describing a HER2-targeted TCB therapy with low anti-CD3 affinity that has greater accumulation in tumour compared to T-cell-rich tissues, the author discussed the effect that affinity for target has on biodistribution.[47,48] It is possible that targets such as PSMA, which have rapid internalisation, may require TCBs that have low PSMA affinity to reduce the impact of target-mediated degradation, whereas targets with low rates of turnover may benefit from higher affinities to their target. This theory has yet to be borne out in the clinic and as a result we eagerly await the results of next-generation PSMA-targeted TCBs while also questioning whether PSMA is the right target.

Cancer vaccines

Another promising strategy in the genre of oncology immuno-therapeutics are cancer vaccines, which stimulate anti-tumour immunity with antigen-specific T cells from the host immune system. Ideally, they would overcome the immune suppression in tumours to stimulate both cellular and humoral immunity. PROSTVAC, a viral vector-based immunotherapy using recombinant poxviruses expressing PSA along with immune-enhancing costimulatory molecules, was safe and well tolerated in a large randomised phase III clinical trial of patients with mCRPC, but the study was terminated due to lack of efficacy, with no effect on survival.[49] GVAX is a vaccine consisting of two prostate cancer cell lines, LNCaP and PC-3, transfected with a human GM-CSF gene. While phase I and phase II studies demonstrated clinical activity and safety of this vaccine, the phase III trials VITAL-1 and VITAL-2, comparing GVAX alone or in combination with docetaxel to docetaxel–prednisolone in asymptomatic and symptomatic mCRPC patients, were terminated due to futility and increased deaths in the GVAX-docetaxel combination arm.[50,51] An autologous dendritic cell-based immunotherapy, DCVAC/PCa was compared to placebo in combination with chemotherapy followed by maintenance treatment in a phase III trial of 1182 mCRPC patients. Although it was well tolerated, no survival benefit was reached.[52]

The COVID-19 pandemic has made the broader public aware of mRNA-based vaccines; meanwhile, cancer researchers have been exploring mRNA vaccines as a therapeutic strategy against cancer for many years. mRNA-based vaccines are well tolerated, easily degraded, and do not integrate into the host genome and have potential to induce both humoral and cell-mediated immunity. The number of clinical trials with therapeutic mRNA cancer vaccines is rapidly expanding. Therapeutic mRNA cancer vaccines are most likely to succeed in combination with other immunotherapeutic treatment methods.

In prostate cancer, multiple therapeutic anti-cancer vaccines remain in development. PSMA is being explored as a promising target for prostate cancer vaccines due to its molecular properties, and abundant expression on the surface of prostate cancer cells, and limited expression in other tissues.[53,54]

CAR-T-cell therapy

CAR-T-cell therapy is an emerging immunotherapy that has made significant breakthroughs in recent years. It involves harvesting autologous or allogeneic T cells and genetically engineering them to add a CAR directed against a specific cancer antigen.[55] The activated T cells are then expanded before being reinfused back into the patient. Lymphodepleting chemotherapy or radiotherapy is required to allow 'space' for the clonal expansion of CAR-T cells. Because CAR-T cells are engineered to combine the effector function of T cells with the ability of antibodies to identify specific antigens, they do not require antigen presentation by antigen presenting cells and can recognise intact proteins. Therefore, the use of CAR-T cells enables several mechanisms of immunological tolerance to be overcome.[56]

While CAR-T therapy has demonstrated impressive and durable clinical benefit in haematological malignancies, it has yet to achieve the same efficacy in solid organ malignancies, despite some early promising results in mesothelioma.[57] Researchers have been focussed on overcoming several challenges including identifying the best TAA or TSA to target, improving the delivery of CAR-T cells to tumour sites, overcoming the immune-suppressive TME to achieve durable responses, and managing toxicities such as CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).[56,58] In prostate cancer, specific barriers to CAR-T cell therapy include markedly elevated levels of transforming growth factor-β (TGFβ) and indoleamine 2,3 dioxygenase in the TME, which inhibit T-cell-mediated cytotoxicity, along with high degree of suppressive myeloid cell infiltration in the TME, and the formidable stromal barrier in bone metastases which may prevent CAR-T cells from infiltrating into the tumour bed.[46]

PSMA, with its high expression in mCRPC, represents a promising TAA for CAR-T-cell therapy. Slovin *et al.*[59] demonstrated that patients could be safely treated with PSMA-targeted CAR-T cells following lymphodepletion with cyclophosphamide in a small cohort of seven patients in a phase I dose-escalating study presented in 2013. In this study, one patient had stable disease for >6 months, another for >16 months. CAR-T cells persisted in the circulation for up to 2 weeks. In another phase I trial, five patients underwent chemotherapy conditioning and infusion of PSMA-targeted CAR-T cells, in combination with a continuous infusion of low dose IL2. The 20% engraftment target was met or exceeded in three patients, and no anti-PSMA or anti-CAR toxicities were detected. Two patients achieved PSA50 responses.[60] In another phase I trial, investigators attempted to overcome the high levels of inhibitory TGFβ in the immunosuppressive TME by arming PSMA-targeted CAR-T cells with a dominant-negative TGFβ receptor.[61] Preliminary evidence for anti-tumour function was observed, with approximately 30% of treated patients achieving a PSA reduction of ⩾30%. Of the 13 patients who received therapy across four dose levels, five developed grade ⩾2 CRS, with one patient experiencing fatal toxicity due to CRS and sepsis (while also demonstrating a rapid and marked PSA decline of >98%) and a second fatal toxicity due to macrophage activation syndrome (MAS). This study has offered insight into the safety and efficacy profile of TGFβ-armoured CAR-T therapy directed to PSMA, with some promising signs of being able to overcome to 'cold' TME of prostate cancer. Further work is required to develop strategies to improve the persistence of these CAR-T cells while reducing severe toxicities.

TAA candidates alternative to PSMA, are also being considered for CAR-T cells, including prostate stem cell antigen (PSCA), highly expressed on the surface membrane in mCRPC.[56] A PSCA-CAR-T cell has been developed and data presented from the first-in-human study by Dorff *et al.* after treatment of 12 patients. Preliminary anti-tumour effect was seen, including a radiographic response and 95% PSA decline, at the starting dose of 100 million CAR-T+ cells with lymphodepletion. However, two patients experienced grade 3 cystitis (dose-limiting toxicity), likely in part due to a higher dose of lymphodepleting cyclophosphamide, although PSCA expression in the urothelium makes this potentially an on-target, off-tumour toxicity. Further data from dose escalation are eagerly awaited.[62]

Human KLK2 is expressed predominantly in prostate tissue, co-localised with KLK3, which is also known as PSA. Like PSMA, it is an androgen receptor-controlled gene yet remains highly expressed as castration resistance develops. A CAR-T-cell therapy targeting KLK2 is currently in clinical testing (JNJ-75229414).[63] Notably, this target is also being studied in a trial with a TCB (JNJ-78278343) and a radiopharmaceutical (JNJ-69086420).[45,64]

While there are still many challenges to overcome, CAR-T cells have the potential to become an important therapeutic option for mCRPC, though novel dosing strategies, including combination therapy, may be necessary to achieve success approaching that seen in haematologic malignancies. Management of toxicity may require predictive models for CRS, MAS and ICANS to guide identification and interventions.[46] As this complex field continues to evolve, further modifications to CAR-T cells, or the addition of adjunct therapies, may be needed to overcome the immunosuppressive TME of solid tumours such as prostate cancer.

One interesting example that illustrates the difficulty of developing CAR-T cell therapy in solid tumours is CTX130, an allogeneic CAR-T that targets CD70. Phase I trials of CTX130 have been conducted in both T-cell lymphoma and renal cell carcinoma (RCC). In the T-cell lymphoma study, where median CD70 expression was 90%, the overall response rate was 70% with complete response rate of 29%.[65] In the RCC study, there was one response, and overall response rate was 8%.[66] While it is highly likely that the greater immunosuppressive TME in RCC compared to T-cell lymphoma is driving the disparate response rates, it is also possible that differences in CD70 expression are also playing a role. Historical data suggest that CD70 expression in RCC is much lower compared to T-cell lymphoma, with one study describing only 22% of clear cell RCC having >50% of IHC expression of CD70.[67] Noting the CD70 experience in T-cell lymphoma and RCC, and understanding that alternative targets are more highly expressed in prostate cancer than PSMA, while the field invests heavily in developing CAR-T cell therapies to overcome an immunosuppressive TME, we should not forget the importance of careful target selection.

Conclusion

In this early era of PSMA-targeted immunotherapy, we have not yet achieved the substantial benefits that have been seen with PSMA-targeted radionuclide therapy. For PSMA-targeted immunotherapy approaches such as TCB therapies, cancer vaccines and CAR-T therapies, this is in part due to the dependence on overcoming an immunosuppressive TME to allow activated T cells to engage cancer cells. While for PSMA-targeted ADCs, the reduced benefits compared with radionuclide therapy may relate to a narrow therapeutic index. The next generation of ADCs, TCB therapies, cancer vaccines and CAR-T cell therapies in prostate cancer are being developed to overcome many of these challenges. However, one additional matter that should be addressed is target selection. While PSMA has been the 'front runner' target for novel immunotherapeutic techniques, it may not be the ideal target for immunotherapy; as we have outlined, there are other TAAs in prostate cancer that warrant further exploration. Although the role of immunotherapy in prostate cancer currently remains limited, we are confident that with the rapid progress we are making, targeted immunotherapy will soon become a highly effective option for our prostate cancer patients.

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Ethics approval and consent to participate

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Consent for publication

Not applicable.

Author contribution(s)

Felicity C Martin: Conceptualisation; Writing – original draft; Writing – review & editing.

Tanya B Dorff: Conceptualisation; Writing – review & editing.

Ben Tran: Conceptualisation; Project administration; Writing – original draft; Writing – review & editing.

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