A Pilot Study of ^{89}Zr-J591 Anti-Prostate-Specific Membrane Antigen Monoclonal Antibody in Patients with Glioblastoma Multiforme

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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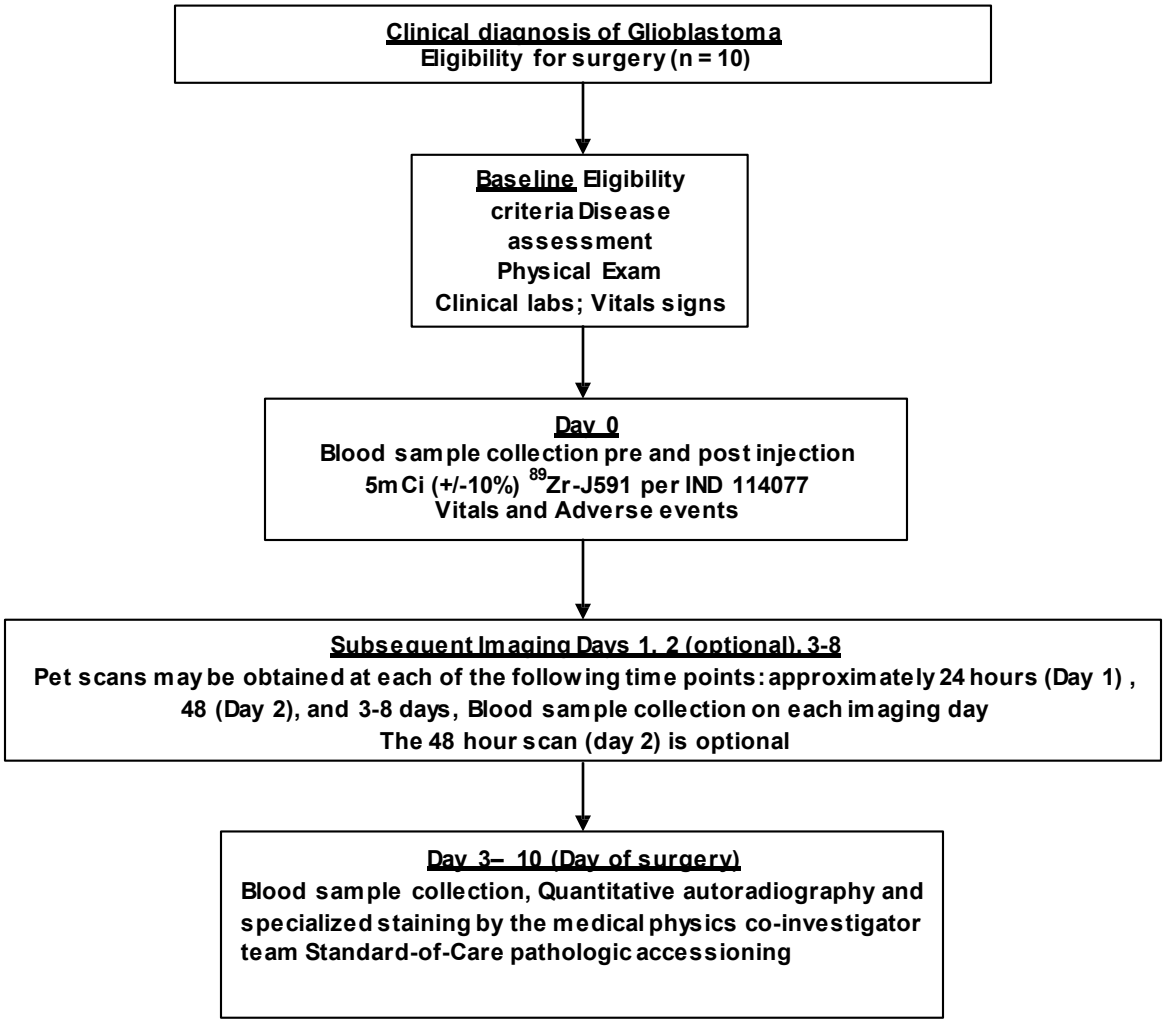
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Immuno-PET with radiolabeled antibody ^{89}Zr-J591 will assess quantitatively the tumor vasculature-specific expression of the prostate-specific antigen (PSMA) in patients with Glioblastoma Multiforme. Glioblastoma is a cerebral neoplasm with a uniformly poor prognosis—a disease for which targets for new treatments are constantly sought. One such target might be prostate-specific membrane antigen (PSMA), which is expressed in prostate carcinoma and, more importantly in this context, in the endothelium of vessels in most malignant solid tumors including glioblastoma [1]. The purpose of this experiment is to assess the binding of ^{89}Zr-J591 in patients (n=10) with glioblastoma multiforme. An assessment of binding will ascertain whether this target is expressed at adequate levels for sustained radionuclide or antibody-drug conjugate targeting directed towards the vessels or cells within the perivascular niche.

Schema



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoints

1a To determine the binding of ^{89}Zr-J591 for the vasculature of glioblastoma multiforme in human subjects.
1b To confirm that pre-surgical tumor localization of radiotracer is related to PSMA expression based on correlation with post-surgical histopathologic analysis.

3.0 BACKGROUND AND RATIONALE

Glioblastoma multiforme (GBM) is the most common cancer arising from the brain. It is also the most aggressive subtype (WHO grade IV) among gliomas, a collection of tumors including oligodendrogliomas and astrocytomas. Malignant gliomas are diffusely infiltrative and hence all locally directed therapies such as surgery or radiotherapy are inherently palliative. Even with maximum treatment at initial diagnosis, malignant gliomas have a dismal prognosis with estimated 5-year survival rates of 10% [2]. Standard management is maximal surgical resection followed by involved field radiotherapy with concomitant temozolomide given daily at 75 mg/m2 and followed by monthly cycles of adjuvant temozolomide given at 150-200 mg/m2/d on days 1 to 5 for a total of 6 cycles. However, GBMs are relentlessly progressive, and median survival with this treatment is only 14 months [2].

The treatment of recurrent malignant gliomas represents a therapeutic challenge. The treatment options at recurrence remain currently limited [3]. There are currently few salvage treatment options that have consistently shown efficacy for recurrent GBMs [4]. A review of 225 GBM patients with recurrent GBM enrolled in 8 previous phase II studies, in which none of the treatments were considered particularly effective, showed a 6 month PFS of 15% for GBM [5]. Systemic administration of the DNA alkylator BCNU results in a 6mPFS (6 month progression free survival) rate of only 17.5% for recurrent GBM. Glioblastomas are highly hypoxic tumors with strong endogenous expression of HIF-1a and of VEGF and its receptors and a consequently vigorous angiogenic phenotype. Anti-angiogenic therapies with antibodies (bevacizumab) and tyrosine kinase inhibitors of the VEGF receptor (e.g. Enzastaurin, SU11248) are already demonstrating an important impact in glioblastoma treatment. Bevacizumab was approved by the FDA for the treatment of recurrent GBMs based on promising efficacy in a landmark Phase II trial [4, 6]. Tumor vascular targeting, exploiting the phenotypic and genotypic variations of tumor (versus normal) vessels, is another potentially valuable anti-angiogenic approach for glioblastoma.

The endothelium of malignant brain tumors is a particularly attractive target for vascular-targeted radio-immunotherapy, because:

1. Glioblastomas are highly vascular,
2. Radiation-resistant glioma stem cells appear to reside, at least in part, in a perivascular niche sustained largely by endothelium [7]
3. Endothelium can be exposed to radiolabeled antibody much more readily than can the tumor substance, which is protected by the blood-brain barrier.

PSMA is expressed in prostate carcinoma and, more importantly in this context, in the endothelium of vessels in most malignant solid tumors [8, 9]. We have immuno-stained the blood vessels of 32 paraffin-fixed glioblastoma specimens with the anti-PSMA mAb 3E6 and found positive PSMA staining in the endothelium in 100% of the cases [9, 10].

Table 1. Extent of Vascular Staining for PSMA

Extent	<5%	6-25%	26-50%	51-75%	75-100%
No. of Tumors	0	8	2	15	7

Table 2. Intensity of Staining for PSMA

Intensity	0	1+	2+	3+
No. Tumors	0	3	15	14

J591 is an anti-PSMA antibody that binds with high affinity to the external domain of PSMA. There has been extensive clinical experience at Weill-Cornell and at MSKCC with the naked antibody and with ^{177}lutetium-labeled antibody in the treatment of prostate cancer and, more recently, in the vascular-targeted therapy of a variety of other solid tumors. We are in the early stages of designing a radio-immunotherapy trial with radiolabeled J591as an anti-angiogenic agent for glioblastoma but before proceeding we desire to demonstrate physiologic binding of J591 to the tumor vessels. ^{89}Zr-J591 PET has been used safely in patients with prostate cancer both primary disease and metastatic castration resistant disease [11]. Our plan is to demonstrate binding of J591 with ^{89}Zr-J591 PET and also optimize ^{89}Zr-J591 PET in glioblastoma patients for the possibility of measuring response to radiolabeled J591 and other anti-angiogenic agents.

J591

The J591 mAb is a humanized monoclonal antibody directed at the extracellular domain of human PSMA [12]. J591 was derived from murine J591 using Biovation's (Biovation, Aberdeen, Scotland, UK) de-immunization 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. 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 humanized 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

Table 3. ^{89}Zr-DFO-J591 Absorbed Doses in 70-kg Standard Man

^{89}Zr-DFO-huJ591 Patient Dosimetry

			# of Injections/CT scans	Dose per CT scan/cGy	CT Extent
Activity of ^{89}Zr-DFO-huJ591	**5**	mCi	**1**		
Low dose WB CT scan	**80**	mA	**0**	0.90	WB
Low dose Head CT scan	**80**	mA	**3**	0.90	Head only
Ultra low dose WB CT scan	**10**	mA	**0**	0.11	WB

	Absorbed Dose			
	[1] 89Zr-DFO-huJ591		**CT**	**TOTAL Absorbed Dose**
Target Organ	cGy/mCi	cGy per admin	cGy	cGy
Adrenals	2.03	10.1	0.00	**10.1**
Brain	0.52	2.6	2.70	**5.3**
Breasts	0.82	4.1	0.00	**4.1**
Gallbladder Wall	2.76	13.8	0.00	**13.8**
LLI Wall	0.81	4.1	0.00	**4.1**
Small Intestine	1.09	5.4	0.00	**5.4**
Stomach Wall	1.22	6.1	0.00	**6.1**
ULI Wall	1.23	6.2	0.00	**6.2**
Heart Wall	3.17	15.8	0.00	**15.8**
Kidneys	3.53	17.6	0.00	**17.6**
Liver	7.69	38.4	0.00	**38.4**
Lungs	2.14	10.7	0.00	**10.7**
Muscle	0.85	4.2	0.00	**4.2**
Ovaries	0.90	4.5	0.00	**4.5**
Pancreas	1.86	9.3	0.00	**9.3**
Red Marrow	1.19	5.9	0.00	**5.9**
Osteogenic Cells	1.16	5.8	0.00	**5.8**
Skin	0.57	2.9	0.00	**2.9**
Spleen	2.72	13.6	0.00	**13.6**
Testes	0.58	2.9	0.00	**2.9**
Thymus	1.16	5.8	0.00	**5.8**
Thyroid	0.69	3.4	2.70	**6.1**
Urinary Bladder Wall	0.77	3.8	0.00	**3.8**
Uterus	0.87	4.4	0.00	**4.4**
Total Body	1.06	5.3	0.00	**5.3**
Effective Dose Equivalent (rem/mCi)	1.99	9.96	0.08	**10.05**

[1] Pandit-Taskar et al, 89Zr-huJ591 immuno-PET imaging in patients with advanced metastatic prostate

cancer.

Eur J Nucl Med Mol Imaging, published online Aug, 2014: DOI 10.1007/s00259-014-2
Dosimetry was performed in accordance with the methods recommended by the MIRD Committee of the Society of Nuclear Medicine and Molecular Imaging as implemented in the OLINDA/EXM software application

DFO-J591

In order to radiolabel J591 with β^+ emitting radionuclides such as ^{89}Zr, the J591 antibody molecule is first conjugated to a macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane- N, N', N'', N'''-tetraacetic acid (DFO) by direct coupling of one of the four carboxylic acid groups of DFO to the primary amines present in the protein structure. The DFO conjugated antibody is formulated in 0.3 M ammonium acetate, pH 7.0 at a nominal concentration of 8 mg/mL.

Radiolabeled J591

The DFO-J591 antibody molecule is labeled with radio-metal ^{89}Zr 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 auto-radiolysis 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.

Anti-PSMA Monoclonal Antibodies

The PSMA gene has been cloned, sequenced, and mapped to chromosome 11 [13]. PSMA is anchored to the cell membrane. Initial validation of PSMA as an *in vivo* target has been borne out by imaging trials with mAb 7E11/CYT-356 marketed as ProstaScint® (Capromab) [14-17]. Molecular mapping, however, indicates that capromab targets a portion of the PSMA molecule that is within the cell's interior and not exposed on the outer cell surface [10, 18]. In living cells, this internal binding site is not accessible to antibody. Successful imaging with capromab relates to targeting of dead/dying cells within tumor sites. It has been noted that a mAb to the extracellular domain of PSMA would provide benefits including improved localization in patients and enhanced imaging and therapy. At Weill Medical College, Liu et al have reported the development of 4 IgG mAb to the external domain of PSMA ($PSMA_{ext}$) [19]. These antibodies to $PSMA_{ext}$ demonstrate high affinity binding to PCa cells in tissue culture, on tissue sections, and in animal models *in vivo*. Furthermore, unlike capromab, these mAb can bind to viable cells because the target-binding site is present on the exterior of the cell. In *in vitro* and *in vivo* animal models of prostate cancer, for which these antibodies were developed, ^{177}Lu -J591 has demonstrated substantial anti-tumor activity. In these studies, immune-deficient 'nude' mice are implanted intramuscularly with PSMA-expressing human prostate cancer cells [18]. Cancers are allowed to 'establish' for a period of approximately 2 weeks during which time the cancer develops a blood supply allowing further growth. At the time of treatment initiation, the cancer implants average 1.0 cm in diameter (or approximately 5% of the animal's body weight. Results demonstrate that ^{177}Lu -J591 induces an average of >90% tumor reduction compared to control-treated mice (saline or non-radioactive antibody or ^{177}Lu -irrelevant

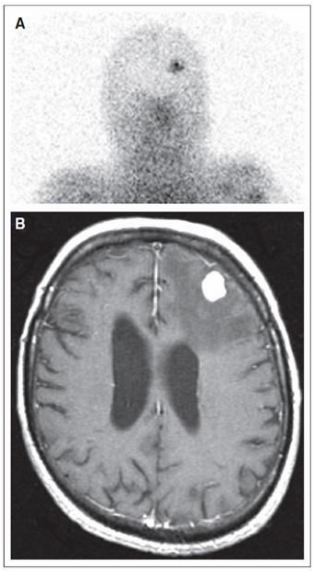
antibody). A portion of the animals showed complete disappearance of tumor. These studies also demonstrate significant improvement in survival of the ^{177}Lu -J591-treated animals, with a large proportion of cured animals. Cancers not expressing PSMA do not respond to treatment demonstrating the specificity of the treatment. Animals treated with multiple, low doses of ^{177}Lu -J591, rather than single, larger doses of ^{177}Lu -J591, appear to have better tumor reduction responses, better survival, and less toxicity.

Prior studies/Preliminary results

The first step in evaluating this hypothesis in human subject will be to evaluate ^{89}Zr-J591 bio-distribution, dosimetry and tumor binding in patients with glioblastomas.

CLINICAL EXPERIENCE:

<u>^{111}Indium J591- (Cornell protocol 1099-905)</u>



Patient with metastatic renal cell carcinoma to brain. 111In-J591 and companion CT demonstrate lesion in left frontal lobe.

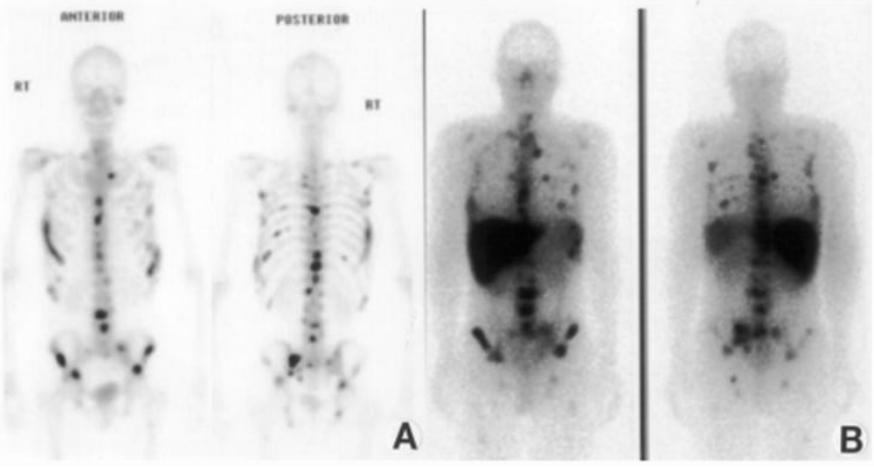
Fourteen patients were entered in a Phase 1 study where patients received 4 weekly doses of ^{111}Indium labeled J591. One patient, at the highest dose level, developed an anaphylactic reaction associated with a too rapid infusion rate, and he received only a single dose. He recovered promptly and completely but, due to the reaction, was not given further doses. The infusion rate has since been limited to 5 mg/minute. Another patient received only a single dose due to rapid disease progression and loss of protocol eligibility. The remaining 12 patients, who received total doses ranging from 62.5 mg/m^2 to 500 mg/m^2, demonstrated the following Grade 1 to 3 (CTCAE) hematological adverse events: neutropenia, lymphocytopenia, leukocytopenia, hemoglobinemia, and thrombocytopenia.

Observed Adverse Events

All of these hematological toxicities were transient in nature and returned to baseline levels during the course of the study. Imaging studies, done in all patients, demonstrated excellent antibody targeting to tumor sites without significant targeting to normal tissue sites. Results demonstrated no clinical or laboratory evidence of immunogenicity of the J591 antibody.

<u>^{90}Yttrium J591- (Cornell protocol 0200-119)</u>

The objectives of this trial were to study the targeting, dosimetry, toxicity, pharmacokinetics and the immunogenicity of the humanized antibody (HAHA) as well as the preliminary therapeutic efficacy. Patients received an initial dose of



Patient with metastatic prostate cancer. Patient underwent bone scan (A) and subsequently received ^{90}Yttrium J591 demonstrating widely metastatic disease.

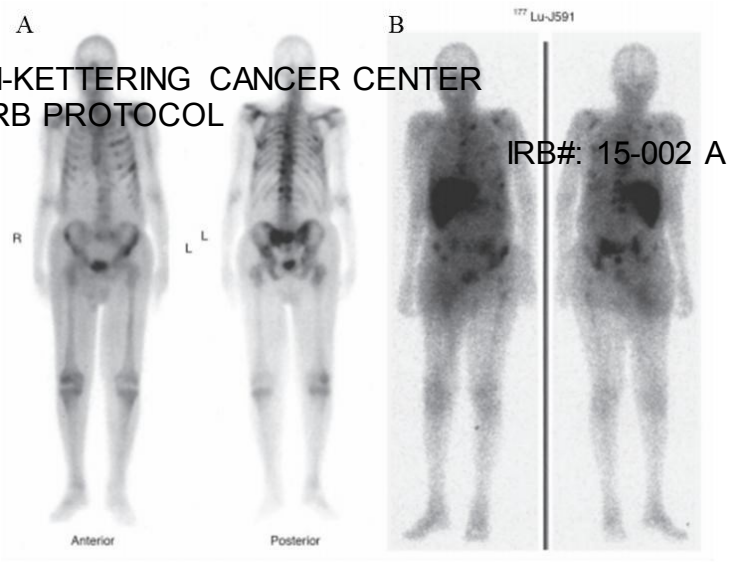
IRB PB

^{111}In-DFO-J591-GS (20 mg, 5mCi) for pharmacokinetic and bio-distribution determinations, followed one-week later, with a dose of ^{90}Y-DFO-J591-GS (20 mg). The dose schedule was selected to allow multiple imaging sessions prior to ^{111}In decay as well as clearance of the J591 from the initial dose prior to delivering the 2nd dose. The ^{90}Y dose was selected based on prior published experience with other antibodies. The first dose utilizes 4-5 mCi of ^{111}In and allows imaging for approximately one week. Eligible subjects were hormone-refractory with progressing prostate cancer. Twenty-nine subjects were entered at the following dose levels: 5, 10, 15, 17.5 and 20 mCi/m^2. Patients were eligible for up to three re-treatments if platelet and neutrophil recovery were satisfactory. Four patients were re-treated. Dose-limiting toxicity was seen at 20 mCi/m^2 with two patients experiencing thrombocytopenia with non-life threatening bleeding episodes requiring platelet transfusions. The 17.5 mCi/m^2 dose level was determined to be the maximum tolerated dose. No re-treated patients experienced dose-limiting toxicity. Non-hematologic toxicity was not dose-limiting. Among the 29 patients receiving ^{111}In-DFO-J591-GS, 19 patients had bone lesions and 13 patients had soft tissue lesions. 17 of 19 (89%) patients with bone lesions and 9 of 13 (69%) with soft tissue lesions were accurately targeted resulting in an overall targeting sensitivity of 26 of 32 (81%). Two patients treated at the 20 mCi/m^2 dose level exhibited 85% and 70% declines in PSA lasting 8 and 8.6 months prior to returning to pre-treatment values. In addition, these two patients had objective measurable disease responses with 90% and 40% decrease in the size of pelvic and retroperitoneal lymphadenopathy. Both patients were hormone-refractory with lymph node-only disease and had not received prior chemotherapy. The second patient was re-treated with ^{90}Y-DFO-J591-GS on day 119. An additional 6 patients experienced PSA stabilization by week 12.

^{177}Lutetium J591- (protocol 1100-472)

35 patients with androgen-independent prostate cancer were entered on a phase I trial of ^{177}Lu-J591. Patients received 10 mg/m^2 J591 with doses of ^{177}Lu ranging from 10 mCi/m^2 - 75 mCi/m^2. Several patients were re-treated. Of the 3 patients at the 75 mCi/m^2 dose level, one experienced dose-limiting (grade 4) thrombocytopenia while the remaining 2 patients experienced grade 3 thrombocytopenia. All 3 of these patients experienced grade 4 neutropenia, one of which was dose-limiting neutropenia of 6 days duration. As 2 of 3 patients at this dose level experienced DLT, no additional patients were entered at this dose. At the prior dose level of 70mCi/m^2, 6 patients were entered. 2 patients had transient grade 4 neutropenia not meeting the definition of DLT; 1 of these patients had grade 4 thrombocytopenia. As there was only 1 DLT in these 6 patients, the 70 mCi/m^2 dose level was determined to be the MTD. Among the 35 patients receiving ^{177}Lu -J591, 30 (86%) had metastatic disease detected on screening imaging studies. Specifically, 21 (60%) patients had bone-only metastases, 6 (17%) had soft tissue-only metastases and 3 (9%) had both bone and soft tissue disease. In all of these 30 patients, known sites of metastatic disease were successfully imaged by ^{177}Lu-J591 scintigraphy.

All 35 patients in this trial had abnormal, rising PSAs and 7 patients had measurable disease. None of the 7 patients with measurable disease had an objective tumor response nor a ≥ 50% PSA decline. Based on PSA, 14 demonstrated progressive disease (PSA increase of ≥ 25%) after treatment while 21 of the 35 patients had evidence of biologic activity. 4 patients had ≥ 50% PSA declines lasting 3+ to 8 months, and 16 patients had PSA stabilization (< 25% increase from baseline) of ≥ 28 days. The median duration of PSA stabilization was 60 days with a range of 28-601+ days.



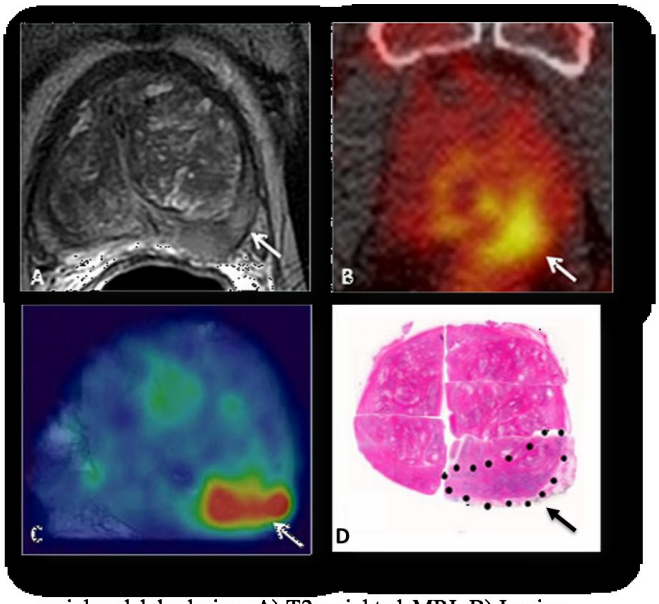
Patient with metastatic prostate cancer. Patient underwent bone scan (A) and subsequently received ^{177}Lutetium J591 demonstrating widely metastatic disease.

Observed Adverse Events

The observed adverse events of this therapeutic protocol were predicted by the prior Indium study. *Please note: these prior studies were therapeutic and diagnostic nuclides like ^{89}Zr are unlikely to have a similar effect on the bone marrow and with toxicity.*

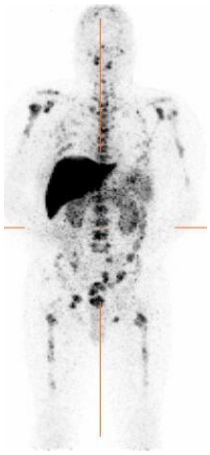
^{89}Zirconium J591

Localized Prostate (Cornell protocol 1202012209): The objectives of this trial were to study the targeting, dosimetry, toxicity, pharmacokinetics and the immunogenicity of the humanized antibody ^{89}Zr-J591under IND 115521. A total of eleven patients received an initial dose of ^{89}Zr-J591 (20 mg, 5mCi) for pharmacokinetic and bio-distribution determinations. Patients were imaged 5-6 days after injection with all patients undergoing whole body PET and a limited scan of the pelvis. Eleven Patients were injected and scanned. None of the patients experiences any adverse effects. Imaging studies, done in all patients, demonstrated excellent antibody targeting to tumor sites without significant targeting to normal tissue sites. Results demonstrated no clinical or laboratory evidence of immunogenicity of the J591 antibody. Results of this pilot trial were published in Journal of Urology in 2013.



peripheral lobe lesion. A) T2 weighted MRI, B) In vivo 89Zr-J591 PET, C) Ex vivo 89Zr-J591 microPET, D) histopathology of prostatectomy specimen.

Metastatic Prostate



Currently over 50 patients have been successfully imaged with ^{89}Zr-DFO-J591 for men with metastatic prostate cancer. These results have been published. An estimated 98% of lesions identified on standard imaging (including bone scan, FDG PET, and CT) were visualized by immuno-PET (personal communication). Furthermore, there were a significant number of lesions (~10%) that were solely identified by immuno-PET. Biopsy samples were performed on a subset of patients, and an estimated 90% of patients who had positive J591 PET scans that were otherwise negative by standard imaging, were histopathologically confirmed to be prostate cancer.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Patients with recurrent glioblastoma are eligible. Additionally, patients with a newly diagnosed biopsy-proven glioblastoma requiring re-resection prior to initiation of therapy are eligible. Patient with a newly diagnosed brain lesion identified on standard-of-care imaging modalities such as CT or MRI that show typical imaging characteristics of a glioblastoma are also eligible. The patients will undergo ^{89}Zr-J591 PET imaging. Surgical resection will be carried out post completion of imaging and part of the resected tumor stained for PSMA and graded by percentage of cells stained and by staining intensity.

Standard imaging procedures:

- CT scan
- MRI

Investigational diagnostic imaging agent

- ^{89}Zr-J591

This study is not designed to confirm the imaging accuracy of ^{89}Zr-J591 and thus, a *truth standard has not been defined* for the purpose of data analyses. Efficacy studies with an appropriate sample size to allow for the assessment of imaging accuracy against a truth standard will be conducted in the future as a Phase II study. At that time, more refined eligibility criteria are likely to be applied to study candidates.

4.2 Intervention

The intervention is the administration of an injection of 18-19mg of unchelated J591 to reach the total administered dose of antibody (IND11407) followed by 5 mCi (+/- 10%) of ^{89}Zr-J591 (1 to 2 mg) . After administration of the experimental tracer, the patient will undergo a Brain PET/CT scan 24 hours, 48 hours post injection and 3-8 days. The 48 hour scan is strongly suggested, but optional.

No clinical management decisions will be made based on ^{89}Zr J591 imaging.

5.0 DIAGNOSTIC AGENTS

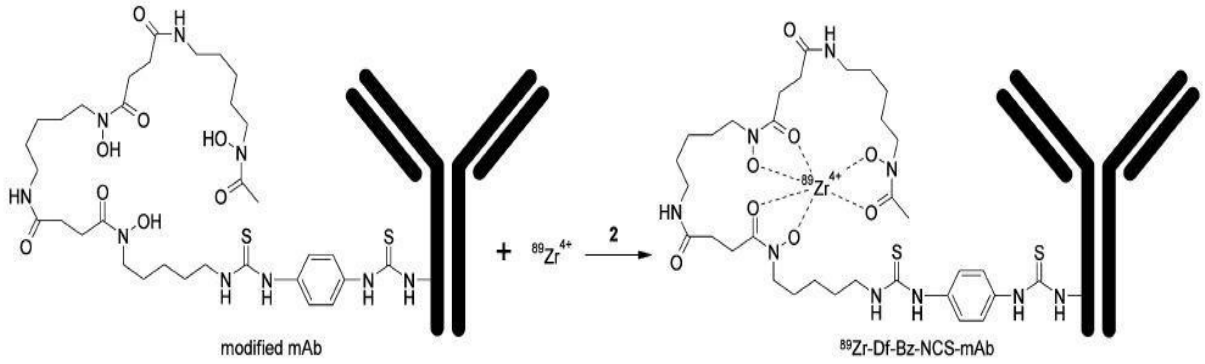
^{89}Zr-J591

J591 is a humanized antibody that targets the external domain of PSMA, and has been studied as therapy as an unconjugated ("cold") antibody, and labeled with Yttrium-90, and Lutetium-177. Several experiments have shown that J591 is an excellent means of targeting the tumor neovasculature, particularly in glioblastoma multiforme. This protocol will extend these studies into the realm of imaging for diagnostic and, ultimately, potential therapeutic applications. The radio-antibody ^{89}Zr-J591 has characteristics that have the potential to outperform other radiotracers in use for glioblastoma multiforme by targeting tumor-specific angiogenesis.

1. The antigen target, PSMA, is uniquely expressed in the tumor neovasculature for multiple solid tumors, particularly glioblastoma multiforme (Chang S, et al. Cancer Res, 1999).
2. The long half-life of the ^{89}Zr makes it possible to image at late times after injection, when background activity has cleared from blood and soft-tissue.
3. ^{89}Zr is a Positron emitter, and PET imaging has much higher sensitivity and resolution characteristics compared to conventional nuclear medicine imaging procedures, such as SPECT.

We will use Zirconium-89, a positron-emitting radionuclide, labeled to J591. The final drug product is ^{89}Zr-J591 in human serum albumin/ saline, sterile filtered in a sterile vial, sealed with rubber septa and closed with aluminum stopper. ^{89}Zr is chelated by the DFO of the DFO-J591 conjugate. Human serum albumin is USP grade and has been adequately tested for HBV, HCV, and HIV-1. No other materials of animal origin are used in the manufacture of ^{89}Zr-J591. Manufacture of first DFO-J591 and then ^{89}Zr-J591 is performed by the Radiochemistry & Molecular Imaging Probes core facility at MSKCC. J591 is provided under IND# 114077 from Dr. Neil Bander of Cornell, which we are cross-referencing for information regarding its chemistry, manufacturing and controls. Cold antibody will be administered separately according to the IND.

Zr conjugation technique



6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Patients age > 25 years old < 80 years old
2. Patients with reoccurrence of brain tumor
   - The principal investigator or co-PI must review MRI and CT findings based on the radiologic assessment provided they meet the following imaging criteria (as established in the clinical trial 09-177)

   OR

   Patients with newly diagnosed GBM, and one of the following options:
   - Eligible for surgery after the last research scan.
   - Significant residual disease after initial surgery
     - The principal investigator or co-PI must review MRI and CT findings and agree with the presence of significant residual disease
   - Treatment (non-surgical) naïve
3. Karnofsky Performance Score ≥ 70

6.2 Subject Exclusion Criteria

1. Laboratory values:
   - Serum creatinine >2.5 mg/dL.
   - AST (SGOT) >2.5x ULN.
   - Bilirubin (total) >1.5x ULN.
   - Serum calcium >11 mg/dL.
2. Pregnant or breastfeeding (if a female is of childbearing potential, and unsure of pregnancy status, a standard pregnancy test should be done).
3. If an initial biopsy demonstrates neoplasm other than GBM
4. Presence of any other co-existing condition which, in the judgment of the investigator, might increase the risk to the subject.
5. Presence of serious systemic illness, including: uncontrolled inter-current infection, uncontrolled malignancy, significant renal disease, or psychiatric/social situations, which might limit compliance with study requirements
6. Prior treatment.
7. Other serious illness (es), which might preclude completion of this, study or interfere with determination of causality of any adverse effects experienced in this study.

7.0 RECRUITMENT PLAN

A member of the patient's treatment team at hospital will identify potential research subject. He or she will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their

treating physician will be referred to the investigator/research staff of the study. Adult patients with recurrence of GBM, or newly diagnosed GBM, based on MR scan confirmation (as defined by IRB approved protocol 09-117), will be eligible for this trial. Additional therapies to temozolomide and radiation are allowable. Should the concomitant agent be available through another clinical trial, the site will need to ensure treatment details (dose, time of administration, and any interruptions in therapy).

8.0 PRETREATMENT EVALUATION

Standard clinical imaging studies will be performed within 6 weeks prior to study entry. No intervening new therapy is allowed between conventional imaging studies and ^{89}Zr-J591:

- MRI and/or CT

Laboratory tests, as part of standard of care, will be obtained within 4 weeks prior to study entry.

- Serum creatinine
- AST (SGOT)
- Bilirubin
- Serum calcium
- Pregnancy test if applicable (within 2 weeks of study entry)

Pre-surgical planning: Preoperative MRI per routine and PET-CT imaging p.i.^{89}Zr-J591 will be performed and co-registered for identification of potential biopsy target/s. The surgeon will prospectively delineate the planned resection volume (PRV) on pre-operative neuro-navigational MRI co-registered to the PET-CT (iPlan workstation, BrainLAB AG). Biopsy target regions will be identified on the basis of tracer uptake. Regions of tracer uptake are considered potential targets if (1) they are within the PRV and (2) are at least 1 cm^3 in volume.

9.0 TREATMENT/INTERVENTION PLAN

Injection details:

Patients will not be required to fast prior to imaging with ^{89}Zr-J591 injection or imaging. The total dose of humanized mAb J591 will be 20mg. Patients will first receive an injection of 18-19mg of unchelated J591 to reach the total administered dose of antibody (IND11407) followed by 5 mCi (+/- 10%) of ^{89}Zr-J591 (1 to 2 mg). Administration of the cold antibody will be followed by the labeled compound.

The adverse events to this injection protocol from IND 114077 are detailed in section 11.0. We have injected greater than 50 patients at MSKCC with this agent with no severe AEs.

Blood Samples:

Bloods samples will be drawn immediately before and approximately 30 minutes after ^{89}Zr-J591 injection. Blood samples will also be drawn on subsequent days of imaging and day of surgery. This data will be used to determine the blood clearance of radiotracer and will inform the accumulation of the

same in the target tissue. With these additional metrics, specific binding will be easier to determine and safety (particularly possible follow-up therapeutic protocols will be more easily determined.

Radiation Dosimetry

Method and Analysis:

Normal-organ radiation absorbed doses and the effective dose for ^{89}Zr-DFO-J591 in human were estimated based on based on MSKCC clinical study of ^{89}Zr-DFO-J591 in 10 patients: dosimetry estimates by Joe O'Donoghue using the formalism of the Medical Internal Radionuclide Dosimetry (MIRD) Committee of the Society of Nuclear medicine (SNM).

Assuming a 5 mCi administered activity of ^{89}Zr-DFO-J591 and a low-dose head CT scan is to be performed, for 2-3 time points the predicted human radiation dosimetry for ^{89}Zr-DFO-J591, total normal-organ absorbed doses and effective dose are tabulated below.

The human normal-organ radiation doses thus derived were found to be comparable to those of other commonly used diagnostic radiotracers. In the radiation dosimetry analysis, the critical organ was determined to be the kidneys, receiving a dose-equivalent of 1.97 rem/mCi. In the trial proposed, a 5 mCi injected-dose of ^{89}Zr-DFO-J591 is to be administered initially. If needed to get adequate PET images, the radioactive compound dose could be increased. Based upon the predicted human dosimetry, even with an administered dose as high as 12 mCi, the total absorbed dose to the kidneys should be less than 28 rem.

SCANNING DETAILS:

Imaging session

On Day 0 each patient would receive 20mg/5 mCi ±10% intravenous injection of the investigational agent followed by PET/CT imaging approximately 24 hours (day 1), 48 hours (day 2, optional) post injection, and 3-8 days.

CT:

- kVp 80
- Qual. Ref. mAs 30
- Slice 3.0 mm Acq 16 x 1.2 mm
- Pitch 1.5
- Kernel B31f medium smooth + (H19sLowDose for ECT for AC CT)

PET Acquisition:

- No of beds: 2
- Scan duration/bed: 3 min/bed
- Field of view (FOV): Brain
- Total scan time: ~20 minutes

MRI:

Structural MRI, scans will be acquired on a 3.0 Tesla scanner (General Electric, Milwaukee, WI). High resolution T_1 and T_2-weighted images will be acquired prior to contrast injection. DWI will be acquired using a spin-echo echo planar sequence with b = 1000 s/mm^2. A 4-slice ^{1}H-MRSI scan will be performed using the method of Duyn et al., with a 15 mm slice thickness, 3.5-mm interslice gap, TE/TR 280/2300 ms, field-of-view (FOV) 240 mm, 24x24 matrix and 512 points with a scan time of 17 minutes producing 1.0 cm^3 voxels ([i]). Unsuppressed water spectra will be acquired for reference allowing detection of individual metabolic variances with respect to water concentration independent of peak area ratios. Dynamic susceptibility contrast enhanced (DSC) perfusion weighted imaging will be performed using an injection of 0.2 mM/kg Gd-DTPA (Magnevist, Berlex, Wayne,NJ) and a GRE-EPI sequence with TE/TR 30/1500 ms to estimate rCBV. Post-contrast T_1-weighted 3D GRE imaging will be acquired followed by T_2-weighted Fast Spin Echo and Fluid Attenuated Inversion Recovery image sets.

AUTORADIOGRAPHY:

The major components of our quantitative autoradiography system include a digital cryostatic microtome (MICROM 500M) and our recently installed state-of the-art GE Typhoon 7000IPphosphor plate autoradiography system capable of spatial resolution as low as 25 µm. Following acquisition of autoradiographic images, sections may then be stained with either histo- or immuno-histochemical (IHC) techniques, and scanned digital images acquired at very high resolution (< 1 µm/pixel). All image sets will then be registered using a combination of mutual information and external fiduciary markers placed on the sections. These techniques have previously been used at MSKCC in a similar mamnner to study 124I-A33 uptake and sub-tumoral distribution.

Infusion reactions

Infusion reactions with J591 are generally mild if they occur at all. In the even of fever, rigors, shortness of breath, or other evidence of infusion reaction, patients may receive diphenhydramine 25 mg IV and Tylenol 650 mg as felt to be clinically appropriate by the treating physician. This has been the accepted protocol since MSKCC IRB 11-126 for the injection of ^{89}Zr-J591.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Primary Outcomes

Positive lesions on ^{89}Zr-J591 PET will be defined as those with higher activity than adjacent or contra lateral background that is deemed not to be physiologic. The gold standard of positive will consist of lesion identified on conventional imaging, (CT/MRI, bone scan) consistent with metastatic disease. Antibody scan will be read blinded from clinical history and conventional imaging modalities. Two different readers will visually analyze the scans, SUV max will be determined, and the results will be merged when the data are complete. A combined list will be generated that will then contain individual SUVmax measurements.

Laboratory Safety Assessments: Hematology and blood chemistry assessments (CBC, serum BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, albumin, and blood glucose levels) will be done at the time points described in Table 4.

Performance Status: Performance status will be assessed using the Karnofsky Performance Status scale.

Vital Signs: Blood pressure and heart rate will be obtained at the time points outlined in the flowchart.

Table 4: Study Calendar

	Baseline (within 4 weeks of study entry)	**Day 0**	**Day 1 (24 hours post injection)**	***Day 2*[2] (48 hours post injection)**	**Days 3-8**	**Day of Surgery**[3]
Informed consent	X					
Medical history	X					
Physical examination	X					
Routine clinical laboratory	X					
Pregnancy test (if applicable)	X					
Vital signs	X	X[4]				
Concomitant medications	X					
Adverse events	X	X	X	X	X	
Standard imaging[1]	X					
^{89}Zr-J591 injection		X				
^{89}Zr-J591 PET/CT scans			X	X	X	
Tissue sampling						X
Research Blood Draw		X	X	X	X	X

[1] Standard imaging includes CT and/or MRI and can be completed within 6 weeks prior to study entry
[2] Day 2 (48 hours post injection) PET/CT scan is optional
[3] Surgery should occur after the completion of last PET/CT scan.
[4] Vitals on Day 0 will be done pre-injection and post-injection of ^{89}Zr-J591.

Tissue sampling for surgical patients

Surgical resection with targeted tissue acquisition will take place per routine, with integrated frameless stereotactic tracking used to annotate sites of biopsies, and updated by intraoperative MRI (iMRI, 1.5T Siemens magnet). Tissue samples from several regions (from contrast enhanced portion of the tumor) will be collected within and around the tumor after adequate specimens have been obtained for diagnostic purposes, as determined by the attending neurosurgeon and pathologist.

Samples will be obtained during surgery at various locations at the site of the lesion during a routine resection procedure. Each sample will be placed into separate preweighed 10% formalin-containing vials, reweighed, and immediately counted in a calibrated Wallac gamma spectrometer (located just outside of the operating room). Decay-corrected radioactivity of each sample (Bq/g tissue) will be

determined, and available samples ranging from high to low radioactivity (Bq/g tissue) will be submitted to pathology in a "blinded manner" for routine fixation and pathological scoring. In the event that the neurosurgeon requires a frozen section during the procedure, the resected sample will be divided: one portion for immediate frozen section analysis (which will include histological confirmation by MSKCC) and another for radioactivity measurement and processing as a study sample. If the surgeon judges the resected tissue sample to be too small or heterogenous to be divided without compromising diagnosis, the clinically relevant frozen section analysis will take precedence. An inservice from radiation safety will be conducted with the OR staff and neuro-surgeons involved prior to the first patient.

Histopathology, molecular characterization, and digital autoradiography of excised specimens. Excised brain tumor biopsy specimens will be divided and a portion flash-frozen in liquid nitrogen, cryosectioned, and transferred for H&E staining and immunohistochemical staining for PSMA expression; remaining frozen material will be stored at -80°C. This excess frozen material at -80^0 C for seven years or if consent is withdrawn, the tissue will be destroyed immediately. Unfrozen portions will be processed for autoradiography to visualize the distribution of this agent along the endothelium of tumor neovasculature.

Processing of samples for molecular characterization and digital autoradiography will be carried out under the direct supervision of Dr. Sean Carlin, Assistant Attending in the Radiochemistry and Imaging Sciences Service. Specimens will be flash-frozen and mounted and sectioned immediately following receipt. Sections will be exposed to a storage phosphor plate for an appropriate length of time, and images subsequently acquired using a GE Typhoon 7000IP plate reader. Sequential sections will be stained manually to determine PSMA and CD34 expression, and digital microscopic images obtained using an Olympus BX60 microscope equipped with a computer-controlled stage and high-sensitivity CCD camera.

PSMA assay and manual staining will be carried out in Dr. Carlin's laboratory, Z1733 center laboratory, which if fully equipped to carry out these procedures

11.0 TOXICITIES/SIDE EFFECTS

Risks

^{89}Zr-J591 PET/CT Scans

As part of this scan there is radiation delivered from the ^{89}Zr and from the low dose CT scan that are performed as part of the CT for attenuation correction and co-registration. There is a low theoretical risk of developing a cancer at some point later in life as a result of the radiation exposure received in this study. This risk is particularly low for adults given the fact that the radiation from the scans will be over several weeks. Participants should not father a baby while on this study. Acceptable birth control methods include abstinence, double barrier method, surgically sterilized patient or partner.

J591

Potential risks associated with J591 are allergic reactions, characterized by fever, chills, and sometimes rashes or hives. Less likely shortness of breath can occur. Rare allergic reactions can present as infection, shock or death or swelling of the throat. Allergic reactions such as these have

not been seen with J591. However, some patients have developed the fever and chills and shortness of breath when J591 has been used in the past. Such reactions are usually addressed by stopping the administration of the drug, administering steroids, acetaminophen and/or diphenhydramine, and restarting the drug at a slower rate if the reaction is not severe.

There is a very small risk of infection. This could cause itching or redness at the area on the patient's arm where the IV was placed.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Positive lesions on ^{89}Zr-J591 will be defined visually as a focus of accumulation of radioactivity that is deemed to not be physiologic and is higher than adjacent or contra lateral background. Antibody scan will be read blinded from clinical history and conventional imaging modalities.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will remain on study until day of surgery. Participation in the study is voluntary. Patients have the right to withdraw from the study at any time. If a patient chooses to withdraw, he or she must inform the investigator immediately. In addition, the investigator has the right to terminate participation of any patient at any time if it is deemed in the patient's best interest. The reason and circumstances for premature discontinuation will be documented in the patient's medical records. Possible examples for reasons of premature study withdrawal include withdrawal of consent, SAE or intolerable AE, or any other medical illness at investigator's discretion.

For patients who are enrolled without prior histological confirmation of glioblastoma, if the surgery is found not to meet histological criteria for glioblastoma, the patient will be removed from the study and replaced until 10 evaluable patients complete the protocol.

14.0 BIOSTATISTICS

Objective 1a of this study is to determine the binding of ^{89}Zr-J591 for the vasculature of glioblastoma multiforme in human subjects. This will be measured by J591 uptake in PET scan.

Two sets of analyses are planned for objective 1a. In the first set the unit of analysis is patient and the only planned analysis is to present the number of patients with any uptake (a binary variable as defined in Sections 10 and 12) at each time point along with a 95% exact confidence interval. If, for example, 8 of the 10 patients have an uptake the confidence interval for this proportion will be 0.44-0.97.

The second set of analyses will use uptake as a continuous variable and primarily consist of summary statistics. Since some patients will have multiple lesions a lesion-based analysis with necessary corrections for the intra-patient correlation will be used. These analyses will be performed separately for each scan (time point). While it is also of interest to compare the uptake across time points using generalized estimating equations, this will be done with the understanding that statistical power will be limited.

Objective 1b (correlating PMSA expression with uptake) will be accomplished using lesion-based analysis where PSMA expression will be obtained from the surgical samples and uptake from the pre-operative scans. Since both variables are continuous we will use a random-coefficients regression if the number of lesions per patient is sufficient. If not, standard metrics of rank correlation will be estimated. This analysis will be based on surgically-sampled lesions.

Sample size was determined based on logistics and availability of funding.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

NA

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.
The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record. Study personnel will record clinical data in each patient's source documents (i.e., the patient's medical record). The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the data stored in the database used for data collection.

Dr. Neil Bander is involved with the development of the tracer and therefore will be provided with the de-identified study results to contribute throughout the study. All data provided will be de-identified before being sent outside of MSKCC electronically.

16.1 Quality Assurance

Regularly scheduled registration reports will be generated to monitor patient accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the principal investigator for discussion and action.

The study team will conduct random-sample data quality and protocol compliance audits at least once a year, more frequently if indicated.

16.2 Data and Safety Monitoring

The data and safety monitoring (DSM) plans at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the policies set forth by the NCI in the document entitled *Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials*, which can be found at http://cancertrials.nci.nih.gov/clinicaltrials. The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSM plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/html/70775.cfm.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and the monitoring procedures will be established at the time of protocol activation.

For this protocol, we will use the following patient safety monitoring plan and monitoring for adverse events, in terms of the test performed and their timing relative to injection (see Table 1 and 2). Patient will be observed closely during infusion and vital signs will be obtained pre- and post-injection of radiotracer.

Safety reviews will be performed by the MSKCC-DSMC with yearly review by the IRB.

Section 16.3 Regulatory Documentation

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

17.0 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonization, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

This protocol does not have therapeutic intent and does not offer patients therapeutic benefit. This will be clearly conveyed to patients when communicating the potential toxicities/side effects of participating in this trial. Participation in the trial is voluntary and there will be no financial benefit (or burden) for the patients. Participants will not be charged for ^{89}Zr-J591 radiotracer and PET scans, and research testing on resected tumor tissue.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

NA

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to

participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

NA