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PSMA targeting in metastatic castration-resistant prostate cancer: where are we and where are we going?

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***Abstract*:** Prostate-specific membrane antigen (PSMA) is highly expressed on the membrane of most prostate cancer cells and to a lesser extent in normal tissues. Many vectors targeting this protein have been created over the past decade and numerous clinical studies have positively demonstrated the tolerance and efficacy of radiolabeled prostate-specific membrane antigen ligands for PSMA radioligand therapy (PRLT). Preliminary results are encouraging that PRLT will become an important addition to the current therapeutic options in a number of settings. Improvement in radiopharmaceutical targeting and combination with other oncological agents are under investigation to further improve its therapeutic efficacy. These encouraging results have led to the development of other therapies using PSMA as a target, such as PSMA–targeted chimeric antigen receptor T-cells, PSMA–targeted antibody drug conjugates, and PSMA–targeted bi-specific T-cell-directed therapy. This narrative review details the current state and advancements in prostate-specific membrane antigen targeting in prostate cancer treatment.

Keywords: immunotherapy, prostate cancer, PSMA, radionuclide therapy

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Introduction

Prostate cancer is the second most frequently diagnosed cancer in men, with an estimated 1.3 million new cases expected in 2018 [World Health Organization (WHO)]. Prostate cancer is the third most common cause of cancer mortality among men, accounting for just over 10% of all cancer-related deaths. Metastases appear in approximately 20% of patients. The treatment landscape now moves far beyond the use of androgen deprivation therapy (ADT), which has been the mainstay of treatment since the 1970s. Options for patients with both castration-sensitive and castration-resistant prostate cancer now include multiple types of chemotherapy (docetaxel, cabazitaxel) and novel hormonal agents (abiraterone, enzalutamide, apalutamide, darolutamide), all of which improve survival and quality of life across the disease spectrum. However, despite the impressive activity and substantial improvement in survival for patients with advanced prostate cancer, these treatments will inevitably fail and survival for patients who have progressed following standard therapies remains poor.[1]

Prostate-specific membrane antigen (PSMA) is a non-secreted membrane enzyme with the activity of a caboxypeptidase and folate hydrolase, presenting with a large extracellular domain. The PSMA receptor has an oncogenic signaling role in prostate cancer cells, acting on glutamate receptors and activating the Pi3 K and Akt growth pathways.[2,3] It is overexpressed in 90% of metastatic prostate cancer[4] while having a low level of physiological expression in normal tissues (prostate, small intestine, salivary and lachrymal glands, and kidney). Cellular studies have demonstrated that once the PSMA-ligand binds to the PSMA receptor, there is internalization that leads

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to intracellular trapping with prolonged retention of the ligand. This appears to happen predominantly within tumor cells, while in normal tissues, where there may be non-specific uptake, there is relatively rapid washout. This phenomenon is demonstrable by repeated scintigraphic imaging using PSMA ligands radiolabeled with gamma-emitter isotopes with differential clearance kinetics from tumor sites compared to normal tissues. These features make PSMA an ideal target for novel prostate cancer therapies, either by radiolabeling PSMA ligands in the case of radionuclide therapy or by targeting PSMA using immunotherapeutic approaches.

Part 1: PSMA radioligand therapy (PRLT)

Development

Radioligand or radionuclide therapy is a form of treatment that leverages the theranostic paradigm consisting of a diagnostic and therapeutic procedure which is tightly coupled. In regard to PSMA radioligand therapy (PRLT), the first step involves a diagnostic scan using PSMA Positron Emission Tomography (PET)/computed tomography (CT) to evaluate tumor PSMA expression. Unlike histopathology from a single tumor site, this enables evaluation of tumors heterogeneity. In case of favorable biodistribution, the therapeutic procedure is followed using radiolabel PSMA ligands with isotope-emitting particles (beta particles such as Lutetium 177, or alpha particles such as Actinium 225).

The initial studies used radiolabeled anti-PSMA antibodies, mostly J591. A phase I-II study observed a relationship between the dose of one injection of Lutetium-177-J591 (^{177}Lu-J591) and Prostate Serum Antigen (PSA) decline; however, myelotoxicity was also often observed. The 70 mCi/m^2 dose, when compared with the 65 mCi/m^2 dose, resulted in a greater number of 30% reduction in PSA (46.9% *versus* 13.3%, $p=0.048$) and longer survival (21.8 *versus* 11.9 months, $p=0.03$), but also increased grade 4 hematologic toxicity and platelet transfusions.[5,6] Fractioning the dose using three injections of 30 mCi (1.11 GBq)/m^2 appeared less myelotoxic.[7]

Efficacy for antibodies is limited by longer circulation half-life, which contributes to increased marrow radiation dose and toxicity, and poor tumor penetrability, particularly for bone metastases. Subsequently, small molecules (PSMA-ligands) have been developed for PRLT. They are able to be radiolabeled with similar high tumor/background ratio and when compared to antibodies, have more favorable biodistribution with less myelotoxicity. The development was mostly done by teams in Germany.[8–10] Numerous observational studies have been reported worldwide, and the results of the first two randomized studies have been recently presented: The phase II TheraP clinical trial conducted in Australia[11] and the international phase III VISION clinical trial.[12] Based on the increasing experience, the European Association of Nuclear Medicine now includes guidelines for PRLT.[13]

Efficacy and side effects

An exhaustive review reported the results of 17 studies, including 14 prospective studies evaluating the effect of PRLT in 744 patients.[14] A decrease in PSA was objectively observed in 493/671 (69%) patients evaluated, including 46% with >50% reduction in PSA (PSA50). The median survival for treated patients was 13.7 months (8–14 months), close to that of Abiraterone (14.8 months), despite patients being treated at later lines, many of whom had previously progressed on Abiraterone. A third of the patients had an improved quality of life.

Side effects have been heterogeneously reported in the studies. Grades 3–4 concern mostly hematological toxicity occurring in less than 10%. The extent of bone marrow metastases may increase the hematotoxicity, however, among 319 heterogeneous patients, two-thirds of those presenting with more than 20 lesions or a diffused bone marrow involvement did not demonstrate hematological issues.[15] Despite intense physiological renal and salivary gland uptake, there have been no reports of nephrotoxicity (0–20%) or xerostomia (5.5–33.5%) greater than grade 2. Grades 1–2 fatigue and nausea were less common. There appears to be no additional toxicity in patients previously treated with Radium 223.[16] However, pre-existing renal failure has been a contraindication for PRLT in reported series and subsequently, it is recommended that kidney scintigraphy to assess kidney function and exclude obstruction in the urinary tract is performed prior to PRLT. However, unlike other radionuclide therapy, for PRLT there is no need for concomitant amino acid infusion to protect kidney function.

Von Eyben *et al.* conducted two extensive reviews of the literature to compare, in the absence of phase III study data available at that time, the efficacy of PRLT to third-line systemic treatment of metastatic castration-resistant prostate cancer (mCRPC).[17,18] A PSA50 is observed in 44% of patients with PRLT compared to 22% for third-line systemic therapy ($p = 0.0002$, t test). In addition, the objective response rate was greater for PRLT compared to third-line systemic therapy (28% *versus* 16%, $p = 0.004$); as was median survival, albeit not significantly so (14 months *versus* 12 months, $p = 0.32$). Side effects were responsible for discontinuation of treatment for 0/469 PRLT patients compared to 22/66 patients treated with third-line systemic therapy ($p < 0.001$). In the latest review, the authors pointed out that PRLT resulted in a 1.3 times higher rate of median PSA decline ⩾50% than treatment with abiraterone, enzalutamide, mitoxantrone, or cabazitaxel ($p = 0.00001$), as well as a 1.1 times higher 6-month rate of median radiographic progression-free survival.

In a non-randomized phase II study conducted by a group at Peter MacCallum Cancer Centre in Melbourne, Australia, the reported overall response rate to PRLT as defined by (Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 71% (complete response and partial response).[19] The Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group has recently reported the results of TheraP, a phase II open label, randomized, multicentre trial that enrolled patients with mCRPC, aiming to determine the activity and safety of ^{177}Lu-PSMA compared to cabazitaxel in men with progressive mCRPC previously treated with docetaxel (NCT03392428, TheraP).[20] Of 291 men who were screened, 200 were eligible on PET imaging combining FluoroDeoxyGlucose (FDG) PET and PSMA-PET criteria. Since the presence of FDG-positive/PSMA-negative disease was an exclusion criteria for this trial but not used in most other series, the results obtained in TheraP may not be reproduced in other series that do not use both tracers for patient selection. PSA50 was significantly higher with ^{177}Lu-PSMA-617, 66% *versus* 37%, while grade 3–4 adverse events were also lower, 35% *versus* 54%.[11] In seven patients who demonstrated an exceptional response based on PSA and complete metabolic response on post-treatment scintigraphy, treatment was paused; however, patients were allowed to re-commence up to the maximum of six cycles of PRLT upon subsequent progression.

The multi-national phase III VISION trial (Endocyte, NCT03511664) enrolled 831 patients with mCRPC in a 2:1 ratio to receive either six cycles of 7.4 GBq of ^{177}Lu-PSMA-617 plus best supportive/best standard of care (SOC) ($n = 551$) *versus* SOC only ($n = 280$).[12] The difference in OS was statistically significant, with an estimated 38% reduction in risk of death in the ^{177}Lu-PSMA-617 arm compared to the best standard of care only arm (median OS, 15.3 months *versus* 11.3 months, hazard ratio 0.62, $p < 0.001$). The incidence of adverse events of grade 3 or above was higher with 177Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected. In the ^{177}Lu-PSMA-617 plus standard of care (SOC) arm, 11.9% of patients discontinued ^{177}Lu-PSMA-617 and 8.5% discontinued SOC; this compares favorably to the SOC alone arm where 7.8% of patients discontinued treatment. Acute kidney injury was only observed in 3.0% of the ^{177}Lu-PSMA-617 arm compared with 2.5% on the SOC only arm. All the key secondary end points significantly favored 177Lu-PSMA-617.

Predicting for response and survival with PRLT

Responses to PRLT can be highly disparate. There is a need for predictive factors. Ferdinandus' multivariate analysis revealed that the most significant independent predictive factors were platelet count and regular need for pain medication for the 50 patients included in a prospective phase II. The response was independent of the amount of PSMA uptake on ^{68}Ga-PSMA PET as well as previous therapies, and other measured factors.[21] Presence of visceral metastases and elevated lactate dehydrogenase (LDH) were associated with worse treatment outcomes.[22]

An early marker of response to PRLT is the decrease in PSA, 2 months after the first cycle, correlating with progression-free survival and overall survival (68 weeks if PSA decreases after the first cycle *versus* 33 weeks if it does not).[23] However, in patients who do not sustain a PSA response following the first cycle, treatment should not be discontinued as nearly one-third of patients show a delayed response following additional cycles.[24]

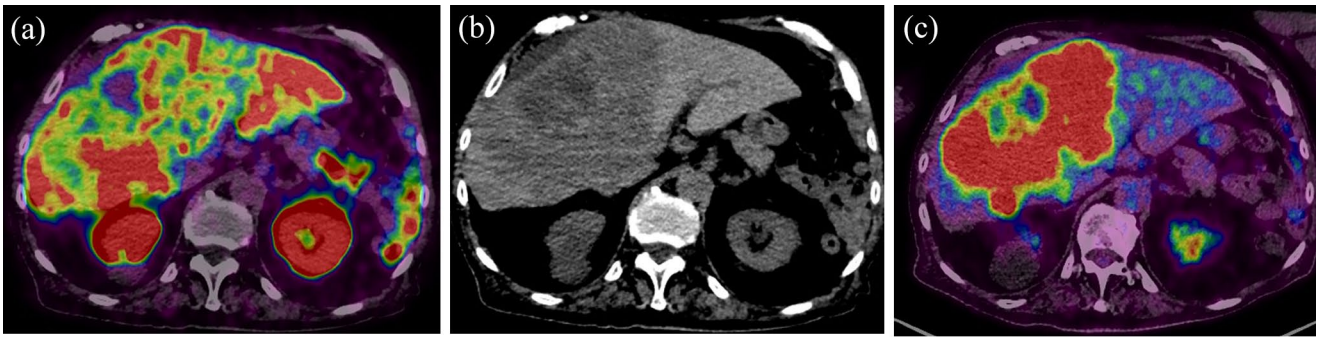


Figure 1. PSMA and FDG screening. Patient presenting with enlarged liver metastases demonstrating low PSMA uptake on ^{68}Ga-PSMA compared to normal liver and compared to FDG, leading to patient ineligibility for 177Lu-PSMA. Axial view of the (a) ^{68}Ga-PSMA PET-CT and (b) the CT component. (c) Axial view of the ^{18}F-FDG PET-CT showing intense FDG uptake in the PSMA-negative areas of the lesion, ruling out the hypothesis of a purely necrotic origin for the absence of PSMA expression of the lesion.

Like most therapies in prostate cancer where the presence of measurable lesions is uncommon, PSA is the dominant biomarker used to evaluate treatment response to PRLT. ^{68}Ga-PSMA PET/CT may play a major role for therapeutic response assessment and even predict survival for PRLT,[25,26] but this has yet to be confirmed in prospective studies. A panel of experts suggested the use of the following criteria to assess disease response on ^{68}Ga-PSMA PET/CT: 'Complete response': complete disappearance of any lesion with tracer uptake; 'partial response': reduction of uptake and tumor volume by $>30\%$; 'SD': change of uptake and tumor volume $\pm \leqslant 30\%$ and no new lesions; 'progressive disease': appearance of two or more new lesions and increase of uptake or tumor PET volume $>30\%$.[27]

The Peter MacCallum team also compared dosimetry and clinical data in these patients. Given the extent of the disease and the tumor heterogeneity, tumor dosimetry can be difficult to assess. They suggested an estimate of the mean total body tumor dose alongside lesional tumor dosimetry, postulating that this may be more clinically relevant. A 3-timepoint (H4, H24, and H96) 3D dosimetry study allowed assignment of voxel-based cumulative activity for tumors on Single Photon Emission Computed Tomography-Comuted Tomography (SPECT-CT). These cumulative activities extrapolated to tumor dose can be considered in a similar vein to area under the curve assessments for pharmacokinetics of systemic therapies. They appeared to be correlated with PSA response at 12 weeks with a median corresponding dose of 14.1 Gy in patients achieving PSA50 *versus* 9.6 Gy for those not achieving PSA50.

Despite encouraging results, one-third of patients do not respond to treatment. In addition, responses are often followed by rapid progression.[9] Due to the low toxicity, it is possible to retreat patients at progression and achieve a further transient response.[28,29] In fact, in one series, patients who received PRLT following progression had significantly improved OS compared with patients who ceased PRLT at progression (12 and 9 months, respectively).[11]

Although it remains unclear, there are multiple reasons for resistance to PRLT. Heterogeneity of PSMA expression between metastases in the same patient is a commonly cited cause.[4] The hypoxic tumor microenvironment (TME) of prostate cancer metastases is another cause, given it can induce radiation resistance.[30] Molecular profile may also contribute to PRLT, with one case of resistance in a patient with BRCA2 overexpression,[31] while defective DNA repair, namely alterations in genes such as BRCA2 and ATM, are associated with higher PSMA expression and therefore possibly greater benefit from PRLT. It is clear that there is more to understand in terms of mechanisms of response or resistance to PRLT.[4]

Improving PRLT outcomes

Patient selection. Improving outcomes to PRLT may depend on many factors, the most important of which is likely to be patient selection. It is important to clearly define patient selection criteria for PRLT. PSMA expression demonstrates intra- and inter-patient heterogeneity, is increased in patients with mCRPC when compared with patients with hormone-sensitive mPC, and appears sometimes lowered in liver metastases,[4] as seen in Figure 1.

^{68}Ga-PSMA PET is used to evaluate the *in vivo* PSMA expression in all metastases. In the Peter MacCallum phase II pilot study, a threshold of tumor uptake greater than 1.5 times physiologic hepatic activity was used. In addition, the study utilized FDG PET/CT with the presence of FDG-positive, PSMA-negative disease being an exclusion criterion.[29,32] For the ANZUP TheraP trial, the selection criteria were modified as follows: at least one site of metastatic disease required a SUVmax of 20, and SUVmax >10 for measurable soft tissue lesions of at least 1 cm. F-FDG PET/CT was also utilized with the same exclusion criterion. Using these criteria, approximately 30% were deemed not suitable: 10% due to low PSMA expression at all sites and 20% owing to sites of FDG-positive, PSMA-negative disease. FDG positive but PSMA negative were excluded, thus enriching for patients most likely to respond. Other studies, including the VISION study, have not required both FDG and PSMA PET to be performed as part of eligibility. The VISION trial has used a visual criteria of uptake intensity greater than liver and used CT/magnetic resonance imaging (MRI) to identify sites >2 cm with no PSMA uptake leading to 12.6% dropout on screening.

Further post hoc analyses of these studies may enable optimization of selection criteria for PRLT. Ferdinandus did not find a relationship between the level of tracer uptake within disease sites on PSMA-PET and the response to PRLT.[29] However, even in patients deemed suitable for treatment, a high metabolic tumor volume on baseline FDG PET was an adverse prognostic factor.

Optimizing dosing. To date, there is no defined maximum tolerated dose (MTD) of ^{177}Lu-PSMA. Given disease response seems to correlate with increasing dose,[33] it may be theoretically interesting to increase the tumor absorbed dose by increasing the administered activity of ^{177}Lu-PSMA. However, this must be balanced with the risk of marrow toxicity, particularly in patients with extensive medullary involvement, or those who have been heavily pretreated with chemotherapy or extensive external beam radiotherapy. The doses used for PRLT align with doses used for peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE for treating neuroendocrine tumors in the NETTER-1 trial that led to regulatory approval of this agent.[34] However, these doses are not based on an established MTD or rigorous dosimetry. The low toxicity observed at these doses suggests they are well below a MTD and that there is likely to be a significant therapeutic window to increase dose to tumor while still having an acceptable toxicity profile.

The dosing schedule within TheraP started at 8.5 GBq and then reduced by 0.5 GBq for every subsequent cycle given (i.e. to 6.0 GBq on the sixth cycle, if reached). This approach allows treatment with a higher initial dose, potentially reducing the number of radioresistant clones that may appear after additional cycles.

Dosimetry can also be used to calculate the cumulative activity. We can set the MTD in normal tissue to calculate the maximal cumulated dose throughout the cycles without risking increased toxicity, similar to what is done for external beam irradiation (EBI). By default, we use the MTD in normal tissues irradiated with EBI. For PRLT, we would use 28 Gy for the kidneys and 30–65 Gy for the parotids as reported by Emami *et al.*,[35] and the 2 Gy bone marrow constraint.[36] This method allows an increase or decrease in the maximal cumulated dose with great tolerance as demonstrated in PRRT.[37–39] It reduces the number of patients who would be overtreated or undertreated by applying the usual schema of four cycles of 7.4 GBq of ^{177}Lu labeled somatostatin analogues (^{177}Lu-Dotatate). Studies are required to evaluate the applicability of PRLT. Ultimately, there is balance between adopting a dosimetry-based approach and phase I dose-escalation approach to optimize PRLT dosing.[40]

Alpha particle emitters. In order to increase DNA damage, modifications of the radiopharmaceutical have been made using PSMA ligands radiolabeled with alpha particle-emitting isotopes, such as Actinium 225, with sometimes spectacular results but frequent xerostomia that can be absolute and thus adversely impact quality of life. The team from Heidelberg reported the preliminary experience with 40 patients treated with three cycles of 100 kBq/kg of ^{225}Ac-PSMA-617, each 2 months apart.[41] Patients were selected for these treatments based on having a large tumor volume, or a diffuse osteomedullary invasion making it dangerous for beta particle emitters, which travel longer distances than alpha particles. Five patients had to stop treatment due to ongoing progressive disease and four due to xerostomia. The median survival time was 5 months and five patients had a prolonged survival of more than 2 years. Interestingly, the same team treated 26 patients who progressed after 177Lu-PSMA with PSA50 achieved in 17/26

patients and median OS 7.7 months. Hematological grade 3/4 toxicities were anemia (35%), leucopenia (27%), and thrombocytopenia (19%). All patients experienced at least grade 1–2 xerostomia. Two and six patients stopped due to hematological toxicity and xerostomia, respectively.[42]

Increasing PSMA expression. PSMA expression can be regulated by the androgen receptor (AR).[43,44] In the presence of androgen, the stimulation of AR leads to the blocking of PSMA synthesis. On the contrary, in the absence of androgen, the AR is in an intracytoplasmic position and therefore non-stimulable, allowing PSMA overexpression. An increase in tumor PSMA expression under androgen blockade was confirmed in a small animal experiment, and in one patient after 1 month of androgen blockade, leading to a marked increase in the intensity of the foci already visualized and the appearance of 13 new foci.[45] This suggests a possible synergistic effect of androgen blockade and PRLT. However, the antiproliferative effect of effective androgen blockade may similarly reduce radiosensitivity, given non-cycling cells are less sensitive to radiation. A recent study demonstrated an increased ^{68}Ga-PSMA uptake compared to normal tissues in 10 patients with mCRPC after a mean of 11.8 days of enzalutamide 160 mg/day, while PSA values did not change significantly.[46] Interestingly, the effect appears heterogeneous but seems to depend on the hormone-sensitivity status.[47] Indeed, at day 9, PSMA expression decreased on repeated ^{68}Ga-PSMA PET after androgen blockade in 6/7 metastatic hormone-naïve patients, in concordance with PSA decrease, but increased in 9/9 patients with mCRPC.[4868]Ga-PSMA PET may be used to select hormonal sensitivity of metastases. However, a heterogeneous response was observed within the same patient, as some lesions increased in intensity and could therefore reflect an early clonal resistance to hormonal treatments. The ENZA-P clinical trial (NCT04419402) is currently testing this hypothesis in a randomized phase II design comparing enzalutamide to the combination of ^{177}Lu-PSMA-617 and enzalutamide in a high-risk mCRPC population.

Combination therapies. Checkpoint inhibitors in prostate cancer have very little activity.[49] However, combining radiotherapy and checkpoint inhibitors may be synergistic and improve efficacy, through an increased expression of tumor-associated antigens and activation of cytotoxic T cells in the TME. The benefit of the association of immunotherapy with ^{177}Lu-PSMA in patients with mCRPC will be evaluated in two prospective phase I/II trials, NCT03658447 in Australia and NCT03805594 in the United States. The American team has reported encouraging first results in an abstract at the ASCO 2021 congress: ^{177}Lu-PSMA-617 followed by pembrolizumab was well tolerated in 18 patients and led to durable responses in four patients with mCRPC who did not have high mutational burden or microsatellite instability, suggesting a possible immunogenic priming effect of radioligand therapy.[50]

PARP inhibitors (PARPi) are proven to improve survival in prostate cancer patients who harbor DNA repair defects. While only ~20% of patients with prostate cancer will harbor DNA repair defects, their presence may be enriched in patients who are resistant to PRLT: The team from Heidelberg have performed biopsies of seven metastases resistant to ^{225}Ac-PSMA despite intense ligand uptake and observed the presence of DNA repair genes alterations.[51,52]

Treating patient at earlier stages. Given the benefits observed in using docetaxel, abiraterone, and enzalutamide in the hormone-sensitive setting, the outcomes from PRLT may be greatly improved by using it in earlier phases of prostate cancer. The UpFrontPSMA study is a randomized phase II study that will recruit 140 men with newly diagnosed PSMA-PET defined high-volume metastatic disease to two cycles of ^{177}Lu-PSMA-617 followed by six cycles of docetaxel to docetaxel alone, both arms receiving concomitant ADT.[53] The NCT04443062 trial will evaluate the benefit of PRLT in oligometastatic patients defined on the ^{18}F-PSMA PET has having up to five lesions. The NCT04430192 trial will even address the 20 expected patients to two cycles of PRLT in neo-adjuvant situation.[54]

Part 2: PSMA-targeted immunotherapy

Led by immune checkpoint inhibitors, immunotherapy has revolutionized the landscape of oncological treatment and is now standard of care in many cancers. Unfortunately, as discussed, immune checkpoint inhibitors have limited efficacy in prostate cancer.[55] This modest activity is thought to be multifactorial, related to an immunosuppressive TME, associated with low levels of PD-L1, a low tumor mutation burden, and other poorly understood factors.[56] However, the

promise of complete responses and sustained benefit from immuno-oncological approaches in other cancers, along with the survival benefit observed with the use of autologous cellular immunotherapy sipuleucel-T, continues to drive research aimed at making immunotherapy effective in prostate cancer.[57]

PSA50 response rates from immune checkpoint inhibitors, either alone or in combination, have been low at 5–20%.[55,58,59] While PSA50 response rate from sipulecel-T was also low, there was an overall survival benefit observed in the phase III study, which was not observed for ipilimumab as a single agent.[57,58] While the precise mechanism of sipuleucel-T is unknown, it is thought to work by stimulating T-cell immune response targeted against prostatic acid phosphatase (PAP), an antigen that is highly expressed in most prostate cancer cells.[57] Given this targeted approach resulted in an overall survival benefit, there are now multiple immunotherapies being developed for prostate cancer.

PSMA is the perfect candidate for targeted immunotherapies. Not only is it highly expressed in advanced and castration-resistant prostate cancer, its large extracellular domain makes it a perfect target for immune approaches.[60] In addition, the activity seen with PSMA-targeted radionuclide therapy, as described above,[14] validates it as an excellent target in prostate cancer.

PSMA-targeted immunotherapy can be classified into four major categories: antibody drug conjugates (ADC), chimeric antigen receptor T-cells (CAR-T), PSMA-directed vaccines, and bispecific T-cell re-directed therapy.

Antibody drug conjugates

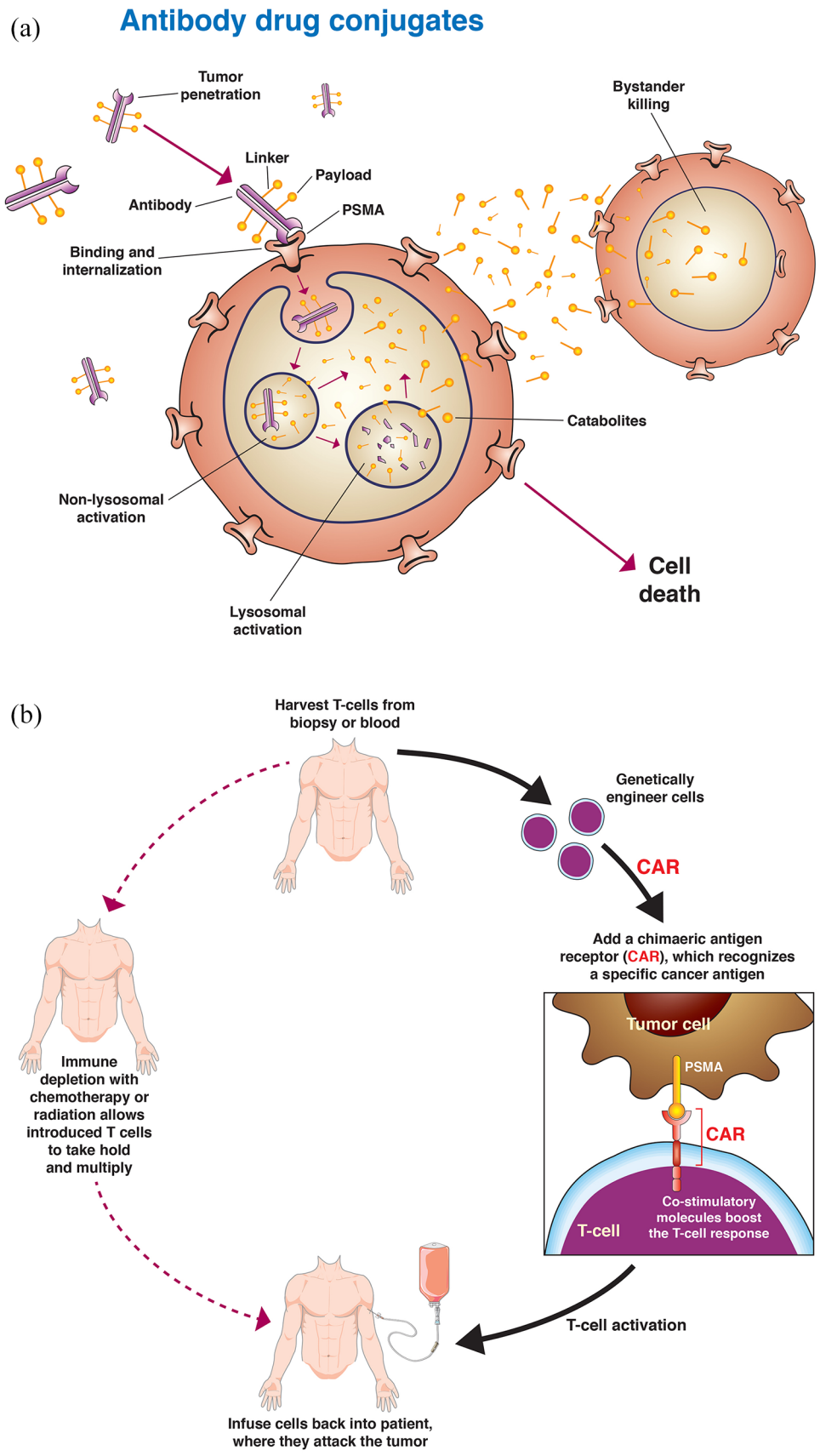
ADCs are an emerging therapeutic approach in oncology that combines a monoclonal antibody with high selectivity for specific targets, along with a cytotoxic agent. In solid cancers, three ADCs have received regulatory approval, all in breast cancer, trastuzumab emtansine, and trastuzumab deruxtecan for HER2-positive breast cancer, and sacituzumab govetecan for triple-negative breast cancer.[61] In urological cancers, enfortumab vedotin has recently demonstrated improved overall survival in urothelial cancer, and the FDA has granted accelerated approval.[62] These approvals demonstrate the potential efficacy of ADCs in other tumor types.

A key requirement for ADC development includes target antigen selection. The target needs to fulfill several requirements, including high expression in tumor with no/low expression in healthy cells, expression on the surface of tumor cells, and finally internalization properties that will facilitate the ADC to transport into the cell.[63] As a target, PSMA possesses all of these requirements.

ADCs consist of an antibody moiety which should be highly specific for the target and have high target-binding affinity, along with low immunogenicity and low cross-reactivity. Linkers are then attached to the antibody, which allow chelation of the cytotoxic drug (Figure 2(a)). There are several types of cytotoxic payloads or warheads that can be attached. The selection of the payload is important, given it must have sufficient potency to destroy the targeted tumor cell, even at low doses. Common payload classes include microtubule-disrupting agents and DNA-damaging agents.[63]

In prostate cancer, several ADCs are currently in clinical development, with targets including PSMA, STEAP-1, TROP2, CD46, and B7-H3. Results from early phase studies of PSMA-targeted ADCs have demonstrated some activity, albeit modest.[64]

- MLN2704 includes a humanized J591 antibody linked to the payload maytansinoid-1. In a study of 62 patients treated with different schedules, PSA50 responses were seen in 5 (8%). Adverse events including peripheral neuropathy, 10% grade 3 or higher, were observed.[65,66]
- Petrylak *et al.* reported results from a phase II study of PSMA ADC, a fully humanized IgG1 monoclonal antibody conjugated to monomethyl auristatin E (MMAE). In 119 patients who had progressed following abiraterone or enzalutamide, PSA50 responses were seen in 14%. Adverse events including neutropenia in 32% of patients and grade 3 neuropathy in 8% led to treatment cessation in 31% of patients.[67]
- De Bono *et al.* reported results from a phase I study of MEDI3726, a PSMA targeted ADC using pyrrolobenzodizepine dimer payloads. In the 33 patients reported, treated at varying dose levels, there were 3 (9%) PSA50 responses. Adverse events including capillary leak syndrome and skin toxicities lead to treatment discontinuation in 39%.[68]



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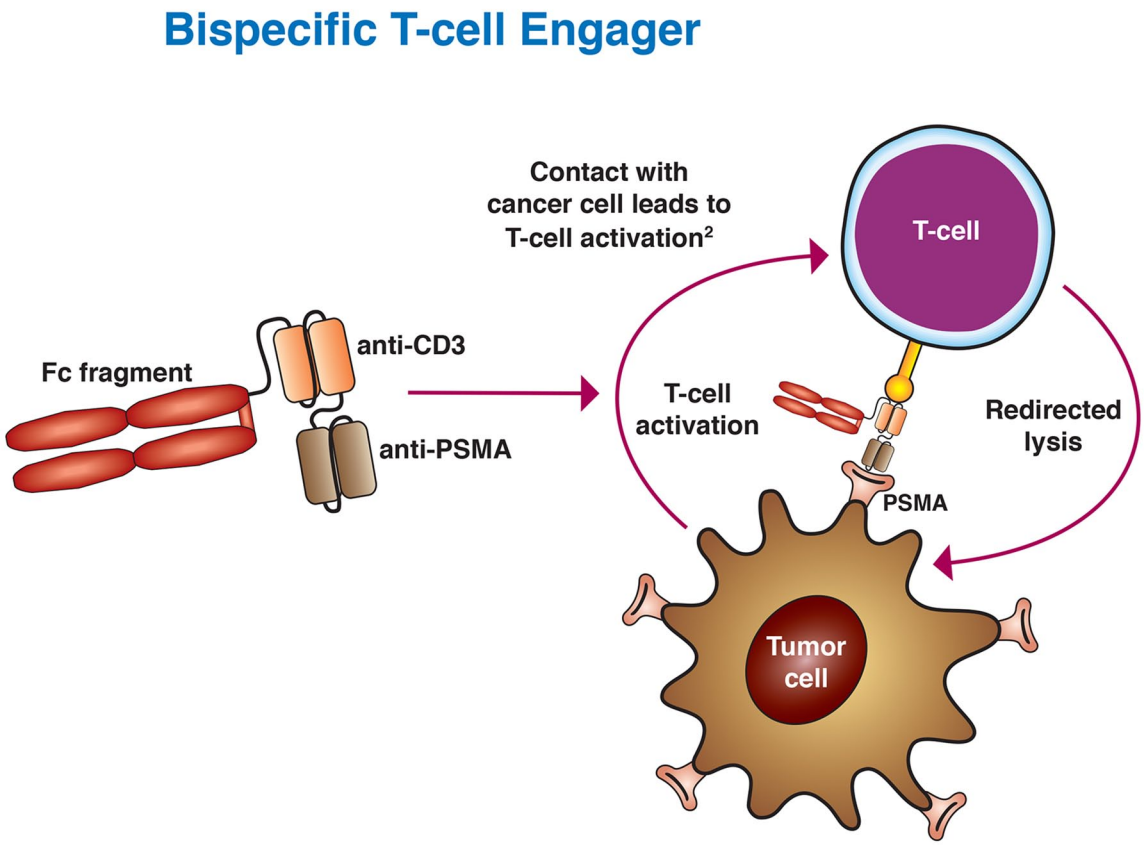

Figure 2. (a) PSMA-targeted antibody drug conjugates, (b) PSMA-targeted CAR-T cell therapy, and (c) PSMA-targeted bispecific T-cell re-directed therapy.

Based on these three studies, PSMA-targeted ADCs do have some activity in CRPC; however, treatment-related adverse events limit the ability to deliver treatment.

Chimeric antigen receptor T cells

Chimeric antigen receptors (CARs) are genetically engineered T-cell receptors with an antibody-based extracellular domain that specifically recognizes a tumor antigen, a transmembrane portion, and an intracellular domain that activates the T-cell. CAR-T cells are produced by inserting specific CAR genes via viral vectors into autologous or allogeneic T-cells[69] (Figure 2(b)).

CAR-T cells have demonstrated impressive clinical activities in hematological malignancies; however, in solid tumors, much work is yet to be done. This includes identifying ideal tumor-specific antigens, improving trafficking of CAR-T cells to tumor sites, overcoming the immune-suppressive TME, and managing on-target adverse events, including cytokine release syndrome.[69] In prostate cancer, several CAR-T cell studies are currently ongoing, with many targeting PSMA.

- Junghans *et al.* published results from a phase I trial of a PSMA-targeted CAR-T cell. In this study, five patients received conditioning chemotherapy, followed by PSMA-targeted CAR-T cells along with continuous infusion of low-dose IL-2. Engraftment was confirmed in all patients, with two patients achieving PSA50 responses. CRS was not observed in any patients.[70]
- Slovin *et al.*[71] presented results from seven patients who received PSMA-targeted CAR-T cells following conditioning chemotherapy, with CAR-T cells persisting in blood for up to 2 weeks, and one patient having stable disease for >16 months.
- While PSMA appears to be an ideal target for CAR-T cell therapy, overcoming the immune-suppressive TME and improving

trafficking to tumor sites remains a potential barrier to efficacy. One novel approach presented by Narayan *et al.* involves co-expression of TGF-β-receptor on PSMA-directed CAR-T cells. Data from this study are eagerly awaited.[72]

PSMA-directed vaccines

Therapeutic cancer vaccines are designed to increase immune response against malignant cells by expanding antigen-specific T cells from the existing host immune system. In prostate cancer, vaccine strategies have demonstrated little benefit thus far. Gulley *et al.*[73] conducted a large randomized phase III trial of PROST-VAC, a vector-based vaccine targeting PSA, in patients with mCRPC and demonstrated no effect on overall survival. However, given the potential of vaccines to result in efficacy with limited adverse events, ongoing exploration of novel approaches continues, including utilizing novel viral and bacterial vectors, along with combinatorial approaches. Given its ideal features, PSMA continues to be explored as a target for prostate cancer vaccines.[74]

Bispecific T-cell re-directed therapy

One strategy to overcome the underlying immunosuppressive TME in prostate cancer is to activate T-cells in the presence of prostate cancer. Bispecific T-cell re-directed therapy adopts this approach.[75] It has been utilized successfully in acute lymphoblastic leukemia, where blinatumomab is now considered a standard of care.[76] It is also being utilized in many other tumor types, including glioblastoma multiforme and colorectal cancer.[77]

Bispecific T-cell-directed therapies generally involve a bispecific antibody which targets the tumor-associated antigen, in addition to CD-3. In doing so, it activates T-cells and induces targeted tumor cell death independent of endogenous T-cell recognition or MHC restriction (Figure 2(c)). CD3 bispecific antibodies can be efficacious, even in immunosuppressive environments. Cytokine release syndrome is a common feature of CD3-targeted bispecifics. This is mainly a result of systemic cytokine release, mainly IL-6, TNF-α, and IFN-γ, as T-cells are activated.[75,77]

Like the other targeted immunotherapy approaches described here, PSMA is an attractive target for prostate cancer for bispecific T-cell therapy.

- AMG 212 [MT112 (Micromet Inc.); BAY 2010112 (Bayer AG)] was a first-generation Bispecific T-cell Engager (BiTE™) molecule targeting PSMA that demonstrated early evidence of clinical activity in a phase I study. However, like other CD3-targeted bispecifics, AMG 212 had a short half-life that required administration by continuous intravenous (cIV) infusion.[78]
- AMG 160 is a next-generation PSMA-targeted BiTE molecule, with an extended half-life that enables administration at longer dosing intervals. Tran et al. presented preliminary results from a phase I study of AMG160 which demonstrated PSA50 response in 34% of patients.[79] Adverse events observed included cytokine release syndrome; however, mitigation strategies adopted during the study resulted in these being manageable and predominantly grade 1–2. This promising phase I study continues, including a cohort combining AMG160 with pembrolizumab. Of all immunotherapy approaches tested so far, AMG160 appears to have the most potential.[75]

For all these therapies, molecular imaging to demonstrate PSMA expression will be a key factor in a precision medicine approach to patient selection.

Conclusion

PSMA is an excellent target to improve outcomes for men with prostate cancer. PRLT has demonstrated a low toxicity and a high efficacy in men with prostate cancer who have progressed after standard therapies and also in comparison with cabazitaxel. Results of the phase III VISION trial have demonstrated improved overall survival and we hope this translates to regulatory approval and another option for our patients with prostate cancer. However, as most patients tend to relapse, there is a need to explore strategies to attain deeper and more durable responses. Non-radioactive approaches targeting PSMA are also of emerging interest. Of these, bispecific T-cell re-directed therapy is the most promising immunotherapy based on early phase trials.

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Conflict of interest statement

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