New Prostate Cancer Targets for Diagnosis, Imaging, and Therapy: Focus on Prostate-Specific Membrane Antigen

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The rising incidence rate of the cancer in the prostate gland has increased the demand for improved diagnostic, imaging, and therapeutic approaches. Prostate-specific membrane antigen (PSMA), with folate hydrolase and carboxypeptidase and, internalization activities, is highly expressed in the epithelial cells of the prostate gland and is strongly upregulated in prostatic adenocarcinoma, with elevated expression correlating with metastasis, progression, and androgen independence. Recently, PSMA has been an active target of investigation by several approaches, including the successful utilization of small molecule inhibitors, RNA aptamer conjugates, PSMA-based immunotherapy, and PSMA-targeted prodrug therapy. Future investigations of PSMA in prostate cancer (PCa) should focus in particular on its intracellular activities and functions. The objective of this contribution is to review the current role of PSMA as a marker for PCa diagnosis, imaging, and therapy.

Keywords: prostate cancer, prostate-specific membrane antigen, PSMA, small molecule inhibitors, RNA aptamer conjugates, PSMA-based immunotherapy, PSMA-targeted prodrug therapy, positron emission tomography

INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a type 2 integral membrane glycoprotein with folate hydrolase and carboxypeptidase, and internalization activities. This internalization capability is increased up to 3-fold when PSMA is linked to anti-PSMA antibodies. PSMA expression is highest in prostate tissue (secretory acinar epithelium), but detectable levels of PSMA protein are also found in the kidney (proximal tubules), the small bowel (i.e., jejunal brush border), neuroglia (Schwann cells and astrocytes), and salivary glands (1, 2). Notably, PSMA is highly expressed in prostate cancer cells and the vessels of various non-prostatic solid tumors (it is not expressed in the normal vasculature) (3).

With the rise and evolution of several targeted approaches to examine prostate cancer using PSMA, the aim of this contribution is to review the current role of PSMA as a marker for PCa diagnosis, imaging, and therapy.
EXPRESSION AND ROLE OF PSMA IN PCA

PSMA was originally discovered using the monoclonal antibody 7E11 obtained from the cell membrane of the LNCaP cell line (4). It has been shown by immunohistochemistry that expression of PSMA at the tissue level increases through the progression from normal prostate to high-grade prostatic intraepithelial neoplasia (HGPIN) and to PCa (3) (Figure 1). There exists a strong positive correlation between PSMA expression and Gleason score. Elevated PSMA expression is strongly correlated with a high serum PSA. These indications are associated with increased tumor angiogenesis and lack of ets-related gene (ERG) expression which leads to reduced vitamin D and androgen receptor expression (5). PSMA expression is regulated by the androgen receptor (AR). PSMA expression increases dramatically during androgen-deprivation therapy (6).

Downregulation of PSMA expression by AR may be associated to the presence of an enhancer region although no androgen response elements have been identified (7).

PSMA expression is significantly correlated with prostate growth and differentiation (8). In particular, in vitro expression of PSMA is associated with an increased cellular folate content. This induces a proliferative property to cells expressing PSMA (9, 10). In addition, PSMA stimulates PCa cell proliferation, migration and survival through the phosho-p38 (P-p38) MAPK pathway in LNCaP cancer cells (11). Guo et al. demonstrated that PSMA knockdown in a LNCaP cell line was associated with not only the inhibition of the pathway of phosphatidylinositol 3-kinase/Akt signaling but also decreased cell proliferation, migration and survival (12).

PSMA is involved in the development of PCa metastases. Xu et al. evaluated four prostate cancer cell lines (i.e., DU145, LNCap, PC-3, and 22RV1) for metastasis-related genes potentially involved in PCa metastasis regulated by PSMA. In their study, CDH6, MMP3, and MTSS1 were seen as PSMA-related genes. Their expression was inversely related with the stage of cancer, thus suggesting their possible involvement in the suppression of PCa metastasis by PSMA (13).

PSMA-BASED IMAGING IN PATIENTS WITH PCA

Conventional imaging techniques, such as ultrasound, CT, bone scintigraphy and Magnetic Resonance Imaging (MRI), are at present utilized to detect primary PCa and its metastatic deposits. However, the limitation of such traditional imaging techniques and modalities is their low sensitivity in the detection of recurrent or metastatic PCa. Improved imaging modalities are needed to optimize the management of the patients with PCa.

Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT) with emerging radiopharmaceuticals provide more accurate staging for primary cancer, detection of metastatic disease, and restaging of tumor recurrence. PSMA has received considerable attention as a useful marker for imaging purposes in patients with PCa (14, 15). Several PSMA-based approaches have been developed, including antibodies, nanobodies, and small molecule inhibitors.

Antibodies and Nanobodies

Indium-111 capromab pendetide (111In-capromab, ProstaScint®) was the first monoclonal antibody against PSMA used in PCa immunoscintigraphy. Correlation of scan results with tissue specimens showed that 111In-capromab detected soft tissue metastases, with an average negative predictive value of 70%, sensitivity of 60%, and positive predictive value of 60% (16–18). However, 111In-capromab lacks sensitivity because it recognizes an intracellular epitope of PSMA, thereby targeting only apoptotic/necrotic or damaged cells.

Unlike 111In-capromab, J591 is an antibody against the extracellular domain of PSMA. 111In-labeled J591 has been evaluated against conventional imaging techniques in the evaluation of bone metastases. 111In-labeled J591 identifies 93.7% of skeletal lesions detected by a conventional imaging technique. Thirteen out of Eighteen bone deposits detected only with 111In-labeled J591 were successively confirmed to be metastases (19). In a more recent study, J591 has been radiolabeled with 89Zr (20) and 64Cu (21) for PET imaging and demonstrate robust targeting of skeletal, nodal and soft tissue metastasis (22).

A new strategy in the development of high-contrast nuclear imaging is the utilization of specific antibody fragments, called nanobodies. Nanobodies contain antibody-derived smaller fragments (typically the variable domain alone of heavy chain antibodies) that largely retain the specific antigen binding properties of the original antibodies, but with more rapid pharmacokinetics and lower immunogenic potential. Evazalipour et al. compared the properties of different nanobodies radiolabeled with 99 m-Technetium (99 mTc) in PSMA+ LNCaP and PSMA− PC3 cell lines and in PSMA− and PSMA+ tumor-bearing xenografts through SPECT/micro-CT imaging and tissue analysis. Among the evaluated molecules, nanobody PSMA30 resulted in an important compound for future applications in PCa imaging trials (23).

Interesting results were also obtained with minibodies, i.e., IAB2M, an 80-kDa minibody genetically engineered from the parent antibody J591 that targets the extracellular domain of PSMA. A phase I dose-escalation study in patients with metastatic prostate cancer demonstrated PET imaging with 89Zr-Df-IAB2M is feasible and well tolerated, and targets both bone and soft-tissue disease (24).

Small Molecules

The identification of the functional (25) and structural (26) homology between N-acetylaspartylglutamate peptidase or NAAALDASE (for which a number of enzymatic inhibitors had been identified) (27, 28) and PSMA has been a major step forward for the development of PSMA-targeted radiotracers. Generally, small molecule PSMA inhibitors consist of zinc binding compounds linked to a glutamate isostere or glutamate. Phosphonate-, phosphate-, and phosphoramidates (1) and ureas (2) constitute the two main families of compounds. Based on NAAALDASE homology, several compounds have been
developed and labeled with 123I (20, 29, 30), 99mTc (21, 31), 18F (32), 111In (33), and 68Ga (34). 123I-MIP-1072 and 123I-MIP-1095 were the first small molecule inhibitors of PSMA adopted in the clinic. SPECT/CT using these compounds showed a rapid detection of PCa deposits in the bone, soft tissue, and prostate gland of men with metastatic PCa (35). A phase I trial on 131I-MIP-1095 in men with mCRPC is now active (NCT03030885).

Among the emerging PSMA small molecule inhibitors, N-((S)-1,3-dicarboxypropyl) carbamoyl)-4-(18F)fluorobenzyl-L-cysteine (18F-DCFBC) is under evaluation in several ongoing studies. Using 18F-DCFBC, PSMA$^+$ PC-3 PIP xenografts were early visualized with little radioactivity in the PSMA$^-$ isogenic PC-3 flu xenografts. After 2 h, the PC-3 PIP xenografts remained visible, with clearance of background radioactivity from kidneys, liver and blood (36, 37).

The use of 18F-DCFBC has been investigated in a few patients with Gleason scores between 7 and 9 and with radiological evidence of metastatic PCa. Bone scans or CT identified 21 lesions (5 bone and 16 lymph node lesions), while 32 lesions were visible with 18F-DCFBC PET. Ten of Eleven additional lesions were located in the bone and were suggestive of early bone deposits, indicating the potential of 18F-DCFBC PET in this subpopulation (38). Currently, the use of 18F-DCFBC PET/CT is under evaluation in a study enrolling patients scheduled for surgical prostate (Group 1), or with biochemical recurrence after surgery or radiotherapy (Group 2), or in metastatic PCa patients (Group 3) (NCT02190279). In addition, another ongoing phase I/II study is assessing the potential of 18F-DCFBC PET in the detection of primary PCa, nodal and bone metastases in men at initial diagnosis (NCT01496157) (Table 1).

As for the PSMA inhibitor 18F-DCFPyL (2-(3-{1-carboxy-5-((6-((18F)fluoro- pyridine-3-carbonyl)-amino)-pentyl)-ureido}-pentanedioic acid), Chen et al. evaluated its use in immunocompromised mice utilizing isogenic PSMA PC3 PIP and PSMA-PC3 flu xenografts, suggesting that this agent could be viable and effective in this setting (32). A phase I study is now assessing the biodistribution and pharmacokinetic of 18F-DCFPyL in patients with advanced PCa (NCT02151760).

The early distinction between local disease and metastasis is crucial in the management of patients with PCa. 18F-choline can distinguish lesions with moderate to good sensitivity, but its activity is limited to patients with a PSA $>$ 1 ng/mL (39). The results obtained by 68Ga-labeled PSMA inhibitors showed a high potential in the detection of small recurrent PCa lesions in patients with low levels of serum PSA (40–42). Indeed, 68Ga-labeled PSMA inhibitors are characterized by accumulation in small metastatic deposits and a rapid clearance from the tissue in the background (43). Recently, a comparison between PET/CT and PET/MRI hybrid systems using a 68Ga-labeled PSMA compound for the detection of recurrent PCa has been performed. The results showed that Ga-PSMA PET/MRI was far more accurate in the detection of PCa and, at the same time, associated with lower radiation exposure (34).

Beyond 68Ga-labeled compounds, 99mTc-labeled inhibitors of PSMA have shown great promise in the detection of PCa lesions. Presently, a phase II study is testing 99mTc-MIP-1404 PSMA inhibitor in patients with high-risk PCa scheduled for radical prostatectomy (RP) surgery including extended pelvic lymph node (LN) dissection compared to histopathology (NCT01667536). Results are expected from the completed phase 3 trial proSPECT-AS (NCT02615067). Primary outcome measures of the study are sensitivity and specificity of 99mTc-MIP-1404 SPECT/CT image assessments to correctly detect clinically significant prostate cancer when compared to histopathology following either RP or prostate biopsy in men with newly diagnosed PCa whose biopsy indicates a histopathologic Gleason Score of $\leq 3 + 4$.

Furthermore, BAY1075553 [2-PMPA analogs (2S, 4S)-2-18F-fluoro-4-(phosphonomethyl) pentanedioid acid] has...
demonstrated high uptake in PSMA+ LNCaP tumor xenografts (44). The phase I study showed that BAY1075553 was able to detect primary PCa, lymph node and bone metastases, although its high uptake with degenerative bone lesions may limit its use in assessing bone disease (45).

Worth mentioning is the registrational phase II/III OSPREY study (NCT02981368) that evaluated the diagnostic accuracy of 18F-DCFPyL PET/CT relative to histopathology, for detecting PCa in pelvic lymph nodes in patients with high risk localized prostate cancer who are planned for RP with lymphadenectomy, and in patients with locally recurrent or metastatic disease willing to undergo biopsy.

### Imaging at Diagnosis of PCa

A number of recent studies has dealt with the use of PSMA-based imaging for the purpose of diagnosing primary PCa (Figure 2). Fendler et al. assessed the accuracy of ⁶⁸Ga-PSMA-11 PET/CT in identifying PCa at the initial diagnosis in men with...
biopsy-proven PCa (46). They found that the optimal $SUV_{\text{max}}$ cutoff for distinction of histopathology-positive segments from histopathology-negative segments is of 6.5. With this approach they obtained 67% sensitivity, 92% specificity, 97% positive predictive value, and 72% accuracy.

Woythal et al. (47) evaluated the association of intraprostatic $^{68}$Ga-PSMA PET/CT features and PSMA immunohistochemical expression in 31 patients who underwent RP and preoperative $^{68}$Ga-PSMA-11 PET/CT. $^{68}$Ga-PSMA-11 PET/CT demonstrated sensitivity and specificity of 87 and 97%, respectively, in the detection of PCa. However, there was no correlation between Gleason Score (GS) and the SUV$_{\text{max}}$. On the other hand, Uprimny et al. (48) found that PCa with a GS of 6, 7a (3 + 4) and 7b (4 + 3) showed lower $^{68}$Ga-PSMA-11 uptake, with SUV$_{\text{max}}$ of 5.9, 8.3, and 8.2, respectively, compared to men with a GS greater than 7 (median SUV$_{\text{max}}$: 21.2). In addition, men with a PSA of 10.0 ng/mL or above it showed a greater uptake than those patients with PSA levels below 10.0 ng/mL.

The correlation of intraprostatic PSMA uptake with clinical parameter, such as PSA value, GS and d’Amico risk score, was analyzed by Koerber et al. in 104 patients with newly diagnosed PCa (49). Results of this study indicated that men with higher PSA, higher d’Amico risk score and higher GS had greater intensity of PSMA uptake on PET/CT.

The comparison between the multiparametric Magnetic Resonance Imaging (mpMRI) and $^{68}$Ga-PSMA-11 PET/CT findings showed a concordance in the detection of intraprostatic tumor lesions, with the highest GS of 89.55%. By giving additional molecular imaging information to the mpMRI features, this method can be improved to avoid false-negative results or understaging tumors, in particular the detection of those with the highest GSs. In addition, PSMA PET/ MRI may prove useful in finding lower rates of indolent cancer detection and a great number of intermediate- and high-risk tumors.

**Imaging at Staging of PCa**

For pre-operative staging, current guidelines recommend at least abdomino-pelvic cross-sectional imaging (MRI or CT) and a bone scan, for intermediate- and high-risk PCa (50) only. In a prospective study 30 patients with intermediate- and high-risk PCa underwent preoperative $^{68}$Ga-PSMA PET/CT followed by RP and extended pelvic LN dissection. Using pathology as reference, $^{68}$Ga-PSMA PET/CT showed a sensitivity of 64% for the evaluation of LN metastasis, with a 95% specificity, 88%, positive predictive value, and 82% negative predictive value (51).

In a prospective, phase II, single center study, Gorin et al. analyzed the diagnostic value of PSMA targeted $^{18}$F-DCFPyL PET/TC in the preoperative staging of 25 patients considered to be at high risk for having metastatic PCa, despite a negative conventional staging result. With this technique, they obtained a sensitivity and specificity of 71 and 88%, respectively, per patient analysis and 66 and 92% per LN packet analysis (52).

The retrospective study conducted by Maurer et al. (53) involved a 130 men with intermediate and high risk PCa staged with $^{68}$Ga-PSMA-PET/magnetic resonance tomography or PET/CT. The sensitivity, specificity and accuracy of $^{68}$Ga-PSMA-PET were 65.9, 98.9, and 88.5%, and those of morphological imaging were 43.9, 85.4, and 72.3%, respectively. Such figures are higher than those for traditional imaging techniques and other alternative PET tracers. Hence, the addition of $^{68}$Ga-PSMA PET to traditional approaches has the potential to replace current standard imaging, enabling more complete and accurate primary staging.

**Imaging at Biochemical Recurrence of PCa**

In men with biochemical recurrence (BCR) after RP or radiotherapy the detection rate of $^{68}$Ga-PSMA PET/CT increases with higher pre-scan PSA value. In the post-RP patients the rate of $^{68}$Ga-PSMA-PET/CT was 11.3, 26.6, 53.3, 79.1, and 95.5% for serum PSA levels of 0.01 to <0.2 ng/mL, 0.2 to <0.5 ng/mL, 0.5 to <1 ng/mL, 1 to <2 ng/mL, and ≥2 ng/mL, respectively. In the post-radiotherapy patients, the rate was 33.3% for PSA 0.01 to <0.5 ng/mL, 71.4% for PSA 0.5 to <1 ng/mL, 93.3% for PSA 1 to <2 ng/mL, and 100% for PSA ≥2 ng/mL (54). Such figures are in agreement with the meta-analysis data by Perera et al. (55). In that study, on per-patient analysis, the sensitivity and specificity of $^{68}$Ga-PSMA-11 PET were both 86%. On per-lesion analysis, the sensitivity and specificity were 80 and 97%. $^{68}$Ga-PSMA PET positivity increased with a shorter PSA doubling time.

Higher rates have been reported by Raucher et al. (56) in a cohort of men with PSA value between 0.2 and 1 ng/mL after RP. The rate of detection was 55% in men with “very low” serum PSA (0.2–0.5 ng/mL) and of 74% in patients with “low” PSA (0.5–1.0 ng/mL). In such investigation the most relevant predictors for $^{68}$GaPSMA-ligand PET/CT positivity in multivariable analysis were concurrent androgen deprivation therapy and serum PSA value. Identification of the sites of recurrent disease is of great importance, thus avoiding unnecessary localized treatments in patients of systemic recurrence and avoid the side effects of systemic treatments in men with localized recurrence (57, 58).

**Table 1** summarizes the completed trials on PSMA and imaging. For additional trials please visit: https://clinicaltrials.gov.

$^{18}$F-fluciclovine (Axumin®) (18F-FACBC) is an amino-acid targeting radiotracer and not a PSMA based PET/CT agent (59).
The sensitivity of 18F-fluciclovine PET for identifying recurrent disease changes with PSA levels, with reported detection rates in the post-prostatectomy biochemical failure setting of 72.0% (for PSA values of less than 1 ng/mL) 83.3% (for PSA 1-2 ng/mL), and 100% for PSA levels of 2 or more ng/mL (60). In patients with pathologically enlarged lymph nodes, presence of true-positive lesions was noted in 29% patients with 18F-fluciclovine vs. 7% patients with CT (61, 62). A prospective study compared overall detection rate of 18F-FACBC and 11C-Choline PET/CT on 28 patients with biochemical relapse after RP. Anti-3-18F-FACBC PET/CT detected 60% additional tumor lesions including 5 (17.8%) additional patients (63).

**PSMA-Targeting Strategies for PCa Therapy**

PSMA has been widely utilized as a target antigen due to its constitutive or induced internalization property as well as to its high expression in PCa. Several strategies, including peptides, monoclonal antibodies and aptamers, have been utilized as nanoparticles or prodrugs to improve targeting efficiency in PCa cells. The discovery and development of anticancer aptamers may prove to be relevant contribution to PCa molecular imaging.

Aptamers are short DNA, RNA or peptide oligomers able to assume a specific and stable three-dimensional shape in vivo (64). Their high affinity and specificity, similar to antibodies, is achieved by a three-dimensional conformation complementary to the target surface. At this regard, Lupold et al. identified two RNA aptamers (A9 and A10) characterized with high binding affinity to PSMA, leading to the inhibition of its NAALADase/glutamate carboxypeptidase II activity (65). Successively, Xu et al. conjugated A10 aptamer on the surface of micelles, showing high drug uptake in PSMA+ cancer cells both in vitro and in vivo investigations (66).

PSMA can be used as target for delivery of therapeutic agents such as in antibody-drug conjugated (ADC) therapy. PSMA ADC is a fully human anti-PSMA monoclonal antibody conjugated to monomethyl auristatin E through a valine-citrulline linker.

Wang and his group assessed the antitumor activity of PSMA ADC in PCa cell lines in vitro and in a novel in vivo model of taxane-refractory human PCa. They observed that in vitro cytotoxic activity was efficient for PCa cells with increased PSMA expression (>105 molecules/cell; IC50 0.022 nmol/L). In addition, PSMA ADC showed high in vivo activity in treating xenograft tumors that have progressed on previous docetaxel therapy (67).

Petrylak et al. (68) reported data from a phase II trial based on PSMA-ADC at 2.5 mg/kg in patients with taxane-refractory metastatic castration-resistant PCa (CRPCa). Thirty-Nine Percent of the patients had been treated with both cabazitaxel and docetaxel, while 58% had received both enzalutamide and abiraterone. Dosing was started at 2.5 mg/kg and adjusted at 2.3 mg/kg for tolerability. The study demonstrated that PSA decline of 30% or more was observed in 36% (2.3 mg/kg) and 16% (2.5 mg/kg). Circulating tumor cell (CTC) decline of ≥50% was seen in 74% patients in both 2.3 and 2.5 mg/kg. Duration of therapy on 2.3 mg/kg was far longer than on 2.5 mg/kg, as well as the rate of

**FIGURE 3** | The targeting ligand binds to PSMA on prostate cancer cells. Once bound to the neoplastic cell, 177Lu atom releases energetic β and γ particles. This results in a DNA-damaging radiation.
serious adverse events (37 vs. 59%). Notably, PSA and CTC decline was associated with higher PSMA expression + CTC level, while PSA responses alone were correlated with lower neuroendocrine (NE) marker expression, thus suggesting that NE differentiation may have a role in this context. On the basis of such results, this study has been further extended (see NCT02020135).

Phage display technology has been used by researchers in the identification of peptide sequences, which can bind to PSMA and, at the same time, inhibit its enzymatic activity. Denneade et al. conjugated a PSMA-specific peptide to an inhibitor (i.e., Thapsigargin) of the sarcoplasmic/endoplasmic reticulum calcium adenosine triphosphate (SERCA) pump. The type of pump shares the catalytic properties of ion-motive ATPases of the P-type family. It transports calcium ions from the cytoplasm into the sarco-endoplasmic reticulum. Its activity is needed for viability by all types of cells. The conjugate remains inactive until the PSMA-specific peptide is cleaved, thereby starting SERCA inhibition. In xenograft models, thapsigargin induced tumor regression at doses that appeared to be minimally toxic.

### TABLE 2

| NCT identifier | Study phase | Drug | Study objectives (Number of patients) | Study results |
|----------------|-------------|------|--------------------------------------|---------------|
| NCT01695044  | Phase 2    | PSMA ADC | Assess total serum PSA response, CTC response, overall radiologic response in mCRPC pts (119 pts- completed 17 pts) in two groups: (1) CHT-experienced and (2) CHT naïve. | -PSA response: >30% Decrease in PSA: 29% (1); 32% (2). >50% Decrease in PSA: 11% (1); 21% (2). -CTC response >30% Decrease in CTC: 81% (1), 92% (2). >50% Decrease in CTC: 74% (1), 85% (2). - Overall radiologic response Stable disease 61% (1), 69% (2); Progressive disease: 13% (1), 9% (2); Partial response: 0 (1), 6% (2) |
| NCT02020135 | (Extension Study) | PSMA ADC | Determine the maximum tolerated dose of PSMA ADC (13 weeks) (52 pts) | No results posted |
| NCT01414283 | Phase 1 | PSMA ADC | Safety and tolerability of PSMA ADC as measured by all adverse events in mCRPC patients (10 pts) | No results posted |
| NCT01414296 | Extended 39-Week | PSMA ADC | Safety, tolerability, and immune response of vaccine therapy with increasing dose levels of rsPSMA protein (14 pts) | No results posted |
| NCT00705835 | Phase 1 | Rs-PSMA | Immunization with PSMA peptide vaccine followed by injection of Interleukin-12 in Metastatic PCa patients, determine disease response (13 pts) | No results posted |
| NCT00015977 | Phase 2 | PSMA peptide vaccine | Immunization with PSMA peptide vaccine followed by injection of Interleukin-12 in Metastatic PCa patients, determine disease response (13 pts) | No results posted |
| NCT01140373 | Phase 1 | Autologous T cells targeted to PSMA | Safety and tolerability using increasing doses of engineered autologous T cells targeted to PSMA after cyclophosphamide in CMPC patients (13 pts) | No results posted |
| NCT02202447 | Phase 1 | EC1169 | Safety, pharmacokinetic profile and preliminary efficacy of PSMA Targeting-Tubulysin Conjugate EC1169 in Patients With Recurrent Metastatic CRPC (40 pts) | No results posted |
| NCT00694551 | Not Applicable | Polypeptide vaccines: PSMA27-35-PSMA687-701 | Pilot immunotherapy study of combination PSMA and TARP peptide with Poly I:C-LC adjuvant in patients with elevated PSA after initial definitive treatment (29 pts) | Adverse events (Grade 3 or higher): 0 pts PSA doubling: 19/29 pts; No PSA doubling: 10/29 pts |
| NCT00916123 | Phase 1 | 177Lu-J591 | Effectiveness of 177Lu-J591 antibody in combination with docetaxel chemotherapy against metastatic CRPC (15 pts) | No results posted |

For a full list of trials please visit: https://clinicaltrials.gov PSMA ADC, Prostate Specific Membrane Antigen Antibody Drug Conjugate; CHT, chemotherapy; PSA, prostatic specific antigen; CTC, Circulating tumor cells; 177Lu-J591, Anti-prostate-specific Membrane Antigen Monoclonal Antibody; CMPC, Castrate Metastatic Prostate Cancer; TARP, T-cell receptor γ alternate reading frame protein; CRPC, castrate-resistant prostate cancer; Rs-PSMA, Recombinant Soluble PSMA.
PSMA represents an attractive target for the detection and treatment of patients with PCa. PSMA immunohistochemical evaluation should be further investigated as a predictive marker in men with metastatic PCa, to guide clinicians in the selection of the most appropriate imaging technique and therapy in individual patients. The choice of emerging PSMA-targeted tracers and therapeutic agents requires further investigation in order to identify the most specific compound for the distinct sites and phases of the disease (83–85). As our understanding of the role of PSMA in prostate carcinogenesis advances and molecular techniques become more refined, PSMA-based strategies will have a crucial role in the evolving diagnostic and therapeutic landscape of patients with PCa.

**AUTHOR CONTRIBUTIONS**

RM and MSc conception and design. AC and MSa drafting the manuscript. MC, FM, and AG review of the literature. NB and AL-B critical revision of the manuscript.
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