

## CCR Translations

See related article by Tagawa et al., p. 5182

**What's in a Label? Radioimmunotherapy for Metastatic Prostate Cancer**

Charles B. Simone II and Stephen M. Hahn

Prostate cancer has a highly tumor-restricted prostate-specific membrane antigen (PSMA) and may be the ideal solid-organ malignancy for treatment with radioimmunotherapy. Encouraging results using lutetium-177-labeled anti-PSMA monoclonal antibody J591 from a phase II study by Tagawa and colleagues support the continued clinical and preclinical development of radioimmunotherapy for solid tumors. *Clin Cancer Res*; 19(18); 4908–10. ©2013 AACR.

In this issue of *Clinical Cancer Research*, Tagawa and colleagues report their findings from a phase II study of lutetium-177-labeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (<sup>177</sup>Lu-J591) for metastatic castration-resistant prostate cancer (mCRPC) (1). This is one of the few reported phase II studies of disease-specific single-agent radioimmunotherapy for solid malignancies and significantly advances this new era of targeted radiotherapy using disease-specific monoclonal antibodies.

Brachytherapy and external beam radiotherapy have well-established roles for definitive therapy of localized prostate adenocarcinoma (2). However, radiotherapy for mCRPC has historically been solely for palliation. This role is expanding with recent interest in radionuclide and radioimmunotherapy. Although radioimmunotherapy is most established for non-Hodgkin lymphoma, its applications to solid malignancies have been limited. Prostate cancer, however, allows for a highly tumor-restricted antigen in PSMA, and patients with mCRPC often have limited-volume disease confined to bone marrow and lymph nodes that is more easily accessed by circulating antibodies.

In the study by Tagawa and colleagues, among 47 patients with prostate-specific antigen (PSA) progression after hormonal therapies with or without chemotherapy treated at two centers with single administration of <sup>177</sup>Lu-J591, 15 initially received 65 mCi/m<sup>2</sup> and 32 subsequently received the maximum tolerated dose (MTD) of 70 mCi/m<sup>2</sup> (1). Overall, 10.6% experienced more than 50% PSA decline, and 36.2% experienced more than 30% decline. This included 46.9% with more than 30% PSA decline among those treated at the MTD (*n* = 32). Furthermore, 9 of 12 (75%) patients with radiographically measurable disease

had some measure of disease control (1 = partial response, 8 = stable disease), and 8 of 12 (67%) assessed for circulating tumor cells (CTC) had more than 50% decline in tumor cell counts 4 to 6 weeks after treatment.

Importantly, Tagawa and colleagues used postadministration imaging of <sup>177</sup>Lu-J591 to assess tumor targeting (1). Also, <sup>111</sup>In-J591 imaging was performed before <sup>177</sup>Lu-J591 administration in selected patients. Overall, 93.6% had accurate targeting of known sites of disease compared with pretreatment computed tomography, MRI, and/or bone scans based on planar gamma camera imaging 3 to 7 days after <sup>177</sup>Lu-J591 infusion. Furthermore, patients with imaging densities suggesting low PSMA expression were somewhat less likely to have PSA responses.

In an *ad hoc* analysis, median overall survival was significantly greater for patients receiving 70 mCi/m<sup>2</sup> than for those getting 65 mCi/m<sup>2</sup> (21.8 vs. 11.9 months; *P* = 0.03). These findings are similar to the historical median survival of mCRPC of less than 2 years (3) and recent phase III trial reports for mCRPC (4, 5). Furthermore, patients with PSA declines had improved median survivals (22.2 vs. 11.4 months; *P* < 0.01). Notably, only a minority of patients had measurable disease, yet radioimmunotherapy still affected survival compared with historical controls. The authors suggest that immune mechanisms may affect clinical outcomes independent of immediate tumor response; however, this mechanism cannot be confirmed with the current study.

Systemic radioisotope therapy with unsealed radiation sources like samarium-153 (β-emitter), strontium-89 (β-emitter), and radium-223 (α-emitter) can decrease PSA, reduce pain, improve quality of life, and even improve overall survival in patients with mCRPC with bone metastasis (6–8). In a groundbreaking radionuclide study, patients with mCRPC and multiple or painful bone metastases needing external beam radiotherapy were randomized to radium-223 or placebo. Radium-223 reduced bone-alkaline phosphatase concentration (*P* < 0.0001), increased time to PSA progression (*P* = 0.048), resulted in numerically fewer skeletal-related events (*P* = 0.065), and increased median overall survival [65.3 vs. 46.4 weeks;

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$P = 0.066$ ; HR adjusted for baseline covariates 2.12 (1.13–3.98; ref. 9)].

Radioimmunotherapy offers distinct advantages over other radionuclide therapies. PSMA, a nonsecreted cell membrane protein, has expression highly restricted to prostate epithelium, and it is expressed in nearly all prostate cancers. J591 is a deimmunized monoclonal antibody against the extracellular domain of PSMA (Fig. 1). Agents like samarium-153, strontium-89, and radium-223 target sites of increased bone metabolism but do not target tumor directly. They instead impart antitumor effects from radiopharmaceutical accumulation adjacent to malignant cells or stroma and, therefore, do not appreciably treat extraosseous visceral metastases. By radiolabeling tumor-specific PSMA monoclonal antibody, delivering cytotoxic therapy to both bone and soft tissue and visceral metastases is achievable. Yttrium-90 and lutetium-177 have both been used for radiolabeling in clinical trials. Lutetium-177, used in the study by Tagawa and colleagues, may prove the superior option because it has a longer half-life, higher activity at the MTD, and is both a short-range (0.2–0.3 mm) beta particle and gamma particle emitter, allowing for lower radiation dose to bone marrow (1).

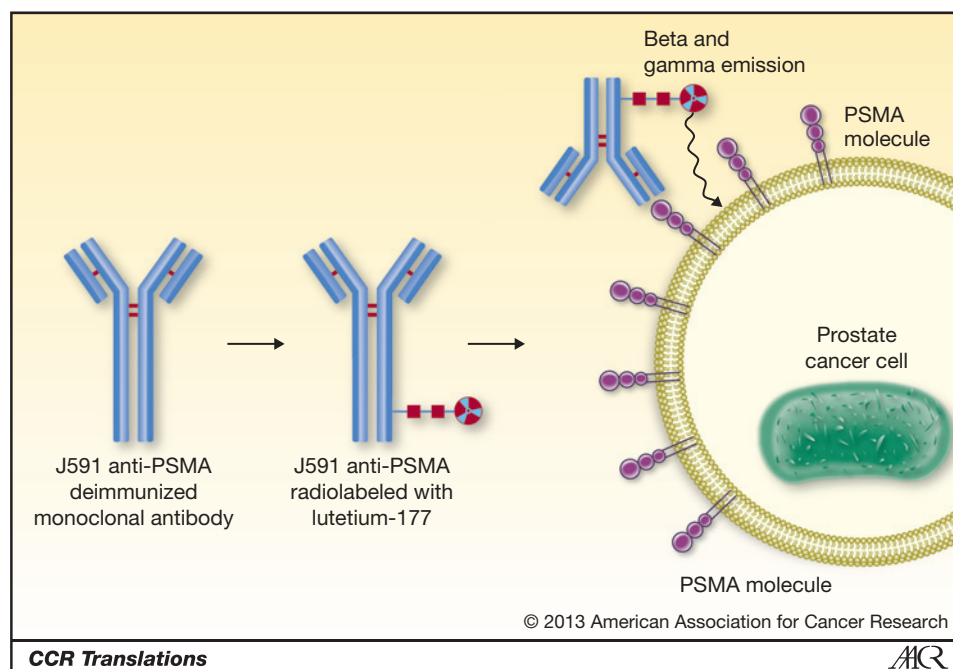
Radionuclide therapy for prostate cancer is generally well tolerated, with reversible hematologic toxicities from samarium-153, strontium-89, and radium-223. Because a larger fraction of administered activity remains in various organs and body spaces, radioimmunotherapy has the potential of increased toxicity compared with radionuclide therapy. The specificity of tumor-specific PSMA monoclonal antibody is likely to mitigate this risk. Nonetheless, in the study by Tagawa and colleagues, all the patients experienced hematologic toxicities, including grade 4 thrombocyto-

penia in 46.8% lasting a median of 7 days and grade 4 neutropenia in 25.5% lasting a median of 5 days (1). Higher rates were recorded in patients treated at 70 mCi/m<sup>2</sup>. Myelosuppression, although typically transient, was of concern, as 7 patients did not recover a normal platelet count. Such bone marrow suppression is significant and may limit the ability to deliver other subsequent therapies or combine <sup>177</sup>Lu-J591 with other cytotoxic agents. Therefore, careful consideration is required when determining integration of radioimmunotherapy with other therapies for mCRPC.

In the 2013 guidelines from the American Urologic Association, symptomatic mCRPC patients with good performance status are recommended to receive docetaxel chemotherapy, or otherwise mitoxantrone (evidence level grade B), ketoconazole (grade C), or radionuclide therapy (grade C). In addition, radionuclides should be considered in patients with mCRPC with poor performance status treated with prior docetaxel or if they have not had prior docetaxel but are unable or unwilling to receive abiraterone plus prednisone (3). In the months since these guidelines were devised, with May 2013 U.S. Food and Drug Administration approval of radium-223 to treat patients with mCRPC with symptomatic bony metastasis, it is expected that future mCRPC guidelines will recommend an even larger role for radionuclide and radioimmunotherapy.

Tagawa and colleagues should be commended for their work showing that <sup>177</sup>Lu-J591-targeted radiotherapy has a measurable response rate in mCRPC. Prospective assessment of tumor targeting with radioimmunotherapy agents is also promising and should be further developed to better select patients and perhaps improve the therapeutic index of these agents. Survival was not the primary

**Figure 1.** Mechanism of cytotoxicity for <sup>177</sup>Lu-J591. Prostate-specific membrane antigen (PSMA) is a nonsecreted cell membrane protein upregulated in nearly all prostate cancers. J591 is a deimmunized monoclonal antibody against the extracellular domain of PSMA (left). J591 anti-PSMA is radiolabeled with lutetium-177 linked via a DOTA chelate to J591 (middle). When <sup>177</sup>Lu-J591 binds to PSMA, lutetium-177 comes into close contact with prostate cancer cells and can achieve cytotoxic effects to both bone and soft tissue and visceral metastases via short-range beta and gamma emission (right).



endpoint of this study, and therefore, limited conclusions can be made regarding the impact of  $^{177}\text{Lu}$ -J591 on mCRPC natural history. As the authors suggest, randomized phase III data using  $^{177}\text{Lu}$ -J591-targeted radiotherapy are required to further develop this agent (1).

Although Tagawa and colleagues have reasonably shown the safety of  $^{177}\text{Lu}$ -J591 in a heavily pretreated patient population, there are concerns regarding hematologic toxicity with radioimmunotherapeutic use. Safety and efficacy data combining  $^{177}\text{Lu}$ -J591 with other therapies or administering it sequentially or in the salvage setting after docetaxel should be assessed. Rational selection of patients based on PSMA expression, perhaps using quantitative pretreatment imaging, is likely to prove desirable if PSMA expression level is found to correlate with response to PSMA-targeted therapy (1).

Although mCRPC remains an incurable condition and is projected to result in up to 29,720 deaths in the United States this year (10), several new agents have been developed over the past 5 to 10 years to treat this disease

that are improving the outlook for this patient population. The results of Tagawa and colleagues suggest that radioimmunotherapy with targeted agents such as  $^{177}\text{Lu}$ -J591 is a promising new therapeutic strategy to explore (1).

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** C.B. Simone, S.M. Hahn

**Development of methodology:** C.B. Simone

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** C.B. Simone

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** C.B. Simone

**Writing, review, and/or revision of the manuscript:** C.B. Simone, S.M. Hahn

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** C.B. Simone

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