Why targeting PSMA is a game changer in the management of prostate cancer – a Urologist’s point of view

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NOTEWORTHY

- PSMA has been a molecular target of interest in prostate cancer since its discovery in 1986 (page 4)
- A variety of antibodies and small-molecule imaging agents targeting PSMA have demonstrated excellent early results for a variety of disease states (page 5)
- Radioimmunotherapeutic and radioligand agents are currently being investigated for use in the mCRPC setting, with several demonstrating encouraging clinical responses (page 11)
- The effect of these agents on overall-survival remains a subject of investigation (page 13)
ABSTRACT

Prostate-specific membrane antigen (PSMA), is a transmembrane glycoprotein that is highly expressed on prostate adenocarcinomas, exhibits only limited expression in benign and extra-prostatic tissues, and thus represents an ideal target for the diagnosis and management of prostate cancer. Since its discovery over 30 years ago, significant effort has been made to develop clinical technology targeting PSMA. The last 5 years have seen an explosion of development of new agents targeting PSMA for diagnostic and therapeutic use. Imaging agents targeting PSMA have been developed for single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging platforms. PSMA PET imaging appears to outperform traditional imaging in the high risk localized disease state, in patients with biochemical recurrence following treatment, and in advanced disease. To date, the majority of reported clinical studies of therapeutic agents utilize PSMA-targeted radiometals to deliver beta radiation to metastatic disease sites, with Lutetium-177 being the most widely-investigated therapeutic radio-isotope. Studies of both antibodies and small molecule agents have been published and have demonstrated encouraging results. Safety appears generally limited to mild transient bone-marrow toxicity and xerostomia owing to uptake of the small molecule agents in the salivary glands. Radiologic responses can be dramatic and decreases in pain have been observed. The effect on overall survival, however, has yet to be demonstrated.
INTRODUCTION

Advances in the early detection and treatment of prostate cancer have resulted in a 50% decrease in mortality from prostate cancer in the United States over the last 25 years(1). Despite these strides, a subset of men either present with de novo metastatic disease, or will progress to the metastatic disease state despite attempts to cure at the localized disease state. While androgen deprivation therapy slows disease progression, metastatic tumors ultimately develop castration resistance and are generally incurable. The past decade has seen the development of treatments of various modalities for the metastatic castration-resistant prostate cancer (mCRPC), including second generation endocrine manipulation, cytotoxic chemotherapy, cellular immunotherapy, and Ra 223 dichloride. While these agents have been shown to prolong overall survival, the benefits conferred are modest, and mCRPC remains a leading cause of cancer death, killing over 300,000 men worldwide annually(2).

BACKGROUND

Prostate-specific membrane antigen (PSMA) is a 750 amino acid type II transmembrane glycoprotein encoded by the folate hydrolase 1 gene located on the short arm of chromosome 11(3). The name PSMA is a misnomer, as the protein is expressed on both benign and malignant prostate epithelium, but also on a variety of extra-prostatic tissues, including proximal renal tubules,(4) the jejunal brush border,(5) salivary glands,(5) and in the neovasculature of several solid tumors(6). Structurally, the transmembrane protein consists of a 19-amino-acid intracellular domain, a 24-amino-acid transmembrane domain and a large, 707-amino-acid extracellular domain(7).
Histologically, PSMA is detectable at modest levels in the epithelium of benign prostate tissue, but demonstrates 100x–1000x fold expression levels on the epithelium of prostate adenocarcinomas(4,8). It is expressed in a majority of tumors, and a positive correlation has been observed between higher PSMA expression and various measures of tumor aggressiveness, including Gleason grade(8), tumor stage(9), biochemical recurrence(10), and castration resistance(11). The cytoplasmic domain of PSMA contains an internalization motif which results in bound PSMA being internalized via clathrin coated pits(12). This process provides the possibility that PSMA-targeting agents could be internalized and concentrated within tumor cells. PSMA is thus an attractive target for diagnostic and therapeutic targeting for a number of reasons, including (1) high expression on prostate cancer cells (2) limited expression on benign prostate tissue (3) limited expression on non-prostate tissue (4) an extracellular domain which can be targeted by antibodies (5) a well-characterized binding-site which can be targeted by small-molecule ligands, and (6) an internalization motif that results in bound agents being internalized and concentrated within malignant cells.

TARGETING AGENTS

Antibodies

The first steps in targeting PSMA took place in the late 1980s and involved the generation of the 7E11-C35 antibody, which is specific for an epitope at the intracellular domain of PSMA(13). This antibody was then labeled with $^{111}\text{In}$, allowing for use with SPECT imaging. This agent, known as capromab pendetide (Prostascint®) was FDA approved in 1996 for the detection of soft-tissue metastases. When evaluated for use in initial staging, two large multicenter trials demonstrated sensitivities ranging from 52–62%, with specificities of 72–96%,
using pelvic lymphadenectomy as the truth standard, outperforming both computed tomography (CT) and magnetic resonance imaging (MRI)(14). When used for the detection of suspected recurrent or residual cancer following treatment of the primary tumor, Prostascint® demonstrated a sensitivity of 49–77% and specificity of 35–71%(14). Despite this modestly improved performance compared with traditional imaging, Prostascint’s relatively poor sensitivity in the setting of low PSAs, difficulties in anatomic localization owing to the limitations of SPECT, and significant operator dependence resulted in relatively limited use.

In an effort to improve upon these limitations, huJ591, a humanized monoclonal IgG1 antibody which binds an extracellular epitope of PSMA, has been developed for use with both gamma and photon-emitting metalloradionuclide agents(15). The antibody has been employed in a number of early-phase clinical trials for both imaging and therapeutic purposes(16–19) (Supplemental Table 1). Because IgG antibodies are not filtered at the glomerulus and remain within the blood pool for several days, imaging must be performed 6–8 days following infusion in order to allow clearance of the antibody from the blood pool. An 80-kDa minibody that has been genetically engineered to lack the Fc-receptor domain, known as $^{89}$Zr-Df-IAB2M, was synthesized with the aim of generating faster blood clearance in order to allow for imaging at a shorter time interval(20). The initial studies suggest that a 48-hour wait time between infusion and imaging may still be required.

**Small-molecule PSMA Ligands**

Characterization of the active substrate-recognition site of the PSMA molecule has allowed for the development of numerous agents engineered to bind to this site. Small molecules have the theoretical advantage over antibodies of achieving better tumor penetration and more
rapid clearance from the blood pool, allowing for infusion and imaging to be performed during a single patient-visit. Numerous small-molecule agents, labeled with a range of radionuclides for use with both SPECT and PET imaging, as well as for the delivery of radiometallonuclides for treatment purposes, have been developed and are in various stages of clinical use and development (Table 1, Supplemental Table 1). Several of the more promising small molecule agents are discussed below.

$^{68}$Ga-PSMA-HBED-CC ($^{68}$Ga-PSMA-11) is the most widely utilized PET agent for PSMA-targeted imaging. First described in 2012, the agent consists of the HBED-CC chelator to which the Gallium is bound, a lipophilic linker, and a urea-based Glu-CO-NH-Lys motif which binds to the active site of the PSMA molecule(21). It displays low-level natural uptake in the kidneys, salivary and lacrimal glands, liver, spleen and bowel, and has demonstrated the ability to detect prostate cancer within the prostate gland, within small nodal metastases, bony lesions, and even within more widespread de-differentiated tumors(22–24). Because the agent is filtered at the glomerulus, high levels of activity are present in the urine, potentially making the detection of local recurrences more difficult; however nodal metastases near the bladder have been detected(24). A systematic review was published in 2016 by Perera et al. evaluating the sensitivity and specificity of $^{68}$G-PSMA-HBED-CC in various clinical settings(25). Further details of the agent’s performance will be discussed below.

Another area of robust investigation in PSMA ligands involves agents which utilize Fludeoxyglucose-18, a radionuclide which has several theoretical advantages over Gallium-68, including better image resolution owing to shorter positron range and higher positron yield. Like the Gallium agents, $^{18}$F agents can be infused and imaged at the same visit. The first of these agents to be tested clinically was $^{18}$F-DCFBC, which has been evaluated for use in disease
assessment both within the gland(26) as well as for the detection of metastases(27,28). While initial results were encouraging, the significant blood pool activity of the agent prompted efforts to refine the agent and improve its performance. The result of these efforts was a second-generation agent, $^{18}$F-DCFPyL, which was initially evaluated in a cohort of 9 patients with metastatic disease(29,30). As hoped, the agent demonstrated a marked improvement in maximum tumor-uptake-to-blood-pool-uptake ratios,(30) allowing for improved visual conspicuity of suspected disease. Another agent, $^{18}$F-PSMA-1007, is also in development, and has shown the ability to detect micrometastases(31) in the biochemically recurrent setting.

**DIAGNOSTIC TARGETING**

**High Risk Initial Diagnosis**

At least 4 published studies have evaluated the performance of PSMA-targeted agents for use in initial staging of intermediate and high-risk patients in which histopathologic correlation was performed(32–35). All of these studies utilized the $^{68}$G-PSMA-HBED-CC tracer, and in all 4 studies, $^{68}$G-PSMA-HBED-CC PET outperformed traditional CT or MRI for lymph node staging, with both improved sensitivity and specificity on both the per-patient and per-template basis. On the per-patient basis, sensitivities ranged from 33–91%, with specificity ranging from 67–100%. On the per-template basis, sensitivities ranged from 74–86%, with specificity ranging from 88–99%.

**Biochemical Recurrence**

At present, biochemical recurrence can be detected long before imaging technology allows anatomic localization of disease. This provides challenges for management because local
radiotherapy, which is known to prolong both disease-free and overall survival(36), is most effective when applied at low PSA levels, when, at present, local recurrence can only be inferred from pathologic data and PSA kinetics. Given reticence to proceed with local salvage radiotherapy without definitive evidence of a local recurrence, imaging technology to improve the localization of disease recurrence is of paramount interest, and represents one of the most robust areas of PSMA-targeted imaging research. Afshar-Oromieh et al. published the largest study for this indication, an analysis of 1007 men with biochemically recurrent disease(22) who underwent PET using the $^{68}$G-PSMA-HBED-CC tracer. In 79.5% of patients, at least 1 lesion suggestive of prostate cancer was identified, including lesions in bone, soft tissue, and viscera. There was a clear relationship between the likelihood of positive scan and PSA level: 46% ($\leq 0.5$ng/mL), 73% (0.51–1.0ng/mL), 80% (1.1–$\leq 2.0$ng/mL), 86% (2.1–$\leq 3.0$ng/mL), 91% (3.1–$\leq 5.0$ng/mL), 94% (5.1–$\leq 7.0$ ng/mL), 91% (7.1–$\leq 10$ng/mL), 96% ($> 10$ng/mL). A multivariable logistic regression analysis found that log PSA and receipt of androgen deprivation therapy predicted a positive scan, but that Gleason score did not. These results are generally consistent with a report from Eiber et al. who published on cohort of 248 consecutive patients with biochemical recurrence after radical prostatectomy. PSMA-PET is especially relevant at low PSA values given that guidelines for salvage radiotherapy recommend treatment at the <0.5 PSA level, and that other PET tracers such as choline demonstrated limited sensitivity at this level (19–36%). Apropos of this point, Bluemel et al. published a report of 125 patients with biochemical recurrence after radiation or radical prostatectomy, who underwent $^{18}$F-choline PET, and if negative, underwent $^{68}$G-PSMA-I&T PET/CT(37). These investigators found that $^{68}$G-PSMA-I&T detects sites of BCR in 44% of patients with a negative $^{18}$F-Choline PET/CT,(37)
with the incremental benefit of the PSMA study most pronounced in the subset of patients with a PSA <1 ng/mL.

**Metastatic**

The majority of published studies demonstrate that PSMA-targeting agents, both antibody-based and small molecule ligands, are safe and provide high sensitivity and specificity for staging lymph node, soft tissue, and bony metastases\(^{(20,27,29,30,38–41)}\). One study by Rowe et al., in which a head-to-head comparison of the performance of conventional imaging versus \(^{18}\text{F}-\text{DCFPyL}\), demonstrates some of the key considerations in this arena\(^{(30)}\). First, \(^{18}\text{F}-\text{DCFPyL}\) detected over 3 times the number of metastatic lesions when compared with conventional imaging. Secondly, they discuss the ability of \(^{18}\text{F}-\text{DCFPyL}\) to detect metastases in small lymph nodes, noting the failure of simple size cutoff to distinguish between benign and malignant lymph nodes. Finally, \(^{18}\text{F}-\text{DCFPyL}\) detected metastatic disease in the periprostatic soft tissues, an area which is difficult to assess with either CT or MRI, and highlight a case in which a patient with a normal MRI pelvis was noted on \(^{18}\text{F}-\text{DCFPyL}\) PET to have a peri-rectal metastasis. The main limitation of this study as well as others in this area is the lack of a systematic formal histologic evaluation on a lesion-by-lesion basis to serve as the truth-standard. As such the true performance of PSMA-targeted imaging for metastatic disease remains incompletely evaluated at this time. Despite this, the initial studies provide strong preliminary evidence that PSMA-targeted imaging agents are likely to outperform traditional imaging procedures for the detection of metastatic disease. It is important to note that the value of molecular imaging to monitor therapy is, at present, unproven with respect to overall survival. Unfortunately, molecular imaging is not included in ongoing large trials in advanced disease.
THERAPEUTIC TARGETING

Targeted cancer therapy aims to achieve sensitive and specific on-target, on-tumor cell death while sparing normal tissues. Great effort has been made to develop agents which target PSMA for treatment in the mCRPC disease state, with the appreciation that prostate cancer is radiosensitive prompting investigation into the use of radiopharmaceuticals as potential candidate effector agents. Most published studies of nascent radiopharmaceuticals are small molecule agents which utilized Lutetium-177 as the radiometal, but early-phase studies have evaluated antibody-based therapies as well. A summary of the key published reports is provided in Table 1. Several notable agents are discussed below. No randomized studies exist to date.

The first PSMA-targeted radioimmunotherapeutic studies utilized the huJ591 antibody. Two phase 1 dose-finding studies, one using $^{90}$Y and one using $^{177}$Lu, were published(18,19), followed by a phase 2 study using $^{177}$Lu and published in 2013 by Tagawa et al(17). In the phase 2 study by Tagawa et al. 47 patients were treated at two treatment doses (2405 MBq/m² and 2590 MBq/m² dose). Key outcomes included a $\geq 50\%$ PSA decline in 10.6% of patients and any PSA decline in 59.6% of patients. Median overall survival for the entire cohort was 17.6 months, with higher dose patients surviving almost twice as long (21.8 mos vs 11.9 mos). Myelosuppression was the main observed side-effect, including grade 4 thrombocytopenia in almost half the patients, but was noted to be reversible. No significant hemorrhages occurred.

More recent attention has been focused on small-molecule PSMA-targeting radioligand therapy, many of which utilize theranostic agents. Theranostic agents are those in which the chelator is capable of binding radiometals for both imaging (Gallium-68) and treatment (Lutetium-177). Similar to imaging agents, small-molecule radioligand agents have the
advantage of more rapid clearance from blood when compared to antibodies, resulting in lower doses of radiation delivered to normal tissues.

The best studied PSMA-targeted radioligand therapeutic agent is $^{177}$Lu-PSMA-617. The first reported cohort was published in 2015\(^{(42)}\), and since that time multiple investigator groups have published results evaluating $^{177}$Lu-PSMA-617\(^{(43–46)}\) (Table 2). The largest study to date is a retrospective multicenter cohort of 145 patients from 12 centers across Germany\(^{(47)}\). Some variation in efficacy outcomes is seen across the studies: following a single treatment, 59–79% of patients experienced a PSA decrease, with 32–45% of patients experiencing ≥50% decrease in PSA. In the studies by Rahbar et al.\(^{(47)}\) and Kratochwil et al.\(^{(43)}\), there is the suggestion that patients who receive multiple treatments continued to respond to subsequent treatments at a similar, if not increasing, rate. The large German multicenter study demonstrated that the presence of visceral metastases and alkaline phosphatase ≥220 U/L predicted a lower rate of treatment response. In the study by Ahmadzadehfar et al., they observed that responders to the initial cycle of treatment survived over twice as long as non-responders\(^{(45)}\). In all cohorts leukopenia and thrombocytopenia were reported, but were mild. Xerostomia was seen but was mild and transient and rarely required salivary replacement.

$^{177}$Lu-PSMA-I&T ($^{177}$Lu-DOTAGA) is yet another PSMA-targeted radioligand therapeutic agent with early promising results. Baum et al. reported on a group of 56 patients with mCRPC who underwent multiple treatments\(^{(48)}\). Overall, 80% of patients had a PSA decrease, with >50% PSA decreased noted in 59% of patients. Again, mild, self-limited xerostomia was noted in 2 patients, with clinically insignificant decreases in leukocyte and erythrocyte counts seen. RECIST morphologic response assessment by CT demonstrated partial response in 20%, stable disease in 53%, and progressive disease in 28%, while response
assessment by $^{68}$G-PSMA-PET demonstrated partial response in 56%, stable disease in 8%, and progressive disease in 36%. The authors point out that changes detectable by standardized uptake values on PET/CT may occur before changes in lesion or lymph node size, and could be responsible for the discrepancy in response rates.

The PSMA-617 agent has also been tested in early clinical trials with the alpha-emitting radiometal Actinium-225, in an attempt to reduce potential hematologic and salivary toxicities, owing to the shorter range of alpha particles, and to potentially break through radioresistance to Lutetium-225. In a 14-patient dose-finding cohort, Kratochwil et al. found a dose of 100kBq/kg was the maximum tolerable dose, and that a schedule of every-2-month dosing appeared feasible. Efficacy was suggested, and plans for further study are in progress.

While dramatic radiologic responses have been noted in many of these early-phase PSMA-targeting radioligand and radioimmunotherapeutic trials, and results suggest a role for these agents in the management of mCRPC, there is, at present, no level 1 evidence demonstrating a benefit in overall survival. The impact of co-targeting approaches that create synthetic lethality from DNA damage with PARP inhibitors, next generation androgen ablation, and platinum based chemotherapies have not yet been explored.

CONCLUSION

PSMA is a promising molecular target in prostate cancer management for a number of reasons, including high levels of expression on the majority of prostate cancer cells with limited expression on benign tissues, proven in vivo safety and feasibility of targeting PSMA using antibodies and small molecules, and an internalization motif which provides for internalization and concentration of agents. Performance characteristics of PET-based imaging assays have been
shown in several studies to outperform standard imaging techniques, and appear poised to 
become a new standard in prostate cancer imaging. Early-phase therapeutic trials of unsealed 
radiometals have produced promising results in mCRPC, however more study will be required to 
prove their effect on meaningful endpoints. PSMA-targeting is likely to play a central role in 
prostate cancer management in the future.
REFERENCES


<table>
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<tr>
<th>First Author</th>
<th>PMID</th>
<th>Report Date</th>
<th>Agent</th>
<th>n</th>
<th>Key efficacy outcomes</th>
<th>Key safety outcomes</th>
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<td>Bräuer</td>
<td>28624848</td>
<td>September 2017</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>59</td>
<td>↓PSA in 91% of patients; ≥50% ↓PSA in 53% of patients; median OS 32 weeks; decrease in PSA after 1 cycle and alkaline phosphatase &lt;220 U/L were associated with longer OS</td>
<td>Grade 3 leukopenia and thrombocytopenia in 2 patients each; new-onset xerostomia in 12 patients</td>
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<td>Ahmadzadehfar</td>
<td>28488028</td>
<td>August 2017</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>52</td>
<td>↓PSA in 81% of patients after 1 cycle; ≥50% ↓PSA in 44% of patients after 1 cycle; 50% of cycle 1 nonresponders did not respond to subsequent treatment; cycle 1 responders lived &gt; twice as long as cycle 1 nonresponders (68 vs 33 weeks)</td>
<td>Not reported</td>
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<tr>
<td>Afshar-Oromieh</td>
<td>28280855</td>
<td>June 2017</td>
<td>$^{131}$I-MIP-1095</td>
<td>34</td>
<td>≥50% ↓PSA in 70.6% of patients; first dose was most effective; no association between applied activity and PSA response, median OS 17 months</td>
<td>Measurable leukopenia and thrombocytopenia, significant xerostomia transient but worsened with increasing # of treatments</td>
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<tr>
<td>Kratochwil</td>
<td>28408529</td>
<td>April 2017</td>
<td>$^{225}$Ac-PSMA-617</td>
<td>14</td>
<td>At 100 kBq/kg duration of ↓PSA was &lt;4 months; if therapy was repeated every 2 months patients experienced additive anti-tumor effects</td>
<td>Severe xerostomia became a DLT at over 100kBq/kg</td>
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<td>Rahbar</td>
<td>27765862</td>
<td>January 2017</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>145</td>
<td>↓PSA in 60% of patients; ≥50% ↓PSA in 45%; elevated alkaline phosphatase &amp; visceral metastases were negative predictors of response</td>
<td>10%, 4%, and 3% of patients experienced anemia, thrombocytopenia, and leukopenia, respectively; 8% with xerostomia</td>
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<td>Fendler</td>
<td>27683041</td>
<td>January 2017</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>15</td>
<td>2 cycles of 3.7 GBq (n=5) or 6.0 GBq (n=10). ↓PSA in 80% of patients; 67% had partial response or stable disease; pain relief in 70% of symptomatic patients</td>
<td>3 patients had grade 3 events (nausea, leukopenia, anemia)</td>
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<td>Kratochwil</td>
<td>26985056</td>
<td>August 2016</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>30</td>
<td>↓PSA in 70% of patients; ≥50% ↓PSA in 43% of patients; PSA response was &gt;24 weeks in 8/11 pts receiving 3 cycles</td>
<td>9 patients had worsening of anemia; 8 patients had leukopenia; 6 patients had thrombocytopenia</td>
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<td>Baum</td>
<td>26795286</td>
<td>January 2016</td>
<td>$^{177}$Lu-PSMA-I&amp;T</td>
<td>56</td>
<td>↓PSA in 80.4% of patients; ≥50% ↓PSA in 58.9% of patients 72% partial response or stable disease by CT; 64% partial response or stable disease by $^{68}$Ga-PSMA PET.</td>
<td>Transient xerostomia in 2 patients; statistically significant / clinically insignificant decreases in leukocyte and erythrocyte counts</td>
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<td>Tagawa</td>
<td>23714732</td>
<td>September 2013</td>
<td>$^{177}$Lu-huJ591 mAb</td>
<td>47</td>
<td>↓PSA in 59.6%; ≥50% ↓PSA in 10.6%</td>
<td>Grade 4 thrombocytopenia in 46.8%; grade 4 neutropenia in 25.5%</td>
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<td>Milowsky</td>
<td>15173215</td>
<td>July 2004</td>
<td>$^{90}$Y-huJ591 mAb</td>
<td>29</td>
<td>↓PSA of 85% and 70% in 2 patients; 6 patients with PSA stabilization</td>
<td>Two patients with thrombocytopenia and non-life-threatening bleeding</td>
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Bq – Becquerel; DLT – dose-limiting toxicity; mAb – monoclonal antibody; mCRPC – metastatic castrate-resistant prostate cancer; PET – positron emission tomography; PMID – Pubmed ID; PSA – prostate specific antigen; PSMA – prostate specific membrane antigen; OS – overall survival
## Supplemental Table 1. PSMA-targeted radiotracers and select reports

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<th>Setting</th>
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<td>Antibody</td>
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<td>SPECT</td>
<td>Villabhoshula – 2005</td>
<td>Metastatic</td>
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<td>8Zr-J591</td>
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<td>Antibody</td>
<td>PET</td>
<td>Osborne – 2014</td>
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<td>PET</td>
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<td>123I-MIP-1072, 123I-MIP-1095</td>
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<td>Barrett – 2013</td>
<td>Localized &amp; Metastatic</td>
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<td>18F-DCFPyL</td>
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<td>Small molecule</td>
<td>PET</td>
<td>Schmuck – 2017</td>
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hrs. – hours; N.A. – not applicable given the large number of studies of this agent; sens. – sensitivity
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<td>Engineered autologous T-cells</td>
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<td>Recruiting</td>
<td>Dose limiting toxicity</td>
</tr>
<tr>
<td>NCT03089203</td>
<td>CAR T-cells</td>
<td>CART T-cells +/- cyclophosphamide</td>
<td>Phase 1, 3 arm sequential assignment</td>
<td>taxane-naïve or taxane-exposed</td>
<td>18</td>
<td>Recruiting</td>
<td>Adverse events, radiologic and PSA response</td>
</tr>
<tr>
<td>NCT02202447</td>
<td>EC1169</td>
<td>PSMA-targeted tubulin inhibitor</td>
<td>Phase 1</td>
<td>taxane-exposed</td>
<td>40</td>
<td>Recruiting</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>NCT02552394</td>
<td>huJ591</td>
<td>Monoclonal antibody</td>
<td>Phase 1</td>
<td>taxane-naïve or taxane-exposed</td>
<td>24</td>
<td>Recruiting</td>
<td>Decrease in CTC count</td>
</tr>
</tbody>
</table>

*as listed ClinicalTrials.gov (accessed 5/23/17), accessed via search of “PSMA”, only trials “completed” or “recruiting” are listed
ADC – antibody drug conjugate; CTC – circulating tumor cells; mCRPC – metastatic castrate resistant prostate cancer; PSA – prostate specific antigen
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