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## Phase II study of lutetium-177 labeled anti-prostate-specific membrane antigen (PSMA) 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 monoclonal antibody J591 (<sup>177</sup>Lu-J591) by PSA decline, measurable disease response, and survival.

**Experimental Design**—In this dual-center phase II study, 2 cohorts with progressive metastatic castration-resistant prostate cancer received one dose of <sup>177</sup>Lu-J591 (15 patients at 65 mCi/m<sup>2</sup>, 17 at 70 mCi/m<sup>2</sup>) with radionuclide imaging. Expansion cohort (n=15) received 70 mCi/m<sup>2</sup> to verify response rate and examine biomarkers.

**Results**—47 patients who progressed after hormonal therapies (55.3% also received prior chemotherapy) received <sup>177</sup>Lu-J591. 10.6% experienced 50% decline in PSA, 36.2% experienced 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. 25.5% experienced grade 4 neutropenia with 1 episode of febrile neutropenia. The phase I maximum tolerated dose (70 mCi/m<sup>2</sup>) 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 non-hematologic toxicity occurred. Those with poor PSMA imaging were less likely to respond.

**Conclusion**—A single dose of <sup>177</sup>Lu-J591 was well-tolerated with reversible myelosuppression. Accurate tumor targeting and PSA responses were seen with evidence of dose-response. Imaging biomarkers appear promising.

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**Conflict of interest:** NHB is an inventor on patents that are assigned to Cornell Research Foundation (“CRF”) for the J591 antibody described in this article. Dr. Bander is a paid consultant to and owns stock in BZL Biologics, the company to which the patents were licensed by CRF for further research and development.

## Keywords

Prostate Cancer; Prostate-specific Membrane Antigen; Radioimmunotherapy; Monoclonal Antibody

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## 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 demonstrated clinical benefit, including decreased pain, some PSA declines, and most importantly improvement in survival for Ra-223.(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 soft tissue and visceral metastases. This approach combines the specificity of mAb targeting with the tumoricidal effects of beta radiation.

Prostate-specific membrane antigen (PSMA) is a non-secreted cell membrane protein with expression that is highly restricted to prostate epithelium and upregulated in prostate cancer. (5-10) 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 utilizing radiolabeled mAb 7E11 (CYT-356, capromab), though 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 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 performed using Yttrium-90 (<sup>90</sup>Y) or Lutetium-177 (<sup>177</sup>Lu) linked via a DOTA chelate to J591 in patients with metastatic castration-resistant prostate cancer (CRPC).(24, 25) These trials defined the maximum tolerated dose (MTD), dosimetry, pharmacokinetics, and human anti-humanized antibody (HAHA) response, and demonstrated preliminary evidence of anti-tumor activity.

<sup>177</sup>Lu was chosen for further development based upon its physical properties, emitting both a short-range (0.2-0.3 mm) beta particle as well as gamma emission. As a result, it delivers a lower radiation dose to bone marrow relative to higher energy beta particles such as <sup>90</sup>Y. (26) The gamma emission from <sup>177</sup>Lu allows for *ex vivo* imaging in contrast to <sup>90</sup>Y that, as a pure beta emitter, requires use of a surrogate isotope such as <sup>111</sup>In 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)<sup>177</sup>Lu also has a longer physical half-life (6.7 days compared with 2.7 days for <sup>90</sup>Y), resulting in longer tumor residence times. Because of these properties, higher activities can be delivered using <sup>177</sup>Lu; in the phase I trials of radiolabeled J591, the MTD of <sup>177</sup>Lu-J591 was 70 mCi/m<sup>2</sup> compared with 17.5 mCi/m<sup>2</sup> for <sup>90</sup>Y-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 <sup>177</sup>Lu-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 LHRH 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 ECOG performance status 0 – 2, absolute neutrophil count  $2000/\text{mm}^3$ , platelet count  $150,000/\text{mm}^3$ , serum bilirubin  $1.5\times$  upper limit of normal (ULN), AST  $2\times$  ULN, PT/INR and aPTT  $1.3\times$  ULN (unless on anticoagulation) and serum creatinine  $2.5$  mg/dL.

Exclusion criteria included prior radiotherapy to  $> 25\%$  of skeleton, prior  $^{89}\text{Sr}$  or  $^{153}\text{Sm}$  containing compounds, bone scan demonstrating 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  $^{177}\text{Lu}$ -J591 was performed as previously described.(25) Subjects received a single dose of  $^{177}\text{Lu}$ -J591 consisting of J591 chelated at a specific activity of 12-15 mCi of  $^{177}\text{Lu}$  per mg of antibody plus sufficient non-radiolabeled, 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/m<sup>2</sup>,(25) based upon limited prior clinical experience with  $^{177}\text{Lu}$ -labeled mAbs as directed by the Food and Drug Administration, an initial cohort of 15 subjects received a dose of  $^{177}\text{Lu}$  of  $65$  mCi/m<sup>2</sup> followed by 17 subjects at  $70$  mCi/m<sup>2</sup>. After analysis of the initial 32 subjects, an additional 15 were enrolled, underwent infusion of  $^{111}\text{In}$ -J591 with subsequent imaging to prospectively evaluate non-invasive assessment of PSMA expression as a predictive biomarker, then received a single dose of  $^{177}\text{Lu}$ -J591 at  $70$  mCi/m<sup>2</sup>. Each dose was administered without pre-medication by an IV infusion at a rate not to exceed  $5$  mg/min.

### Evaluation During the Study

Subjects were monitored for at least 4 hours post mAb infusion. Complete blood counts (CBC) were performed at least weekly beginning 3 weeks after  $^{177}\text{Lu}$ -J591 infusion until 6 weeks or recovery and were repeated at least twice per week during periods of grade (Gr) 4 neutropenia and at least 3 times per week during periods of Gr 4 thrombocytopenia. Transfusions, filgrastim or pegfilgrastim (but not sargramostim), and red blood cell growth factors were permitted at the discretion of the treating physician. Chemistry panel including liver tests and PSA was performed at least every 4 weeks. Expansion cohort subjects had a baseline circulating tumor cell (CTC) count by CellSearch (Veridex) methodology at baseline and 4-6 weeks following  $^{177}\text{Lu}$ -J591 infusion.

A planar gamma camera image was obtained 5-7 days after  $^{177}\text{Lu}$ -J591 infusion (expansion cohort subjects also had pre-treatment imaging 3-4 days after  $^{111}\text{In}$ -J591 infusion) with SPECT 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 2 methods. A five point visual scale was performed by

two independent radiologists and scored 0 (no uptake), 1 (weakly positive), 2 (definitely positive), 3 (equal intensity to liver), 4 (greater uptake than liver). Tumor Targeting Index (TuTI), a novel metric designed to semi-quantitatively 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.  $TuTI = (\text{lesion ROI count density} - \text{background count density}) / (\text{total body count density})$ . Assessment of accurate uptake of radiolabeled mAb by known sites of disease was performed comparing visual scores and TuTI to areas of known metastatic disease on bone scan and CT/MRI. CT or MRI of abdomen/pelvis and bone scans were repeated 3 months after  $^{177}\text{Lu}$ -J591 infusion and every 3 months thereafter until progression. Radiographically measurable disease was defined as lymph nodes of at least 20 mm and non-osseous 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 post-treatment PSA decline rate, which was originally defined as the percent of patients who achieved a 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/m<sup>2</sup> dose to 32 subjects allowed a two-sided 95% CI to be constructed to be within  $\pm 11\%$  of the expected 50% PSA decline response rate. A 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; the 32 subjects allowed a 2-sided CI within  $\pm 17\%$  of the expected 30% PSA decline response rate. Kaplan-Meier survival analysis was used to estimate overall survival (OS), with median OS and 95% CI's described. Descriptive statistics were performed to characterize the study sample.

Based upon observations made after study initiation, additional analyses were performed in post hoc fashion in the initial cohorts and prospectively in the expansion cohort. Fisher's exact test was used to compare 30% PSA decline response proportions between the 65 mCi/m<sup>2</sup> and 70 mCi/m<sup>2</sup> dose cohorts and between quartiles of mean TuTI. The log-rank test was employed to compare OS between the two dose cohorts and between levels of PSA decline (30% vs <30% PSA decline). Median OS and 95% confidence intervals 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 performed in SAS Version 9.2 (SAS Institute, Inc., Cary, NC) and STATA Version 11.0 (StataCorp, College Station, TX).

## 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 1-4 lines of chemotherapy including docetaxel. There were no significant differences in any demographic or prognostic variables between the cohorts.

## Anti-tumor Effects and Survival

All subjects had progression by PSA prior to enrollment. Overall, five patients (10.6%; 95% CI=2.0-25.0%) experienced 50% decline in PSA from baseline, seventeen (36.2%) experienced 30% decline, and twenty eight (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 Figure 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/m<sup>2</sup> cohort (the phase I MTD),(25) leading to the expansion cohort, confirming the dose-response relationship as depicted in Table 2, with 46.9% vs 13.3% with 30% PSA decline (p=0.048).(Individual PSA changes by dose received is depicted in Supplemental Figure 1A) Twelve of the 15 patients in cohort 3 had CTC counts measured at baseline and at 4-6 weeks following treatment (2 lab failures and 1 missed blood draw); 8 (66.7%) had 50% decline in CTC counts and 3 (25%) were unchanged at 0 or 1 per 7.5 mL blood (1 declined 27%).(Supplemental Figure 1B)

Only twelve (25.5%) patients had measurable disease; 1 experienced a partial response by RECIST(31) with confirmed 55% decrease in nodal metastases, 8 had stable disease, 2 with progressive disease, and 1 was lost to follow up prior to repeat image (with PSA increase of 10% from baseline at last evaluation).(Supplemental Figure 1C)

Median overall survival (OS) for all patients was 17.6 months (95% CI = 15.2, 20 months), with improved survival for the 70 mCi/m<sup>2</sup> cohort as compared with the 65 mCi/m<sup>2</sup> 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) (Figure 2). As 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 between dose, PSA changes, and survival. In the overall study (all 3 cohorts), median OS for those with any PSA decline was 22.2 months [18.6, 25.7] compared to 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 to 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 performed 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, though those with liver metastases were difficult to assess because of the antibody's partial hepatic clearance (Figure 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 TuTI's (i.e. those with lowest PSMA expression by imaging), 12.5% experienced 30% PSA decline (0% with >50% decline), whereas in the 3 remaining quartiles 37.5% experienced 30% PSA decline (8.3% with >50% decline) (p=0.19). Prospective evaluation of this association using <sup>111</sup>In-J591 imaging prior to <sup>177</sup>Lu-J591 treatment in cohort 3 demonstrate the same trend (p=0.19). No association between imaging and toxicity was seen.

## Toxicity

Without pre-medication, 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 four (8.5%) received pharmacologic intervention

(diphenhydramine and/or acetaminophen; 2 received meperidine). Eight (17%) experienced transient grade (Gr) 1 transaminase elevation; 2 with Gr 2 (1 of whom had Gr 1 elevation at baseline). Treatment emergent adverse events are summarized in Table 3.

All experienced hematologic toxicity, with nadir platelet and neutrophil counts occurring at a median of 4 weeks after  $^{177}\text{Lu}$ -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 experienced significant hemorrhagic episodes. Three had Gr 1 ecchymosis at blood draw or other traumatic sites. Thirty nine (82.9%) experienced complete (i.e. at least 150,000/mcL) platelet recovery within a median of 25 days. Seven experienced recovery to Gr 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 Gr 4 neutropenia 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/m<sup>2</sup> 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, though 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  $^{177}\text{Lu}$  dose) and for those with lower baseline platelet counts (p=0.11). There was no difference in Gr 4 neutropenia with previous chemo- or radiotherapy.

## DISCUSSION

Although RIT was first studied in solid tumors, the largest experience with RIT to date involves targeting the CD20 antigen ( $^{131}\text{I}$  tositumomab or  $^{90}\text{Y}$  ibritumomab tiuxetan) in non-Hodgkin's lymphoma. Radioimmunotherapy for solid tumors has lagged behind for several reasons, including a dearth of antigens of adequate tumor-specificity and concerns regarding tumor radio-resistance 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). (32) Prostate cancer is not subject to these limitations: (i) a highly tumor-restricted antigen, PSMA, has been identified; (ii) PC is radiosensitive; and (iii) metastatic PC can be identified at the stage of small volume lesions in bone marrow and lymph nodes that are well accessed by circulating antibody.

Radiation therapy 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 utilized. Samarium-153 and Strontium-89 are approved  $\beta$ -emitting agents for palliation of painful bony metastases. (1-4) Recently, an  $\alpha$ -emitting agent has demonstrated a survival benefit in men with metastatic CRPC to bone. (4, 33) While bone-seeking radiopharmaceuticals may be seen as targeted agents with proven efficacy, they do not target tumor directly. Rather, their anti-tumor 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 over-expressed 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 AR-axis lead to increased PSMA expression.(34) We demonstrated safety and accurate tumor-targeting in previous studies using trace-labeled J591 in patients with advanced PC, but responses to the unarmed antibody in this patient population were limited.(22) These studies led to anti-PSMA-based RIT studies utilizing  $\beta^-$  emitting radionuclides. Two phase I studies in patients with metastatic CRPC formed the basis for the current study.(24, 25) While a few efficacy studies have utilized 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 utilizing 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 anti-tumor efficacy observed in the phase I studies was supported,(24, 25) with the majority of subjects demonstrating PSA declines. Though 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 [NHB, unpublished data], PSA declines vs. 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) though preliminary, would suggest that patients with PSA declines lived significantly longer ( $P=0.01$ ).

Numerous publications evaluating PSMA expression have indicated that 84-100% of prostate cancers are PSMA-positive.(8, 11-14) Therefore, patient selection based on PSMA expression was not performed 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. Since using  $^{177}\text{Lu}$ -J591 as the imaging agent carries the toxicity associated with beta-emission, we performed a pre-treatment scan utilizing  $^{111}\text{In}$ -J591 in the prospective cohort, demonstrating 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 (PET),(34,47) 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 the methods section, initial plans were for a single-arm phase II study at the phase I MTD / recommended phase II dose (70 mCi/m<sup>2</sup>). Based upon limited prior experience with  $^{177}\text{Lu}$  and discussions with the FDA, a cohort treated at a slightly lower dose (65 mCi/m<sup>2</sup>) 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 which led to an expansion cohort which validated the increased PSA response rates seen with a single infusion of 70 mCi/m<sup>2</sup> of  $^{177}\text{Lu}$ -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) Whereas PSMA/J591 is an

excellent antigen/antibody pair in PC, the physical properties of  $^{177}\text{Lu}$  theoretically make it most optimal for patients with micro-metastatic disease. Consequently, the patients treated in this phase II trial may be a less suitable cohort in which to demonstrate durable responses. The observed anti-tumor activity together with the additional safety data suggest that  $^{177}\text{Lu}$ -J591 targeted radiotherapy may be safe and effective in PC patients with micro-metastatic disease. A multi-institutional trial has begun to test this hypothesis (clinicaltrials.gov NCT00859781) and pre-clinical work is ongoing on J591-alpha 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 to cytotoxic chemotherapy.(49) Myelodysplastic syndrome and acute leukemia have been reported with anti-CD20 based RIT for non-Hodgkin's lymphoma,(50) though 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). While 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 post-docetaxel.(53, 54) In preliminary review of our overall anti-PSMA-based RIT experience through 2009 (109 patients), excluding re-treated patients, 98% and 87% had full recovery of neutrophils and platelets respectively.(55) Of the remaining, all but 4 recovered to Gr 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  $^{177}\text{Lu}$ -J591 was well-tolerated with reversible myelosuppression. PSA responses were seen with evidence of a  $^{177}\text{Lu}$  dose-response relationship. This study further validates PSMA as an excellent PC-restricted target as well as the performance of the J591 antibody in vivo. The anti-tumor activity seen suggests 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 utilizing imaging and CTC and immunohistochemical PSMA-expression analysis, ii) improving therapeutic margin with dose-fractionation, (23, 56) iii) utilizing taxane radiosensitization and tumor debulking (combination studies),(23, 57) and iv) "targeted salvage radiotherapy" exploring  $^{177}\text{Lu}$ -J591 in the biochemically recurrent population, a setting in which the physical properties of  $^{177}\text{Lu}$  should be more optimally suited.(23,58,59) In addition, a randomized phase III registration trial in men with metastatic CRPC is planned.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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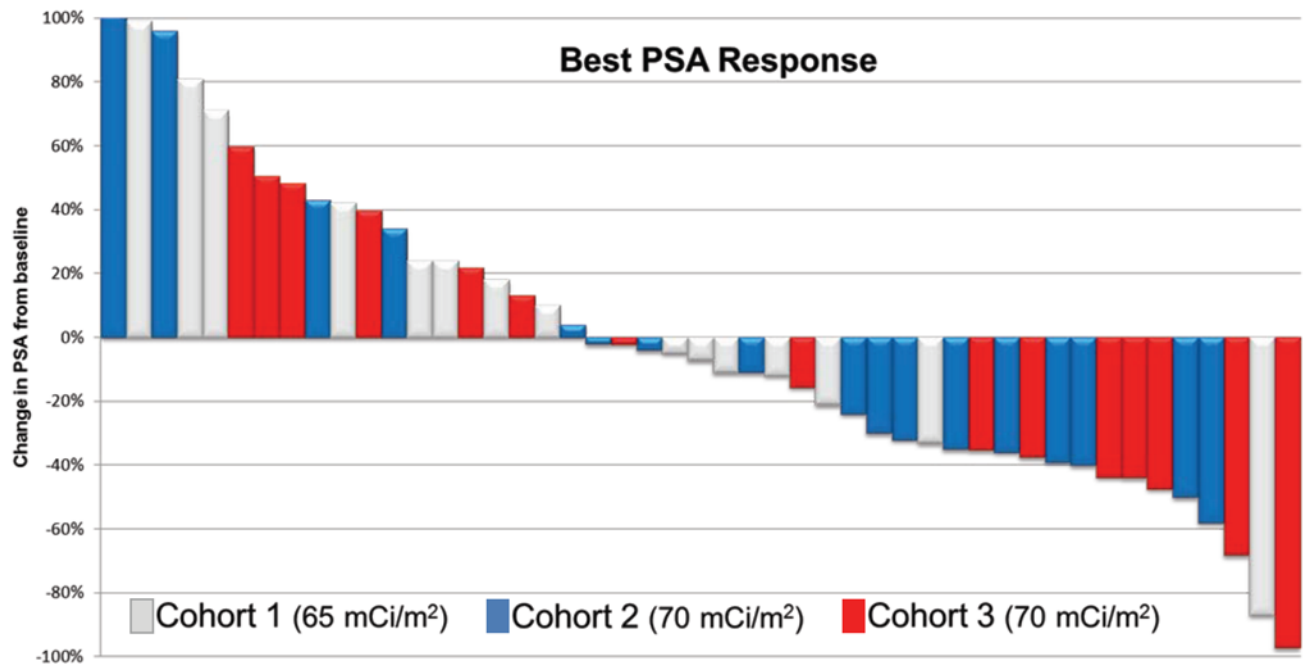
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### STATEMENT OF TRANSLATIONAL RELEVANCE

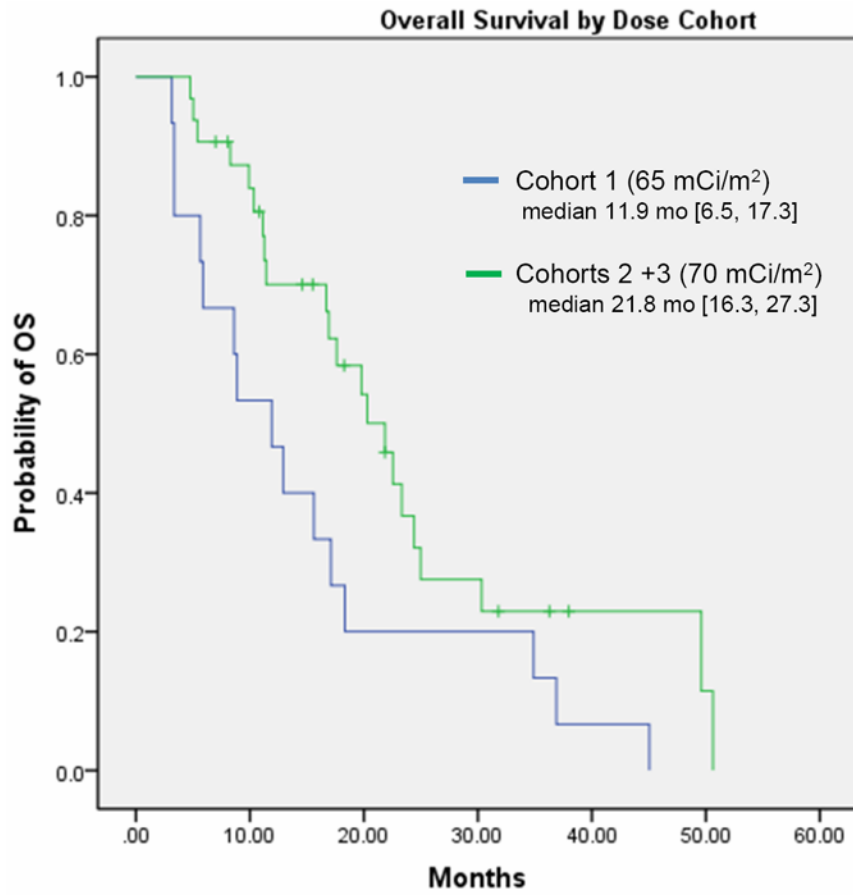
Targeted therapies are of relevance to many fields of medicine. Prostate specific membrane antigen (PSMA) represents a highly restricted, over-expressed prostatecancer cell-surface protein. J591, a de-immunized monoclonal antibody targeting the external domain of PSMA has been successfully radiolabeled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



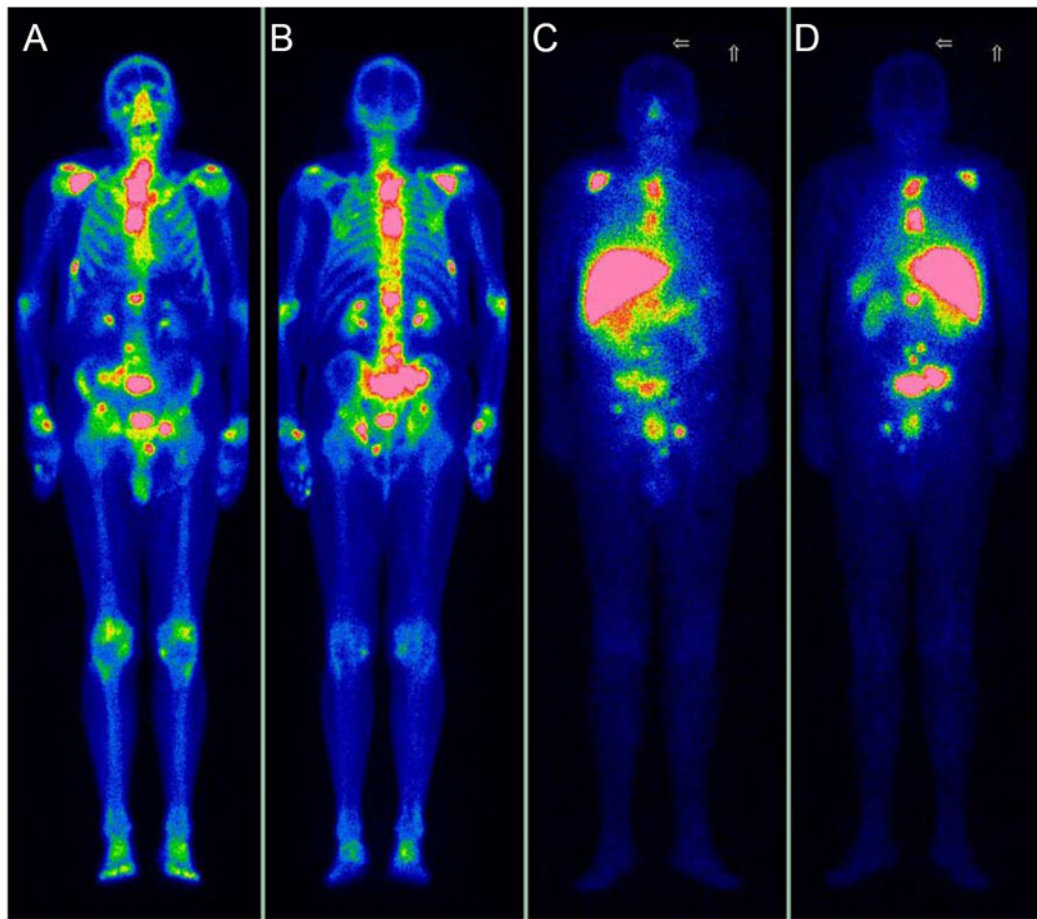
**Figure 1.**

PSA waterfall plot

Each individual subject's best PSA response on study. Those subjects treated with 65 mCi/m<sup>2</sup> of <sup>177</sup>Lu-J591 (Cohort 1) are indicated in light gray while those that received 70 mCi/m<sup>2</sup> of <sup>177</sup>Lu-J591 (the phase I trial maximum tolerated dose) are indicated in blue (Cohort 2) or red (Cohort 3).



**Figure 2.**  
 Overall survival  
 Probability of survival by dose received. [OS:overall survival; mo: months]



**Figure 3.**

**Imaging**

*Left:* <sup>99m</sup>Tc-MDP bone scan: Anterior (A) and posterior (B) images of pretreatment bony metastases. *Right:* <sup>177</sup>Lu-J591 scan: Anterior (C) and posterior (D) total body images obtained via dual head gamma camera of sites of uptake 7 days after <sup>177</sup>Lu-J591 administration. (Note: Radiolabeled antibody is partially cleared via the liver resulting in non-specific <sup>177</sup>Lu localization).



**Table 1**

## Baseline Characteristics (N=47)

Age, years	
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
# Previous Hormonal Therapies	
1	6 (12.7%)
2	21 (44.6%)
3	14 (29.8%)
4	6 (12.7%)
# 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*	1 (2.1%)

\* Other: 1 subject received prior investigational radioimmunotherapy

**Table 2**

DOSE (mCi/m <sup>2</sup> ) COHORT N	65 Cohort 1 n=15	70 Cohort 2 n=17	70 Cohort 3 n=15	70 Cohorts 2+3 n=32	p value for dose comparison
Any PSA Decline	46.7%	70.6%	60.0%	65.6%	0.35
30% PSA Decline *	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 *	11.9 mo	19.8 mo	NR	21.8 mo	0.032
Platelets Gr 3	40%	13%	6.7%	9.4%	--
Platelets Gr 4	27%	53%	53.3%	56.3%	0.069
Platelet Transfusion *	7%	41%	40.0%	40.6%	0.019
Neutropenia Gr 3	53%	13%	46.7%	28.1%	--
Neutropenia Gr 4 *	0%	48%	26.7%	37.5%	0.005

\* p<0.05 for comparison between 65 and 70 mCi/m<sup>2</sup>

**Table 3**

## Treatment emergent adverse events

CTCAE Toxicity	Grade 1-2	Grade 3	Grade 4	Total
<u>Non-Hematologic</u>				
ALT (SGPT)	6 (12.8%)			6 (12.8%)
Anorexia	11 (23.4%)			11 (23.4%)
AST (SGOT)	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, GI: 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%)
<u>Hematologic</u> (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%)