

Phase II Study of Lutetium-177–Labeled Anti-Prostate-Specific Membrane Antigen Monoclonal Antibody J591 for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: To assess the efficacy of a single infusion of radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (lutetium-177; ¹⁷⁷Lu) by prostate-specific antigen (PSA) decline, measurable disease response, and survival.

Experimental Design: In this dual-center phase II study, two cohorts with progressive metastatic castration-resistant prostate cancer received one dose of ¹⁷⁷Lu-J591 (15 patients at 65 mCi/m², 17 at 70 mCi/m²) with radionuclide imaging. Expansion cohort ($n = 15$) received 70 mCi/m² to verify response rate and examine biomarkers.

Results: Forty-seven patients who progressed after hormonal therapies (55.3% also received prior chemotherapy) received ¹⁷⁷Lu-J591. A total of 10.6% experienced $\geq 50\%$ decline in PSA, 36.2% experienced $\geq 30\%$ decline, and 59.6% experienced any PSA decline following their single treatment. One of 12 with measurable disease experienced a partial radiographic response (8 with stable disease). Sites of prostate cancer metastases were targeted in 44 of 47 (93.6%) as determined by planar imaging. All experienced reversible hematologic toxicity, with grade 4 thrombocytopenia occurring in 46.8% (29.8% received platelet transfusions) without significant hemorrhage. A total of 25.5% experienced grade 4 neutropenia, with one episode of febrile neutropenia. The phase I maximum tolerated dose (70 mCi/m²) resulted in more 30% PSA declines (46.9% vs. 13.3%, $P = 0.048$) and longer survival (21.8 vs. 11.9 months, $P = 0.03$), but also more grade 4 hematologic toxicity and platelet transfusions. No serious nonhematologic toxicity occurred. Those with poor PSMA imaging were less likely to respond.

Conclusion: A single dose of ¹⁷⁷Lu-J591 was well tolerated with reversible myelosuppression. Accurate tumor targeting and PSA responses were seen with evidence of dose response. Imaging biomarkers seem promising. *Clin Cancer Res*; 19(18); 5182–91. ©2013 AACR.

Introduction

Prostate cancer is a radiosensitive disease, and radiotherapy is an established form of definitive treatment for clinically localized prostate cancer and for palliation of painful bone metastases. Unsealed radiation sources (samarium-153, strontium-89, radium-223) targeting sites of increased bone metabolism/turnover as an indirect means to target bone metastases have showed clinical benefit, including de-

creased pain, some prostate-specific antigen (PSA) declines, and most importantly improvement in survival for ²²³Ra (1–4). We have investigated the application of a tumor-targeted monoclonal antibody (mAb) as a means to deliver a cytotoxic payload directly and specifically to prostate cancer metastases not only in bone but also in soft tissue and visceral metastases. This approach combines the specificity of mAb targeting with the tumoricidal effects of β radiation.

Prostate-specific membrane antigen (PSMA) is a nonsecreted cell membrane protein with expression that is highly restricted to prostate epithelium and upregulated in prostate cancer (5–10). Results from pathology studies indicate that PSMA is expressed by virtually all prostate cancers (8, 11–14). PSMA was initially validated as an *in vivo* target for imaging using radiolabeled mAb 7E11 (CYT-356, capromab), although results from therapeutic studies were disappointing (15–18). Recognition that PSMA represented a prostate cancer–restricted target and that 7E11 targets an internal domain and is unable to bind to viable cells led to the development of mAbs to the exposed, extracellular

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Translational Relevance

Targeted therapies are of relevance to many fields of medicine. Prostate-specific membrane antigen (PSMA) represents a highly restricted, overexpressed prostate cancer cell-surface protein. J591, a deimmunized monoclonal antibody targeting the external domain of PSMA, has been successfully radiolabeled with β -emitting radionuclides. Here we report a phase II trial of a single dose of ¹⁷⁷Lu-J591 that successfully targets known sites of disease in men with progressive metastatic, castration-resistant prostate cancer (CRPC). Declines in prostate-specific antigen were showed, with a dose-response relationship seen. Circulating tumor cell count control occurred in the majority of patients tested. Noninvasive assessment of PSMA expression via imaging may prove to be a predictive biomarker. Based upon this study and other clinical trials and the physical properties of ¹⁷⁷Lu (short path length), a randomized study is ongoing targeting a theoretically more optimal micrometastatic disease population (i.e., CRPC without metastases), and a phase III registration trial is planned.

domain of PSMA (5, 9, 19–22). J591, a deimmunized mAb against the extracellular domain of PSMA, is the lead clinical candidate (22, 23).

Two independent phase I radioimmunotherapy (RIT) trials have been conducted using yttrium-90 or lutetium-177 linked via a DOTA chelate to J591 in patients with metastatic castration-resistant prostate cancer (CRPC; refs. 24 and 25). These trials defined the maximum tolerated dose (MTD), dosimetry, pharmacokinetics, and human antihumanized antibody response and showed preliminary evidence of antitumor activity.

Lutetium-177 was chosen for further development based upon its physical properties, emitting both a short-range (0.2–0.3 mm) β particle as well as γ emission. As a result, it delivers a lower radiation dose to bone marrow relative to higher energy β particles such as ⁹⁰Y (26). The γ emission from ¹⁷⁷Lu allows for *ex vivo* imaging in contrast to ⁹⁰Y, which, as a pure beta emitter, requires use of a surrogate isotope such as indium-111 for imaging. With RIT, tumor lesion geometry has been proposed to be an important factor, and it has similarly been proposed that the emission characteristics of the isotope should probably be appropriately matched to the lesion size/volume to be treated to ideally focus energy within the tumor rather than in the tissue surrounding the lesion/s (27). Lutetium-177 also has a longer physical half-life (6.7 days compared with 2.7 days for ⁹⁰Y), resulting in longer tumor residence times. Because of these properties, higher activities can be delivered using ¹⁷⁷Lu; in the phase I trials of radiolabeled J591, the MTD of ¹⁷⁷Lu-J591 was 70 mCi/m² compared with 17.5 mCi/m² for ⁹⁰Y-J591, with lower activity in bone marrow per amount of blood radioactivity (24–26). Here we report safety and efficacy data for a phase II study of ¹⁷⁷Lu-J591 in patients with metastatic CRPC.

Patients and Methods

Adult subjects with progressive metastatic CRPC were eligible for enrollment. Histologic or cytologic confirmation of prostate cancer (primary or metastatic site) was required. Progressive CRPC was defined using modified Prostate-Specific Antigen Working Group (PCWG1) criteria (28). Continuous leutenizing hormone-releasing hormone agonist therapy was required for subjects who had not undergone bilateral orchiectomy. Any number of previous regimens was allowed, provided the subject had not received anti-PSMA based therapy. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, absolute neutrophil count $\geq 2,000/\text{mm}^3$, platelet count $\geq 150,000/\text{mm}^3$, serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase (AST) $\leq 2 \times$ ULN, prothrombin time international normalized ratio and activated partial thromboplastin time $\leq 1.3 \times$ ULN (unless on anticoagulation), and serum creatinine ≤ 2.5 mg/dL.

Exclusion criteria included prior radiotherapy to $>25\%$ of skeleton, prior ⁸⁹strontium- or ¹⁵³samarium-containing compounds, bone scan showing confluent lesions involving both axial and appendicular skeleton ("superscan"), other active cancers, or clinically significant cardiac, renal, hepatic, pulmonary, thyroid, or psychiatric disease. Concurrent corticosteroids and/or adrenal hormone inhibitors, PC-SPEs, finasteride, or dutasteride were not allowed. This registered study (clinicaltrials.gov NCT00195039) was approved by the Institutional Review Boards of Weill Cornell Medical College and Memorial Sloan-Kettering Cancer Center, and all subjects provided written informed consent.

Treatment

Preparation and quality control of ¹⁷⁷Lu-J591 was conducted as previously described (25). Subjects received a single dose of ¹⁷⁷Lu-J591 consisting of J591 chelated at a specific activity of 12 to 15 mCi of ¹⁷⁷Lu per mg of antibody plus sufficient nonradiolabeled, non-DOTA-conjugated ("naked") J591 to achieve a total antibody dose of 20 mg. Although the MTD of the phase I dose escalation study was 70 mCi/m² (25), based upon limited prior clinical experience with ¹⁷⁷Lu-labeled mAbs as directed by the U.S. Food and Drug Administration (FDA), an initial cohort of 15 subjects received a dose of ¹⁷⁷Lu of 65 mCi/m² followed by 17 subjects at 70 mCi/m². After analysis of the initial 32 subjects, an additional 15 were enrolled, underwent infusion of ¹¹¹In-J591 with subsequent imaging to prospectively evaluate noninvasive assessment of PSMA expression as a predictive biomarker, and then received a single dose of ¹⁷⁷Lu-J591 at 70 mCi/m². Each dose was administered without premedication by an i.v. infusion at a rate not to exceed 5 mg/min.

Evaluation during the study

Subjects were monitored for at least 4 hours after mAb infusion. Complete blood counts were done at least weekly beginning 3 weeks after ¹⁷⁷Lu-J591 infusion until 6 weeks or recovery and were repeated at least twice a week during periods of grade 4 neutropenia and at least 3 times a week during periods of grade 4 thrombocytopenia.

Transfusions, filgrastim or pegfilgrastim (but not sargramostim), and red blood cell growth factors were permitted at the discretion of the treating physician. A chemistry panel including liver tests and PSA was conducted at least every 4 weeks. Expansion cohort subjects had a baseline circulating tumor cell (CTC) count by CellSearch (Veridex) methodology at baseline and 4 to 6 weeks after ^{177}Lu -J591 infusion.

A planar gamma camera image was obtained 5 to 7 days after ^{177}Lu -J591 infusion (expansion cohort subjects also had pretreatment imaging 3 to 4 days after ^{111}In -J591 infusion) with single-photon emission computed tomography images obtained in selected patients. Radiolabeled J591 images were compared to baseline clinical bone scintigraphy and cross-sectional imaging. After planar gamma camera imaging, images were scored using two methods. A 5-point visual scale was conducted by two independent radiologists and scored 0 (no uptake), 1 (weakly positive), 2 (definitely positive), 3 (equal intensity to liver), and 4 (greater uptake than liver). Tumor targeting index (TuTI), a novel metric designed to semiquantitatively score images, was calculated for the most prominent lesions in each subject using the ratio of lesion count density (corrected for background) to whole body count density: $\text{TuTI} = (\text{lesion region of interest count density} - \text{background count density}) / (\text{total body count density})$. Assessment of accurate uptake of radiolabeled mAb by known sites of disease was conducted by comparison of visual scores and TuTI to areas of known metastatic disease on bone scan and computed tomography (CT)/MRI. CT or MRI of abdomen/pelvis and bone scans were repeated 3 months after ^{177}Lu -J591 infusion and every 3 months thereafter until progression. Radiographically measurable disease was defined as lymph nodes of at least 20 mm and nonosseous visceral disease of at least 10 mm in greatest diameter.

Statistical plan

The primary endpoint of the study was response rate, evaluated by the measurable-disease response rate and posttreatment PSA decline rate, which was originally defined as the percentage of patients who achieved a $\geq 50\%$ decrease in PSA from baseline without requirement for confirmation. With an initial sample size of 32 patients, a two-sided 95% confidence interval (CI) for the response proportion was estimated to extend 0.10 from the observed proportion for an expected proportion of 10%. For an expected proportion of 15%, the CI was estimated to extend 0.12 from the observed proportion. The expansion cohort to bring the 70 mCi/m² dose to 32 subjects allowed a two-sided 95% CI to be constructed to be within $\pm 11\%$ of the expected $\geq 50\%$ PSA decline response rate. A $\geq 30\%$ response rate was added to the primary endpoint as an amendment based upon the survival association in chemotherapy trials published after this study began (29, 30) and a retrospective analysis of radiolabeled-J591 studies with a similar survival association; use of 32 subjects allowed a two-sided CI within $\pm 17\%$ of the expected $\geq 30\%$ PSA decline response rate. Kaplan–Meier survival

analysis was used to estimate overall survival (OS), with median OS and 95% CIs described. Descriptive statistics were conducted to characterize the study sample.

Based upon observations made after study initiation, additional analyses were conducted in *post hoc* fashion in the initial cohorts and prospectively in the expansion cohort. The Fisher exact test was used to compare $\geq 30\%$ PSA decline response proportions between the 65- and 70-mCi/m² dose cohorts and between quartiles of mean TuTI. The log-rank test was used to compare OS between the two dose cohorts and between levels of PSA decline ($\geq 30\%$ vs. $< 30\%$ PSA decline). Median OS and 95% CIs for median OS were stratified by dose cohort and level of PSA decline. All *P* values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were conducted in SAS version 9.2 (SAS Institute, Inc.) and STATA version 11.0 (StataCorp).

Results

In the initial portion of the trial, 32 subjects were treated between November 2004 and February 2008 at 2 centers; 15 additional subjects were treated in the expansion cohort between June 2009 and February 2012. Baseline demographics including prognostic variables are summarized in Table 1. All had progressed on multiple lines of hormonal therapy and the majority (55.3%) progressed on 1 to 4 lines of chemotherapy including docetaxel. There were no significant differences in any demographic or prognostic variables between the cohorts.

Antitumor effects and survival

All subjects had progression by PSA before enrollment. Overall, 5 patients (10.6%; 95% CI, 2.0–25.0%) experienced $\geq 50\%$ decline in PSA from baseline, 17 (36.2%) experienced $\geq 30\%$ decline, and 28 (59.6%) experienced any PSA decline with median time to progression of 12 weeks (range, 8–47 weeks) following their single treatment. Each subject's best PSA response is depicted in Fig. 1. Although the study was initially designed to have both cohorts analyzed together, a suggestion of dose–response was observed in favor of the 70 mCi/m² cohort (the phase I MTD; ref. 25), leading to the expansion cohort, confirming the dose–response relationship as depicted in Table 2, with 46.9% versus 13.3% with $\geq 30\%$ PSA decline (*P* = 0.048; individual PSA changes by dose received is depicted in Supplementary Fig. S1A). A total of 12 out of 15 patients in cohort 3 had CTC counts measured at baseline and at 4 to 6 weeks following treatment (2 lab failures and 1 missed blood draw); 8 (66.7%) had $\geq 50\%$ decline in CTC counts, and 3 (25%) were unchanged at 0 or 1 per 7.5 mL blood (1 declined 27%; Supplementary Fig. S1B).

Only 12 (25.5%) patients had measurable disease; 1 experienced a partial response by Response Evaluation Criteria in Solid Tumors (31) with confirmed 55% decrease in nodal metastases, 8 had stable disease, 2 had progressive disease, and 1 was lost to follow-up before repeat image (with PSA increase of 10% from baseline at last evaluation; Supplementary Fig. S1C).

Table 1. Baseline characteristics (N = 47)

Age, y	
Median	73.9
Range	49.7–90.4
Gleason sum	
6	6
7	10
8–10	29
Unknown	2
PSA (ng/mL)	
Median	74.4
Range	3.31–2184.6
Sites of metastases	
Bone	46 (97.9%)
Lymph node	28 (59.6%)
Lung	11 (23.4%)
Liver	4 (8.4%)
Other	3 (6.4%)
ECOG performance status	
0	13 (27.7%)
1	34 (72.3%)
2	0
LDH	
Median	217.5
Range	134–647
Hemoglobin	
Median	11.9
Range	9.8–14.1
Alkaline phosphatase	
Median	99
Range	23–1170
CALGB prognostic score (60)	
Median	149
Range	88–184
No. of previous hormonal therapies	
1	6 (12.7%)
2	21 (44.6%)
3	14 (29.8%)
4	6 (12.7%)
No. of previous chemotherapy regimens	
0	21 (44.6%)
1	19 (40.4%)
≥2	7 (14.9%)
Prior radiation	
Prostate/prostate bed	21 (44.7%)
Palliative to bone metastasis	3 (6.4%)
Other ^a	1 (2.1%)

Abbreviations: CALGB, Cancer and Leukemia Group B; LDH, lactate dehydrogenase.

^aOther: One subject received prior investigational radio-immunotherapy.

The median OS for all patients was 17.6 months (95% CI, 15.2–20 months), with improved survival for the 70 mCi/m² cohort as compared with the 65 mCi/m² cohort [median

OS = 21.8 months (95% CI, 16.3–27.3 months] vs. 11.9 months (95% CI, 6.5–17.3 months), respectively, *P* = 0.03; Fig. 2]. Because only a minority of patients had measurable disease, therapies with potential immune mechanisms may provide survival benefits independent of immediate response, and we had adequate follow-up for survival analysis, we explored relationships among dose, PSA changes, and survival. In the overall study (all three cohorts), median OS for those with any PSA decline was 22.2 months (18.6, 25.7) compared with 11.4 months (8.4, 14.4) for those without PSA decline (*P* < 0.01). The 17 patients with ≥30% PSA decline had a median OS of 22.2 months (95% CI, 18.4–25.9 months) compared with 15.7 months (95% CI, 10.2–21.3 months) among those with less than a 30% PSA decline (*P* = 0.06).

Imaging

Planar gamma camera imaging was done on all patients. Forty-four subjects (93.6%) had accurate targeting of known sites of disease when compared to baseline CT/MRI and bone scan images, although those with liver metastases were difficult to assess because of the antibody's partial hepatic clearance (Fig. 3). As our initial imaging data suggested significant variability of PSMA expression levels across the patient population, we therefore retrospectively explored the correlation between TuTI and PSA response in the initial cohorts. In the lowest quartile of mean TuTIs (i.e., those with lowest PSMA expression by imaging), 12.5% experienced ≥30% PSA decline (0% with >50% decline), whereas in the three remaining quartiles 37.5% experienced ≥30% PSA decline (8.3% with >50% decline; *P* = 0.19). Prospective evaluation of this association using ¹¹¹In-J591 imaging before ¹⁷⁷Lu-J591 treatment in cohort 3 showed the same trend (*P* = 0.19). No association between imaging and toxicity was seen.

Toxicity

Without premedication, 11 subjects (23.4%) experienced transient, reversible infusion reactions consisting of feelings of warmth (with or without temperature changes), cold (without episodes of hypothermia), flushing, rigors, or elevation of blood pressure. All completed drug infusion and 4 (8.5%) received pharmacologic intervention (diphenhydramine and/or acetaminophen; 2 received meperidine). Eight (17%) experienced transient grade 1 transaminase elevation; 2 with grade 2 (one of whom had grade 1 elevation at baseline). Treatment for emergent adverse events is summarized in Table 3.

All of the subjects experienced hematologic toxicity, with nadir platelet and neutrophil counts occurring at a median of 4 weeks after ¹⁷⁷Lu-J591 administration. Grade 4 thrombocytopenia occurred in 22 (46.8%), lasting a median of 7 (range 3–17) days; 14 received platelet transfusions (median 2, range 1–4 transfusions). None of the subjects experienced significant hemorrhagic episodes. Three had grade 1 ecchymosis at blood draw or other traumatic sites. Thirty-nine (82.9%) experienced complete (i.e., at least 150,000/mL) platelet recovery within a median of 25 days. Seven

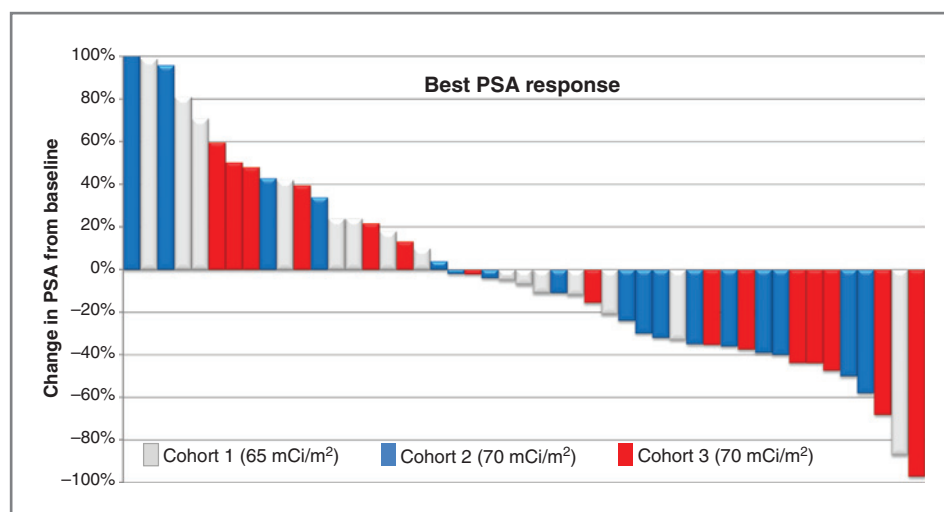


Figure 1. PSA waterfall plot. Each individual subject's best PSA response on study. Those subjects treated with 65 mCi/m² of ¹⁷⁷Lu-J591 (Cohort 1) are indicated in light gray whereas those that received 70 mCi/m² of ¹⁷⁷Lu-J591 (the phase I trial MTD) are indicated in blue (Cohort 2) or red (Cohort 3).

experienced recovery to grade 1 (range 118–130,000/mcL peak platelet counts). One recovered to only grade 2 (59,000/mcL). Of those with incomplete recovery, all had concurrent progressive disease by PSA. Three who experienced partial platelet count recovery (i.e., increase from nadir) and subsequent decline had concurrent PSA rises and significant prostate cancer infiltration of bone marrow with otherwise normal hematopoietic elements on bone marrow biopsy. Twelve (25.5%) experienced grade 4 neutropenia of up to 17 days in duration (median 5, range 2–17 days); 1 had febrile neutropenia. Nine patients (19.1%) received filgrastim or pegfilgrastim. Hematologic toxicity was greater in the 70 mCi/m² cohort (Table 2), with significantly more platelet transfusions and grade 4 neutropenia. No correlation between toxicity and sites of disease or number of bone metastases was observed, although there was a trend for more platelet transfusions in those who previously received radiotherapy ($P = 0.15$ in univariate analysis; $P = 0.25$ when correcting for ¹⁷⁷Lu dose) and for those with lower

baseline platelet counts ($P = 0.11$). There was no difference in grade 4 neutropenia with previous chemotherapy or radiotherapy.

Discussion

Although RIT was first studied in solid tumors, the largest experience with RIT to date involves targeting the CD20 antigen (¹³¹I tositumomab or ⁹⁰Y ibritumomab tiuxetan) in non-Hodgkin lymphoma. RIT for solid tumors has lagged behind for several reasons, including a dearth of antigens of adequate tumor specificity and concerns about tumor radioresistance and antibody penetration. Other practical reasons have included difficulties in stably linking radionuclides to existing mAbs, shortfalls in existing (and readily available) radionuclides, and difficulty in clinical use (coordination between different specialties; ref. 32). Prostate cancer is not subject to these limitations: (i) a highly tumor-restricted antigen, PSMA, has been identified; (ii)

Table 2. Dose response and toxicity

Dose (mCi/m ²) Cohort	65 Cohort 1 n = 15	70 Cohort 2 n = 17	70 Cohort 3 n = 15	70 Cohorts 2 + 3 n = 32	P for dose comparison
Any PSA decline	46.7%	70.6%	60.0%	65.6%	0.35
≥30% PSA decline ^a	13.3%	47.1%	46.7%	46.9%	0.048
≥50% PSA decline	6.7%	12.8%	13.3%	12.5%	1.00
Median survival ^a	11.9 mo	19.8 mo	NR	21.8 mo	0.032
Platelets grade 3	40%	13%	6.7%	9.4%	–
Platelets grade 4	27%	53%	53.3%	56.3%	0.069
Platelet transfusion ^a	7%	41%	40.0%	40.6%	0.019
Neutropenia grade 3	53%	13%	46.7%	28.1%	–
Neutropenia grade 4 ^a	0%	48%	26.7%	37.5%	0.005

Abbreviation: NR, not reported.

^a $P < 0.05$ for comparison between 65 and 70 mCi/m².

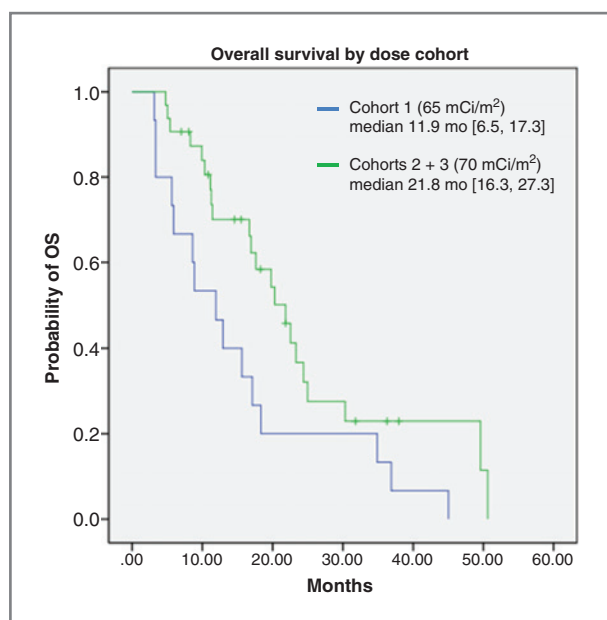


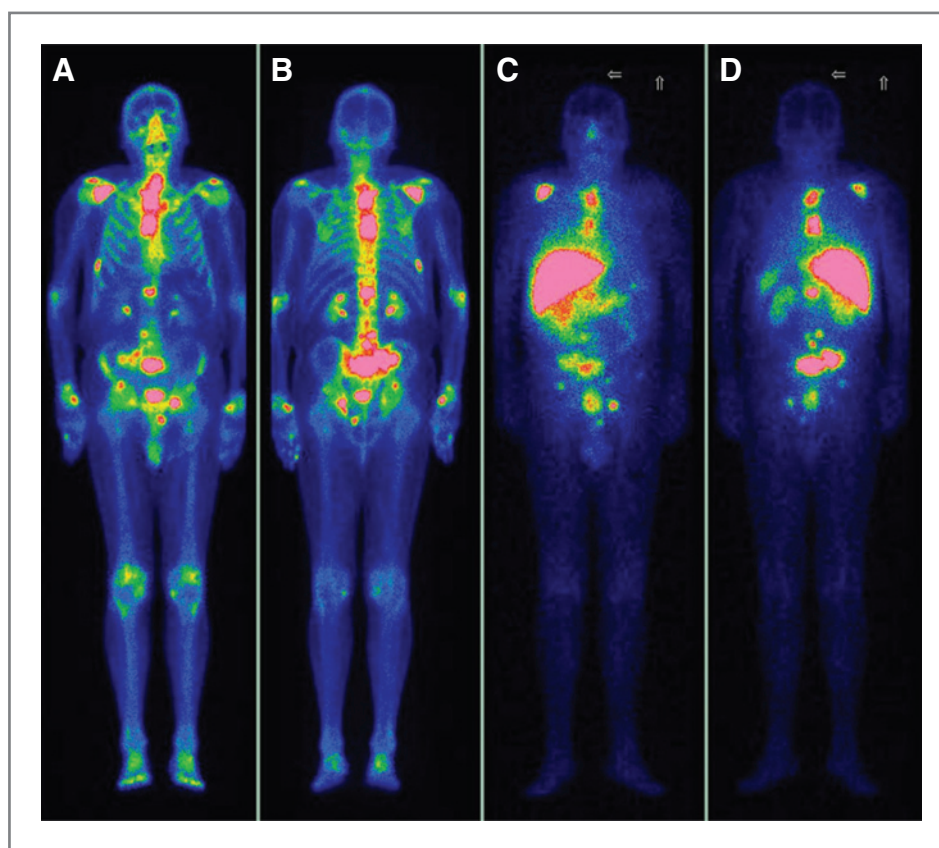
Figure 2. Probability of survival by dose received.

prostate cancer is radiosensitive; and (iii) metastatic prostate cancer can be identified at the stage of small volume lesions in bone marrow and lymph nodes that are well accessed by circulating antibody.

Radiotherapy may be delivered to primary and secondary sites of prostate cancer for curative or palliative intent via external beam or brachytherapy. Systemic radioisotope therapy targeting bone has also been successfully used. Samarium-153 and Strontium-89 are approved β -emitting agents for palliation of painful bony metastases (1–4). Recently, an α -emitting agent has shown a survival benefit in men with metastatic CRPC to bone (4, 33). Although bone-seeking radiopharmaceuticals may be seen as targeted agents with proven efficacy, they do not target tumor directly. Rather, their antitumor effect derives from radiopharmaceutical accumulation in proximity to malignant cells and/or stroma; these agents entirely ignore soft tissue and extra-osseous visceral metastases.

Targeted therapeutics offer a potential advantage in cancer therapy by sparing normal tissues. In prostate cancer, PSMA is an ideal target, as it is highly overexpressed by virtually all prostate cancers, and not significantly expressed by normal cells. The few sites that do express low levels of PSMA (e.g., renal proximal tubule lumen and brush border of small intestine) have minimal exposure to anti-PSMA mAb-based therapy, as these sites are not accessible to circulating intact mAb. In addition, recent therapeutic advances in targeting the androgen receptor axis lead to increased PSMA expression (34). We showed safety and accurate tumor targeting in previous studies using trace-labeled J591 in patients with advanced prostate cancer,

Figure 3. Imaging. Left, ^{99m}Tc-MDP bone scan: anterior (A) and posterior (B) images of pretreatment bony metastases. Right, ¹⁷⁷Lu-J591 scan: anterior (C) and posterior (D) total body images obtained via dual head gamma camera of sites of uptake 7 days after ¹⁷⁷Lu-J591 administration. (Note: radiolabeled antibody is partially cleared via the liver, resulting in nonspecific ¹⁷⁷Lu localization.)



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Table 3. Treatment of emergent adverse events

CTCAE toxicity	Grades 1–2	Grade 3	Grade 4	Total
Nonhematologic				
ALT	6 (12.8%)			6 (12.8%)
Anorexia	11 (23.4%)			11 (23.4%)
AST	9 (19.2%)			9 (19.2%)
Bruising (without thrombocytopenia)	2 (4.3%)			2 (4.3%)
Constipation	5 (10.6%)			5 (10.6%)
Creatinine	5 (10.6%)			5 (10.6%)
Diarrhea	4 (8.5%)			4 (8.5%)
Dizziness	1 (2.1%)			1 (2.1%)
Dyspepsia	2 (4.3%)			2 (4.3%)
Dyspnea	3 (6.4%)			3 (6.4%)
Edema: limb	1 (2.1%)			1 (2.1%)
Fatigue	17 (36.2%)			17 (36.2%)
Fever (without neutropenia)	1 (2.1%)			1 (2.1%)
Hemorrhage, gastrointestinal: oral cavity	1 (2.1%)			1 (2.1%)
Hypersensitivity (aka infusion reaction)	11 (23.4%)			11 (23.4%)
Nausea	5 (10.6%)			5 (10.6%)
Pain—abdomen NOS	2 (4.3%)			2 (4.3%)
Pain—joint	1 (2.1%)			1 (2.1%)
Petechiae/purpura	1 (2.1%)			1 (2.1%)
Rash/desquamation	1 (2.1%)			1 (2.1%)
Rigors/chills	1 (2.1%)			1 (2.1%)
Taste alteration (dysgeusia)	1 (2.1%)			1 (2.1%)
Weight loss	1 (2.1%)			1 (2.1%)
Hematologic (see Table 2 for dose comparisons)				
Hemoglobin	19 (40.1%)	5 (10.6%)		24 (51.1%)
Leukocytes (total WBC)	14 (29.8%)	22 (46.8%)	4 (8.5%)	40 (85.1%)
Neutrophils (ANC)	7 (14.9%)	17 (36.2%)	12 (25.5%)	36 (76.6%)
Febrile neutropenia		1 (2.1%)		1 (2.1%)
Platelets	4 (8.5%)	10 (21.3%)	22 (46.8%)	36 (76.6%)

Abbreviations: aka, also known as; ALT, alanine aminotransferase; ANC, absolute neutrophil count; NOS, not otherwise specified; WBC, white blood cell count.

but responses to the unarmed antibody in this patient population were limited (22). These studies led to anti-PSMA-based RIT studies using β -emitting radionuclides. Two phase I studies in patients with metastatic CRPC formed the basis for this study (24, 25). Although a few efficacy studies have used mAbs against non-tumor-specific targets alone or in combination in solid tumor RIT (35–40), this trial represents one of the few reported phase II studies of disease-specific single-agent RIT (i.e., targeted radiotherapy using a disease-specific mAb) with mature follow-up in solid tumor oncology (41).

In this study, we successfully targeted known sites of metastatic disease in 93.6% of unselected metastatic CRPC subjects, confirming our previous results. More importantly, the initial evidence of antitumor efficacy observed in the phase I studies was supported (24, 25), with the majority of subjects showing PSA declines. Although PSA changes have never fully met criteria for surrogate endpoints, it is important to note that unlike other therapies including docetaxel

(42–44), J591 has no direct effect on PSA transcription, expression, or secretion (N.H. Bander; unpublished data), PSA declines versus increases following radiolabeled J591 therapy have been associated with radiographic response or progression (24), and the data from this study as well as retrospective analysis of other radiolabeled J591 studies (45), although preliminary, would suggest that patients with PSA declines lived significantly longer ($P = 0.01$).

Numerous publications in which PSMA expression was evaluated have indicated that 84% to 100% of prostate cancers are PSMA-positive (8, 11–14). Therefore, patient selection based on PSMA expression was not conducted in this study. Even though receptor sites are not saturated, it has been shown that the amount of radiolabeled mAb uptake is proportionate to the level of antigen expression (46); it is logical that the level of PSMA expression might correlate with response to PSMA-targeted therapy and provide a predictive parameter to identify those less likely to respond (i.e., those with no or low PSMA expression).

Post hoc analysis of the initial cohorts suggested imaging-based scoring of PSMA expression may correlate with subsequent response. Because using ¹⁷⁷Lu-J591 as the imaging agent carries the toxicity associated with β-emission, we conducted a pretreatment scan using ¹¹¹In-J591 in the prospective cohort, showing the same trend for a lower likelihood of response for poor imagers. However, planar or even SPECT imaging is qualitative by nature, which may limit clinical utility. Use of quantitative imaging, such as anti-PSMA-based positron emission tomography (refs. 34 and 47), may be more effective in selecting the best candidates (or more practically ruling out poor candidates given general expression levels) for a PSMA-targeted therapeutic.

As described in Patients and Methods, initial plans were for a single-arm phase II study at the phase I MTD/recommended phase II dose (70 mCi/m²). Based upon limited prior experience with ¹⁷⁷Lu and discussions with the FDA, a cohort treated at a slightly lower dose (65 mCi/m²) was used with the expectation that neither efficacy nor toxicity would be significantly different. In the initial cohorts, we observed preliminary evidence suggestive of a dose-response relationship that led to an expansion cohort that validated the increased PSA response rates seen with a single infusion of 70 mCi/m² of ¹⁷⁷Lu-J591; this group also experienced improved survival.

In RIT clinical trials, factors such as antibody internalization and the physical properties of the radionuclide, including the type of particle(s) emitted, half-life, and path length, are important in designing the appropriate clinical strategy (27, 48). Although PSMA/J591 is an excellent antigen/antibody pair in prostate cancer, the physical properties of ¹⁷⁷Lu theoretically make it most optimal for patients with micrometastatic disease. Consequently, the patients treated in this phase II trial may be a less suitable cohort in which to show durable responses. The observed antitumor activity together with the additional safety data suggest that ¹⁷⁷Lu-J591-targeted radiotherapy may be safe and effective in prostate cancer patients with micrometastatic disease. A multi-institutional trial has begun to test this hypothesis (clinicaltrials.gov NCT00859781), and pre-clinical work is ongoing on J591 α-particle emitters.

One concern related to RIT is the possibility that treatment may result in damaged bone marrow that might prevent patients from receiving subsequent therapy. The dose-limiting toxicity of RIT in general is transient myelosuppression, which typically occurs in a delayed fashion compared with cytotoxic chemotherapy (49). Myelodysplastic syndrome and acute leukemia have been reported with anti-CD20-based RIT for non-Hodgkin lymphoma (50), although larger studies have not substantiated this effect (51, 52). In this study, all subjects were treated at or near the MTD (i.e., at or near a dose leading to significant myelosuppression). Although all subjects recovered normal neutrophil counts, 7 did not fully recover a normal platelet count. This effect cannot be attributed solely to the radioisotope, however, because all of these subjects had clinically progressive prostate cancer and the 3 who underwent bone marrow biopsy revealed infiltrative metastases, so it is

plausible that their lack of complete recovery was secondary to progression of their prostate cancer. As with patients receiving chemotherapy, not all have full recovery of blood counts, as evidenced by the patients treated on recent post-chemotherapy studies with baseline and ongoing thrombocytopenia following treatment with docetaxel (53, 54). In a preliminary review of our overall anti-PSMA-based RIT experience through 2009 (109 patients), excluding retreated patients, 98% and 87% had full recovery of neutrophils and platelets, respectively (55). Of the remaining subjects, all but 4 recovered to grade 1 neutropenia and/or thrombocytopenia. The most common reason for lack of complete hematologic recovery was CRPC progression (PSA and/or scan progression with confirmatory bone marrow biopsy revealing significant prostate cancer metastases). No cases of post-RIT myelodysplasia and/or leukemia have been observed (55).

In summary, a single dose of ¹⁷⁷Lu-J591 was well tolerated with reversible myelosuppression. PSA responses were seen with evidence of a ¹⁷⁷Lu dose-response relationship. This study further validates PSMA as an excellent prostate cancer-restricted target as well as the performance of the J591 antibody *in vivo*. The antitumor activity seen suggests the clinical potential of targeting other types of cytotoxic agents to PSMA. Future directions in progress with anti-PSMA RIT include (i) studies to improve patient selection using imaging and CTC and immunohistochemical PSMA-expression analysis; (ii) improving therapeutic margin with dose-fractionation (23, 56); (iii) using taxane radiosensitization and tumor debulking (combination studies; refs. 23 and 57); and (iv) "targeted salvage radiotherapy" exploring ¹⁷⁷Lu-J591 in the biochemically recurrent population, a setting in which the physical properties of ¹⁷⁷Lu should be more optimally suited (23, 58, 59). In addition, a randomized phase III registration trial in men with metastatic CRPC is planned.

Disclosure of Potential Conflicts of Interest

M.J. Morris is a consultant/advisory board member of Atlab Pharma, Bayer, and Janssen. H.I. Scher is a consultant/advisory board member of BIND. N.H. Bander has ownership interest (including patents) and is a consultant/advisory board member of BZL Biologics, Inc. No potential conflicts of interest were disclosed by the other authors.

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