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Prostate-Specific Membrane Antigen–Directed Therapy for Metastatic Castration-Resistant Prostate Cancer

Min Yuen Teo, MB, BCh and Michael J. Morris, MD

Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Prostate-specific membrane antigen (PSMA) is highly expressed on both benign and malignant prostatic tissue. Prostate-specific membrane antigen–directed therapy is conceptually promising, with a potential to additionally serve as a theranostic model in management of advanced prostate cancer. To date, various approaches have been devised and tested, including radiolabeled PSMA antibodies and inhibitor and antibody-drug conjugates. However, development and progress have faced challenges in determining the optimal combination of payload, PSMA-binding moiety, and linker technology. We review the available clinical data to date in PSMA-directed therapies and discuss the challenges faced.

Keywords

Prostate cancer; PSMA; Therapy

Historically, the clinical benefits of systemic cytotoxic chemotherapy have been countered by a narrow therapeutic index and treatment-related toxicities. This is exemplified by both docetaxel and cabazitaxel in the treatment of metastatic castration prostate cancer. While both drugs have been shown to prolong survival,^{1,2} this benefit is frequently countered by side effects that can have a detrimental effect on patients' quality of life.³

Against this background, the advent of targeted therapies has evoked considerable interest and enthusiasm. The theoretical advantages of targeted chemotherapy are multifold—by direct delivery of a cytotoxic agent to sites of disease, higher doses of therapy might be administered while sparing normal tissue. Coupled with radioisotopes that are suitable for imaging, treatment could perhaps be titrated and dosed in a personalized manner. In fact, targeted chemotherapy has already been demonstrated conceptually in other disease types, which resulted in practice-changing successes as witnessed with HER2-overexpressed breast cancer with trastuzumab-DM-1 (maytansinoid-1)⁴ and refractory Hodgkin disease with brentuximab vedotin.⁵ Clinical benefits are achieved by conjugation of a cytotoxic compound, frequently via a linker, to either an antibody or small molecule with the ability to bind to an identifiable cell surface protein. Upon binding to the surface target, the payload is

Reprints: Michael J. Morris, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. morrism@mskcc.org.

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internalized, and the linker dissolved by cytosolic lysozymes, therefore leading to intracellular release of cytotoxic agents.

While radiotherapy has conventionally been regarded as a locoregional therapeutic modality, the above principle can also be extended to the delivery of targeted radiotherapy.

Radioactivity-emitting radioisotopes can similarly be chelated to agents that home in on disease-specific targets and therefore deliver small but focal radiotherapy to all sites of disease while having the advantage of imaging to guide dosing. This has long been standard practice for diseases such as neuroendocrine tumors with somatostatin analogs.⁶

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein with folate hydrolase activity, although its role in vivo remains unclear. Its structure is similar to that of glutamate carboxypeptidase II and folate hydrolase I, and it harbors substrate and pharmacologic characteristics of a neuropeptidase.⁷ Prostate-specific membrane antigen is highly specific for both benign and malignant prostate epithelial cells. Expression by immunohistochemistry can be detected in up to 99.4% of prostatic epithelial and adenocarcinomatous tissues⁸ and further intensified with androgen deprivation therapy.⁹ However, PSMA expression is also detectable in other nonprostatic tissues including duodenal mucosa, proximal renal tubules,¹⁰ and non-prostatic tumor-related tumor neovasculature.¹¹ Unlike PSA, PSMA is nonsecretory and membrane bound.^{9,12} Binding of ligands to PSMA leads to internalization via clathrin-coated pits.¹³ These features render PSMA an attractive and ideal target for drug delivery for both diagnostic and therapeutic intentions.

Indeed, multiple efforts have been undertaken over the last 15 years to take advantage of PSMA's unique physicochemical properties. However, these early-phase clinical studies in castration-resistant prostate cancer (CRPC) have faced a variety of challenges that have inhibited development to late-phase clinical trials (Table 1). All 3 constitutional components of PSMA-directed therapies, namely, the PSMA-binding molecule and the therapeutic agent, connected via a linker, to date have presented with different developmental and biological challenges, which are discussed in detail below.

PSMA-Directed Radioimmunotherapy J591

huJ591 is a humanized anti-PSMA monoclonal antibody that binds with 1nM affinity to the extracellular domain of PSMA. Naked J591 has been shown to induce prolonged antibody-dependent cellular toxicity in a dose-dependent manner, although the effect was not likely to be clinically meaningful, with only 1 in 14 patients demonstrating PSA decline of greater than 50% in a small phase I study.¹⁴ Because of the large size of the J591 molecule, the majority of the antibody is cleared slowly from the plasma and therefore confers a long terminal half life of 44 ± 15 hours. In fact, blood radioactivity can still be detected 6 to 7 days after injection and could therefore be a disadvantage for radioimmunotherapy or chemoconjugates where circulating drug could confer additional toxicity (Fig. 1).

The therapeutic basis of radioimmunotherapy is the conjugation of a radioligand to either an antibody or small molecule inhibitor. Radiometals are small isotopes with radiation-emitting

capability. The principle lies in targeted delivery of radiation-emitting particles selectively to the sites of disease for cancer cell kill while minimizing toxicities to normal tissues. The physical properties of a chosen radiometal could assert substantial influence on the clinical activity of the agent, including features such as optimal tumor size for treatment and toxicity profile. This is important as, for example, the geometry of a tumor might lead to underdosing of portions distant from the radioligand and off-target toxicity in normal tissues proximate to the drug.

^{90}Y -Yttrium (^{90}Y) and ^{177}Lu -lutetium (^{177}Lu) were the 2 radioisotopes selected for initial phase I evaluation of radiolabeled huJ591, both of which are either pure or predominant β emitters. ^{90}Y has a shorter half-life of 2.7 days, higher energy, and a longer range of emission (maximum 12.0 mm), whereas ^{177}Lu has a comparatively longer half-life (6.7 days), lower energy max of 0.5 MeV, and a shorter emission range of 2.2 mm. Based on various mathematical models, the ideal tumor sizes for both ^{90}Y and ^{177}Lu were 28 to 42 mm and 1.2 to 3.0 mm, respectively.¹⁵ The radioisotopes were linked to J591 (discussed below) via 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (more conveniently known as DOTA) as a chelator.

Both studies enrolled patients with progressive CRPC and carried the standard 3 + 3 dose escalation design with determination of maximum tolerated dose as the primary endpoint. As ^{90}Y is a pure β emitter, the patients in the ^{90}Y -DOTA-J591 study were administered a dose of ^{111}In -indium-DOTA-huJ591 for pharmacokinetics, biodistribution, and dosimetric determinations 1 week prior to treatment. For patients in the ^{177}Lu -DOTA-huJ591 study, γ emission permitted capturing of postinfusion images to evaluate biodistribution of the agent. Both trials allowed for up to 3 retreatments with at least 6-week interval, provided hematologic parameters were adequate.^{16,17}

Because of prostate cancer's propensity for osseous metastatic deposits, the longer range of β emissions can increase predisposition to marrow toxicity. Unsurprisingly, both trials reported dose-dependent hematologic toxicities. Of the 29 patients enrolled in the ^{90}Y -DOTA-J591 trial, grade 3 thrombocytopenia and grade 3 or 4 neutropenia were observed in 12 (41.4%) of 29 and 13 (44.8%) of 29 patients, respectively, whereas 10 (28.6%) of 35 and 9 (25.7%) of 35 experienced grade 3 or 4 thrombocytopenia and neutropenia on the ^{177}Lu -DOTA-huJ591 trial. The majority of patients who received a single dose of treatment in both studies eventually attained full hematologic recovery.

Although these are dose-finding studies, limited clinical activity was observed and reported. In the ^{90}Y -DOTA-huJ591 trial, 2 patients (6.9%) who received 20 mCi/m² (dose level 5) achieved 85% and 70% declines in PSA lasting 8.0 and 8.6 months, respectively, 90% and 40% decreases in the sizes of nodal disease. In the ^{177}Lu -DOTA-huJ591 phase I trial, 4 patients (11.4%) had more than 50% decline in PSA lasting from 3 to 8 months before returning to baseline, and 16 patients had stabilization of their PSA, defined as less than 25% PSA increase from baseline for more than 28 days. No objective radiographic responses were observed in the 7 patients with measurable disease. Dose-limiting toxicity was observed at 75 mCi/m², and the recommended phase II dose was determined to be 70 mCi/m².¹⁶

The phase II study of ^{177}Lu -DOTA-huJ591 enrolled 47 heavily pretreated patients who had progressed on multiple lines of hormonal therapy, of whom 55.3% of patients had progressed on 1 to 4 lines of systemic chemotherapy including docetaxel. The first 15 subjects in the phase II study received 65 mCi/m^2 with the following 17 patients treated at the 70 mCi/m^2 dose. Overall, 17 (36.2%) of 47 patients and 5 (10.6%) of 47 experienced PSA declines of greater than 30% and 50%, respectively. Interestingly, a possible dose-response relationship was observed, with 46.9% of patients treated with 70 mCi/m^2 achieving PSA decline of greater than 30% compared with only 13.3% of patients on the 65 mCi/m^2 dose.¹⁸ Only 12 patients (25.5%) had measurable disease, in which 1 patient experienced a partial response by RECIST (Response Evaluation Criteria In Solid Tumors) criteria with confirmed 55% reduction in nodal metastases. Median overall survival for the entire cohort was 17.6 months, although it was longer in the subgroup that was treated at the higher dose (21.8 vs. 11.8 months).

The safety and clinical activity of ^{177}Lu -DOTA-huJ591 were further refined in a phase I/II dose fractionation study. A total of 49 metastatic CRPC patients were enrolled, of whom 16 were involved in the dose-finding phase of the study. The recommended phase II dose was determined to be 2 doses of ^{177}Lu -DOTA-huJ591 at 40 or 45 mCi/m^2 administered 2 weeks apart, with growth factor support for the higher dose level. Predictable and reversible hematologic toxicities were observed. For the entire cohort, 32.7% and 16.3% of patients experienced greater than 30% and 50% PSA decline, respectively. For the 17 patients who were dosed at 45 mCi/m^2 , greater than 30% and 50% PSA declines were observed in 58.8% and 29.4% of patients, along with numerically longer median overall survival compared with the entire cohort, further confirming the dose-dependent clinical activity of the treatment. The study authors also observed that the level of PSMA expression by imaging might correlate with the likelihood to respond, supporting the role of PSMA expression as potential predictive biomarker of response.¹⁹

Radioligands With Small Molecules

Kozikowski and colleagues²⁰ first described urea-based PSMA inhibitors in 2001. These agents consist of a glutamate-urea-*X* motif, which functions as a heterodimeric inhibitor of PSMA, where *X* can be a series of peptides that affects the molecule's binding affinities.²¹ In pharmacokinetic evaluation, these small molecules are able to move out of vascular compartment into extravascular space, rapidly resulting in low total-blood exposure and short mean residence time. Rapid clearance can be observed, with up to 75% clearance within 72 hours of administration.²² These properties could potentially alter the balance of toxicity and efficacy compared with antibody-based agents.

MIP-1095, also known as (s)-2-(3-((S)-1Carboxy-5-(3-(4-iodophenyl)ureido) pentanedioic acid, is one of the urea-based PSMA inhibitor that has high affinity for PSMA with K_i of 0.24 nmol/L in preclinical studies and could form stable conjugates with both 124-iodine (^{124}I) and 131-iodine (^{131}I).²³ Although not formally tested in a prospective trial, ^{131}I -MIP-1095 has been available in Germany on a compassionate use basis for progressive metastatic CRPC. Zechmann and colleagues²⁴ reported their early experience in 28 patients and observed substantial biochemical activity with greater than 50% PSA decline in 60.7%

of patients, whereas 24.0% of patients had more than 75% decline in their PSA levels. The median time to PSA progression was 126 months (range, 62–469 months), and a decrease in PSA was frequently associated with a decrease in number and/or intensity of the lesions on posttreatment imaging studies. In fact, 11 of 13 patients with disease-related bone pain at baseline reported partial or complete resolution of the symptom. Hematologic toxicities were frequent but mild, with leucopenia noted in 14 of 28 patients with 1 grade 3 leukopenia and 11 of 28 patients with all-grade thrombocytopenia, with 2 attaining grade 3 severity.²⁴ As ¹³¹I-MIP-1095 is a pure β emitter, the additional administration of ¹²⁴I-MIP-1095 is required for imaging purposes.²⁵

On the other hand, investigators at Technical University of Munich developed a ¹⁷⁷Lu-DOTAGA analog, with which has demonstrable improved affinity, higher tumor uptake, and faster renal clearance.²⁵ Two groups have independently reported their clinical experience with this modified agent under a compassionate access protocol for patients with advanced prostate cancer in Germany. With a combined number of patients of 54, the majority of the patients have had prior exposure to enzalutamide, abiraterone, or both and at least 1 or more lines of taxanes and other cytotoxic chemotherapies. At least 18 patients were previously treated with radium-223 (²²³Ra). In contrast to other radiolabeled PSMA-targeting agents studied to date, reported rates of hematologic toxicities were low, and pronounced clinical activities were observed. Only 3 patients developed grade 3 anemia, and 1 developed grade 3 thrombocytopenia, but half of these had diffuse pattern bone marrow infiltration on prior imaging suggestive of high disease burden and limited marrow reserve. In the cohort of 30 patients reported by Kratochwil and colleagues,²⁶ 21 patients demonstrated a decrease in PSA, 18 (60.0%) of whom with greater than 25% decline, whereas 13 (43.3%) enjoyed greater than 50% decline in PSA. Eleven patients received 3 treatment cycles of at least 8-week intervals, all patients enjoyed at least 25% decline in their PSA level, whereas 8 of 11 had decline of greater than 50%. Ten of 11 patients with evaluable scans showed responsive disease, although it should be noted that response criteria were not standardized because some were restaged with PSMA–positron emission tomography/computed tomography (CT), whereas some were imaged with technetium 99m–PSMA–single-photon emission CT/CT or CT scans.²⁶ Similarly, in the second but smaller study, 79.1% of patients experienced decline in PSA at first evaluation 8 weeks after first treatment, of whom 61.9% and 47.6% of patients experienced a decline of greater than 30% and greater than 50%, respectively. Twenty-two patients received a second cycle of treatment, of whom 68.2% and 60% experienced a PSA decline of greater than 30% and greater than 50%, respectively.²⁷

PSMA-Directed Chemotherapy

Antibody-Based Agents

MLN2704 is an antibody-drug conjugate (ADC) in which the antibody component of the drug was huJ591. The antibody was linked to DM-1 through a disulfide bridge to thiopentanoate group, whereas DM-1 is a microtubule inhibitor, which is an analog of maitansine with high potency compared with conventional cytotoxic agents.²⁸ Two early-phase trials were initiated to study different dosing levels and schedules. It was observed that the toxicity profile differs substantially from other PSMA-targeted therapies and is more

typical of systemic chemotherapy, with nausea, fatigue, and diarrhea being the most commonly encountered adverse effects. In the first study, asymptomatic increases in hepatic transaminases were noted in 1 of 3 patients at 120 mg/m² and 5 of 6 patients at 343 mg/m², whereas 8 of 23 patients developed low grade neuropathy, which appeared more frequent at higher doses.²⁹ In the second study with 61 progressive metastatic CRPC patients, most commonly encountered toxicities were also nausea, fatigue, and schedule-dependent neurotoxicity. Dose limiting toxicity was determined to be grade 3 transaminitis.¹⁷ It became evident that deconjugation of MLN2704 occurred based on the presence of DM-1-SH and free MLN591 in the serum, whereas the terminal elimination half-life for the drug was observed to be markedly shorter than that for the total antibody.²⁹ Consequentially, this led to suboptimal drug delivery to the intended sites of disease, as reflected in the low rate of clinical activity, with only a total of 4 patients experiencing PSA decline of greater than 50% across both studies.²⁹

The MLN2704 experience provides a valuable lesson in challenges that one faces in linker technology. Besides connecting the therapeutic agent and PSMA-binding molecule together, the linker also serves to ensure that the linkage is maintained until the drug is internalized into the cancer cells to fulfill the role of targeted drug delivery. A linker's length, polarity, size, flexibility, presence of aromatic groups, or hydrophobic functionality can significantly influence the pharmacokinetics and internalization potency of PSMA inhibitors.³⁰

While MLN2704 succumbed to technological limitations, interests in PSMA-targeted delivery of cytotoxic agents remain high, further spurred on by activities seen with microtubule-targeting agents such as docetaxel and cabazitaxel.^{1,2}

Ma and colleagues³¹ reported a PSMA-targeting monoclonal antibody conjugated to monomethylauristatin E (MMAE) through a valine-citrulline linkage designed to maintain serum stability while maximizing intracellular drug release by human cathepsin B. Monomethylauristatin E is a synthetic antimetabolic agent related to a natural product called dolastatin and was shown to be approximately 200 times more potent in vitro than conventional chemotherapeutic agents, with significant activity in in vitro and in vivo CRPC models.³¹ In its first-in-human study, the drug appeared to be safe with low level of free MMAE in circulation. The early development of this agent involved 52 subjects dosed over 9 different dose levels, starting at 0.4 mg/kg administered once every 3 weeks for a maximum of 4 cycles. Initial clinical signal was not observed until 1.6 mg/kg,³² with dose-limiting toxicity identified eventually at 2.8 mg/kg in the form of neutropenia with consequential transaminitis and death.³²⁻³⁴

The drug was brought forward to phase II investigation at the maximum tolerated dose of 2.5 mg/kg in patients with progressive metastatic castration-resistant disease following taxanes and next-generation AR signaling inhibitors. Treatment dose had to be reduced from 2.5 to 2.3 mg/kg after 34 patients because of high rates of neutropenia, with 2 cases of resultant sepsis and death. Overall, 83 taxane-exposed and 35 chemotherapy-naïve patients were enrolled. For the entire cohort, PSA declines of greater than 30% and greater than 50% were observed in 30% and 14% of patients, respectively, and circulating tumor cell conversion rate was 47%. However, radiographic response rates were low among evaluable patients,

observed only in 6% of taxane-pretreated patients and 17% of chemotherapy-naïve patients. Treatment-related toxicities were common, with 22% of chemo-naïve and 25% of taxane-exposed patients developing grade 3 or higher neutropenia.^{35,36}

PSMA-Directed Nanoparticles

BIND-014 is a novel, tumor PSMA-targeted nanoparticle containing docetaxel. The technology is based on encapsulation of drugs in long-circulating, biodegradable, and biocompatible, polymeric particles functionalized with targeted ligands. When administered intravenously, these nanoparticles are designed to circulate in the vascular compartment for long periods, accumulate in the diseased tissue, and release the encapsulated drug in a controlled manner.

A phase I study in solid tumors demonstrated a dose-linear pharmacokinetic profile distinct from that of docetaxel with P2RD determined to be 60 mg/m².³⁷ A phase II trial was subsequently carried out in 42 docetaxel-naïve metastatic CRPC patients. Seventy-four percent of the patients were previously exposed to abiraterone, enzalutamide, or both, with 19% having progressed within 6 months of AR-targeting agents. The results were recently reported in the American Society of Clinical Oncology Genitourinary Cancers Symposium, with median radiographic progression-free survival of 7.1 months and PSA decline of 50% or greater observed in 12 (30%) of 40 patients. Circulating tumor cell conversion occurred in 13 (50%) of 26 patients, and radiographic objective response rate was 32%. Rates of low-grade toxicities were high, including lymphopenia (26%), anemia (19%), fatigue (69%), nausea (55%), diarrhea (45%), dyspnea (36%), and neuropathy (33%).³⁸

While concerns with deconjugation have been overcome with these new agents, the observed clinical activities and toxicity profiles did not appear to differ substantially from that of systemic administration of docetaxel, raising the question on the specificity and affinity of the target in vivo.

PSMA-Directed Therapies—Ongoing Challenges

The development of PSMA-directed therapies elucidates the many challenges that the field has faced—a bone-based tumor that is in close proximity to the patient's reservoir of bone marrow, targeting agents that have long circulating half-lives, and linkers that may not effectively retain their payload. Nonetheless, the hypothesis that anticancer treatments can be specifically delivered to cancer cells leveraging those cells' biology while sparing normal tissues and minimizing bystander effects remains promising. Furthermore, the technological aspects of optimizing approach improves with each generation of drug development, using agents with superior linkers, more rapid clearance, and the possibility of reducing the impact on the bone marrow.

Encouraging results from the phase III ALSYMPCA trial, which demonstrated the clinical benefit and safety of α -emitting ²²³Ra,³⁹ raise the interests for α -particle-based radiometals as payload. Meanwhile, MIP-1095, which demonstrated considerable clinical activity in the Heidelberg experience, is due for prospective evaluation in the future. While MLN2704 was limited by linker deconjugation, next-generation cytotoxic-bound ADCs such as BIND-014 and MMAE ADC have successfully demonstrated the potential of improved pharmacology.

Newer agents are continued to be tested, including an ongoing phase I study of EC1169, a PSMA-targeting moiety linked to tubulysin B hydrazide, which have shown highly favorable toxicity profile to date (NCT02202447).⁴⁰ Both in vitro^{41,42} and mice model⁴³ studies have shown synergisms between PSMA ADC and newly available agents such as abiraterone, enzalutamide, and rapamycin, offering a wealth of combination, which have not been evaluated in human studies. As PSMA is highly restricted to prostatic tissue, it has also been actively investigated as a target for therapeutic vaccine and immunotherapy, which is being covered in detail in a different article elsewhere in this issue.

These novel therapeutic approaches are highly needed beyond existing strategies of AR inhibition, bone-seeking radiopharmaceuticals, and systemic chemotherapy. Prostate-specific membrane antigen has the potential to provide a large theranostic advantage over existing therapeutics in prostate cancer. Theranostics, a portmanteau of diagnostics and therapeutics, involves the detection of the target with molecular imaging prior to treatment administration, ensuring that only patients who will benefit from PSMA-directed therapy proceed to receive the treatment. Despite early limitations, PSMA-directed therapies, with the ability to preselect patients who might derive benefit from the treatment, tailor dosing to patients' individual metabolic rates, and minimize adverse effects while maximizing anticancer effects, remain an important area of investigation with the ability to fill an unmet need in advanced prostate cancers.

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FIGURE 1.
Mechanisms of action of PSMA-directed therapies.

TABLE 1

List of PSMA-Directed Therapy Clinical Studies

Study	Year	Phase	Sample Size	Treatment	Targeting Agent	Payload	RP2D	Clinical Activity
Milowsky et al. ¹⁷	2004	1	29	⁹⁰ Y-DOTA-huJ591	huJ591	⁹⁰ Y	17.5 mCi/m ²	
Bander et al. ¹⁶	2005	1	35	¹⁷⁷ Lu-DOTA-huJ591	huJ591	¹⁷⁷ Lu	70 mCi/m ²	
Morris et al. ¹⁴	2005	1	7	Unlabelled huJ591	huJ591	N/A		>50% PSA decline: 10.6%, >30% PSA decline: 36.2%
Tagawa et al. ¹⁸	2013	2	47	¹⁷⁷ Lu-DOTA-huJ591	huJ591	¹⁷⁷ Lu		>50% PSA decline: 60.7%
Zechmann et al. ²⁴	2014	Retro	28	¹³¹ I-MIP-1095	MIP-1095	¹³¹ I		>50% PSA decline: 43.3%, after 3 treatments: 72.7%
Kratochwil et al. ²⁶	2016	Retro	30	¹⁷⁷ Lu-PSMA-617	PSMA-617	¹⁷⁷ Lu		After 1st treatment: >50% PSA decline: 41.6%, >30% PSA decline: 54.2%; after 2nd treatment: >50% PSA decline: 60.0%, >30% PSA decline: 68.2%
Ahmadzadehfar et al. ²⁷	2016	Retro	24	¹⁷⁷ Lu-PSMA-617	PSMA-617	¹⁷⁷ Lu		
Galsky et al. ²⁹	2008	1	23	MLN2704	huJ591	DM-1	Not defined	
Petrylak et al. ³⁴	2013	1	52	PSMA ADC	PSMA mAb	MMAE	2.5 mg/kg	
Petrylak et al. ³⁶	2015	2	119	PSMA ADC	PSMA mAb	MMAE		Entire cohort: >50% PSA decline: 14.0%, >30% PSA decline: 30.0%; chemotherapy naive: >50% PSA decline: 31.0%, >30% PSA decline: 20.0%
Autio et al. ³⁸	2016	2	52	BIND-014	PSMA targeting nanoparticle	Docetaxel		>50% PSA decline: 30.0%

Retro indicates retrospective study; RP2D, recommended phase II dose.