Protocol and Statistical Analysis Cover Page
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A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

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Weill Cornell Medical College

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INVESTIGATOR AGREEMENT

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I have read the protocol entitled "A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy."

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal investigator printed name

_____ _____

Principal investigator signature **Date**

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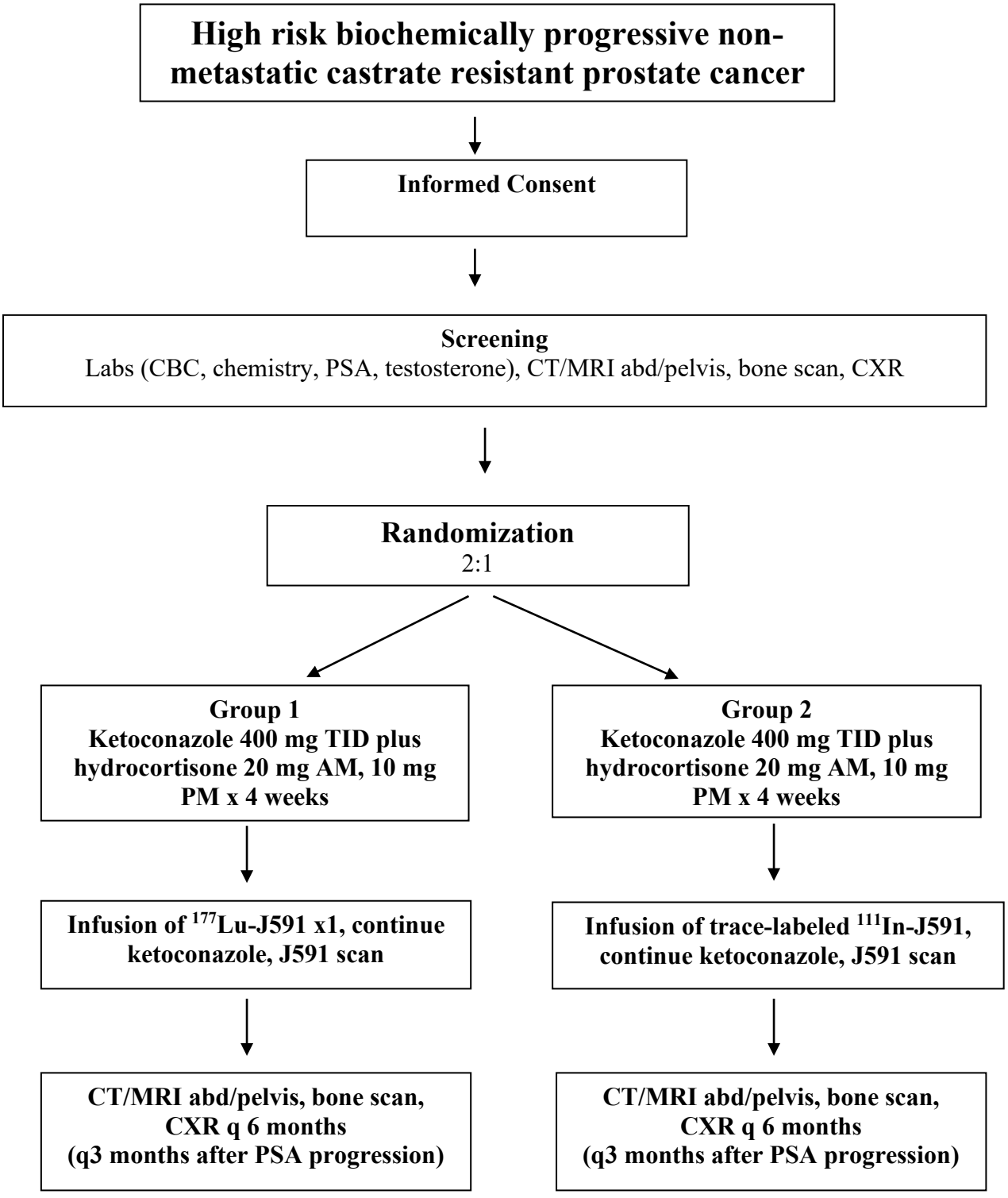
Investigational site or name of institution and location (printed)

SCHEMA


High risk biochemically progressive non-metastatic castrate resistant prostate cancer
Informed Consent
Screening
Labs (CBC, chemistry, PSA, testosterone), CT/MRI abd/pelvis, bone scan, CXR
Randomization
2:1
Group 1
Ketoconazole 400 mg TID plus hydrocortisone 20 mg AM, 10 mg PM x 4 weeks
Group 2
Ketoconazole 400 mg TID plus hydrocortisone 20 mg AM, 10 mg PM x 4 weeks
Infusion of 177Lu-J591 x1, continue ketoconazole, J591 scan
Infusion of trace-labeled 111In-J591, continue ketoconazole, J591 scan
CT/MRI abd/pelvis, bone scan, CXR q 6 months (q3 months after PSA progression)
CT/MRI abd/pelvis, bone scan, CXR q 6 months (q3 months after PSA progression)

PROTOCOL SUMMARY

Study Title:	**A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) with Ketoconazole in Patients with High Risk Castrate Biochemically Relapsed Prostate Cancer after Local Therapy**
Principal Investigator:	Scott T. Tagawa, MD (New York Presbyterian Hospital-Weill Cornell Medical College)
Number of Study Centers Planned:	10-16
Clinical Phase:	Phase 2 (Randomized)
Study Rationale:	To determine the clinical activity of ^{177}Lu -J591 with ketoconazole for the treatment of patients with castrate resistant biochemically progressive prostate cancer
Study Objectives:	**Primary Objective** Compare the rate of progression to radiographically apparent metastatic disease at 18 months with ^{177}Lu -J591 plus ketoconazole versus ketoconazole plus trace-labeled ^{111}In-J591 (placebo) **Secondary & Exploratory Objectives** • Compare progression free and metastasis free survival • Define the PSA response rate (50% reduction, with 30% reduction exploratory analysis). • Define the duration of PSA response • Define the toxicity of ^{177}Lu-J591 given as single dose plus ketoconazole in men with castrate resistant biochemical disease. • Assess the overall and prostate cancer specific survival rate of patients following treatment. • Assess the prognostic implications of baseline adrenal hormone levels in men with castrate resistant non-metastatic prostate cancer receiving ketoconazole • Define the toxicity and need for dose modifications with "high dose" ketoconazole in men with biochemically progressive castrate resistant prostate cancer • To explore the ability of ^{177}Lu-J591 or ^{111}In-J591 to image metastatic sites in patients who are NED on bone scan CT/MRI of abdomen/pelvis and CXR (selected sites) • To assess the prognostic implications of baseline circulating tumor cell (CTC) counts in men with castrate resistant non-metastatic prostate cancer receiving ketoconazole and to explore the implications of serial

	changes in CTC counts (centrally assessed, optional) • To explore the feasibility of quantitative assessment of PSMA expression in CTCs and explore prognostic and predictive implications of PSMA expression in circulating tumor cells prior to therapy with Lu-J591 (centrally assessed, optional) • To assess the implications and changes with therapy of plasma markers of hemostasis, fibrinolysis, and angiogenesis in biochemically progressive castrate resistant prostate cancer (centrally assessed, optional. • To describe reasons for lack of participation in study treatment • To assess patient reported outcomes in the setting of non-metastatic CRPC and with the development of metastases
Methodology:	Subjects will be randomized in a 2:1 fashion to receive ketoconazole with 70 mCi/m^2 of ^{177}Lu-J591 or trace-labeled ^{111}In-J591. Subjects will be stratified by site and method of primary therapy (surgery vs radiation). All subjects will receive ketoconazole (400 mg po TID) plus hydrocortisone (20 mg am, 10 mg pm) for 4 weeks followed by a single infusion of ^{177}Lu-J591 or trace-labeled ^{111}In-J591, then continue ketoconazole/hydrocortisone until progression/toxicity. Patients will be followed for response (biochemical), disease progression, and toxicity with the primary endpoint of time to radiographically apparent metastatic disease
Number of Patients Planned:	55
Statistical Methods	Based upon entry criteria, we expect 50% of patients to have developed metastasis at 18 months with ketoconazole + ^{111}In-J591. With a sample size of 50 (2:1 randomization), the study will have ≥80% power, with a pre-set one sided alpha of 10%, to determine an absolute difference in the 18-month metastasis-free survival (MFS) between groups of 30% (e.g., 80% vs 50%). An additional 10% will be enrolled to account for unevaluable subjects and loss to follow-up, resulting in a planned final n = 55.

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1. OBJECTIVES

1.1. Primary Objectives

To compare the rate of progression to radiographically apparent metastatic disease at 18 months with ^{177}Lu -J591 plus ketoconazole versus trace-labeled ^{111}In-J591 plus ketoconazole**.**

1.2. Secondary Objectives

To define the PSA response rate (50% reduction, with 30% reduction exploratory analysis).

To define the duration of PSA response

To define the toxicity of ^{177}Lu-J591 given as single dose plus ketoconazole in men with castrate resistant biochemical disease.

To assess the overall and prostate cancer specific survival rate of patients following treatment.

To define the toxicity and need for dose modifications with "high dose" ketoconazole in men with biochemically progressive castrate resistant prostate cancer

To assess the prognostic implications of baseline adrenal hormone levels in men with castrate resistant non-metastatic prostate cancer receiving ketoconazole

To explore the ability of ^{177}Lu-J591 to image metastatic sites in patients who are NED on bone scan CT/MRI of abdomen/pelvis and CXR (selected study sites)

To assess the changes with therapy and implications of plasma markers of hemostasis, fibrinolysis, and angiogenesis in biochemically progressive castrate resistant prostate cancer (optional)

To assess patient reported outcomes with high-risk, non-metastatic CRPC and with the development of metastases

1.3 Exploratory Objectives

To assess the prognostic implications of baseline circulating tumor cell (CTC) counts in men with castrate resistant non-metastatic prostate cancer receiving ketoconazole and to explore the implications of serial changes in CTC counts

To explore the prognostic and predictive implications of PSMA expression in circulating tumor cells

To explore the prognostic and predictive implications of PSMA expression in archival surgical or biopsy material in subjects being treated with anti-PSMA RIT

To describe reasons for lack of participation in study treatment (i.e. reasons for pre-screen and screen failures)

2. BACKGROUND

2.1 Disease

Prostate cancer is the leading cause of noncutaneous cancer in men in the United States, accounting for 29% of all cancers with 218,890 estimated new cases in 2007 (1). It is the second leading cause of cancer-related death, with 27,050 US men estimated to die from this disease in 2007(1). Clinically localized adenocarcinoma of the prostate is treated primarily with surgery or radiation therapy, with or without hormonal or chemotherapy, although another option for some men with newly diagnosed prostatic adenocarcinoma is active surveillance or observation, since some men will continue to be asymptomatic until death from another cause (2, 3). Although therapy for localized disease may be successful at eradicating the disease, some patients suffer recurrence or present with advanced disease. First line therapy for advanced adenocarcinoma of the prostate usually includes androgen deprivation with a mean duration of efficacy of 12-18 months (4), although there is a wide variation in response in this heterogeneous disease.

Unfortunately, after primary therapy with surgery or radiotherapy, some men suffer relapsed disease. In the current PSA era, the majority of these relapses are initially "biochemical" only, i.e. with a rising PSA despite no evidence of cancer on scans (5, 6), affecting approximately 50,000 or more men per year in the U.S. alone. Some of these men may be "salvaged" with appropriate therapy for local relapse (radiation for those that had surgery first, and surgery or cryotherapy for those with locally relapsed disease after radiotherapy) (6). Although there is no proven overall survival benefit in a prospective randomized trial, radiotherapy as a salvage regimen after radical prostatectomy can lead to long-term survival in selected individuals (7-10). However, most patients who receive local or regional radiotherapy with the hopes of cure after biochemical relapse following surgery subsequently suffer systemic progression. We have demonstrated J591-based therapy's ability to successfully target known sites of disease and have positive signals of ^{177}Lu-J591's efficacy in the advanced setting (see below). Since forms of radiotherapy have been validated in the clinically localized as well as salvage setting, "targeted radiotherapy" in the form of radioimmunotherapy is at least theoretically an attractive option with the possibility of even greater efficacy in the minimal disease (biochemical only) setting. The most studied form of radioimmunotherapy to date uses targeting of the CD20 antigen (I^{131} tositumomab and Y^{90} ibritumomab tiuxetan) in non-Hodgkin's lymphoma. While approved in the relapsed setting, it appears that these therapies have their greatest impact in the minimal disease setting (11-16). In addition, the decay characteristics of ^{177}Lu with its relatively short range beta emission is preferably suited for small volume, rather than bulky, disease sites.

Prostate specific membrane antigen

Prostate specific membrane antigen (PSMA) is the single, most well-established, highly restricted prostate epithelial cell membrane antigen known (17-22). The PSMA gene has been cloned, sequenced, and mapped to chromosome 11p (18, 23). Although first thought to be entirely prostate-specific (17-19), subsequent studies demonstrated that PSMA is also expressed by cells of the small intestine, proximal renal tubules and salivary glands (21). However, the level of expression in these non-prostate tissues is 100-1000-fold less than in prostate tissue (22),

and the site of PSMA expression in these normal cells (brush border/luminal location) are not typically exposed to circulating Ab. In contrast to other well known prostate-restricted molecules such as PSA and prostatic acid phosphatase (PAP) that are secretory proteins, PSMA is a type II integral cell-surface membrane protein that is not secreted, thereby making PSMA an ideal target for mAb therapy. Pathology studies indicate that PSMA is expressed by virtually all prostate cancers (23). Moreover, PSMA expression increases progressively in higher grade cancers, metastatic disease and hormone-refractory prostate cancer (19, 20, 24, 25).

PSMA has been found to have folate hydrolase and neurocarboxypeptidase activity (26). Although its role in PC biology is unknown, the consistent finding of PSMA upregulation correlating with increased aggressiveness of the cancer implies that PSMA has a functional role in PC progression. Inhibition of enzymatic activity *in vitro* or in xenograft models has not demonstrated significant growth inhibitory effect (27). Nevertheless, the expression pattern of PSMA makes it an excellent target for mAb based targeted therapy of prostate cancer.

PSMA as a target in prostate cancer

Use of capromab penditide (Prostascint ®) has validated PSMA as an *in vivo* target for imaging (28, 29), although clinical treatment studies with capromab have been disappointing (30, 31). Molecular mapping revealed that capromab targets a portion of the PSMA molecule that is within the cell's interior and not exposed on the outer cell surface (32-34) and cannot bind to viable cells (17, 34). Recognition of these features led Neil Bander at WCMC and others to propose that mAbs to the exposed, extracellular domain of PSMA had the potential to significantly improve *in vivo* targeting likely resulting in enhanced imaging and therapeutic benefit (34, 35). These antibodies (J591, J415, J533 and E99) demonstrate high affinity binding to viable PSMA-expressing LNCaP cells in tissue culture and are rapidly internalized (34, 36).

Pre-clinical experience with J591

Murine monoclonal Ab J591 (muJ591) was chosen for clinical development and has been extensively studied in pre-clinical models (37-39). The affinity of J591 is 1 nm which other studies have shown to be the optimal affinity in therapeutic models, lower affinity providing less binding and higher affinity interfering with antibody penetration into tumor masses (40).

Immunohistochemistry studies with mAbs to $PSMA_{ext}$ confirmed the highly restricted expression pattern of PSMA with binding to prostate epithelial cells and weak binding to the brush border of renal proximal tubular and small bowel epithelium. Unexpectedly, immunohistochemical studies of a variety of malignant tissues found that tumor vascular endothelium of all solid tumors, but not normal vascular endothelium, bound anti-PSMA antibodies (34). This further raised the interest in anti-PSMA antibodies as a potential way to specifically target not just prostate cancer but all solid tumors using a vascular targeting approach.

Animal studies utilized nude mice implanted subcutaneously with PSMA-expressing LNCaP cells. After allowing the tumors to establish and reach a diameter of 7-10 mm, the animals were treated with J591 radiolabeled with different isotopes, including ^{131}Iodine (^{131}I-J591), ^{177}Lutetium (^{177}Lu-J591) and ^{90}Yttrium (^{90}Y-J591). These studies showed that ^{90}Y and ^{177}Lu provide better dosimetry due to their longer intracellular half-lives and radioiodine's relatively rapid clearance and that anti-tumor responses were seen with all radionuclides with an apparent dose response relationship. Higher cumulative doses of either ^{90}Y or ^{177}Lu could be

delivered using fractionated dosing (multiple sub-MTD doses rather than a single MTD dose). Median survival of the animals improved by 300% for fractionated ^{90}Y-J591 therapy (150 days vs. 52 days (control). With fractionated dose ^{177}Lu-J591, >80% of the mice were cured (39). A major limitation of using a mouse mAb in patients is the development of a human anti-mouse antibody (HAMA) response that precludes repetitive dosing. Therefore, mAb J591 was de-immunized by using a next generation approach to humanization developed by Biovation, Ltd. (Aberdeen, UK) into a humanized form (huJ591).

Clinical experience with J591

Initial phase I studies using huJ591 trace-labeled with ^{111}In using a DOTA chelate showed that repetitive dosing was well tolerated with total doses of up to 500 mg/m^2 without the development of a human anti-humanized (de-immunized) antibody (HAHA) response (41, 42). No dose limiting toxicity occurred and the maximum tolerated dose 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 in 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 although, as seen in other trials using radiometals, the liver is the primary site of excretion. Per-cent injected dose in the liver diminished with increasing dose of antibody, and higher doses were associated with longer plasma clearance times (43-45).

Choice of Radionuclide

For targeted radionuclide therapy, monoclonal antibodies and peptides can be labeled efficiently with several radionuclides emitting beta particles (Table 1-1). 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 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 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.

Table 1-1: 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. for β^- radiation		0.389	1.9886	0.314
gamma		0.815	No	0.075

Phase I Trials of Radiolabeled J591.

Two independent phase I clinical trials have been performed at WCMC using ^{90}Y or ^{177}Lu linked via a DOTA chelate to huJ591 in patients with hormone-refractory prostate cancer (46, 47). Briefly, 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 defined by at least 3 serially rising PSAs and/or radiographic studies. As prior studies had demonstrated that all prostate cancers were PSMA-positive (23), no 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 ^{89}Strontium or ^{153}Samarium were not permitted. Other standard laboratory exclusion criteria applied as well (46, 47). Dose limiting toxicity in the 2 trials was defined as: Hematologic toxicity consisting of grade 4 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.

^{90}Y-J591 phase I trial:(46) Twenty nine subjects initially received 5 mCi of ^{111}In linked via a DOTA chelate to 20 mg of mAb J591 for pharmacokinetic and biodistribution determinations. One week later, they received ^{90}Y -DOTA-J591. All patients received 20 mg of mAb J591 with the ^{90}Y dose escalated in cohorts of 3 or more patients at the following planned dose levels: 5, 10, 15, and 20 mCi/m^2. A fifth dose level of 17.5 mCi/m^2 was added to more precisely define the MTD. Toxicity was dose-related and limited to reversible myelosuppression, predominantly thrombocytopenia. The 17.5 mCi/m^2 dose level was determined to be the MTD.

Four eligible patients were re-treated with none experiencing irreversible myelosuppression (no DLTs). J591 imaging of known sites of both bone and soft tissue metastases were seen in 90% of patients. Two patients at the 20 mCi/m^2 dose level (MTD + 1 level) experienced 85% and 70% declines in PSA lasting 8 and 8.6 months, respectively as well as objective measurable disease responses. An additional 6 patients (21%) experienced PSA stabilization. No HAHA response was detected.

^{177}Lu-J591 phase I trial:(47) In the ^{177}Lu trial, 35 subjects received a total of 10 mg/m^2 of J591 with escalating doses of ^{177}Lu ranging from 10 mCi/m^2-75 mCi/m^2. Since ^{177}Lu can be directly imaged and has a longer physical $t_{1/2}$ than ^{111}In, imaging took place during the 2 weeks following dosing. Patients received 10 mg/m^2 J591 with doses of ^{177}Lu ranging from 10 mCi/m^2-75 mCi/m^2. Imaging demonstrated successful targeting of metastatic sites in 100% of the 30 patients with radiographic evidence of disease. The 70 mCi/m^2 dose was defined as the single-dose MTD with grade 4 thrombocytopenia as the DLT. Repeat dosing at 45 to 60 mCi/m^2 resulted in dose-limiting myelosuppression; up to 3 doses of 30 mCi/m^2 could be safely administered. PSA declines of ≥ 50% were seen in 4 patients lasting 3+ to 8 months. An additional 16 subjects (46%) experienced PSA stabilization for a median of 60 days (1 – 21+ months). No HAHA responses were detected.

Cytotoxin conjugated J591.

MLN2704 is a antibody-chemotherapy conjugate designed to target PSMA. J591 is conjugated to maytansinoid 1 (DM1), which is a potent microtubule-depolymerizing compound. Pre-clinical activity was demonstrated (48), leading to a phase I trial designed to explore single ascending doses of the conjugate to define DLT, MTD and PK (49). Twenty three subjects with progressive castrate metastatic prostate cancer received MLN2704 at doses ranging from 18 – 343 mg/m^2 in an accelerated dose escalation scheme; 18 received at least 3 doses. Grade ≥ 3 toxicities occurred in 2 subjects, including 1 episode of uncomplicated febrile neutropenia and transient grade 3 elevation of transaminases. One subject (treated at 343 mg/m^2) achieved a >50% decline in PSA, and another (treated at 264 343 mg/m^2) experienced a PR by RECIST along with a >50% decline in PSA.

A subsequent multicenter phase I/II study was initiated based upon the above results (50). Sixty two subjects received multiple doses of MLN2704. Because of neurotoxicity at every 1 or 2 week doses, the study was amended to include every 3 week dosing and dosing on days 1 and 15 of 42-day cycles. Of the 4 schedules tested, PSA declines were most frequent at 330 mg/m^2 every 2 weeks (2/6 had PSA decrease >50%, 2/6 had PSA stabilization). However, grade 2-3 neuropathy was dose-limiting, and could not be predicted by prior taxane-based chemotherapy, diabetes, or prior neuropathy. Although response was modest, and treatment was limited by toxicity, this trial demonstrated proof of principle that an immunoconjugate utilizing a PSMA antibody has therapeutic potential.

Phase II trial of ^{177}Lu-J591 in metastatic castrate resistant prostate cancer

Based upon the phase I results described above (47), a phase II trial has completed enrollment. In this investigator-initiated study, subjects with progressive metastatic CRPC received one dose of ^{177}Lu -J591 in two-cohorts. Cohort 1 (65mCi/m^2), 15 pts; Cohort 2: (70mCi/m^2), 17 pts. The primary endpoint is PSA and/or measurable disease response; the secondary endpoint is toxicity. A ^{177}Lu-J591 imaging study was done to confirm tumor targeting.

All of the initially planned 32 pts (14 chemo-naïve) have been treated. Preliminary analysis reveals the following (51):

Median age is 71 (range 51 – 88), median baseline PSA 77.92 (range 3.31 – 2184.6). Three pts achieved PSA declines of >50%. Another more preliminary analysis has been performed based upon retrospective analyses in patients on prospective chemotherapy trials demonstrating that 30% declines in PSA are most associated with survival benefits (52, 53). Of the 15 subjects receiving 65mCi/m^2, 2 of 15 (13%) achieved a 30% PSA decline. Of the 17 subjects receiving 70mCi/m^2, 7 (47%) experienced at least a 30% decrease in PSA.

Platelet nadir <25 x 10^9/L occurred in 42% of pts, 9 of whom required 1 – 4 platelet transfusions (median = 2). 29/32 pts recovered normal platelet counts; the remaining 3 pts had rapidly progressive disease with bone marrow involvement. Neutropenia ≤ 0.5 x 10^9/L occurred in 27% of pts, 6 of whom received brief therapy with growth factors. All 32 pts had normal neutrophil recovery and no pt experienced neutropenic fever. No significant drug-related non-hematologic toxicity has occurred. Excellent targeting of known sites of PC metastases has been observed in 31/32 (97%) of pts.

In summary, single dose ^{177}Lu-J591 demonstrates anti-tumor activity in pts with progressive CRPC with reversible myelosuppression. 32 of the initially planned 32 subjects have been treated to date and follow up is ongoing. Because of an FDA mandate, treatment was begun at a lower dose than the phase I MTD. Since there appears to be a dose response relationship (13 vs 47% with >30% PSA decline, 46 vs 71% with any PSA decline), an expansion protocol at the MTD is planned to tighten the confidence intervals for response at the MTD. Based upon acceptable toxicity in both groups and signals for increased efficacy at the higher dose (the MTD based upon the phase I trial), we are proceeding with the current trial.

2.2 Investigational Agent

2.2.1 J591

The J591 Mab is a deimmunized monoclonal antibody directed at the extracellular domain of human PSMA. J591 was derived from murine J591 using Biovation's (Biovation , Aberdeen , Scotland, UK) DeImmunisation technology in which individual amino acids in predicted B and T cell epitopes were replaced with other amino acids such that the epitope would no longer be recognized by the human immune system, thereby decreasing the likelihood of the development of an anti-mAb antibody response in humans.[28] This results in a potentially non-immunogenic antibody, which might be administered to patients on multiple occasions over long periods without inducing an immune response (see Clinical Experience). Furthermore, the deimmunized Mab additionally has been engineered to possess the effect of inducing antibody dependent cellular cytotoxicity (ADCC) with human immune effector cells.

J591 is produced from NS0 cells by Lonza (Lonza Biologics, Slough, UK). The molecular weight of J591 is approximately 147,000 daltons as determined by Matrix Assisted Laser Desorption Mass Spectrometry (MALDI-TOF). The naked antibody is formulated in a 50 mM sodium phosphate, pH 5.5, containing 100 mM sodium chloride and 2 mM EDTA at a nominal concentration of 5 mg/mL.

2.2.2 DOTA-J591

In order to radiolabel J591 with β^- emitting radionuclides such as ^{177}Lu, the J591 antibody molecule is first conjugated to a macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane- N,N',N'',N'''-tetraacetic acid (DOTA) by direct coupling of one of the four carboxylic acid groups of DOTA to the primary amines present in the protein structure.

The DOTA conjugated antibody is formulated in 0.3 M ammonium acetate, pH 7.0 at a nominal concentration of 8 mg/mL.

2.2.3 Radiolabeled J591

The DOTA-J591 antibody molecule is labeled with radiometal ^{177}Lu or ^{111}In in 1.0 M ammonium acetate buffer at pH 7.0. The radiolabeled J591 complex is then purified using size-exclusion column chromatography.

To avoid the effects of autoradiolysis on the antibody, reaction time is minimized and the radiolabeled antibody preparations are formulated in phosphate buffered saline containing not more than 1% Human Serum Albumin (HSA). All reagents used in the conjugation and purification of J591 are made with pyrogen-free water. Radiolabeled J591 is periodically tested for sterility and pyrogenicity.

Each patient dose will be supplied to the study site on the day of or day before treatment by the central radiopharmacy.

The J591 mAb is a deimmunized monoclonal antibody directed at the extracellular domain of human PSMA. For additional details, see Section 1 and/or Investigator Brochure.

Radiolabeled antibody preparations are formulated in phosphate buffered saline containing not more than 1% Human Serum Albumin (HSA).

In order to radiolabel J591 with β^- emitting radionuclides, the antibody molecule is first conjugated to a macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) by direct coupling of one of the four carboxylic acid groups of DOTA to the primary amines present in the protein structure.

The radiolabeling of J591 with ^{177}Lu is achieved by adding the radionuclide to the ammonium acetate buffered J591. To avoid the effects of autoradiolysis on the antibody, reaction time is minimized and the reaction mixture is purified with a size exclusion column prior to administration.

All reagents used in the conjugation and purification of J591 are made from pyrogen-free water. Radiolabeled J591 is tested periodically for sterility and pyrogenicity.
Refer to the Investigator Brochure for further details.

2.2.4 Pharmacokinetics

The pharmacokinetics of J591 antibody was studied in patients with prostate cancer using ^{111}In-J591 as a radiotracer. In a Phase 1 dose escalation study (see above) 4 groups of patients received different amounts of J591 antibody (25, 50, 100, 200 mg/m^2) mixed with a trace amount of ^{111}In-J591 (5 mCi/1-2 mg). In a different Phase 1 dose-escalation study using ^{90}Y-J591 (see above), a group of patients received 20 mg of total J591 antibody mixed with a trace amount of ^{111}In-J591 (5 mCi/1-2 mg) for imaging studies prior to ^{90}Y treatment dose. These studies demonstrated that the plasma clearance kinetics of ^{111}In- J591 antibody is dose-dependent at low doses (<50 mg/m^2). It should be noted that, in these studies, plasma clearance kinetics was determined based on the measurement of radioactivity in the plasma over time. The actual J591 antibody levels have not been measured; there is an assumption that the clearance of radiolabeled antibody does indeed reflect the J591 antibody clearance. The plasma clearance kinetics, based on bi-exponential fitting of plasma-time activity curves indicate that the terminal half-life ($T_{1/2}\beta$) is about 44.2±13.9 hrs at 11 mg/m^2 antibody dose and 59.3±16.6 hrs at 25 mg/m^2 antibody dose. At higher doses of antibody mass, the plasma clearance is relatively slower, but stable. In summary, the plasma clearance of antibody increases at lower doses of antibody (<25 mg/m^2). In addition, repeat administration of J591 antibody over a 4-week period does not affect plasma clearance of radiolabeled J591 in patients with prostate cancer (data not shown).

In a Phase 1 dose-escalation study using 177Lu-J591 (see above), a group of patients received J591 antibody mixed with a ^{177}Lu-J591 (10-70 mCi/m^2 and total J591 10mg/m^2). The plasma clearance kinetics (shown in Table 1-2) demonstrate that there is no difference between ^{177}Lu and ^{111}In labeled J591 antibody.

Table 1-2: ^{177}Lu-J591 Vs. ^{111}In-hJ591: Plasma Clearance Kinetics

Pts.	mg/m^2	$T_{½}\ \alpha$ (hr)	$T_{½}\ \beta$ (hr)	V_d at T_0	Clearance
n=18[#]	10	3.61±5.70	**46.8±12**	3949±1067	72±34
n=16*	11	2.37±1.94	**44.2±14**	4042±863	94±34
n=3[$]	25	3.36±2.17	**59.3±17**	3698±224	56±16
n=3[$]	50	7.83±9.5	**99.7±32**	4156±256	47±6.7
n=3[$]	100	5.7±7.5	**105±38**	4373±566	40±13

[#] = In a Phase 1 Dose escalation protocol, 18 patients were treated with ^{177}Lu-J591

***** = In a Phase 1 Dose escalation protocol, 16 Patients were treated with ^{90}Y-J591 and one week prior to treatment, ^{111}In-J591 kinetics were studied.

[$] = In a Phase 1 Dose escalation protocol with huJ591 cold antibody treatment, 3 patients in each group received different amounts of cold huJ591 mixed with ^{111}In-J591.

2.2.5 Biodistribution

The imaging studies with ^{111}In-J591 in patients with prostate cancer showed that liver is the principal organ with significant uptake of radiolabeled antibody. The liver uptake of J591 is a function of J591 antibody mass administered (Table 1-3): the higher the antibody mass, the lower the relative proportional uptake of radiolabeled antibody by the liver. In addition, at 20 mg of J591 administered in Phase 1 dose escalation trials with ^{111}In-DOTA-J591, the liver uptake increases with time and is at a maximum by day 6 (27.0 ± 1.7 % of injected dose). No significant localization was seen in other major organs, such as spleen and kidneys.

Biodistribution: ^{111}In-J591 vs. ^{177}Lu-J591

The imaging studies were done 5 times over a period of one week with ^{111}In and 2 weeks with ^{177}Lu. The uptake of radioactivity in various source organs (% injected dose/organ) was determined. The imaging studies clearly document that the in vivo distribution of radiolabeled J591 during the first week is quite similar with both ^{111}In and ^{177}Lu radionuclides (Table 1-4).

Table 1-3: ^{111}In-J591: Liver Uptake (% injected dose) as a Function of J591 Antibody Mass

Time	11 mg/m^2	25 mg/m^2	50 mg/m^2
1	13.1 ± 2.5	9.6 ± 1.0	7.9 ± 0.8
24	19.0 ± 3.2	12.9 ± 2.1	11.2 ± 1.2
48	20.8 ± 2.8	ND	11.0 ± 0.4
72	22.5 ± 2.4	14.5 ± 1.2	12.1 ± 1.0
120	24.6 ± 2.8	ND	ND
144	27.0 ± 1.7	17.1 ± 3.2	13.9 ± 1.0

Table 1-4: Biodistribution of Radiolabeled J591 Antibody

	^{111}In-J591		^{177}Lu-J591	
Organ	DAY 0	DAY 6	DAY 0	DAY 7
Whole Body	100.0 ± 0.0	66.1 ± 18.4	100.0 ± 0.0	69.8 ± 9.5
Remainder	52.3 ± 5.7	24.9 ± 16.8	57.5 ± 6.4	34.7 ± 6.9
Heart Contents	8.9 ± 2.3	3.4 ± 1.2	8.8 ± 2.2	3.1 ± 0.9
Kidneys	2.4 ± 0.8	2.5 ± 0.7	2.2 ± 0.5	2.5 ± 0.5
Liver	14.7 ± 3.2	28.0 ± 7.8	15.0 ± 3.8	23.7 ± 7.0
Lungs	9.0 ± 2.0	4.4 ± 1.7	6.9 ± 1.9	3.1 ± 0.7
Red Marrow	10.9 ± 5.0	1.2 ± 1.1	7.4 ± 2.4	0.6 ± 0.4
Spleen	1.8 ± 0.6	1.7 ± 0.8	2.2 ± 1.0	2.1 ± 0.8

2.2.6 Radiation Dosimetry

Based on imaging studies and plasma clearance with ^{177}Lu-J591, the residence times (τ) of radioactivity in various source organs (as shown in Table 1-4) were calculated. Using "S" factors from MIRD tables, radiation dosimetry (cGy/mCi) for ^{177}Lu-J591 was estimated (Table 1-5). Following administration of ^{177}Lu-J591, the liver is the critical organ, receiving 7.77± 2.23 rads/mCi, and the kidneys and spleen receive <7 rads/mCi. The bone marrow dose was estimated to be 1.17± 0.37 rads/mCi based on the assumption that 36% of bone marrow volume represents plasma volume.

Hematopoietic toxicity is usually the dose-limiting factor in RIT (54). Radiation dose of 9.0 Gy to the bone marrow is generally regarded as an "organ injury dose" and the tolerable absorbed doses were usually estimated to be 65% of LD50 (50%) organ injury dose. Therefore, the tolerable absorbed dose for bone marrow is about 3.0 Gy (330 rads). The maximum tolerable radiation doses to kidneys, liver and spleen are approximately 20-25 Gy (2000-2500 rads). Dosimetric studies using radiolabeled antibodies have been effectively used by many investigators to determine patient-specific radiation dosimetry of radiolabeled antibody treatment (55, 56). Based on the dosimetry data shown in Table 1-5, the maximum bone marrow dose following administration of 70mCi/m^2 of ^{177}Lu-J591 would deliver 164 rads to an average person with a BSA of 2.0 m^2. The maximum dose the liver would be about 1100 rads, well below the maximum tolerable liver dose.

Table 1-5: Radiation Dosimetry (rads/mCi) of ^{177}Lu-J591 in Patients with Prostate Cancer

Organ	Mean		S.D.
Adrenals	0.52	±	0.08
Brain	0.40	±	0.07
Gall Bladder	0.55	±	0.08
LLI Wall	0.42	±	0.07
Small Intestine	0.43	±	0.07
Stomach	0.45	±	0.07
ULI Wall	0.44	±	0.07
Heart Wall	3.50	±	0.70
Kidneys	5.20	±	1.29
Liver	**7.77**	**±**	**2.23**
Lungs	2.79	±	0.80
Muscle	0.42	±	0.07
Pancreas	0.52	±	0.08
Red Marrow	**1.17**	**±**	**0.37**
Bone Surfaces	0.70	±	0.14
Skin	0.42	±	0.07
Spleen	7.28	±	3.41
Testes	0.36	±	0.13
Thymus	0.44	±	0.07
Thyroid	0.41	±	0.07
Urin. Bladder Wall	0.97	±	0.22
Total Body	0.71	±	0.10
Effective Dose Equiv.	2.14	±	0.35
Effective Dose	1.33	±	0.19

2.3 **Rationale**

As stated above, we have validated that J591 can target known sites of disease and have preliminary evidence that there is anti-tumor effect of radiolabeled J591. Since forms of radiotherapy have been validated in the clinically localized as well as salvage setting, "targeted radiotherapy" in the form of radioimmunotherapy is at least theoretically an attractive option with the possibility being a higher yield therapy in the minimal disease (biochemical only) setting [see information on anti-CD20 based radioimmunotherapy above].

The objective of this study is to determine the efficacy of the addition of ^{177}Lu -J591 to ketoconazole in men with progressive biochemical (PSA) prostate cancer despite medical or surgical castration. All subjects will receive ketoconazole (400 mg p.o. TID) plus replacement doses of hydrocortisone (20 mg am, 10 mg pm). Subjects will be randomized to receive a single dose of 70 mCi/m^2 ^{177}Lu -J591 or trace-labeled ^{111}In-J591 (i.e. placebo). Subjects will be followed for response, disease progression, safety and toxicity. The treatment phase will last until progression of disease or toxicity necessitating discontinuation of therapy. Subjects will be followed until the primary endpoint, which is the development of radiographically apparent metastatic disease.

2.4 **Correlative Studies Background**

2.4.1 Adrenal androgen levels

Although androgen deprivation therapy with LHRH agonists are successful in suppressing testosterone levels in the majority of cases, adrenal androgen levels are not typically suppressed by significant amounts (57). In addition, some evidence exists that targeting adrenal androgens may play a role in the management of prostate cancer (58, 59), leading to the common use of ketoconazole for this purpose. CALGB 9583 was a randomized trial of antiandrogen withdrawal with or without ketoconazole (60). As part of the correlative sciences portion of this trial (secondary endpoint), adrenal androgen level were prospectively collected. Baseline adrenal androgen levels in men with metastatic castrate resistant prostate cancer were associated with PSA response and overall survival (61). Based upon these data, we plan to prospective assess and validate these results in men with biochemically progressive castrate resistant prostate cancer. As published we will compare the median baseline androgen levels in those with a PSA response vs those without. In addition, we will categorically analyze subsets of baseline adrenal androgen levels and correlate them with time to development of radiographically apparent metastatic disease and overall survival. As the published analysis did not prospectively identify categorical values for analysis (median levels were used), we will also use prospective determined levels based upon the published studies and categorize subsets for analysis.

2.4.2 Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis

Trousseau first published the link between malignancy and thrombosis in 1865 (62). Since then, various physicians and scientists have studied this association in terms of thrombotic mechanisms, determinants of cancer prognosis, and treatment outcomes. Data from the MEGA study, a large population-based, case-control study, revealed that cancer increases the risk of venous thromboembolism 7-fold overall, with a higher risk near the time of diagnosis and with advanced rather than localized disease (63). The presence of a malignancy also increases the risk for recurrent venous thromboembolism (64, 65). In addition, both the Levitan study (64) and data from the Danish registries (66) found that thrombosis in the cancer patient predicts for worse prognosis and a shorter survival.

Even in the absence of clinical thromboembolic disease, abnormalities in coagulation tests in patients with malignancy are common. Elevation of coagulation factor levels, fibrin degradation products, and platelet counts are common (67). Other more specific parameters demonstrative of activation of hemostasis, including thrombin-antithrombin (TAT) complexes, fibrinopeptide A, D-dimers and prothrombin fragment F1+2, are also elevated. The hemostatic activation observed in many cancer patients may be the result of direct activation by the malignant cell or an indirect effect mediated through activated endothelium or monocytes (68, 69).

The link between early activation of hemostasis and cancer prognosis has also been demonstrated in clinical studies. D-dimers are a marker of fibrin formation and degradation by both thrombin and plasmin. The levels of D-dimers are elevated in a variety of clinical situations associated with increased thrombin generation such as disseminated intravascular coagulation and thromboembolic events. Clinical studies have shown that D-dimer levels are significantly elevated in many patients with both disseminated and limited malignancies without evidence of clinical thromboembolism (67). Quantitative measurements of D-dimers, using sensitive immunoassays, have been reported to have prognostic significance. The plasma level of D-dimers predicts survival in patients with both limited and disseminated lung cancer (70-72). Similarly, in women with breast cancer, levels of D-dimers have correlated with malignant versus benign breast lesions (73), the presence of lymph node metastases on surgical pathology (73), and with volume of disease, time to progression, and overall survival in metastatic disease (74). Quantitative D-dimer levels also correlate with levels of IL-6 and VEGF (74). In patients with colorectal cancer, pre-operative levels of D-dimer have been correlated with stage of disease, tumor size and or depth of invasion, lymph node metastases, and distant metastases (75). Levels of D-dimers have also correlated with FIGO stage in women with ovarian cancer (76). Pre-operative levels of plasma TAT complexes, an assay more reflective of immediate thrombin generation, have been correlated with risk of venous thrombosis in patients with cancer undergoing surgery (77). Plasma TAT levels have also been shown to correlate with response to therapy and prognosis in patients treated for lung cancer (78). In addition, there is evidence that inhibitors of coagulation may decrease tumor growth, limit metastases, and improve survival in cancer models (79-82).

Like many other cancers (as discussed above), prostate cancer is linked to thrombosis. In a review of patients with thrombosis with or without cancer using Medicare claims data, prostate cancer was the third most common type of malignancy to be associated with a thrombosis (64). Activation of both the coagulation and fibrinolytic systems has been demonstrated in prostate cancer (83). Clinically, men with carcinoma of the prostate are at increased risk of thromboembolic disease, but may also have increased risk of bleeding (84). The interaction of tumor cells with the coagulation and fibrinolytic systems is likely be important in tumor growth and spread. Markers of activation of coagulation, including D-dimers, TAT, and prothrombin fragment F1+2, are elevated in men with advanced prostate cancer compared to age-matched controls (85). TF expression (using immunohistochemistry) has also been correlated with angiogenesis and PSA level (86). In metastatic disease, immunohistochemical assessment of biopsy specimens for TF correlated with prognosis with androgen deprivation therapy (87). Preoperative levels of IL-6 and its receptor are associated with recurrence and progression in localized prostate cancer (88, 89). Increased VEGF expression correlates with Gleason score and pathologic stage in localized prostate cancer (90). However, in prostate cancer as in other cancers, it is unclear if expression of angiogenic markers in tumor tissue or neighboring normal tissue or stroma is more important prognostically (91-93).

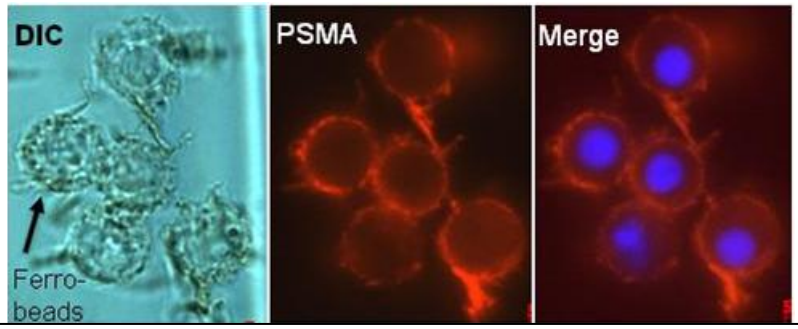
On our own preliminary data set, we have shown that subclinical hemostatic activation is common in men with untreated clinically localized prostate cancer and correlates with objective measures of surgical blood loss with prostatectomy (94). We have confirmed others' observations that trends of several markers increase with age (fibrinogen, $p=0.005$; TAT, $p=0.088$; D-dimer, $p<0.001$; IL-6, $p<0.001$; IL-8, $p=0.059$) (95). We also noted trends for correlations amongst several markers (TAT and D-dimer, $p<0.001$; TAT and IL-6, $p=0.009$; D-dimer and IL-6, $p<0.001$, fibrinogen and D-dimer, $p<0.001$; fibrinogen and IL-6, $p<0.001$; fibrinogen and IL-8, $p=0.076$) (95). In addition, we found a correlation between pre-operative IL-6 levels and pre-operative PSA and a validated post-operative prognostic nomogram-derived score ($p=0.038$) which predicts prostate cancer recurrence at 10 years after radical prostatectomy using pre- and post-operative variables (96)(95). Preliminary data from a pilot study in men with advanced, untreated prostate cancer examining the effect of androgen deprivation on markers of hemostatic activation, fibrinolysis, and angiogenesis, data from the first 3 subjects reveals that levels of markers decrease significantly after only one month of therapy (mean decreases in TAT by 60.9%, IL-8 by 24.9%, IL-6 by 60.5%, and D-dimers by 72.1%). In addition, the reverse has been observed anecdotally in one pt with markers drawn pre-operatively and again upon recurrence (increase in TAT by 316%, IL-8 by 259%, IL-6 by 307%, and D-dimer by 2226%). Our hypothesis is that further hormonal therapy with ketoconazole will affect these markers as well. We will assess baseline values and compare values at 1 month and 6 months after therapy. In addition to assessing changes with therapy, we will perform exploratory analyses examining the use of baseline values as well as percent change in predicting response to ketoconazole.

2.4.3 Circulating tumor cells (CTCs)

Assays to detect CTCs in the peripheral blood of cancer patients have been used clinically to provide prognostic information and to test for minimal residual disease. Typical methods to detect these CTCs are either antibody-based (immunocytochemistry or flow cytometry) or RT-PCR; each has its specific advantages and limitations. For example, RT-PCR can be very sensitive and highly specific when the expression of the target mRNA is limited to malignant tumor cells. Flow cytometry, on the other hand, has been used to detect and authenticate cells as CTCs, but it does not allow visual confirmation of cell morphology or discrimination of changes at the subcellular level (97). The challenges in CTC detection relate to the need for high sensitivity combined with high specificity. Important progress in this field has recently arisen with the development of a semi automated enrichment system, the CellSearch (Veridex LLC, Warren, NJ) that uses an antibody-based immunomagnetic-capture and automated staining methodology (98). The immunomagnetic capture is achieved with the use of a ferrofluid-coated antibody specific for the epithelial cell adhesion molecule EpCAM (99), a 40 KD, transmembrane glycoprotein that consists of two epidermal growth factor-like extracellular domains. EpCAM, encoded by the *GA733-2* gene located on the long arm of chromosome 4 (100), has been described under various names, mostly associated with monoclonal antibodies specific for cell surface antigen (MH99, AUA1, MOC31, 323/A3, KS1/4, GA733, and HEA125 (used in this assay). Litvinov *et al.* first suggested the name EpCAM, which more precisely reflects the molecule's function and tissue specificity. EpCAM is detected at the basolateral membrane of the majority of epithelial tissues, and is overexpressed by the majority of human epithelial carcinomas, including colorectal, breast, prostate, and head and neck carcinomas (101). Thus, use of antibodies to EpCAM allows for circulating epithelial-derived tumor cells to be isolated and concentrated from peripheral blood so they can be further inspected by microscopy. However, as EpCAM, can also be expressed in leucocytes, the specificity of this antibody-based assay to detect CTCs is lowered to 80%. To increase the specificity of detection for epithelial tumor-derived cells, CellSearch technology uses three additional immunostains: an antibody against CD45 conjugated with allophycocyanin to identify white blood cells (WBC), the nuclear dye [4,6-diamidino-2-phenylindole (DAPI)] to fluorescently label the cells' nuclei, and two phycoerythrin-conjugated anti-cytokeratin antibodies recognizing cytokeratins (predominantly cytokeratins 8, 18, and 19) to more specifically identify epithelial cells as such. Stained cells are analyzed on a fluorescence microscope using the Cell Track Analyzer II. Automatically selected images are then reviewed by the operator for the identification and counting of CTCs. The criteria for an object to be defined as a CTC include: round-to oval morphology, a visible nucleus (DAPI staining), positive staining for cytokeratins, and being negative for CD45. In addition, the consensus pathognomonic features of epithelial tumor cells, such as a clearly enlarged nucleus, high nucleus/cytoplasmic ratio and/or clusters of two or more immunopositive cells are also part of the CTC definition criteria, further attesting to the epithelial-tumor specificity developed in the CellSearch method (for review see (102)). The accuracy, sensitivity and linearity of CTC detection by this method has been previously established (98).

Clinical studies of CTCs in humans with cancer: Using this system, Cristofanilli et al. show in a prospective study, that CTC detection provides significant prognostic information for patients with metastatic breast cancer (103). In this pivotal study, the detection of >5 CTCs per 7.5 mL of blood at the start of chemotherapy and after each cycle of therapy was associated with shorter progression-free and overall survival for patients with metastatic breast cancer. Another related study in metastatic breast cancer revealed that CTC counts are more predictive of outcomes than the standard clinical parameters (104). The CellSearch system and reagents have now been Food and Drug Administration–cleared for routine clinical use in metastatic breast, colorectal, and prostate cancer. Recent studies using this technology in prostate cancer also show that a count of >5 CTCs per 7.5 mL of blood is associated with poor overall survival, in this case in patients with metastatic PC (105, 106). Furthermore, in a subset of CRPC patients, the presence of CTCs was shown to be the most significant parameter predictive of survival in both univariate and multivariate analyses (105). These single institution findings have been confirmed with a multi-centered study (Moreno et al., American Society of Clinical Oncology 2007Annual Meeting), leading to an application for FDA approval in prostate cancer. Finally, it has been demonstrated that CTC's isolated using this technology can be analyzed with immunohistochemistry, immunofluorescence, and FISH analysis, which has confirmed the neoplastic nature of these cells and demonstrated amplification of the androgen receptor (107). For these reasons, we believe this technology is the most advanced, sensitive, and appropriate for our CTC study. We will perform cell counting on 7.5 mL samples at baseline, 1 month (pre-J591 for that arm), 2 months, and at 6 months. We will analyze baseline levels (< 5 CTCs/7.5 mL blood vs $\geq$5) as well as changes with treatment for associations with PSA response and time to development of radiographically evident metastatic disease.

WCMC studies using CTCs in prostate cancer: We have been using the CellSearch system to count CTCs. However, using this methodology the enumerated CTCs cannot be retrieved for any further molecular analysis. Thus, we have collected an additional sample of blood which is subjected to automated immunomagnetic selection using the CellSearch profile kit allowing us to selectively collect the EpCAM-positive cells without any additional staining. Following isolation, isolated tumor cells may be assessed using a variety of methods. Since PSMA expression is universal, there has not been any selection of patients treated on any of our clinical trials utilizing J591. We will explore the utility of assessment of PSMA expression by immunohistochemistry (scored in quantitiative fashion) of pre-treatment CTCs with relationship to response to Lu-J591.



PSMA staining in CTCs isolated from the blood of a CRPC patient. T**he EpCAM-enriched cells** were isolated from the blood of CRPC patients and were further immunostained for PSMA (J591) and DAPI. **Left Panel:** Phase image of the ferrobead captured cells, showing the ferrobead loacation and the overall cell integrity. **Middle Panel:** PSMA immunostaining shows a distinct cell-membrane localization. **Right Panel**: Merged image of PSMA and DAPI staining. The diameter of the depicted cells is approximately 15 um.

2.4.4 Patient Reported Outcomes

Quality of life has not been well-described in men with non-radiographically evident CRPC. In addition, while the appearance of radiographically-evident metastatic disease is generally agreed to be a negative prognostic event, studies assessing the initial appearance of metastases have only sub-optimally examined patient symptoms.

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire is a validated tool to assess both global and prostate cancer specific symptoms and quality of life. The FACT-P (version 4) questionnaire will be completed by subjects at baseline and at each radiographic assessment timepoint (prior to results).

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate.

3.1.2 Biochemical progression (rising PSA) after medical or surgical castration

- Subjects who have received antiandrogens (such as bicalutamide) and have experienced PSA decline must have biochemically (PSA) progressed following discontinuation of anti-androgen therapy.
- **PSA**: An increase in PSA determined by two separate measurements taken at least one week apart and confirmed by a third, and if necessary, a fourth measurement. If the third measurement is not greater than the second measurement, then a fourth measurement must be taken; the fourth measurement must be greater than the second measurement for the patient to be eligible for enrollment in the study. Furthermore, the confirmatory PSA measurement (i.e., the third or, if applicable, fourth PSA measurement) must be ≥ 1 ng/mL with prior prostatectomy or ≥ 2 ng/mL without prostatectomy and ≥ 25% above the previous nadir.

3.1.3 High risk of systemic progression defined as:

- Rising PSA as defined above and either:
  - Absolute PSA > 20 ng/mL
    AND/OR
  - PSA DT < 8 months

    PSA doubling time (PSA-DT) will be calculated using a linear regression model. In the model, the logarithm of PSA will be modeled as a linear function of time. The PSA-DT will be calculated as the product of log 2 multiplied by the reciprocal of the slope of the regression equation, for which the logarithm is the natural log function. For standardization purposes across sites, a web-based PSA doubling time calculator developed by Memorial Sloan Kettering, is available at http://www.mskcc.org/mskcc/html/10088.cfm

The minimum PSA value for eligibility will be greater than or equal to 1 with prior prostatectomy or at least 2 ng/mL without prostatectomy. All PSA values of at least 0.1 ng/mL over the past 6 months must go into the equation. A minimum of 3 PSA values with a minimum of 2 weeks between assessments is required (the screening PSA may be used for the 3rd value if necessary).

3.1.4 No evidence of local recurrence or distant metastases within 1 month of enrollment (or following enrollment as part of screening) including:

- Radionuclide bone scan without evidence of metastatic disease
    - In the event of an equivocal bone scan, confirmation is needed with Xray, CT scan, or MRI
- CT or MRI of abdomen/pelvis without evidence of metastatic disease or recurrent disease in the prostate or prostate bed
- If no prior prostatectomy or radiation to the prostate, multiparametric MRI (mpMRI) of the prostate must have been performed and scored with PIRADS v2. The PIRADS score must be <3. (Appendix H: Summary of PIRADS V2 Scoring). mpMRI must be performed within 30 days prior to randomization.
- Chest Xray or CT of chest without evidence of metastatic disease
- Digital rectal exam (DRE) without clinical suspicion of recurrent/persistent prostate cancer

3.1.5 Age ≥18 years.

3.1.6 Serum testosterone ≤ 50 ng/ml

3.1.7 The effects of J591 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, patients capable of fathering children must agree to use an effective method of contraception for the duration of the trial.

3.1.8 Subjects on bisphosphonate therapy or denosumab must be on a stable dose and must have started therapy ≥ 4 weeks prior to protocol therapy. Initiation of bisphosphonate therapy or denosumab is not allowed during the treatment phase.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Use of red blood cell or platelet transfusions within 4 weeks of treatment

3.2.2 Use of hematopoietic growth factors within 4 weeks of treatment

3.2.3 Prior cytotoxic chemotherapy and/or radiation therapy within 4 weeks of treatment

3.2.4 Prior radiation therapy encompassing >25% of skeleton (see Appendix C)

3.2.5 Prior treatment with ^{89}Strontium or ^{153}Samarium containing compounds (e.g. Metastron®, Quadramet®)

3.2.6 Platelet count <150,000/mm^3 or known primary qualitative platelet disorder

3.2.7 Absolute neutrophil count (ANC) <2,000/mm^3

3.2.8 Hematocrit <30 percent and Hemoglobin < 10 g/dL

3.2.9 Abnormal coagulation profile (PT or INR, PTT > 1.3x ULN) unless on therapeutic anticoagulation – see concomitant meds section

3.2.10 Serum creatinine >2.5 mg/dL

3.2.11 AST (SGOT) >2x ULN

3.2.12 Bilirubin (total) >1.5x ULN; subjects with Gilbert's syndrome will be allowed if direct bilirubin is within institutional normal limits

3.2.13 Active serious infection

3.2.14 Active angina pectoris or NY Heart Association Class III-IV

3.2.15 ECOG Performance Status > 2

3.2.16 Life expectancy <12 months

3.2.17 History of deep vein thrombosis and/or pulmonary embolus within 1 month of study entry

3.2.18 Other serious illness(es) involving the cardiac, respiratory, CNS, renal, hepatic or hematological organ systems which might preclude completion of this study or interfere with determination of causality of any adverse effects experienced in this study

3.2.19 Prior investigational therapy (medications or devices) within 4 weeks of treatment. Furthermore, other investigational therapy is not permitted during the treatment phase.

3.2.20 Prior use of ketoconazole for the purposes of prostate cancer therapy for greater than 1 month

3.2.21 Known history of HIV.
The effects of J591 are unknown in this population. Furthermore, ketoconazole has many well-described drug-drug interactions which could affect antiviral therapy. If necessary, this population will be studied separately.

3.2.22 Currently active other malignancy other than non-melanoma skin cancer.
Patients are considered not to have "currently active" malignancy if they have completed any necessary therapy and are considered by their physician to be at less than 30% risk of relapse.

- Known history of known myelodysplastic syndrome

3.2.23 Adrenal hormone inhibitors (other than ketoconazole) within 4 weeks prior to study enrollment.

3.2.24 Finasteride (Propecia® or Proscar®) or dutasteride (Avodart®) within 4 weeks of enrollment.

3.2.25 Patients on corticosteroids prior to enrollment must have either discontinued and shown biochemical progression or have biochemical progression on a stable dose

4. ENROLLMENT AND REGISTRATION PROCEDURES

4.1 Enrollment Procedures

4.1.1 Identification of subjects
Potential subjects will be recruited from the oncology, urology, and radiation oncology practices of participating institutions and affiliates. Public advertisements will be allowed if approved by WCMC and the local IRB. Pre-screening of potential subjects may be performed by investigators or delegates under their direct supervision. Investigational sites may elect to obtain waiver of HIPAA for pre-screening purposes.

4.1.2 Consent process
Potential subjects will have a discussion with the investigator/delegate including the rationale for the study, investigational nature of the protocol and study drug and the voluntary nature of participation, potential risks and benefits, alternatives to participation, and study procedures. Individuals will have the opportunity to read the written informed consent document at their leisure (preferably outside of the clinical area for > 1 day) and the opportunity to have questions answered in a private location with the understanding that should they decide not to participate, they will still be able to receive any available therapy off-trial. Potential subjects will also have the

opportunity to obtain the advice of their treating physician. Investigators or delegates under their direct supervision will verify the subject's understanding of the investigational and voluntary nature of the study, the potential risks and benefits, study procedures, and alternatives prior to signing of the written informed consent.

Documentation of the consent process and that written consent was conducted must be documented in the subject's medical record.

4.2 Central Patient Registration

Patients will be centrally registered with the Weill Cornell Medical College (WCMC), Division of Hematology and Medical Oncology Clinical Research Office. To register a patient, upload the following documents into a pdf file(s) and email to guonc@med.cornell.edu (note that this email address will not accept emails larger than 4.5 MB in size, so large size files may need to be split). If scan/email is not readily available, fax to the Clinical Research Office at 646-962-1611. Fax should be followed by phone call or email to ensure receipt.

- WCMC Patient Enrollment Form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form (if separate from the consent document)
- Eligibility checklist signed and dated by investigator and research nurse
- Source documents verifying eligibility including
  i. Pathology report confirming diagnosis
  ii. Laboratory reports confirming PSA progression
  iii. Radiology reports, bone scan, CT/MRI scan of abdomen/pelvis and Chest x-ray or CT scan
  iv. Laboratory reports confirming all required eligibility criteria have been met
  v. On-study visit note documenting PS and consenting process
- Documentation of any eligibility waivers granted

Central registration information is reviewed and entered into the HemOnc centralized research database. These documents should be emailed (or faxed if email is not feasible) Monday to Friday from 9:00 AM to 4:45 PM EST. Patients will be assigned a sequence number for the protocol. The registering institution will then be faxed a copy of the sequence number as confirmation of a completed registration.

Registration of patients cannot occur until the Coordinating Center has received proper documentation from the registering institution of IRB approval, including a copy of the current approval letter, stamped consent and signed FDA-1572 form. These documents may be emailed to guonc@med.cornell.edu or faxed to the Coordinating Center at 646-962-1611.

5. TREATMENT PLAN

5.1 **Agent Administration**

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for ketoconazole and hydrocortisone are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Ketoconazole (all subjects)

Ketoconazole (Nizoral) will be prescribed at a dose of 400 mg (two 200 mg tabs) to be taken orally (preferably on an empty stomach) three times per day (total daily dose of 1200 mg). For subjects on chronic gastric acid suppressive therapy (chronic administration of proton pump inhibitors or H2 blockers), ketoconazole should be taken with cola or orange juice. The cost of the drug will be billed to the subject's insurance company.

5.1.2 Hydrocortisone (all subjects)

Hydrocortisone (Cortef) will be prescribed at a dose of 20 mg orally each morning, 10 mg orally each evening (total daily dose of 30 mg). The cost of the drug will be billed to the subject's insurance company.

5.1.3 Radiolabeled J591

Eligible patients will receive a single dose of ^{177}Lu-J591 (70 mCi/m^2) or ^{111}In-J591 (5 mCi) on a Thursday or Friday approximately 4 weeks after cycle 1, day 1 consisting of J591 chelated at a specific activity of 12-15 mCi of ^{177}Lu per mg of antibody plus sufficient non-radiolabeled, non-DOTA-conjugated ("naked") J591 to achieve a total antibody dose of 20 mg. Each dose will be administered by an IV infusion at a rate not to exceed 5 mg/min.

5.1.3.1 Radiolabeled-J591 pre-medications

It is suggested that subjects receive pre-medications prior to J591 infusion with diphenhydramine 25 – 50 mg p.o. or IV and acetaminophen 325 – 650 mg p.o.

5.1.3.2 Monitoring post- radiolabeled-J591 infusion

During and after infusion, patients will be monitored for possible allergic reaction. Allergic events will be managed as follows: rash, pruritis, urticaria and wheezing will be treated with diphenhydramine hydrochloride, meperidine and/or steroids as clinically appropriate. Anaphylaxis or anaphylactoid signs or symptoms will be treated with steroids and/or epinephrine as clinically indicated. Patients will be treated in a facility that is equipped for cardiopulmonary resuscitation. Infusion-related reactions (fever, rigors) will be treated with acetaminophen, meperidine and diphenhydramine hydrochloride as clinically appropriate.

5.1.3.3 Vital signs pre/post radiolabeled J591 infusion

Vital signs (temperature, heart rate, blood pressure, respiratory rate) should be documented 0-30 min prior to infusion. 12-18 minutes following infusion of study

drug, temperature, heart rate and blood pressure should be documented. Heart rate, blood pressure, and respiratory rate should then be documented at least every 15 minutes x3, then every 30 minutes x2. In addition to baseline and at 15 min, temperature should be documented at least hourly x2 following infusion of study drug. Subjects experiencing Gr > 0 infusion reactions at 2 hours post-infusion should be monitored for an additional hour. Additional vital signs may be performed at the discretion of the study team. Detailed instructions for vital signs are as follows:
Pre-infusion (0-30 min before infusion): temperature, HR, BP, RR
[Infusion will last a minimum of 4 minutes]
Post infusion #1 (15 min +/-3 following end of infusion): temperature, HR, BP, RR
Post infusion #2 (30 min +/-3 following end of infusion): HR, BP, RR
Post infusion #3 (45 min +/-3 following end of infusion): HR, BP, RR
Post infusion #4 (60 min +/-5 following end of infusion): temperature, HR, BP, RR
Post infusion #5 (90 min +/-5 following end of infusion): HR, BP, RR
Post infusion #6 (120 min +/-10 following end of infusion): temperature, HR, BP, RR

5.1.4 Castration
All subjects who have not been surgically castrated will continue to receive LHRH agonist/antagonists to maintain chemically castrated state (goal testosterone < 50) as part of standard care. Examples of acceptable medications include leuprolide and goserelin.

5.2 General Concomitant Medication and Supportive Care Guidelines

All medications that are administered during the study must be recorded in the patient's CRF and in the source documents. Concomitant medications for other medical conditions are permitted as clinically indicated subject to specific protocol requirements outlined below.

5.2.1 Excluded medications

- Aspirin and/or non-steroidal anti-inflammatory agents possessing anti-platelet activity must be discontinued if the platelet count drops below 150,000. These medicines may be re-initiated at the discretion of the treating physician after confirmed recovery from any thrombocytopenia (after 2 consecutive rises with $2^{nd} \geq 100,000$).

- Anti-platelet medications including, but not limited to, abciximab, cilostazol, clopidogrel, dipyridamole and ticlopidine HCL should be discontinued be discontinued if the platelet count drops below 150,000. These medicines may be re-initiated at the discretion of the treating physician after confirmed recovery from any thrombocytopenia (after 2 consecutive rises with $2^{nd} \geq 100,000$).

- Anti-coagulant medications including, but not limited to, heparins (unfractionated and low molecular weight forms), coumarins (including warfarin sodium), anti-Xa inhibitors (including fondaparinux and abixaban), and direct thrombin inhibitors (including rivaroxaban) at therapeutic doses when platelet count $<50,000/mm^3$. These medications may be re-initiated

upon confirmed recovery of thrombocytopenia (after 2 consecutive rises with the 2nd above 75,000)

- Any investigational mAb based therapy not covered in this protocol. Note that "approved" monoclonal antibody therapy such as denosumab is allowed provided that subjects have initiated therapy and are on a stable dose/schedule at least 1 month prior to enrollment.

- Medication to support platelet count (such as oprelvekin (Neumega®), romiplostim (Nplate), eltrombopag (Promacta)).

- Patients on drugs known to be metabolized by the cytochrome P450 system (specifically CYP 3A4) should be cautioned about potential interactions with ketoconazole. Specifically, cisapride, terfanadine and astemizole are contraindicated (see black box warning in product's label). Any such interactions should be discussed with the patient's treating physician.

5.2.2 Myelosuppression guidelines

5.2.2.1 Thrombocytopenia – monitoring guidelines

- Based upon previous studies, the expected time of platelet nadir is expected to be 4-5 weeks after Lu-J591 infusion. Physicians should search for additional causes of thrombocytopenia when suspected, especially if the platelet count falls < 3 weeks before or > 8 weeks after Lu-J591 infusion.

- During periods of time when the platelet count is < 25,000/mm^3, platelet counts must be monitored <u>at least</u> twice per week.

5.2.2.2 Thrombocytopenia – transfusion guidelines

- Per ASCO guidelines (108), prophylactic platelet transfusion is recommended at a threshold platelet count of 10,000/mm^3.

- Physicians should use their clinical judgment in determining the need for platelet transfusions for the non-bleeding subject with a platelet count > 10,000/mm^3, including factors such as platelet kinetics or factors that might alter platelet kinetics such as fever.

5.2.2.3 Neutropenia – growth factor guidelines

- Per ASCO guidelines (109), WBC growth factors are not recommended for afebrile neutropenia. However physicians may consider prophylaxis with filgrastim or pegfilgrastim for those subjects with severe neutropenia and known risk factors for neutropenic complications, including age > 65. Sargramostim (GM-CSF) should not be used because of its effect against

prostate cancer (110-114), including in combination with ketoconazole in this patient population (115).

5.3 Duration of Therapy and Criteria for Removal From Study

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Development of metastatic disease / Disease progression*,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to discontinue treatment,
- Subject decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

* Subjects with biochemical progression only (rising PSA) should be encouraged to remain on study as long as there is no medical contraindication. Subjects who receive subsequent anti-cancer therapies prior to development of radiographic metastases should continue protocol follow up every 3 months (including scans). Subjects who withdraw from treatment to receive investigational agents should be encouraged to allow reporting of follow up of the primary and secondary endpoints such as development of metastatic disease and death. Subsequent anti-cancer therapies will be documented.

5.4 Duration of Follow Up

Patients will be followed for 3 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Ketoconazole

Subjects experiencing grade 3 or 4 non-hematologic toxicities will have ketoconazole held until resolution to $\leq$ grade 1 (The toxicity should be at least probably related to ketoconazole and does not need to be held if toxicity is unrelated). Subjects experiencing $\geq$ grade 3 non-hematologic toxicity that does not resolve to $\leq$ grade 1 within 4 weeks will be removed from ketoconazole therapy. Subjects experiencing resolution to $\leq$ grade 1 may resume ketoconazole at a lower dose (dose level -1). Further grade $\geq$ 3 toxicities will result in permanent discontinuation of ketoconazole. Dose reduction or discontinuation of ketoconazole for other reasons should be discussed with the study chair.

Dose Level	Agent / Dose
-1*	Ketoconazole 200 mg tabs 1 tab p.o. TID
0	Ketoconazole 200 mg tabs 2 tabs p.o. TID

Subjects who require dose reduction of ketoconazole will have hydrocortisone continued or discontinued at the discretion of the investigator. Should subjects discontinue hydrocortisone, the dose should be tapered (suggestion: taper by 5 mg every three days).

7. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

7.1 **Investigational Agent Risks**

7.1.1 ^{177}Lu-J591 (No additional risks expected from ^{111}In-J591)

Radiolabeled J591 is likely to cause thrombocytopenia and/or neutropenia as well as anemia. Mild to moderate infusion reactions (fever, chills, rigors) are occasionally seen after administration. The following risks are possible after treatment with this experimental drug: allergic reactions, rash, hypotension, hypertension, renal insufficiency, liver enzyme elevations (ALT and/or AST), difficulty breathing and human anti-humanized antibody (HAHA) response.

Precautions/monitoring:

Subjects should receive pre-medication prior to Lu-J591 infusion as described in Section 5.2.3.1. During and after infusion, patients will be monitored for possible allergic reaction. Allergic events will be managed as follows: rash, pruritis, urticaria and wheezing will be treated with diphenhydramine hydrochloride, demerol and/or steroids as clinically appropriate. Anaphylaxis or anaphylactoid signs or symptoms will be treated with steroids and/or epinephrine as clinically indicated. Patients will be treated in a facility that is equipped for cardiopulmonary resuscitation. Infusion-related reactions (fever, rigors) will be treated with acetaminophen, meperedine and diphenhydramine hydrochloride as clinically appropriate.

7.1.2 Ketoconazole

The most common side effects are weakness or lack of strength, gastrointestinal complaints such as nausea or vomiting, liver toxicity, skin reactions, and a potential risk of adrenal suppression.

Precautions/monitoring:
Subjects should take ketoconazole as described in Section 5.2.1. . Regular monitoring of liver enzymes is required. Ketoconazole is metabolized by the cytochrome P450 system and is a 3A4 substrate/inhibitor. Caution should be used with subjects on other medications metabolized by this system. Fatal arrhythmias have been reported in patients taking ketoconazole in combination with certain medications. See excluded medications in Section 5.2.1.

7.1.3 Hydrocortisone
Side effects of hydrocortisone include fluid retention (swelling), electrolyte imbalances (sodium and potassium), elevated glucose, elevated blood pressure, muscle weakness, bone loss, and skin changes.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - **Definite** – The AE *is clearly related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction can be confirmed with a positive re-challenge test or supporting laboratory data.
  - **Probable** – The AE *is likely related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
  - **Possible** – The AE *may be related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
  - **Unlikely** – The AE *is doubtfully related* to the study treatment. The current state of knowledge indicates that a relationship is unlikely.
  - **Unrelated** – The AE *is clearly NOT related* to the study treatment. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.

7.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

7.4 Serious Adverse Event (SAE) Reporting

7.4.1. Definition of SAE

A serious adverse event **(SAE) is any adverse event, occurring at any dose and regardless of causality that:**

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but

would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.4.2. Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the policies of the local IRB. For WCMC patients, reportable SAEs will be reported on the institutional SAE reporting form and comprehensive AE & IND Reporting table. These forms may be downloaded at

http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

For all other institutions: SAE's will be reported to the local IRB per the institutional guidelines.

7.4.3. Reporting of SAE to Weill Cornell Medical College

Institution will notify Weill Cornell Medical College of all serious adverse events that occur within 24 hours of investigator notification by contacting Dr. Scott Tagawa's office at 646-962-2072. A written SAE report should be filed with the local IRB in accordance with the institutional guidelines. The following forms must be emailed to guonc@med.cornell.edu and/or faxed to Weill Cornell Medical College Clinical Trials Office at 646-962-1611 within five (5) business days of investigator notification:

- Completed MedWatch Form
- Completed WCMC SAE Cover Sheet

Note that specified AE/SAE's such as thrombocytopenia or bleeding are required to be reported within 24 hours. The Principal Investigator and Medical Monitor will review all SAEs and copies of all SAEs will be electronically distributed to all participating site for submission to the local IRB.

7.4.4. Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. All completed MedWatch forms will be sent to WCMC for submission to the FDA.

7.5 Secondary AML/MDS

Myelodysplastic syndrome and acute myeloid leukemia has been reported in patients previously treated with anti-CD20 based RIT for non-hodgkin's lymphoma. Some case reports and small series have raised concern for this phenomenon after RIT (116). However, given the increased incidence of MDS/AML in this population, either because of their underlying illness or of their exposure to previous cytotoxic therapy (especially alkylating agents), there is no good evidence

to suggest that there is a significantly increased risk than of a similar population of patients not receiving RIT (117, 118). However, based upon the theoretical increased risk, the incidence of MDS/AML during follow up will be noted and used to increase the investigators' experience and knowledge. Any suspected potential increased risk of MDS/AML will be reported to the IRB and DSMB.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with radiolabeled J591 can be found in Section 7.1.

8.1 Investigational Agent (IND#11,613)

Radiolabeled J591 (**^{177}Lu -J591** and **^{111}In-J591**) are an investigational agents supplied to investigators by Weill Cornell Medical College. Ketoconazole and hydrocortisone are commercially available and should be prescribed as indicated above (see Section 5.1).

8.2 Radiolabeled J591 Ordering

Upon enrollment, sites will notify the WCMC Study Coordinator of the proposed D29 radiolabeled J591 infusion date. The WCMC Study Coordinator will arrange for shipment of the radiolabeled antibody to the treatment site. After confirmation of the date of infusion at the D15 telephone follow up, the site will confirm treatment date with the WCMC Study Coordinator and shipment to the site's nuclear medicine department will be confirmed.

8.3 **Drug Accountability**

The case report forms relating to the preparation, quality control and drug accountability will be completed by the radiochemists in nuclear medicine.

Test articles:
a) mAb HuJ591, 5 mg/ml (non-radioactive, non-DOTA conjugated naked antibody),
b) DOTA-HuJ591-GS, 8.0 mg/ml (non- radioactive antibody for labeling with ^{177}Lu)

Storage: The primary inventory of test articles is stored at Goodwin Biotech, Plantation, FL, a cGMP, FDA-approved facility. This storage facility is monitored around the clock and is equipped with back-up power generators in the event of a power outage. Periodically, as needed, vials of the test articles are shipped to WMC Urologic Oncology where they are stored in a locked, monitored, centrally alarmed refrigerator. Access to the storage area in WMC Urologic Oncology is limited by ID card-required access and a locked refrigerator with a key controlled by the WMC Urologic Oncology Lab administrator (Lana Winter).

Inventory: An official inventory record is kept and updated in real time. On the day of radiolabeling and dose administration to the patient, the radiochemists remove the test articles from the refrigerator and record the number of vials removed from the inventory

and the number remaining in the official inventory record. These records are kept in WMC Urologic Oncology.

The "test article", ^{177}Lu-J591, is prepared by the radiochemists in the Nuclear Medicine laboratory. The radionuclides are received and stored in the nuclear medicine department according to the procedures established by the Institutional Radiation Safety Office. The radiolabeling and quality control data on radiochemical purity, immunoreactivity, sterility and pyrogenicity tests are kept in nuclear medicine. Radiolabeled antibody preparations are kept refrigerated until use.

Disposal: Unused radiolabeled antibody preparations are stored in lead containers for decay and subsequently disposed of according to standard radiation safety guidelines. Unused non-radioactive antibody vials and partially used vials (test articles) are destroyed or recycled to the WMC Urologic Oncology research lab for non-clinical research purposes.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

Additional Correlative Tests will be performed during the trial and will be centrally analyzed.

Only the materials (tubes, shipping box, FedEx airbill) for CTC counts via CellSearch methodology will be provided to the site following site activation. Additional materials should be requested directly by emailing GUONC@med.cornell.edu. The site should use their own supplies for the remainder of the tests.

A unique ID (number) for the Adrenal Androgen, CTC, Plasma markers, Archival Tumor, and HAHA samples will be provided by WCMC via email. Please contact GUONC@med.cornell.edu prior to the date of sample collection (if possible) for the unique ID. Please use the number provided to write it on the label and the lab requisition. The material shipment for these samples should be provided by site.

Please notify GUONC@med.cornell.edu when shipping samples, and provide the tracking number. A Requisition form should be completed (as described in the Lab Manual) detailing the samples that are being shipped for all samples except the CTC counts via CellSearch methodology.

Note: Plasma markers (9.1.2) are the only tests that are optional. All other correlative samples are required. The collection of archival tissue may be waived if no tissue is available.

9.1.1 Adrenal Androgen Levels

Serum levels of adrenal androgen levels will be obtained at screening (any time following consent and prior to therapy initiation on C1D1), Cycle 2 Day 1, and at the

time of PSA progression. Collect 10 mL of peripheral blood in a yellow (SST) or red top tube. Label samples with the unique sample number that will be provided by the Weill Cornell Medical College study coordinator to ensure that laboratory personnel will be blinded to subject and clinical data.

Please refer to the Lab Manual for further details on collecting, handling and shipping of adrenal androgen samples.

9.1.2 Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis (optional)

Plasma samples will be collected on C1D1 prior to therapy (may be collected as part of screening within 1 week of C1D1), Cycle 2 Day 1 (prior to J591 administration), Cycle 3 Day 1, at PSA progression, and at end of study. Refer to the Lab Manual for further details on collecting blood samples for plasma markers. Samples will be labeled with a unique sample ID number to ensure that laboratory personnel will be blinded to subject and clinical data.

Refer to the Lab Manual for details on handling and shipping of blood samples for plasma markers.

* Plasma markers are the only tests that are optional.

9.1.3 Circulating tumor cells

Circulating tumor cells (CTCs) will be assessed in the following manner:
- CTC counts via CellSearch methodology
- CTC analysis for research

9.1.3.1 Collection of specimens for CTC counts (enumeration) via CellSearch Methodology:

Kits (including requisition and FedEx airbill) will be provided for CTC samples for counts via CellSearch methodology. At specified time points [baseline C1D1 prior to ketoconazole, C2D1 (prior to Lu-J591), C3D1, at the time of PSA progression, and at end of study] samples for CTC count via CellSearch methodology will be collected. Use the label from the requisition and place it on the tube to ensure that laboratory personnel will be blinded to subject and clinical data. The name should be the unique ID provided by WCMC coordinator (**NOT** the patient name). Refer to the Lab Manual for further details on collecting, handling and shipping of blood samples for CTC counts via CellSearch methodology.

9.1.3.2 Collection of specimens for CTC analysis for research:

At specified time points (screening/baseline at C1D1 prior to treatment and at end of study), blood samples will be collected as described in the Lab Manual. No Kit will be provided for this test, sites should use their own materials. Samples will be labeled

with a unique sample ID number to ensure that laboratory personnel will be blinded to subject and clinical data.
Refer to the Lab Manual for further details on handling and shipping of blood samples for CTC analysis for research.

9.1.3 Human Anti-Humanized Antibody (HAHA) specimen:

Blood samples will be collected at screening and EOS. Refer to the Lab Manual for further details on collecting, handling and shipping of blood samples for HAHA.

9.1.4 Archival Tumor PSMA expression

9.1.4.1 Specimens

At the screening visit, paraffin-embedded tumor blocks or 10 unstained slides with representative tumor tissue will be collected as described in the Lab Manual. Samples will be labeled with a unique sample ID number to ensure that laboratory personnel will be blinded to subject and clinical data.

For shipping instructions, please refer to the Lab Manual.

9.2 **Special Studies**

9.2.1 Radiolabeled-J591 Imaging

9.2.1.1 Assessment

9.2.1.1.1 Method of Assessment:

Planar imaging will be performed 2-8 days after radiolabeled-J591 administration (scan window will be assigned at randomization). In the case of a suspicious lesion, SPECT of the area may be performed at the nuclear med physician's discretion. In addition a CT/MRI may be obtained for possible confirmation. Identified sites will be followed on subsequent imaging modalities (bone scan, CT or MRI) to define the interval between identification of the lesion/s by radiolabeled-J591 versus other modalities. Images will be captured as specified in the Imaging Manual and provided to WCMC on disc in dicom format.

9.2.1.1.2 Timing of Assessment

J591 scanning will be performed approximately 2-3 or 6-8 days after J591 administration (scan date will be assigned with randomization). Scans will be assessed centrally at WCMC.

10. STUDY CALENDAR

The study flow chart, including all procedures to be performed during the study, is presented below. Prior to engaging in any study procedure, each patient must sign and date an informed consent form.

Baseline evaluations are to be conducted within *1 week* prior to administration of protocol therapy. Scans and x-rays must be done *within one month* of enrollment (or following enrollment as part of screening).

	Screening Period												
	V1	**V2**	**V3[8]**	**V4**	**±**	**V5**	**V6**	**V7**	**V8**	**V9**	**F/U[14]**	**PSA progression**	**EOS[11]**
Study Procedure	Day -28 to -1	C1D1	C2D1	C2 D3-9	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	Every 4 weeks		
Informed consent	X												
Medical History	X	X[++]	X[++]			X[++]				X[++]	X[++]	X[++]	X[++]
Physical Exam (PE)-Complete	X											X	X
PE – Targeted[9]		X	X			X				X	X		
Vital Signs[10]	X	X	X[+]			X				X	X	X	X
Demographics	X												
Previous Therapy Report	X												
Performance Status	X	X	X			X				X	X	X	X
Height, weight	X	X	X			X				X	X	X	X
CBC with differential + platelet count[2,3]	X	X	X		±	X	X[3]	X[3]	X[3]	X	X	X	X
PT or INR, PTT	X												
Electrolytes, BUN, Creatinine	X	X	X			X				X	X	X	X
Total protein, albumin, calcium	X		X			X				X	X	X	X
total bilirubin, AST	X		X			X				X	X	X	X
ALT, LDH, Alk Phos	X		X			X				X	X	X	X
PSA[4]	X	X	X			X				X	X	X	X

Testosterone	X											X	X
Urinalysis	X												
Human anti-J591antibody	X												X
EKG	X												
CT or MRI (abdomen-pelvis)[1]	X										X		
Bone Scan[1]	X										X		
CXR[1]	X										X		
J591 scan				X*									
Adverse Events	X	X	X	X		X				X	X	X	X
FACT-P[13]		X[13]									X[12]	X[12]	X[12]
Concomitant Medications	X	X	X			X				X	X	X	X
Concomitant Procedures		X	X			X				X	X	X	X
^{111}In/^{177}Lu-J591 Administration			X[12]										
Ketoconazole/ Hydrocrotisone[7]		X	X	X		X	X	X	X	X	X	X	
Plasma Markers		X	X			X						X	X
Circulating Tumor Cells[5]		X	X			X						X	X
Adrenal Hormones		X[6]	X[6]									X[6]	
Archival Tissue	X												

A phone assessment will be performed on D15 +/- 3 days to assess compliance and toxicity of ketoconazole/hydrocortisone.
± CBC on D50 +/- 2 days is required for pts on anticoagulation or NSAIDS, suggested in pts with baseline plt count < 200

*J591 scan may be done 2-8 days after infusion (date will be assigned upon randomization). SPECT studies of sites of disease will be obtained in selected patients as necessary.
+ vital signs to be taken prior to infusion and post-infusion as per Section 5.1.3.3
++ interval medical history
[1] Baseline radiographic evaluation should be performed within one month of enrollment (or following enrollment as part of screening). Subsequent scans (CT/MRI abd/pelvis, CXR (or CT chest), and bone scan) should be performed every 6 months until PSA progression, then every three months thereafter unless clinically indicated sooner.
[2] CBC repeated twice a week when platelets <25,000/mm^3 and/or ANC <500/mm^3
[3] CBC's not associated with study visits may be performed at any CLIA certified laboratory
[4] The same lab should be used for all study PSA's if possible
[5] CTC counts via CellSearch (using kit) at C1D1 prior to ketoconazole, C2D1 (prior to Lu-J591), C3D1, at the time of PSA progression, and at end of study. Additional blood samples for CTC analysis for research will be drawn.at C1D1 prior to treatment and at end of study
[6] Adrenal hormone levels should be drawn prior to starting treatment on Cycle 1, Day 1, 1 month, and at PSA progression
[7] Starting after C1D1 assessment and blood draw until toxicity, investigator, or patient decision as per Sections 5.2.1, 5.2.2, 6.1. Distribute medication diary at the beginning of each cycle.
[8] Visit 3 (C2D1): Targeted physical exams can be completed the day prior to the scheduled J591 infusion date.

[9] All references to targeted physical exams throughout the protocol include a heart and lung examination, as well as evaluation of any abnormalities found during the complete physical exam performed at screening

[10] Vital signs include temperature, heart rate, blood pressure, and respiratory rate.

[11] The End of Study Visit occurs when patient shows evidence of metastatic disease. Patient remains on trial until documented metastatic disease. In addition to scans a biopsy can be performed to prove metastatic disease. Patient can receive additional therapy prior to showing metastatic disease and still remain on trial. Site will be asked for information regarding the additional therapy in the case report forms.

[12] In the event that the J591 infusion is delayed, cycle 1 will be extended until the date of the J591 infusion. The date of the J591 infusion will be considered Cycle 2, Day 1.

[13] The FACT-P questionnaire should be completed after enrollment, but prior to therapy (on C1D1 prior to ketoconazole). Questionnaires should also be completed at each radiographic assessment point (q6 months prior to PSA progression, q3 months after PSA progression) – may be performed just prior to scan, on day of scan, or after scan, but BEFORE results of scans are discussed. In addition, FACT-P will be completed at PSA progression and EOS

[14] Follow up is at least every 4 weeks while on ketoconazole and until study drug toxicities have resolved (with the exception of anemia). Following discontinuation of ketoconazole, follow up is at least every 12 weeks (or 3 months)

10. 1 STUDY PROCEDURES: Schedule of Events

The assessments to be performed during the study are outlined below by study period, visit and day. Study assessments through Visit 9 (Day 85) will be completed within ±3 days of the specified day for the visit, except where noted. Visits after Day 169 will be performed within ±7 days of the scheduled visit.

Screening Period (Visit 1, Days -28 to -1) – All subjects
The procedures outlined for Visit 1 must be completed prior to the patient receiving study drug. The following procedures will be conducted at Visit 1:

- Informed Consent
- Medical History
- Concurrent medications
- Complete Physical Exam
- Vital Signs
- Demographics
- Previous therapy
    - Surgical report will include date and type of surgery +/- lymphadenectomy
    - Radiotherapy report will include modality of therapy with prescribed dose and field and dates of therapy
    - Previous hormonal therapy – drugs, doses, dates of therapy
        - Continuous vs intermittent therapy
- ECOG Performance Status
- Height, Weight
- CBC with differential and platelet count.
- PT or INR, PTT
- Electrolytes, BUN, Creatinine
- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- PSA
- PSA DT Calculation

- Alkaline phosphatase
- Testosterone
- Human anti-J591 antibody sample (may also be drawn C1D1 prior to initiation of study drugs)
- Urinalysis
- Archival Tissue (section 9.1.4) - Paraffin-embedded tumor blocks or 5 unstained slides with representative tumor tissue
- EKG, up to 1 month prior to treatment
- CT or MRI (abdomen-pelvis), up to 4 weeks prior to enrollment
- Bone scan, up to 4 weeks prior to enrollment
    - Any confirmatory tests to assess equivocal results of bone scan should also be completed within 4 weeks of enrollment
    - CXR, up to 4 weeks prior to enrollment (if CT chest has been performed within 4 weeks of enrollment, this procedure is waived)

Evaluations and procedures at Visit 2 (C1D1) – All subjects
Following screening procedures, eligible patients will be dosed with ketoconazole and hydrocortisone. See Section 5.1 for details on the dose and administration.
The following assessments are to be collected prior to drug administration unless otherwise noted:

- Interval medical history
- Targeted Physical Examination with vital signs
- ECOG PS
- CBC with differential and platelet count*
- Electrolytes, BUN, Creatinine*
- PSA*
- Adrenal hormone levels
- Plasma markers
- CTC's
- Adverse Events

- Concomitant medications
- Concomitant procedures
- FACT-P questionnaire (prior to ketoconazole/hydrocortisone administration)
- Ketoconazole/hydrocortisone administration instruction (re-inforcement) – prescriptions should have been filled prior to this visit, but no drugs should have been taken prior to blood draw D1
    - Distribute Medication Diary

*Note that treatment day labs are used for baseline (not for assessment of eligibility), though subjects may be withdrawn from the study for safety concerns per the investigator's discretion.

Phone Assessment (Cycle 1, Day 15 +/- 2 days) – All subjects

- Compliance
- Toxicity screening
- Next visit reminder (confirmation of date/time of next visit with J591 infusion should also be confirmed after delivery date of drug is confirmed)

Evaluations and procedures at Visit 3 (C2D1) – All subjects
Following assessment, eligible, randomized patients who have not come off trial for toxicity or noncompliance will be dosed with radiolabeled-J591. See section 5.2.3 for details on the administration.

Note: The J591 infusion days should be scheduled on a Thursday or Friday. If needed, visits can be scheduled on a Wednesday afternoon but the earliest the site will receive drug is Wednesday at noon. Because of the nature of study drug and shipping, dosing outside of specified window should be discussed with WCMC, but will not require a protocol exception provided the date has been pre-approved by WCMC. The exact date of the J591 infusion will be confirmed 2 weeks prior. The site is not responsible for ordering the J591. WCMC will handle ordering and shipping the drug. The shipping material needs to be sent back to WCMC. A return air bill will be included with the shipment.

Note: In the event that the J591 infusion is delayed, cycle 1 will be extended. The date of the J591 infusion will be considered cycle 2, day 1.

Patients will remain at the clinical site for a minimum of 2 hours after completion of radiolabeled-J591 administration to monitor vital signs. The patient should be considered clinically stable by the investigator prior to discharge. The following assessments are to be collected prior to drug administration unless otherwise noted:

- Interval medical history

- Targeted Physical Examination
- ECOG Performance Status
- Vital Signs (pre-infusion, post infusion as per Section 5.1.3.3)
- Verification of ketoconazole/hydrocortisone administration, Collection/Distribution of diary
- CBC with differential and platelet count*
- Electrolytes, BUN, Creatinine*
- PSA*
- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- Alkaline phosphatase
- Plasma markers
- Adrenal hormones
- CTC's
- Concomitant medications
- Concomitant/interval procedures
- Adverse events (pre- and post- infusion)

*Note that treatment day labs are used for radiolabeled-J591 baseline (not for assessment of eligibility)

Evaluations and procedures at Visit 4/J591 Scan (C2D3-9)

- Adverse Events
- Concomitant medications
- Concomitant/interval procedures
- J591 imaging (2-8 days after infusion). At selected study sites, whole body planar radionuclide images will be obtained between 2-8 days post-J591treatment. The date of scan (3 or 4 days vs 6-8 days after J591 infusion) will be assigned at the time of randomization. SPECT studies of sites of disease will be obtained in selected patients as appropriate. These will be used to assess the ability of radiolabeled J591 to image

metastatic sites that do not appear on conventional imaging modalities (bone scan, CT/MRI).

Evaluations and procedures C2D22 (safety CBC for some subjects)
For subjects on aspirin/NSAIDs with anti-platelet properties or anticoagulation, a CBC on approximately Day 50 is **required** (3 weeks +/- 2 days after radiolabeled J591 infusion). For all other subjects, in particular subjects with baseline platelet counts < 200/mm^3 a CBC at this timepoint is suggested, but not required.

- CBC with differential †

Evaluations and procedures C3D1

- Interval medical history
- Targeted Physical Examination
- Vital Signs
- ECOG Performance Status
- Verification of ketoconazole/hydrocortisone administration, Collection/Distribution of diary
- Adverse Events
- Concomitant medications
- Concomitant/interval procedures
- CBC with differential and platelet count.
- Electrolytes, BUN, Creatinine
- Total protein, albumin, calcium
- Total bilirubin, AST, ALT, alkaline phosphatase, LDH
- PSA
- Plasma markers
- CTCs

Evaluations and procedures Cycle 3 D8 *†

- CBC with differential and platelet count

Evaluations and procedures Cycle 3 D15 *†

- CBC with differential and platelet count†

Evaluations and procedures Cycle 3 D22 *†

- CBC with differential and platelet count†

All CBC results during cycle 3 must be either entered into the REDCap eCRF database or emailed to guonc@med.cornell.edu within 24 hours of testing.

***Lu-J591 subjects with platelets < 25,000 and/or ANC < 500 are required to have CBC's performed <u>at least</u> twice per week until recovery to platelets > 25,000 and ANC > 500**

† Lu-J591 CBC evaluations may be performed at approved CLIA certified local laboratories with PI's pre-approval

Evaluations and procedures C4D1 – ALL PTS

- Adverse events
- Concomitant medications
- Concomitant/interval procedures
- Verification of ketoconazole/hydrocortisone administration, Collection/Distribution of diary
- Interval Medical History
- Targeted Physical Exam
- Vital Signs
- ECOG Performance Status
- Weight
- CBC with differential and platelet count.
- Electrolytes, BUN, Creatinine

- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- PSA
- Alkaline phosphatase

J591 subjects who have not yet recovered ANC > 1.5 and/or platelet counts > 150 by Visit 9 (Cycle 4 D1) will continue to have CBC's checked weekly until these criteria satisfied or until permission is granted by the Study Chair

Evaluations and procedures q4 weeks while on ketoconazole and until resolution of study drug toxicities with the exception of anemia until EOS

- Adverse events
- Concomitant medications
- Concomitant/interval procedures
- Verification of ketoconazole/hydrocortisone administration, Collection/Distribution of diary
- Interval Medical History
- Targeted Physical Exam
- Vital Signs
- ECOG Performance Status
- Weight
- CBC with differential and platelet count.
- Electrolytes, BUN, Creatinine
- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- PSA
- Alkaline phosphatase
- Other laboratory assessments and procedures as clinically indicated.

NOTE: For individual subjects deemed to be tolerating ketoconazole well, following 6 months on study (after scans) study evaluations need to be performed by official study investigators at official study sites only every 12 weeks. For those subjects who are

tolerating study drug well (in the opinion of the investigator) and for whom travel is a burden, the other two q4 week evaluations may be performed by a local lab with either local physician and/or phone assessment for adverse events (i.e. at least every third visit must be done on site by official study investigators). In this case, source documents should be collected and drug diaries may be collected by fax/mail/email. Subjects who discontinue ketoconazole for any reason may be followed every 12 weeks following resolution of ketoconazole and study drug toxicities (except anemia).

Radiographic Evaluation and Patient Reported Outcome Evaluation

- Bone scan, CT/MRI abdomen/pelvis, and CXR + FACT-P[#] at baseline
- Bone scan*, CT/MRI of abdomen/pelvis, and CXR + FACT-P[#] will be repeated every 6 months in the absence of biochemical or clinical progression
- Bone scan*, CT/MRI of abdomen/pelvis, and CXR + FACT-P[#] will be repeated every 3 months subsequent to biochemical or clinical progression
- In addition, a bone scan will be performed for subjects with clinical signs or symptoms of bone metastases at the investigators discretion

*During the first 6 months, bone scan progression requires confirmation by a 2nd bone scan. The date of progression is defined as the date of the 1st scan that is subsequently confirmed to be positive.

[#]FACT-P to be administered either prior to imaging or following imaging, but before results of scans are disclosed to subject.

Evaluations and procedures at PSA progression

Note: subjects may remain on ketoconazole/hydrocortisone beyond PSA progression at the discretion of the investigator and/or their treating physician

- Adverse events
- Concomitant medications
- Concomitant/interval procedures
- Verification of ketoconazole/hydrocortisone administration, Collection of diary
- Interval Medical History
- Complete Physical Exam
- Vital Signs
- ECOG Performance Status

- Weight
- CBC with differential and platelet count.
- Electrolytes, BUN, Creatinine
- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- Alkaline phosphatase
- PSA
- Testosterone
- Plasma markers
- CTC's
- Adrenal hormones
- Other laboratory assessments and procedures as clinically indicated.
- FACT-P

Evaluations and procedures at End of Study (EOS = development of metastatic disease on scans)

Note: subjects may remain on protocol past initial scans with evidence of metastatic disease if confirmatory scans are warranted

- Adverse events
- Concomitant medications
- Concomitant/interval procedures
- Verification of keto/hydrocortisone administration, Collection of diary (if relevant)
- Interval Medical History
- Complete Physical Exam
- Vital Signs
- ECOG Performance Status
- Weight

- CBC with differential and platelet count.
- Electrolytes, BUN, Creatinine
- Total protein, albumin, calcium, total bilirubin, AST, ALT, LDH
- Alkaline phosphatase
- PSA
- Testosterone
- Plasma markers
- CTC's
- Human anti-J591 antibody sample
- Other laboratory assessments and procedures as clinically indicated.
- FACT-P

11. MEASUREMENT OF EFFECT

11.1 Primary Endpoint: Proportion free of radiographically evident metastases at 18 months. Bone scans with <3 metastatic lesions should be confirmed with CT/MRI or a repeat scan >4 weeks after the initial scan. Should a subject require confirmatory scans, the date of radiographic progression will be the date of the initial scan showing suspicion of metastasis.

11.1.1 Metastasis-free survival

Time to development of metastatic disease will be calculated from the date of treatment to the date of the first radiographic evidence of metastatic disease. Bone scans with <3 metastatic lesions should be confirmed with CT/MRI or a repeat scan >4 weeks after the initial scan. Should a subject require confirmatory scans, the date of radiographic progression will be the date of the initial scan showing suspicion of metastasis.

11.2 Response Criteria

11.2.1 Biochemical (PSA) response

A PSA decline of ≥50% has been demonstrated to correlate with improved survival in advanced castrate disease (119). In addition, Scher, et al have demonstrated that a PSA which either declines or shows no increase from baseline at either 8 or 12 weeks after initiating therapy correlates with improved survival compared to patients whose PSA rises despite therapy (120). Both of these criteria (≥ 50% PSA decline and no increase from baseline) will be recorded.

PSA response will be determined by comparing the PSA levels after therapy to the baseline, pre-treatment PSA. A decline of ≥ 50%, confirmed by a second PSA value ≥ 2 weeks later, should be reported. Patients must not demonstrate clinical or radiographic (CT and/or MR) evidence of disease progression during this time period.
Analyses of phase III trials of docetaxel versus mitoxantrone chemotherapy in men with metastatic androgen independent prostate cancer have shown that a 30% decrease in PSA levels is most strongly associated with a treatment effect on overall survival (52, 53). A PSA decline of ≥ 30% will be assessed and used for exploratory analysis in the prediction of time to metastatic disease and overall survival.

11.2.2 Duration of PSA response
Duration of PSA response is defined as the time from the first 50% (or 30%) PSA decline until the PSA value is confirmed to increase by 25% above the nadir, provided that the increase is at least 2 ng/mL above nadir.

11.2.3 Progression (see also 11.1)

11.2.3.1 Biochemical progression
Biochemical (PSA) progression is defined as a PSA measured ≥ 12 weeks after treatment which is confirmed (by a repeat assay) to rise ≥ 25% above the baseline, pre-treatment value AND ≥ 2 ng/mL. In the case of a patient whose PSA declines after therapy, PSA progression is defined as a rise in PSA ≥ 25% above the nadir value AND ≥ 2 ng/mL. The time of progression is determined using the date of the 1st (subsequently confirmed) PSA ≥ 25% above baseline or nadir. PSA rise < 12 weeks of initiating treatment is not considered to be progression.

11.2.3.2 Time to biochemical progression
Time to PSA progression is defined as the interval between initiating treatment until the PSA rises 25% above nadir provided that the increase is at least 2 ng/mL

11.2.3.3 Time to PSA progression above baseline
Time to PSA progression above baseline will also be recorded. Time to PSA progression above baseline will be defined as the interval between initiating treatment until the PSA rises above the pre-treatment baseline by at least 2 mg/mL. PSA rise < 12 weeks of initiating treatment is not considered to be progression.

12. DATA REPORTING / REGULATORY CONSIDERATIONS

12.1 Data Collection and Monitoring

The data collection plan for this study is to utilize a user ID/password protected encrypted database created by the WCMC CTSC to capture all treatment, toxicity, and efficacy data for all enrolled patients. Electronic CRF's (case report forms) utilizing unique study ID numbers to minimize potential exposure of PHI will be completed on an ongoing basis by all sites.

The study will be monitored by Weill Cornell Medical College. Data integrity will occur via electronic and fax queries. A review of the majority of source documents to verify CRF integrity is planned for the initial subject treated at each site. Further electronically collected data will be reviewed in real time and electronic queries will be sent. Weill Cornell reserves the right to site audits as necessary. In the event this will occur, the site will be given ample notice prior to the visit.

12.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Study Chair. Weill Cornell will have the opportunity to review and approve the changes prior to submission of these changes to the Weill Cornell IRB and distribution to participating sites.

12.3 Data Safety Monitoring Board

This study will utilize the Weill Cornell Medical College (WCMC) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring this double-blinded study for safety concerns, with ongoing updates from the Study Chair on an ongoing basis. The interim analysis will be performed by the DSMB and the decision to proceed or stop the trial will be provided to the Study Chair.

The Weill Cornell DSMB is comprised of medical specialists and advisors on human rights issues in human subjects research. The DSMB currently has 9 members, meets at quarterly intervals during the year, and carries out ongoing review of protocols submitted throughout the year. Once a protocol has been submitted and approved by the Institutional Review Board (IRB) and is recommended for oversight by the DSMB, the Board determines if the protocol will be reviewed quarterly, semi-annually, or annually.

The DSMB evaluates the accumulated data from the study in order to monitor the safety of subjects throughout the trial and reviews the risks and benefits, as well as the efficacy, of the study. The DSMB will also evaluate the overall trial conduct and progress. Ultimately, the DSMB validates the continuation of the trial or determines if a study needs modification or termination.
Reports to the DSMB will include the following items for review:

1. Completed DSMB Periodic Review Form.
2. Synopsis of the study to date.
3. IRB approved consent form.
4. IRB current protocol.
5. Summary table of study results.
6. Adverse event table.
7. Data safety monitoring plan.

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subject research projects and to protect the safety of human subjects. Safety

monitoring can be viewed as any process during a clinical trial that involves the review of accumulated outcome data for groups of patient-subjects to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998, 2000) specify that all clinical trials should have a system in palce for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities will be commensurate with the nature, size, and complexity of the trial in accordance with institutional policies and will be determined after IRB and DSMB review of the protocol immediately prior to study activation. For a small, single-center study, the monitoring is usually performed by a statistician in conjunction with a Safety Officer. For those single-site, high risk trials, a DSMB may be appropriate. For larger, single or multi-site studies, the monitoring is usually performed by a committee, often called a Data Safety Monitoring Board (DSMB). Ongoing review of the data by an independent individual or committee assures the investigators, the IRB, the study's sponsor, and the funding agency that the trial can continue without jeopardizing subjects' safety.

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

12.4 Initial Safety Review

^{177}Lu-J591 has been shown to be safe at a dose of 70 mCi/m^2 in a phase I dose-escalation trial and a multicentered phase II trial. Because the major toxicity (myelosuppression) is at least in part due to the location of metastases (cortical bone and bone marrow), it is expected that the toxicity in this study population will not exceed that seen in the trials in metastatic CRPC. However, safety data will be monitored on a real-time basis by the Study Chair and shared with the core study investigators. Should there be > 1 subject experiencing a stopping rule as defined by agreement with the FDA during the conduct of the phase II trial in metastatic CRPC (see Appendix B) within the initial 9 subjects (approximately 6 subjects receiving ^{177}Lu-J591), enrollment will be halted pending DSMB review. Enrollment will continue without a pause during the ongoing safety analysis. Completion of initial safety review is anticipated to be completed in summer, 2011.

12.5 Analysis and Data Reporting

Secondary endpoints examining the patient population or treatment with ketoconazole/hydrocortisone without regard to the study drug (radiolabeled J591) may be analyzed without breaking the blinding procedures on an ongoing basis and may be reported during the conduct of the study.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The study is a randomized phase 2 study with a 2:1 ratio favoring ^{177}Lu-J591, with stratification by investigational site and mode of primary therapy (radiation vs surgery). Randomization will be performed by using a series of randomized blocks of 6 within each participating site/primary therapy stratum (with a 2:1 allocation ratio). This will provide assurance that after six patients are enrolled in any given participating site/primary therapy stratum, there will be four patients assigned to the combination regimen (Group 1) and two patients assigned to the single regimen (Group 2). This procedure will allow for each site to contribute similar numbers of ^{177}Lu-J591/ketoconazole patients and ^{111}In-J591 (placebo)/ketoconazole patients within the defined participating site/primary therapy strata.

The primary endpoint is the proportion free of metastases in each group at 18 months. Ninety-five percent confidence intervals (95% CI) will be estimated for the 18-month MFS proportion in both groups via binomial proportions. The MFS proportion will also be descriptively evaluated at 12, 24, 30, and 36 months in each group.

MFS will be measured from the start of the treatment to the date of either documentation of metastatic disease or death. All treated patients will be observed for a minimum of 18 months. The 18-month MFS proportion with ketoconazole + ^{111}In-J591 has been estimated to be 50% {521 Smith, M.R. 2005}; therefore, the target 18-month MFS proportion for the combination of ketoconazole + ^{177}Lu-J591 regimen is hypothesized to be 80%. An intent to treat analysis will include all randomized subjects. However, we will also analyze subjects who received study-drug. This subset will be those subjects who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal within the first 4 weeks, and received infusion of study drug.

With approximately 34 patients in the ketoconazole+J591 arm and 17 patients in the ketoconazole monotherapy arm (2:1 allocation), this design will allow for the detection of a 30% absolute difference in the 18-month MFS proportion between the ketoconazole+J591 arm and the ketoconazole monotherapy arm (80% vs. 50%, respectively) with ≥80% power and a one-sided alpha level of 10%. An additional 10% will be enrolled to account for loss to follow up (total projected number of subjects to be randomized = 55). A 95% CI for the difference in the 18-month MFS proportion between the two treatment arms can be constructed to be within ± 18% of the true difference in 18-month MFS proportions.

13.1.1 ^{111}In-J591 as placebo

We have chosen to infuse ^{111}In-J591 as a placebo in this double-blind study. The infusion procedures and characteristics of this compound are similar to ^{177}Lu-J591. In addition, ^{111}In-J591 will allow imaging studies to be performed. Because ^{111}In is a pure gamma-emitter, there will be no treatment effect as in the beta emission with ^{177}Lu. It is theoretically possible that by infusing ^{111}In-J591, there will be a treatment effect by ADCC, thereby diluting the proportional effect of ^{177}Lu-J591 in the experimental arm. However, clinically meaningful ADCC is not expected, as it has been demonstrated at

much higher doses of the J591 antibody (122), and by giving equal antibody doses in each study arm, we will be able to truly evaluate the effect of ^{177}Lu radioimmunotherapy.

13.2 **Sample Size/Accrual Rate**

The planned sample size is 55 subjects (50 + 10% for in-evaluable / loss to follow-up = 55). Subjects who come off protocol prior to day 29 of treatment (i.e. prior to infusion of study drug) will be replaced. It is anticipated that the average site will pre-screen several subjects per month and enroll approximately 3 subjects per year.

13.3 **Stratification Factors**

Patients will be stratified by treating institution and delivery of primary therapy (surgery and/or radiotherapy vs no primary therapy to the prostate).

13.4 **Analysis of Secondary & Exploratory Endpoints**

Secondary endpoints include biochemical (PSA) response rate, duration of PSA response, biochemical (PSA) progression, time to biochemical (PSA) progression, time to biochemical (PSA) progression above baseline, overall survival, and toxicity. We anticipate that the 95% confidence interval around the PSA response rate will be within ±9% of the true value for Arm 1 and within ±15% of the true value for Arm 2. Time to biochemical (PSA) progression, time to biochemical (PSA) progression above baseline, median MFS-time, and overall survival will be estimated using the Kaplan-Meier method, and 95% confidence intervals will be calculated using Greenwood's formula.

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

Imaging studies: The possibility of identifying sites of metastatic disease not apparent on conventional imaging (CT/MRI abdomen/pelvis, bone scan, and CXR) will be confirmed with serial imaging. Any potential metastatic site on J591 imaging will be followed over time by conventional imaging. Sites of disease appearing on J591 scan and subsequently confirmed by conventional imaging will be labeled as positive. Any site apparent on J591 scan that is subsequently biopsied as part of standard care and confirmed to be metastatic prostate cancer will be labeled as definite. Sites of disease appearing on J591 scan without any corroborating evidence (conventional imaging or biopsy) will be labeled as possible.

Adrenal hormonal levels: Baseline adrenal hormonal levels will be categorized by median baseline levels found in CALGB 9583 (60, 61). In addition, as this may be a different patient population, we will analyze by median as well as quartiles. We will correlate levels with time to radiographic metastatic disease as well as PSA response and overall survival. Changes in adrenal hormone levels will be analyzed with time (baseline, 1 month, 6 months, at progression).

Plasma markers of hemostasis/fibrinolysis/angiogenesis: Baseline levels will be categorically analyzed by median as well as in quartiles and will be correlated with clinical endpoints (time to mets, survival, PSA response). We will also perform exploratory analyses using these values as continuous variables. In addition, a description of changes in levels of these markers with time/treatment will be reported. We will explore changes (decreases) by 50% (and median decrease) in correlation with outcome/response.

CTC's: Change in CTC counts will be summarized descriptively. Baseline counts ≥ 5 CTCs vs < 5 (per 7.5 mL) will be analyzed for time to metastatic disease in the overall population. We will also analyze changes with therapy: Decrease from ≥ 5 to < 5, increase from < 5 to ≥ 5, and stable categorical counts with respect to primary and secondary efficacy endpoints.

13.5 Reporting and Exclusions

13.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment on study. Toxicity of radiolabeled J591 in this population will be evaluated from the time of J591 administration.

13.5.2 **Evaluation of response.** All patients included in the study will be assessed for response to treatment if they have received at least 4 weeks of therapy with ketoconazole and received radiolabeled J591. Subjects dropping out of the study prior to J591 administration will be replaced.

14 Inclusion of Women and Minorities

Women are excluded from the protocol because prostate cancer is a disease of men. No exclusion based upon race/ethnicity will occur.

15. Study Personnel

Study Chair (Scott T. Tagawa, MD): Responsible for patient recruitment and over-all clinical management, protocol design and coordination, assessment of adverse events, safety, toxicity, and effect of treatment. Will communicate with principal investigators and study personnel at all sites and run monthly study teleconferences with the Study Coordinator. Will oversee any changes to the protocol and will be responsible for submitting amendments to the appropriate regulatory agencies (such as IRB, DSMB, sponsors, FDA, etc.). [See also Appendix D]

WCMC Co-Investigators (David M. Nanus, MD, Caryn Ecker, NP, Himisha Beltran, MD, Yuliya Jhanwar, MD, Ana Molina, MD, Meghan Moran NP, Trisha Youn, MD): Responsible for patient recruitment, overall clinical management, assessment of adverse events, safety, toxicity, and effect of treatment. Will assist with protocol design, coordination, and interpretation of scans.

Nuclear Medicine Chairs (Stanley Goldsmith, MD, Shankar Vallabhajosula, PhD**):** Responsible for administration of IND agents (radiolabeled J591 antibodies) for diagnostic and therapeutic studies, will oversee evaluation and quantitation of radiolabeled J591 scans. Will oversee quality control of radiolabeled antibody.

Statistician (Paul Christos, MS, Dr.PH): Assist with study design, data analysis and interpretation, assist with protocol amendments.

Research Nurse Assist with patient recruitment, study drug administration, documentation of adverse events.

Study Coordinator Assist with pre-screening and screening of subjects at WCMC; communicate with DOD; coordinate potential and enrolled subjects at all sites; optimize accurate data collection and entry by communicating frequently with other sites; prepare data for analysis. Will run monthly study teleconferences with principal investigators and other study team members at other sites in conjunction with the Study Chair. Will assist the Study Chair in providing continuing review documents for appropriate regulatory agencies (such as IRB, DSMB, sponsors).

Research Monitor John Leonard, M.D. is responsible to oversee the safety of the research and report observations/findings to the IRB of Record or a designated official. The Research Monitor will review all unanticipated problems involving risk to volunteers or others associated with the protocol and provide an unbiased written report of the event to the IRB of Record. The Research Monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The Research Monitor shall have authority to stop the research protocol in progress, remove individual human subjects from the study, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. The Research Monitor is responsible for promptly reporting their observations and findings to the IRB. [See also Appendix D]

Consultant (Neil H. Bander, MD): Will provide insight and guidance in overall study design, use of antibody, and correlative studies examining PSMA expression. [see also Section 15.1]

15.1 Conflicts of Interest

Neil H. Bander, MD will serve as an unpaid consultant on the study. He holds the patent rights to J591 and has served as a paid consultant to BZL Biologics (company that has assisted in the production of the J591 monoclonal antibody). He will have no access to any of the study data other than the blinded material (circulating tumor cells and archived tissue slides) on which some of his lab personnel may perform PSMA staining. He will have no role in screening of subjects, obtaining informed consent, treatment of the subjects, or analysis and reporting of the data.

16. Funding

This protocol has been initiated with WCMC funding as well as funding via the WCMC CTSC. Funds from WCMC have been and will be supplemented through past grants from the Cancer Research Institute, the David H. Kock Foundation, and the National Cancer Institute. Part of the Study Chair's funding through a K12 mechanism (KL2 RR024997-01 (PI: Imperato-McGinley) K12 Clinical & Translational Research Training Scholars Award) and Prostate Cancer Foundation Young Investigator's award will cover his time and effort in the development of the protocol. The study will be performed at the WCMC CTSC through funds via the WCMC CTSA (UL1 RR024996). Additional study sites have preferentially been chosen because of available CTSA funding. Some of the correlative studies (adrenal androgen levels, plasma markers of hemostasis, fibrinolysis, and angiogenesis) will be performed in the WCMC CTSC core lab and will be funded via the CTSA. The user ID/password protected/encrypted web-based database will also be built and run by WCMC CTSC personnel funded via the CTSA.

Additional funding for the WCMC site will be obtained through the Department of Defense (via a DOD Prostate Cancer Research Program Clinical Trial Award (Funding Opportunity Number W81XWH-08-PCRP-CTA, PC081664). There will be strict non-overlapping budgets, as funds are available from multiple sources. Other sites will be funded via their CTSA and supplemented by the WCMC Urologic Oncology Research Fund.

17. Additional Study Sites

The study protocol has been developed by WCMC investigators. However, the Study Chair and other WCMC investigators have incorporated changes to the study design based upon input from a core group of investigators at additional sites provided via email, teleconferences, and an investigator meeting at the 2008 ASCO Annual Meeting. The core group of study investigators who provided input on study design will be included in initial safety review.

The below additional study sites (and principal investigators) are collaborators on this study protocol:

University of Southern California (David Quinn)
Indiana University (Costantine Albany)
University of Iowa (Dan Vaena)
Emory University (Omer Kucuk, David Schuster)
University of Pittsburgh (Leonard Appleman)
Cedars Sinai (Edwin Posadas)
University of Utah (Neeraj Agarwal)
Georgetown University (George Phillips)
University of Kansas (Peter Van Veldhuizen)
University of Arizona (Parminder Singh)
UF Health – Orlando (Julio Hajdenberg)

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APPENDICIES

- **Appendix A - Performance Status Criteria**
- **Appendix B – Stopping Rules from prior phase II study**
- **Appendix C - % Skeleton for Radiotherapy**
- **Appendix D – Department of Defense Information**
- **Appendix E – Radiographic guidelines**
- **Appendix F – Substitution for ketoconazole (selected countries outside of U.S.)**
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- **Appendix H – PIRADS v2**

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Stopping Rules (from phase 2 single-dose study, to be used as a guideline for DSMB reporting)

In the initial portion of the single-dose phase II study of ^{177}Lu-J591 for men with metastatic CRPC, the FDA required notification with a hold on further enrollment pending review if any of the below criteria were met. For the current study, the DSMB must be notified when any of the below stopping rules occur. Should >1 subject within the initial 9 experience any of the following, further enrollment will be held until DSMB review and FDA permission for continuation is given.

Hematologic

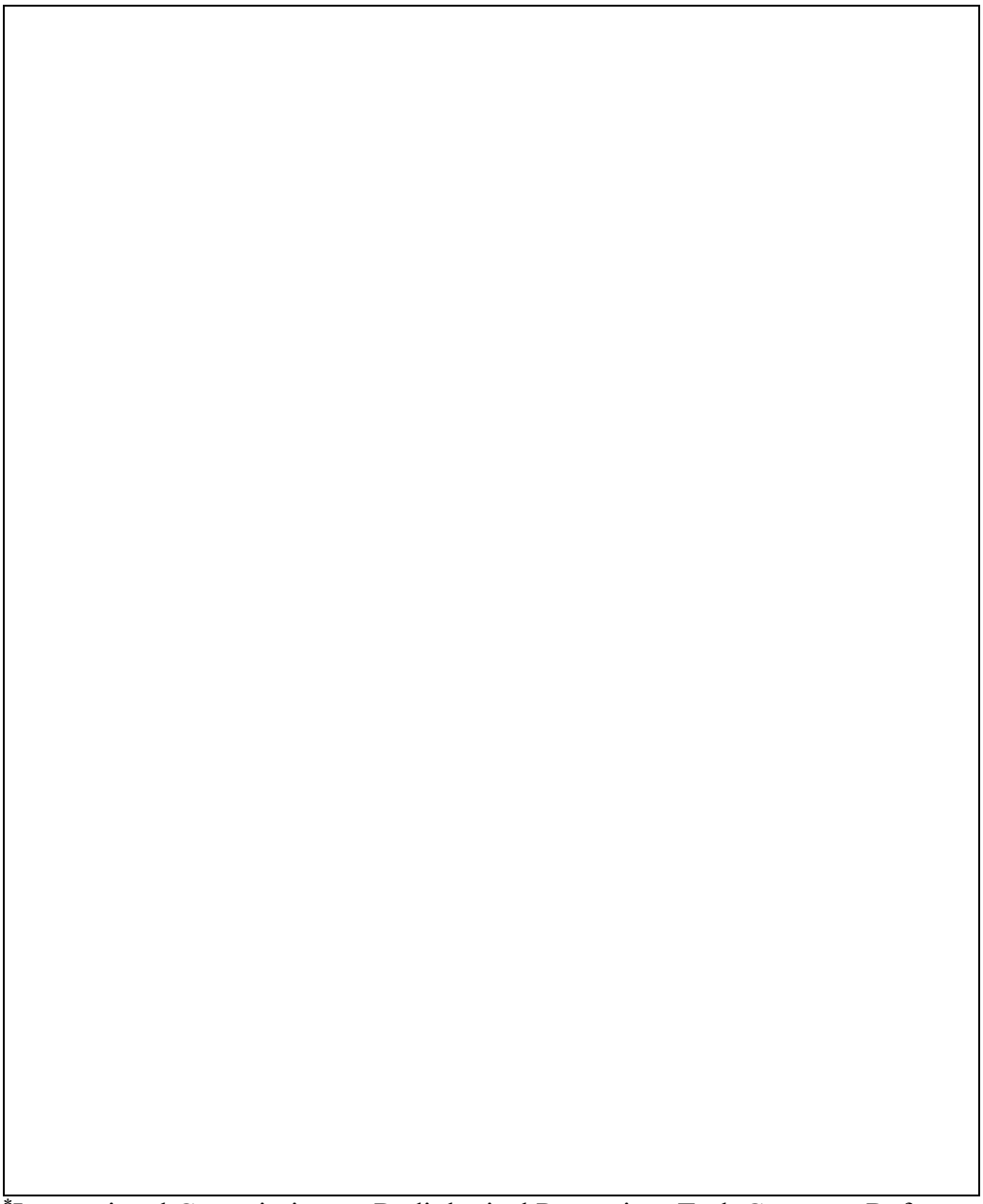
- Grade 4 thrombocytopenia that persists for ≥ 14 days after therapy
- Grade 4 thrombocytopenia that requires > 2 platelet transfusions over a 14 day period (note that multiple units of platelet products given together are considered a single transfusion)
- Grade 3 thrombocytopenia persisting > 30 days
- Grade 4 neutropenia that requires growth factor support for more than 14 days
- Grade 3 neutropenia that persists > 30 days
- Febrile neutropenia

Non-hematologic

- Any ≥ Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug (radiolabeled J591)

The NCI Common Toxicity Criteria for adverse events (CTCAE) version 4.0 will be utilized.

Appendix C Calculation of % Skeleton Involvement*



*International Commission on Radiological Protection: Task Group on Reference Man. Report of the task Group on Reference Man: a report prepared by a task group of Committee 2 of the International Commission on Radiological Protection. Oxford; New York: Pergamon Press, 1975

Appendix D

Protocol Addendum

A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy
IRB # 0810010067
HRPO Log Number A-15378

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

Guidance for the Requirement of a Medical Monitor

Per DoD Directive 3216.02, all greater than minimal risk studies require a Medical Monitor. The USAMRMC ORP HRPO also reserves the authority to require assignment of a Medical Monitor for those protocols assessed as presenting no greater than minimal risk to the subjects participating in the study.

Responsibilities of the Medical Monitor

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

Please indicate the name of the medical monitor and the role they will have in this research study. This individual will be a qualified physician, other than the principal Investigator, not associated with this particular study, able to provide medical care to research subjects for conditions that may arise during the conduct of this study, and will monitor the subjects during the conduct of the study.

Research Monitor: John Leonard, MD

Describe the specific role of the Research Monitor in this research study:

The Research Monitor is responsible to oversee the safety of the research and report observations/findings to the IRB of Record or a designated official. The Research Monitor will review all unanticipated problems involving risk to volunteers or others associated with the protocol and provide an unbiased written report of the event to the IRB of Record. The Research Monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The Research Monitor shall have authority to stop the research protocol in progress, remove individual human subjects from the study, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. The Research Monitor is responsible for promptly reporting their observations and findings to the IRB.

Appendix E

Radiographic Guidelines

This study is designed to include men without radiographic evidence of metastases with the primary endpoint of various measures of time to the development of radiographic appearance of metastatic disease. It is understood that there may be instances when the determination of lack of radiographic evidence of metastases may be equivocal. The following general guidelines should be followed:

Equivocal bony lesions on bone scan should be evaluated by X-ray, CT, or MRI. If the etiology of the bone scan lesion may be explained by another cause (e.g. fracture), the lesion will not be considered evidence of osseous metastatic disease.

In the case of borderline lymphadenopathy, every attempt should be made to obtain historical scans. Should the lesion be present and stable over time and unchanged despite biochemical progression and in the opinion of the investigator does not represent metastatic disease from prostate cancer, the lesion will not be considered evidence of metastatic soft tissue disease.

Equivocal lesions suspicious for metastatic disease should be biopsied if feasible.

Keeping the guidelines in mind, any equivocal lesion should be assessed by the PI and may be discussed with the study chair. Images may also be sent for central review (assuming written informed consent has been provided).

Appendix F

Substitution for ketoconazole

In countries outside of the U.S. where the administration of ketoconazole for prostate cancer is prohibited, substitution of an alternative form of secondary hormonal therapy (or continuation of LHRH agonist/antagonist alone) with approval of the study chair will be allowed.

Appendix G

Functional Assessment of Cancer Therapy – Prostate (FACT-P), version 4

Appendix H

Summary of PIRADS V2 Scoring

Magnetic resonance imaging (MRI) is the reference standard imaging test for the local staging of prostatic carcinoma. Prostate cancer staging is according to the tumor nodes metastases (TNM) criteria established by the American Joint Committee on Cancer.

To overcome variation in the performance, interpretation, and reporting of prostate MRI exams, the European Society of Urogenital Radiology (ESUR) drafted guidelines for the MR imaging and MR reporting of prostate cancer with a specific radiology lexicon referred to as the PI−RADS system. Ever since then the use of PI−RADS version 1 (PI−RADS v1) for the identification and grading of tumor foci with MRI has garnered tremendous interest. However, experience from working with PI−RADS v1 has also revealed several limitations, in part due to rapid progress in the field. In an effort to make PI−RADS standardization more globally acceptable, the American College of Radiology (ACR), ESUR and the AdMeTech Foundation established a Steering Committee to build upon, update and improve upon the foundation of PI−RADS v1. This effort resulted in the development of PI−RADS v2.

Assignment of a PI−RADS v2 Assessment Category is based on multi−parametric MRI (mpMRI) findings only and does not incorporate other factors such as serum prostate specific antigen (PSA), digital rectal exam, clinical history, or the choice of treatment. A sector map (adapted from a European Consensus Meeting and the ESUR Prostate MRI Guidelines 2012) employing thirty-nine sectors/regions: thirty-six for the prostate, two for the seminal vesicles and one for the external urethral sphincter is used for standardized reporting and interpretation.

PI−RADS v2 Assessment Categories:

PIRADS 1− Very low (clinically significant cancer is highly unlikely to be present)
PIRADS 2− Low (clinically significant cancer is unlikely to be present)
PIRADS 3− Intermediate (the presence of clinically significant cancer is equivocal)
PIRADS 4− High (clinically significant cancer is likely to be present)
PIRADS 5− Very high (clinically significant cancer is highly likely to be present)

When assessing the peripheral zone lesions, diffusion−weighted imaging (DWI) component of the mpMRI is the primary determining sequence (dominant technique) for assigning the PIRADS score.

When assessing the transition zone lesions, T2−weighted pulse sequence (T2W) of the mpMRI is the primary determining sequence (dominant technique) for assigning the PIRADS score.

PI−RADS assessment for peripheral zone lesions:

DWI	T2W	DCE	PIRADS
1	Any	Any	1
2	Any	Any	2
3	Any	−	3

3	Any	+	4
4	Any	Any	4
5	Any	Any	5

PI−RADS assessment for transition zone lesions:

T2W	**DWI**	**DCE**	**PIRADS**
1	Any	Any	1
2	Any	Any	2
3	≤4	Any	3
3	5	Any	4
4	Any	Any	4
5	Any	Any	5

PI−RADS scoring for DWI:

Score	**Peripheral Zone (PZ) or Transition Zone (TZ)**
1	No abnormality (i.e. normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI.
4	Focal markedly hypontense on ADC and markedly hyperintense on high b-value DWI; <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

PI−RADS scoring for T2W:

Score	**Peripheral Zone (PZ)**
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity. Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

PI−RADS scoring for T2W:

Score	**Transition Zone (TZ)**
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins. Includes others that do not

	qualify as 2, 4 or 5
4	Lenticlular or non-circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

PI−RADS scoring for DCE:

Score	**Peripheral Zone (PZ) or Transition Zone (TZ)**
(−)	No early enhancement, or diffuse enhancement not corresponding to a focal finding on T2W and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2W
(+)	Focal, and; earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and; corresponds to suspicious finding on T2W and/or DWI

Patients diagnosed with PCa who have been treated earlier with hormonal therapy and are now progressed to castration resistant prostate cancer (CRPC) without any evidence of frank metastasis on conventional imaging modalities (CT scan, Bone scan, CXR) will be required to undergo 3−Tesla mpMRI. If their PI−RADS score is 3 or below, they will be included in the study since they are unlikely to have local disease progression.

EPE Scoring:

Standardized criteria used for assessment of extra-prostatic extension (EPE) at MRI proposed by the European Society of Uroradiology [1].

EPE Score	Original PI-RADS criteria	Modified PI-RADS criteria
1	Abutment	Clearly confined, intervening normal tissue between tumor and intact prostate capsule
2	Not specified	Abutment, tumor abuts but does not deform capsule
3	Irregularity	Irregularity, tumor abuts capsule causing capsular irregularity
4	Bulge, loss of capsule, neurovascular bundle thickening	Tumor bulges, deforms or obscures (loss of) capsule with or without neurovascular bundle thickening
5	Measurable extracapsular disease	Gross/measurable extracapsular disease

Note: 1) For PI-RADS v2 clinically significant cancer is defined on pathology/histology as Gleason score > 7 (including 3+4 with prominent but not predominant Gleason 4 component), and/or volume > 0.5cc, and/or extraprostatic extension (EPE).
2) PI-RADS score of 5 for DWI and/or T2W represents lesion of ≥1.5cm in greatest dimension [Ref: ESUR guidelines]

3) Higher tumor incidence correlates with higher PI-RADS score [1]
4) Imaging features used to assess for EPE include asymmetry or invasion of the neurovascular bundles, a bulging prostatic contour, an irregular or spiculated margin, obliteration of the rectoprostatic angle, a tumor-capsule interface of greater than 1.0 cm, breach of the capsule with evidence of direct tumor extension or bladder wall invasion. [Ref: ESUR guidelines]

Ref:

1. Schieda N, Quon J, Lim C, et al. Evaluation of the European Society of Urogenital Radiology (ESUR) PI-RADS scoring system for assessment of extra-prostatic extension in prostatic carcinoma, Eur J Radiol (2015), http://dx.doi.org/10.1016/j.ejrad.2015.06.016
2. Junker D, Schäfer G, Edlinger M, et al. Evaluation of the PI-RADS Scoring System for Classifying mpMRI Findings in Men with Suspicion of Prostate Cancer. *BioMed Research International*. 2013;2013:252939. doi:10.1155/2013/252939.