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Anti-Prostate Specific Membrane Antigen-based Radioimmunotherapy for Prostate Cancer

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Abstract

Despite recent advances, advanced prostate cancer is suboptimally responsive to current chemotherapeutic agents. Radiolabeled monoclonal antibody therapy that targets prostate specific membrane antigen (PSMA) shows promise and is an area of active investigation. J591 is a deimmunized IgG monoclonal antibody developed to target the extracellular domain of PSMA. Preclinical and early phase clinical studies utilizing radiolabeled J591 have demonstrated efficacy in targeting tumor cells and decreasing levels of PSA. Radiolabeled J591 is well-tolerated, non-immunogenic, and can be administered in multiple doses. The dose limiting toxicity is reversible myelosuppression with little non-hematologic toxicity. Future studies will include approaches to optimize patient selection and incorporate novel strategies to improve the success of anti-PSMA radioimmunotherapy.

Keywords

prostate cancer; prostate specific membrane antigen; radioimmunotherapy; monoclonal antibodies

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in the Western world, accounting for 25% of all new cases of cancer and 14% of deaths from cancer. There was an estimated 186,320 new cases and 28,660 deaths from prostate cancer in 2008.¹ Although many patients present with localized or indolent disease and eventually die of other causes,^{2,3} there is still a significant proportion of patients that present or eventually progress to advanced metastatic disease, for which no curative treatment exists. First line therapy for advanced prostate cancer is androgen deprivation with a mean duration of response of 12-18 months.⁴ Following progression, chemotherapy offers a quality of life as well as progression-free and overall survival benefit, although responses are transient and there is no proven therapy that improves survival beyond initial chemotherapy.⁵⁻⁸

Because metastatic prostate cancer is suboptimally responsive to conventional chemotherapy, novel molecularly targeted therapies are urgently needed. Monoclonal antibodies (mAbs) have been successful in proving therapeutic efficacy in a variety of solid and hematologic malignancies, and antibodies targeting CD20, ErbB2, CD33, CD52, EGFR, and VEGF are currently in clinical practice. Monoclonal antibodies have the benefits of

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being “natural” proteins that possess exquisite specificity and high affinity for their molecular target. In their native naked form, mAbs possess the ability to initiate immunological effects, block receptors, or sequester ligands. Another area of investigation is the use of tumor-targeted mAb as vehicles to deliver highly cytotoxic radionuclides, drugs, or toxins to the desired cell population.^{9, 10}

Because of their success in other cancer types or in targeting prostate cancer in pre-clinical models, several mAbs have been studied in clinical trials in men with prostate cancer. Prostate cancer represents an ideal target for mAb therapy for numerous reasons, including the pattern of spread (bone marrow and lymph nodes, sites that typically receive high levels of circulating antibody), and the small volume of disease that is ideally suited for antibody delivery and antigen access. Prostate cancer is also radiation sensitive, rendering it an excellent target for radiolabeled mAb therapy. A surrogate marker such as PSA allows rapid clinical evaluation of potential therapeutic efficacy.

Prostate Specific Membrane Antigen

Prostate-specific membrane antigen (PSMA) is a prototypical cell-surface marker of prostate cancer. It is an integral, type II membrane protein with abundant and nearly universal expression on prostate epithelial cells, and is strongly upregulated in prostate carcinoma.¹¹⁻¹⁶ In contrast to other well known prostate-restricted molecules that are secretory proteins (PSA, prostatic acid phosphatase), PSMA is an integral cell-surface membrane protein that is not secreted. This makes PSMA an ideal target for mAb therapy.

Pathology studies indicate that PSMA is expressed by virtually all prostate cancers.¹⁷ Although first thought to be entirely prostate-specific,¹¹⁻¹³ subsequent studies demonstrated that PSMA is also expressed by cells of the small intestine, proximal renal tubules and salivary glands.¹⁵ However, the level of expression in non-prostate tissues is 100-1000-fold less than in prostate tissue,¹⁶ and the site of PSMA expression in normal cells (brush border/luminal location) are not typically exposed to circulating Ab. PSMA has also been found to be expressed by vascular endothelial cells of various other solid tumors, leading to the speculation that anti-PSMA antibodies may have the potential to specifically target not just prostate cancer but all solid tumors using a vascular targeting approach.

The physiologic function of PSMA in prostate tumor biology is currently unknown. PSMA expression increases progressively in higher grade cancers, metastatic disease and hormone-refractory prostate cancer,^{13, 14, 18, 19} suggesting that PSMA has a functional role in prostate cancer progression.

The first antibody to PSMA that was developed in 1998 was capromab (7E11/CYT-356), a murine IgG1 produced from hybridoma. The use of this mAb validated PSMA as an *in vivo* target for imaging,^{20, 21} although clinical treatment studies have been disappointing.^{22, 23} Capromab binds to an intracellular epitope of PSMA, requiring internalization or exposure of the internal domain of PSMA externally, and therefore preferentially binds apoptotic or necrotic cells.^{24, 25} As a result, capromab cannot bind viable cells and may therefore not be of therapeutic benefit.^{11, 26} Recognition of these features led to the development of other mAbs (J591, J415, J533 and E99) which target the external domain of PSMA, giving easier and more rapid access to the antigen. This led to enhanced imaging and therapeutic potential.^{26, 27} These PSMA specific antibodies could also be labeled with various isotopes, such as ¹³¹Iodine, ¹⁷⁷Lutetium, ⁹⁰Yttrium, for use as an *in vivo* target for imaging.^{20, 21} Radioisotope labeled antibodies can also be used as a systemic treatment, emitting α or β particles, and delivering radiation to tumor cells.

Radiolabeled J591: Preclinical and Phase I Trials

Murine mAb J591 (muJ591) was chosen for clinical development as it had been extensively studied in preclinical models, demonstrating that it effectively targets PSMA expressed on LNCaP cells.²⁶ J591 has an affinity of 1 nM which has been shown to be an optimal affinity in therapeutic models. Lower affinity provides suboptimal binding, while higher affinity interferes with antibody penetration into tumor masses.²⁸

Testing J591 radiolabeled with various isotopes has been performed utilizing an animal model of prostate cancer in which athymic mice were implanted subcutaneously with PSMA-expressing LNCaP cells. After allowing the tumors to reach a diameter of 7-10 mm, the animals were treated with J591 radiolabeled with different isotopes, including ¹³¹Iodine (¹³¹I-muJ591), ¹⁷⁷Lutetium (¹⁷⁷Lu-muJ591) and ⁹⁰Yttrium (⁹⁰Y-muJ591). These studies showed that ⁹⁰Y and ¹⁷⁷Lu provide better dosimetry due to their longer intracellular half-lives and radioiodine's relatively rapid clearance. Anti-tumor responses were seen with all radionuclides with an apparent dose response relationship. Higher cumulative doses of either ⁹⁰Y or ¹⁷⁷Lu could be delivered using fractionated dosing (multiple sub-maximum-tolerated doses (MTD) rather than a single MTD dose). Median survival of the animals improved by 300% for fractionated ⁹⁰Y-muJ591 therapy (150 days vs. 52 days (control)). With fractionated dose ¹⁷⁷Lu-muJ591, >80% of the mice were cured.²⁹ A major limitation of using a mouse mAb in patients was the development of a human anti-mouse antibody (HAMA) response that precluded repetitive dosing. Therefore, mAb muJ591 was de-immunized by using a next generation approach to humanization developed by Biovation, Ltd. (Aberdeen, UK) into a humanized form (J591).³⁰ The F(ab) region of muJ591 was sequenced, immunoglobulin sequence motifs recognizable by human B and/or T cells were identified and then replaced by human homologous sequences.

Initial phase I studies were performed using J591 trace-labeled with ¹¹¹In using a DOTA chelate. They showed that repetitive dosing was well tolerated with total doses of up to 500 mg/m² without the development of a human anti-humanized (de-immunized) antibody (HAHA) response.³¹⁻³² No dose limiting toxicity (DLT) occurred and the MTD was not reached. After the first dose, total body gamma camera images were obtained within one hour post-infusion (day 0) and on 3 more occasions over the following week. Excellent tumor targeting could be detected at all dose levels of mAb. No mAb targeting to non-prostate cancer sites was observed. As seen in other trials using radiometals, the liver was the primary site of excretion. Percent injected dose in the liver diminished with increasing dose of antibody, and higher doses were associated with longer plasma clearance times.³³⁻³⁵

Two independent phase I clinical trials were subsequently performed using ⁹⁰Y or ¹⁷⁷Lu linked via a DOTA chelate to J591 in patients with castrate resistant prostate cancer.³⁶⁻³⁷ The primary objectives of these trials were to define the MTDs of the isotopes as well as to further define dosimetry, PK, and HAHA of the radiolabeled mAb conjugates. Anti-tumor responses were assessed as a secondary endpoint. The design and entry criteria of the 2 trials were identical. Eligible patients had a prior histologic diagnosis of prostate cancer and evidence of progressing recurrent or metastatic disease. As prior studies had demonstrated that all prostate cancers were PSMA-positive,¹⁷ no prospective determination of PSMA expression was done. Patients were required to have an absolute neutrophil count (ANC) $\geq 2.0 \times 10^9/L$, platelet count $\geq 150 \times 10^9/L$. Prior radiation therapy encompassing > 25% of the skeleton or prior treatment with ⁸⁹Strontium or ¹⁵³Samarium was not permitted. Other standard laboratory exclusion criteria applied as well.³⁶⁻³⁷ Dose limiting toxicity in the 2 trials was defined as: hematologic toxicity consisting of severe thrombocytopenia (platelet <

$10 \times 10^9/L$) and/or grade 4 neutropenia ($ANC < 0.5 \times 10^9$) for greater than 5 days; and other toxicity consisting of grade ≥ 3 non-hematologic toxicity attributable to radiolabeled J591.

Patients enrolled in the ^{90}Y -J591 phase I trial³⁶ received an initial dose of ^{111}In -J591 (20 mg, 5mCi) for pharmacokinetic and biodistribution determinations, followed one-week later, with a dose of ^{90}Y -J591. The dose schedule was selected to allow multiple imaging sessions prior to ^{111}In decay as well as clearance of the J591 from the initial dose prior to delivering the 2nd dose. The ^{90}Y dose was selected based on prior published experience with other antibodies. The first dose utilized 4-5 mCi of ^{111}In and allowed imaging for approximately one week. Twenty-nine subjects were entered at the following dose levels: 5, 10, 15, 17.5 and 20 mCi/m². Patients were eligible for up to three re-treatments if platelet and neutrophil recovery were satisfactory. Four patients were re-treated. Dose-limiting toxicity was seen at 20 mCi/m² with two patients experiencing thrombocytopenia with non-life threatening bleeding episodes requiring platelet transfusions. The 17.5 mCi/m² dose level was determined to be the maximum tolerated dose. No re-treated patients experienced dose limiting toxicity. Non-hematologic toxicity was not dose limiting. Among the 29 patients receiving ^{111}In -DOTA-J591, 19 patients had bone lesions and 13 patients had soft tissue lesions. Seventeen of 19 (89%) patients with bone lesions and 9 of 13 (69%) with soft tissue lesions were accurately targeted resulting in an overall targeting sensitivity of 26 of 32 (81%). Two patients treated at the 20 mCi/m² dose level exhibited 85% and 70% declines in PSA lasting 8 and 8.6 months prior to returning to pre-treatment values. In addition, these two patients had objective measurable disease responses with 90% and 40% decrease in the size of pelvic and retroperitoneal lymphadenopathy. Both patients were castrate-resistant with lymph node-only disease and had not received prior chemotherapy. The second patient was re-treated with ^{90}Y -J591 on day 119. An additional 6 patients experienced PSA stabilization by week 12.

Thirty five patients were enrolled in the ^{177}Lu -J591 phase I trial.³⁷ Patients received J591 radiolabeled with doses of ^{177}Lu ranging from 10 mCi/m² - 75 mCi/m². Several patients were retreated. Of the 3 patients at the 75 mCi/m² dose level, one experienced dose-limiting (grade 4) thrombocytopenia and one experienced dose-limiting neutropenia of 6 days duration. At the prior dose level of 70 mCi/m², 6 patients were entered. Two patients had transient grade 4 neutropenia not meeting the definition of DLT; 1 of these patients had grade 4 thrombocytopenia. As there was only 1 DLT in these 6 patients, the 70 mCi/m² dose level was determined to be the MTD. Re-treatment was allowed after hematologic recovery. Repeat dosing at 45 to 60 mCi/m² 6 to 12 weeks after the initial dose resulted in dose-limiting myelosuppression; up to 3 doses of 30 mCi/m² could be safely administered. Clearly identified sites of metastatic disease were successfully imaged by ^{177}Lu -J591 scintigraphy in 100% of patients (Figure 1). All 35 patients in this trial had rising PSA values including 7 patients with measurable disease. None of these 7 patients had an objective tumor response, nor a $\geq 50\%$ PSA decline. Based on PSA criteria, 14 patients demonstrated progressive disease (PSA increase of $\geq 25\%$) after treatment while 21 of 35 patients had evidence of biologic activity. Four patients had $\geq 50\%$ PSA declines lasting 3+ to 8 months, and 16 patients had PSA stabilization ($< 25\%$ increase from baseline) lasting at least 28 days. The median duration of PSA stabilization was 60 days with a range of 28 to 601 days. No HAHA responses were detected.

Choice of radionuclide

For targeted radionuclide therapy, monoclonal antibodies and peptides can be labeled efficiently with several radionuclides emitting beta particles (Table 1). The higher beta energy particles of ^{90}Y may be good for bulky tumors, but it may not be necessary or even sub-optimal, for small tumors and especially bone or bone marrow metastases. The

relatively low energy beta particles of ^{131}I are ideal, but in vivo dehalogenation of radioiodinated molecules is a major disadvantage for internalizing antibody and peptide molecules. In contrast, ^{177}Lu has a low energy beta particle with only 0.2-0.3 mm range and delivers much lower radiation dose to bone marrow compared to ^{90}Y . In addition, due to a longer physical half-life (compared to ^{90}Y), the tumor residence times are higher. As a result, higher activities (more mCi amounts) of ^{177}Lu labeled agents can be administered with comparatively less radiation dose to marrow. In addition to the favorable properties described above, ^{177}Lu has gamma emission, enabling imaging to be performed using the treatment dose (as opposed to using ^{111}In followed by ^{90}Y in the aforementioned phase I trial). Based on planned future directions (see below), ^{177}Lu has been chosen for further development. However, because of the physical properties of ^{177}Lu , one should note that treatment of bulky metastatic castration-resistant prostate cancer (CRPC) is likely a suboptimal patient population in which to test the true antitumor efficacy of ^{177}Lu -J591 based RIT.

Phase II trial of ^{177}Lu -J591 for metastatic CRPC

Based upon the phase I results described above,³⁷ a phase II trial was initiated at two centers and has now completed enrollment.³⁸ Subjects with progressive metastatic castrate resistant prostate cancer received one dose of ^{177}Lu -J591 in two-cohorts. The MTD of the phase I study³⁷ was 70 mCi/m². However, based upon restrictions imposed by the FDA, the initial cohort of patients on this phase II trial was treated with 65 mCi/m². Cohort 1 (65mCi/m²) enrolled 15 pts; Cohort 2 enrolled (70mCi/m²) 17 pts. The primary endpoint was PSA and/or measurable disease response; the secondary endpoint was toxicity. A ^{177}Lu -J591 imaging study was performed to confirm tumor targeting. In this study, the median age was 71 years (range 51 – 88), median baseline PSA 77.92 ng/mL (range 3.31 – 2184.6). All patients underwent planar ^{177}Lu -J591 scans after treatment. Excellent targeting of known sites of prostate cancer metastases was observed in 30/32 (94%) of patients. Thrombocytopenia was the most common severe hematologic toxicity. No significant drug-related non-hematologic toxicity occurred. PSA declines were observed in more patients receiving the dose of 70 mCi/m² (71%) compared to 65 mCi/m² (46%).

In summary, three trials provide support that radiolabeled J591 is well-tolerated and non-immunogenic. Radiolabeled J591 effectively targets prostate cancer metastases with sensitivity and specificity and produces PSA declines. Both ^{177}Lu -J591 and ^{90}Y -J591 are dose limited by myelosuppression with little non-hematologic toxicity. Patients with metastatic CRPC tolerate anti-PSMA RIT either prior to or after chemotherapy and no long-term effects on bone marrow function have been seen.

Future Directions

The current focus of research with anti-PSMA-based RIT is to develop strategies to improve efficacy.

Improving Patient Selection

Because PSMA expression has been described in virtually all studies evaluating expression in prostate cancer tissue, no selection for PSMA expression has been performed to date. It is unknown if levels of expression are associated with response to anti-PSMA based therapy. In a retrospective post-hoc analysis of patients treated with ^{177}Lu -J591, the quality of imaging as determined by visual scale and semi-quantitative tumor targeting index values (^{177}Lu tumor counts corrected for background/total body counts) correlated with PSA decline.³⁹ This observation is being further studied prospectively in ongoing trials. If the intensity of radiolabeled J591 imaging predicts future response, studies examining the ability to pre-

select appropriate patients with an imaging study to enrich the target population will proceed. In addition, studies examining PSMA expression in circulating tumor cells are ongoing.

Dose Fractionation

In radiotherapy, the anti-tumor response is primarily due to induction of apoptosis.⁴⁰⁻⁴³ However, the degree of anti-tumor response following the administration of radiolabeled mAbs depends on several variables, including total (cumulative) radiation dose to the tumor, dose-rate, and tumor radiosensitivity. Single-agent radioimmunotherapy (RIT), although useful for slowing solid tumor growth, has not been effective in completely eliminating large, aggressive tumors. These tumors often have p53 mutations, and are less susceptible to apoptosis which is the proposed mechanism of cell death from low dose-rate radiation.⁴⁴ Therefore, strategies are being developed to optimize dosimetry to the bone marrow and tumor by dose-fractionation and/or combining RIT with chemotherapy. In addition, studies to optimize patient selection are underway.

Bone marrow is the dose-limiting organ in radioimmunotherapy in the absence of marrow reconstitution. Dose-fractionation is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose-rate.^{43, 45, 46} Dose fractionation may take advantage of the difference between early-responding and late-responding tissue. The radiation effect on early-responding tissue can be reduced by prolonging the treatment time and dose fractionation. The radiation effect on late-responding tissues will not be changed significantly if the total dose is not changed.^{43, 46} Preclinical data have shown that dose fractionation or multiple low dose treatments can decrease toxicity while increasing the efficacy.^{41, 47, 48} Similarly, there is some clinical evidence that bone marrow toxicity can be reduced with some modest increase in the cumulative maximum tolerated dose.⁴⁹⁻⁵¹

To test these concepts using J591, a phase I dose escalation study sponsored by the Department of Defense has begun for men with progressive metastatic castrate resistant prostate cancer.⁵² Cohorts of 3-6 pts with progressive metastatic castrate resistant prostate cancer receive 2 doses of ¹⁷⁷Lu - J591 2 weeks apart: Cohort 1 (20 mCi/m² × 2), dose escalation 5 mCi/m² per dose per cohort. The primary endpoint is to determine dose-limiting toxicity (DLT) and the cumulative maximum tolerated dose (MTD) of fractionated ¹⁷⁷Lu - J591 RIT with pharmacokinetics and dosimetry and secondary endpoints of efficacy. Dose limiting toxicity is defined as severe thrombocytopenia (platelet count < 15 or need for > 3 platelet transfusions in 30 days), grade 4 neutropenia, febrile neutropenia, or grade > 2 non-hematologic toxicity. Initial results appear encouraging with no DLT observed past cohort 4 and PSA declines achieved in subjects at doses above the initial cohort.

Chemo-Radioimmunotherapy

Although there is clear efficacy of anti-PSMA-based RIT in the treatment of metastatic CRPC, the results are limited. All men treated to date with mature follow up have progressed clinically. Following progression on primary hormonal therapy, chemotherapy offers a quality of life as well as survival benefit, although responses are transient and there is no proven therapy beyond initial chemotherapy.^{7, 8} The combination of taxane chemotherapy with radiotherapy has been used in several diseases because of the radiosensitizing effects of taxane-based chemotherapy.⁵³⁻⁵⁵ The combination of taxane chemotherapy with radioimmunotherapy has also been studied in pre-clinical and early clinical studies.⁵⁶⁻⁵⁸ In addition to favorable results from fractionated radioimmunotherapy, and the radiosensitizing effects of taxane-based chemotherapy, it is hypothesized that the additional debulking by chemotherapy will overcome some of the limits imposed by the

physical characteristics of ^{177}Lu . Based upon these data, a phase I trial of docetaxel and prednisone with escalating doses of fractionated ^{177}Lu -J591 will begin accrual in 2009.

Salvage Radioimmunotherapy

In the current era, the majority of relapses after local therapy are initially “biochemical” only, i.e. a rising PSA despite no evidence of cancer on imaging.^{59, 60} This clinical scenario affects approximately 50,000 men per year in the United States alone. Although there is no proven overall survival benefit in a prospective randomized trial, radiotherapy to the prostatic fossa as a salvage regimen can lead to long-term disease-free survival in selected individuals.⁶¹⁻⁶⁴ Unfortunately, most subsequently suffer systemic progression because of subclinical micrometastatic disease outside of the radiation field.

Based on the demonstrated ability of J591-based therapy to successfully target known sites of disease and the clinical efficacy in the advanced setting, it is now under investigation in the salvage setting. “Targeted radiotherapy” in the form of radioimmunotherapy is an attractive option with the possibility of a more effective therapy in the minimal disease (biochemical only) setting. The most studied form of radioimmunotherapy to date targets the CD20 antigen (^{131}I tositumomab and ^{90}Y ibritumomab tiuxetan) in non-Hodgkin lymphoma. While approved in the relapsed setting, it appears that these therapies have their greatest impact in the minimal disease setting.⁶⁵⁻⁷⁰

Based upon acceptable toxicity and demonstrated anti-tumor activity, a multicenter randomized phase II trial in castrate non-metastatic biochemically progressive disease will begin accrual in 2009. The primary objective of this trial is to prevent or delay radiographically evident metastatic disease. Subjects with biochemically progressive prostate cancer after local therapy and initial hormonal therapy (testosterone level < 50) at high risk for early development of metastatic disease (short PSA doubling time or elevated absolute PSA)⁷¹ will be included. Subjects will receive ketoconazole and hydrocortisone and be randomized to a single infusion of ^{177}Lu -J591 or a single infusion of trace-labeled ^{111}In -J591 (i.e. placebo). Radiolabeled J591 imaging will also be performed in all patients as this group of patients have no evidence of metastatic prostate cancer on traditional imaging modalities (bone scan and CT/MRI). The utility of radiolabeled J591 imaging to identify occult sites of disease will be explored.

Conclusion

Prostate specific membrane antigen is the most highly-established prostate cell-surface antigen known. Radioimmunotherapeutic approaches targeting PSMA are well-tolerated and demonstrate anti-tumor activity. Clinical trials are underway to further improve upon efficacy and patient selection.

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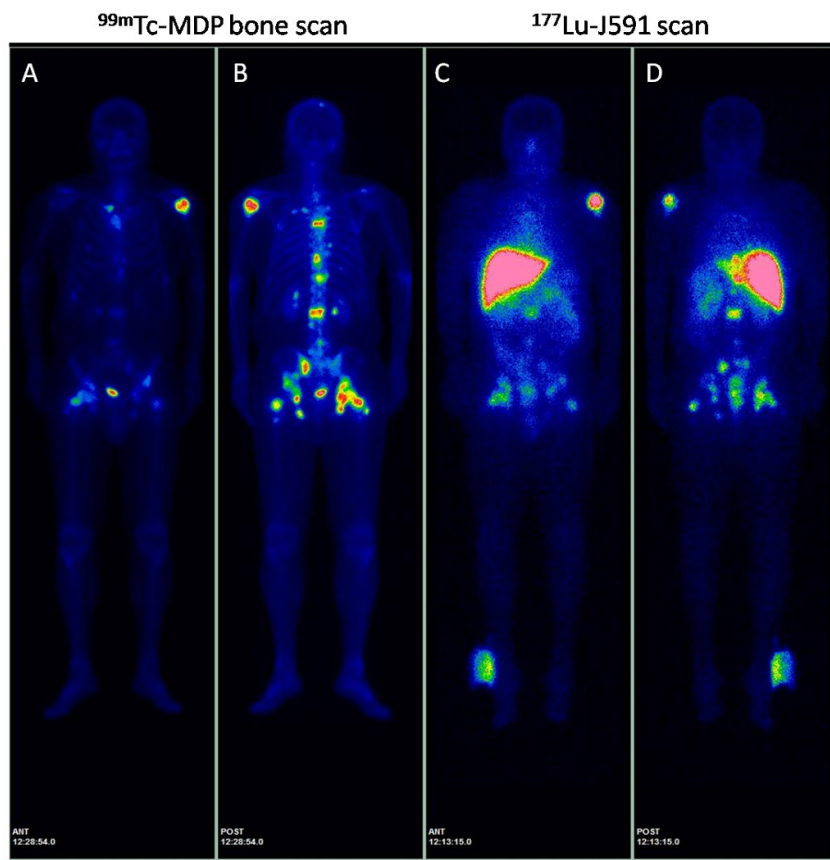


Figure 1.

Left panels: Anterior (A) and posterior (B) ^{99m}Tc -MDP bone scan images of pre-treatment bony metastases. Right panels: Anterior (C) and posterior (D) total body images obtained via dual head gamma camera of sites of uptake 7 days after ^{177}Lu -J591 administration. Note ^{177}Lu -J591 is cleared via the liver.

Table 1**Beta Emitting Radionuclides For Therapy**

	¹³¹ I	⁹⁰ Y	¹⁷⁷ Lu
Physical half-life (days)	8.05	2.67	6.7
β ⁻ particles (MeV)			
Max	0.61	2.280	0.497
Average	0.20	0.935	0.149
Range in tissue (mm)			
Max	2.4	12.0	2.20
Average	0.4	2.7	0.25
Gamma emission (MeV)	0.364 (81%)	None	0.113 (7%) 0.208 (11%)
Equilibrium Dose Constant (rad.g/hr)			
β ⁻ radiation	0.389	1.9886	0.314
gamma	0.815	No	0.075

¹³¹I: ¹³¹Iodine; ⁹⁰Y: ⁹⁰Yttrium; ¹⁷⁷Lu: ¹⁷⁷lutetium