A Phase I/II Study of ^{89}Zr-DFO-MSTP2109A in Patients with Prostate Cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Summary

Metastatic prostate cancer is predominantly bone-tropic, and bone metastases result in blood dyscrasias, cord compression, fracture, pain, neurologic compromise, and death. New therapies are desperately needed, and many novel targeted therapies, androgen receptor (AR)-targeted treatments, chemotherapies, vaccines, immunologic drugs and immunotoxins are currently being tested. Unfortunately, drug development and clinical care for these patients is significantly hampered by the lack of any standard means of accurately assessing the primary reservoir of distant disease, which is embedded in the marrow of the axial skeleton.

Bone scintigraphy demonstrates reactive bone deposition only and not the cancer itself. Bone lesions shown on computerized tomography (CT) and plain radiographs generally only appear as sclerotic lesions that bear no relation to active tumor size, nor can these methods distinguish between the healing effects of successful therapy vs. the osteoblastic response of bone to a tumor that is continuing to progress on therapy.

The lack of good imaging methods hampers decision making in terms of when to apply or modify conventional treatment methods as well as limiting new drug development. Accurate imaging modalities are particularly needed in the age of targeted or biologic therapies, where effective therapies may be cytostatic and may not result in significant prostate-specific antigen (PSA) declines. In such cases, molecular imaging may be the only means by which early biologic activity of a new drug may be detectable in a Phase I or Phase II study. Furthermore when targeted therapies are to be used it is desirable to have an imaging test that identifies that the target is present in order to select patients and that may be also be used to determine if the target is being “hit” or downregulated. Many examples of this target selection and monitoring approach exist. Examples include bone scan for selection of radionuclide therapy with Sm-153 EDTMP or Sr-89 chloride, I-123 MIBG to select patients for I-131 MIBG therapy or In-111/Ga-68 Somatostatin receptor scintigraphy to select patients for Y-90/Lu-177 Somatostatin receptor therapy.

The Memorial Sloan-Kettering Cancer Center (MSKCC) Genitourinary (GU) Oncology Service has long collaborated with the Nuclear Medicine Service and the Department of Radiology to develop novel imaging modalities for prostate cancer. Using the MSKCC clinical states model (Scher and Heller 2000) as a template for radiologic investigations as well as clinical investigations, we have established a methodology for exploring positron emission tomography (PET) in prostate cancer that controls for clinical state, disease progression, scanning algorithm, method of interpretation, data collection, and data analysis. Using these techniques, we have demonstrated that fluorine-18-fluorodeoxyglucose (FDG) PET can be used to detect disease and demonstrate treatment effects and that fluorinated dihydrotestosterone (FDHT) PET can be used to detect disease and demonstrate pharmacodynamic effects of AR-targeted agents (Morris, Akhurst et al. 2002; Larson, Morris et al. 2004; Zanzonico, Finn et al. 2004; Morris, Akhurst et al. 2005). Furthermore we have collaborated on imaging and therapy based antibody approaches targeting Prostate Specific Membrane Antigen (PSMA). These approaches have shown the feasibility of using an antibody to target prostate cancer (Bander, Trabulsi et al. 2003; Nanus, Milowsky et al. 2003; Milowsky, Nanus et al. 2004; Bander, Milowsky et al. 2005; Morris, Divgi et al. 2005; Morris, Pandit-Taskar et al. 2007; Pandit-Taskar, Morris et al. 2008). Currently in collaboration with the chemistry core we have been developing Zirconium-89 (^{89}Zr) , a positron-emitting radionuclide, labeled to J591 has been approved by the IRB (protocol #11-126) and 8 patients have been accrued thus far (up to 4-28-2012) without dose limiting toxicity. J591 is an antibody that recognizes the external domain of prostate-specific membrane antigen. Furthermore

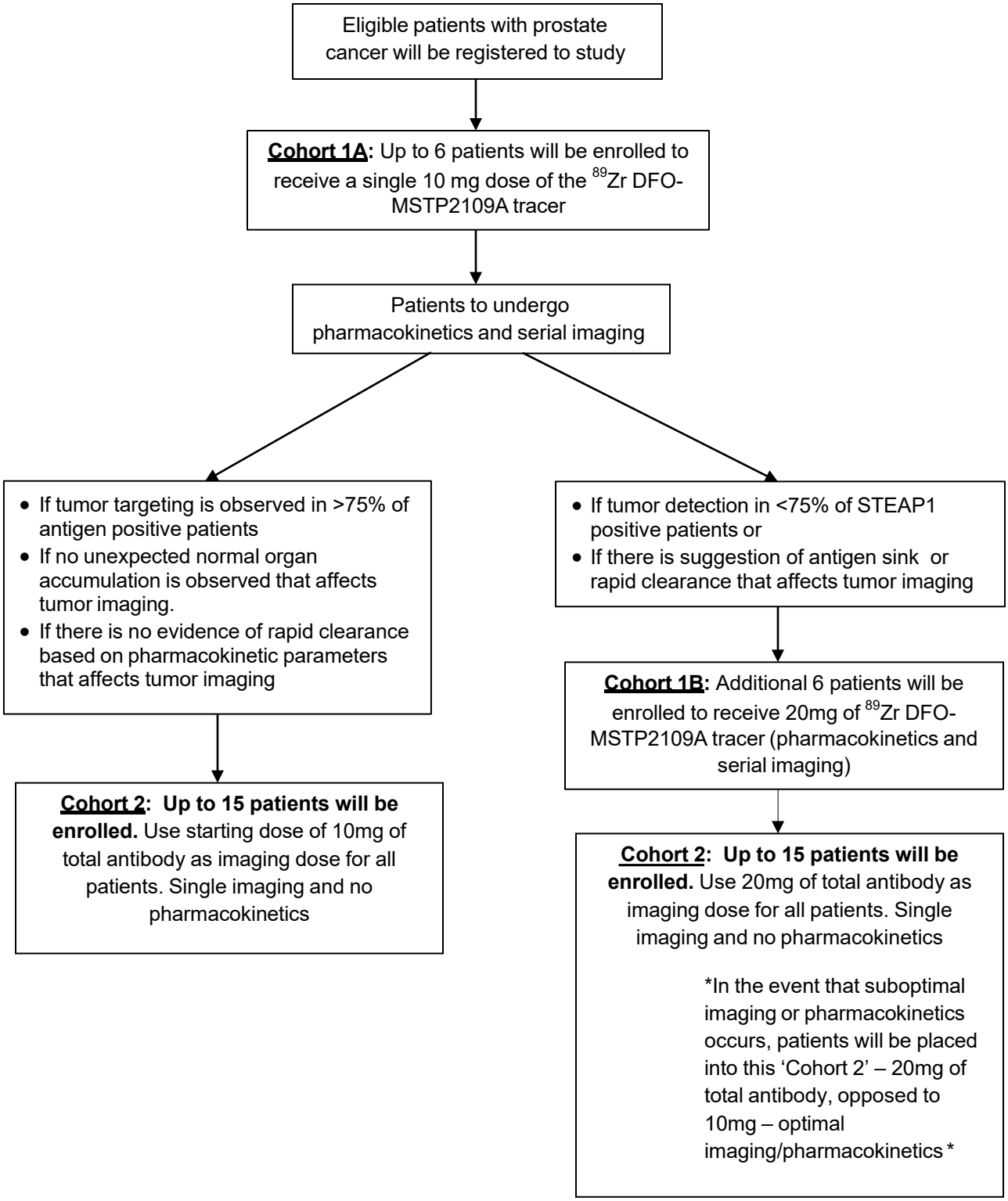
we have prepared clinical grade ^{89}Zr trastuzumab and a protocol is being written. Thus we have in place the technology to develop ^{89}Zr labeling of antibodies of interest.

Six-transmembrane epithelial antigen of the prostate-1 (STEAP1) is a multi-transmembrane, cell-surface antigen of unknown function that is overexpressed in 85% of human epithelial prostate cancers. Genentech has developed an antibody, MSTP2109A that binds to STEAP1. They have developed an antibody drug conjugate (ADC) DSTP3086S that contains the humanized IgG1 anti-STEAP1 monoclonal antibody MSTP2109A and a potent anti-mitotic agent, monomethyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-VC-PAB). This reagent is currently in a phase I therapeutic multicenter trial in which MSKCC is participating (PI Daniel Danila protocol, MSKCC 11-016). Therefore it is desirable to develop an imaging reagent that identifies the presence and intensity of the target by in vivo imaging. In addition, if the tracer appears to identify prostate cancer metastases effectively, then it may further be developed as an imaging biomarker for prostate cancer even independent of the specific STEAP1-targeted therapy.

Schema

Cohort 1A and 1B will each have the same clinical characteristics and inclusion criteria requirements. Both sets of patients will undergo serial pharmacokinetics and serial imaging exams post ^{89}Zr-DFO-MSTP2109A injection.

Upon the completion of pharmacokinetics and serial imaging (post Cohort 1A), patients will proceed accordingly based upon tumor detection observed, and whether there is suggestion of antigen sink or rapid clearance that affects tumor imaging. The difference between the 2 cohorts will be that 1A will receive 10 mg total of DFO-MSTP2109A and if cohort 1B is necessary, because criteria described above of suboptimal imaging or pharmacokinetics, patients will receive 20 mg total of DFO-MSTP2109A. From cohort 1A (10mg) or 1B (20 mg), we will decide what antibody amount (10 or 20 mg) is best and the optimal time of image acquisition. Cohort 2 will then consist of patients with the same characteristics and inclusion criteria as in cohort 1A and 1B, with the only difference being that they will receive the best dose determined from cohort 1A or 1B (10 or 20mg). Furthermore, they will not undergo pharmacokinetics and rather than serial imaging, the patients will only have one scan at an optimal time post injection of antibody determined from serial imaging of Cohort 1A and 1B.


Eligible patients with prostate cancer will be registered to study
Cohort 1A: Up to 6 patients will be enrolled to receive a single 10 mg dose of the 89Zr DFO-MSTP2109A tracer
Patients to undergo pharmacokinetics and serial imaging
If tumor targeting is observed in >75% of antigen positive patients
If no unexpected normal organ accumulation is observed that affects tumor imaging.
If there is no evidence of rapid clearance based on pharmacokinetic parameters that affects tumor imaging
Cohort 2: Up to 15 patients will be enrolled. Use starting dose of 10mg of total antibody as imaging dose for all patients. Single imaging and no pharmacokinetics
If tumor detection in <75% of STEAP1 positive patients or
If there is suggestion of antigen sink or rapid clearance that affects tumor imaging
Cohort 1B: Additional 6 patients will be enrolled to receive 20mg of 89Zr DFO-MSTP2109A tracer (pharmacokinetics and serial imaging)
Cohort 2: Up to 15 patients will be enrolled. Use 20mg of total antibody as imaging dose for all patients. Single imaging and no pharmacokinetics
*In the event that suboptimal imaging or pharmacokinetics occurs, patients will be placed into this 'Cohort 2' – 20mg of total antibody, opposed to 10mg – optimal imaging/pharmacokinetics *

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

- To determine feasibility, safety and tolerability of single dose administration of ^{89}Zr-DFO-MSTP2109A antibody.
- To determine the ability of ^{89}Zr-DFO-MSTP2109A PET to detect sites of metastatic prostate cancer.
- To determine the pharmacokinetics (PK) and biodistribution of ^{89}Zr-DFO-MSTP2109A.

2.2 Secondary Objectives

- To determine the better/"adequate" ^{89}Zr-DFO-MSTP2109A mass amount for tumor imaging (10 or 20 mg) .
- To determine optimal time relative to ^{89}Zr-DFO-MSTP2109A administration for tumor imaging.
- To use quantitative biodistribution data of ^{89}Zr-DFO-MSTP2109A uptake to perform dosimetry estimates.
- To correlate ^{89}Zr-DFO-MSTP2109A uptake in tumors with STEAP1 antigen expression by IHC
- To explore whether ^{89}Zr-DFO-MSTP2109A PET imaging results are related to patient outcome in patients being treated with DSTP3086S.

3.0 BACKGROUND AND RATIONALE

3.1 The Problem Being Addressed: Limitations of Conventional Imaging Modalities for Prostate Cancer Metastases

Progressive prostate cancer spreads to bone more commonly than to any other site, yet monitoring bone metastases to quantify cancer regression and progression remains inconsistent at best. In addition, a significant percentage of patients have soft tissue, predominant nodal disease. The standard Phase II response criteria for solid tumors do not apply, and despite the rapid evolution of imaging modalities for prostate cancer, visualizing of tumor spread to bone is still in the early stages of development. For example, as seen on plain radiographs, when prostate cancer spreads to bone, tumor growth in the marrow results in osteoblastic changes, which, in the end stage, result in the complete replacement of the marrow space. While most physicians accept that sclerotic healing of a lytic lesion constitutes tumor regression, sequential monitoring of lesions that are initially sclerotic is problematic because the bone architecture rarely reverts histologically back to normal. Even if all tumor cells are destroyed, there may be no visible changes on standard scans. In these cases, only a direct biopsy can determine if viable tumor cells are present. Other imaging modalities have significant limitations in identifying viable tumor as described below. Immunotherapy, radioimmunotherapy or antibody drug conjugate (ADC) related therapy are dependent on targeted antigen concentration. While patients may be selected based on antigen expression based on tumor biopsy, this is an invasive technique and is limited by impracticality of multiple tumor biopsy. In contrast, using a radiolabeled antibody approach allows one to non invasively select patients based on antigen content and allows assessment of multiple tumor sites.

Imaging modalities in prostate cancer

3.1.1 Radionuclide bone scanning

In prostate cancer, bone scintigraphy, although useful for staging, has limited usefulness because rather than providing a direct measure of cancer activity, it reflects the reaction of bone to the surrounding cancer. In addition, the common occurrence of the flare phenomenon (a paradoxical increase in intensity after successful therapy) complicates the interpretation of scans on a serial basis.

3.1.2 Cross-sectional imaging

The cross-sectional imaging modalities that are used to evaluate prostate cancer include CT, magnetic resonance imaging (MRI), and the emerging technology of magnetic resonance spectroscopy (MRS). The utility of each of these modalities varies according to the stage of disease. At present, no modality can distinguish viable disease from necrotic or nonmalignant tissue.

CT is well suited for detecting soft tissue disease, but has limited utility in assessing early changes in bone. CT is not sensitive enough to detect small volume nodal disease or tumor in non enlarged lymph nodes. CT also does not effectively evaluate disease that is confined to the prostate and adjacent area.

MRI: To provide the most accurate assessment in the region of the prostate, neurovascular bundles, and seminal vesicles, MRI is considered the modality of choice. In addition, MRI can detect soft tissue disease and is most useful to corroborate bone scintigraphy findings (particularly when the earliest involvement is thought to be present in the bone marrow). MRI is most sensitive in the axial skeleton and pelvis, and is less effective in the ribs, chest wall, and skull.

3.2 Positron Emission Tomography (PET)

PET has advantages over conventional imaging methods because it quantitatively assesses biologic processes in vivo and can assess different processes using specific radiotracers. Processes that can be analyzed with currently available reagents include glucose and amino acid metabolism and proliferation, blood flow, and receptor status (i.e., androgen receptor). Most studies have focused on the accumulation of FDG.

3.2.1 PET scanning with fluorine-18-fluorodeoxyglucose (FDG)

During the past decade, investigators at MSKCC have shown that PET imaging in prostate cancer can be tested prospectively using rigorous, carefully controlled standard clinical trial designs traditionally reserved for therapeutics (Morris, Akhurst et al. 2002; Morris, Akhurst et al. 2005). The method has been to enroll patients registered in therapeutic clinical trials to the imaging trials to undergo imaging in conjunction with their treatment.

3.2.1.1 FDG PET and bone metastases

Previous studies found that the sensitivity of FDG PET for detecting metastases was poor. However, these were not prospective, and the populations studied were not controlled for progression, clinical state, or type of treatment (Apolo, Pandit-Taskar et al. 2008). These trials demonstrated the need for rigorous controls in prostate cancer clinical trials of new tracers. To that end, we examined a uniform cohort of patients with progressive metastatic prostate cancer. We tracked each bone lesion from inception to progression, starting with 1 scan before baseline and 2 follow-up scans after baseline, if feasible. FDG PET was sensitive enough to identify active disease and distinguish it from quiescent or noncancerous lesions (Morris, Akhurst et al. 2002).

3.2.1.2 FDG PET and evaluation of treatment effect

In our prospective study, FDG PET captured, in a single imaging modality, the information usually captured by the standard composite clinical endpoint of PSA, bone scintigraphy, and soft tissue imaging. Twenty-two patients with castrate metastatic prostate cancer registered to clinical trials of anti-microtubule chemotherapy also participated in our imaging study. We followed them to either progression or death. After 4 weeks of chemotherapy, FDG PET and PSA were in agreement in 86% of cases; in 91% of cases, FDG PET correctly identified whether the patient's disease was progressing. After 12 weeks of therapy, FDG PET, PSA, and standard imaging were compared. PET correctly identified the clinical status in 94% of cases. These data suggest that FDG PET, when studied prospectively in a population rigorously controlled for clinical state and disease progression, can effectively demonstrate treatment effects (Morris, Akhurst et al. 2005). FDG PET can demonstrate marked posttreatment changes in response to chemotherapy similar to PSA, furnishes information regarding tumor metabolism, and demonstrates antitumor effects on a lesional basis. By contrast, simultaneous bone scintigraphy demonstrates no such effects and is nearly useless in demonstrating post-treatment changes.

3.2.2 STEAP1 antigen and MSTP2109A antibody

Six-transmembrane epithelial antigen of the prostate-1 (STEAP1) is a multi-transmembrane, cell-surface antigen of unknown function that is overexpressed in 85% of human epithelial prostate cancers, and low and restricted expression only in normal prostate tissue (Hubert, Vivanco et al. 1999; Challita-Eid, Morrison et al. 2007).

Genentech has developed a humanized anti-STEAP1 monoclonal IgG1 antibody MSTP2109A that recognizes this antigen. An anti-mitotic agent monomethyl auristatin E (MMAE) based ADC DSTP3086S has been developed by Genentech, and is currently under clinical evaluation in a multicenter clinical trial in which MSKCC is participating. The ADC as a therapy takes advantage of the targeting capability of the antibody and the cytotoxic activity of MMAE, which binds to microtubules and disrupts the microtubule network. Following antigen-specific binding of the ADC, the complex of the target antigen and the conjugate is internalized and MMAE or MMAE-containing catabolites are

released intracellularly, resulting in inhibition of cell division and growth, and culminating in cell death (Doronina, Toki et al. 2003; Francisco, Cerveny et al. 2003). It is anticipated that presence of the antigen is a prerequisite for tumor targeting and delivery of the toxic pay load. We believe that it would be useful to evaluate a radiolabeled anti-STEAP1 antibody to determine the presence and intensity of target antigen on prostate tumors, in vivo.

Both the anti-STEAP1 antibody, MSTP2109A, and its ADC showed similar and high binding activity (low nanomolar) to human and cynomolgus monkey STEAP1 but no binding to rat or mouse STEAP1 orthologues. The pharmacokinetics and disposition of unconjugated antibody and its ADC are driven mainly by the anti-STEAP1 antibody component and expected to be similar between antibody and ADC.

The pharmacokinetics of anti-STEAP1 antibody, MSTP2109A and its conjugate DSTP3086A were linear in both rats and non-tumor bearing mice, as expected for non-binding species. DSTP3086A also demonstrated linearity in cynomolgus monkeys (a binding species) over the tested dose range i.e., 0.3-5.0 mg/kg), which is expected given the non-detectable level of STEAP1 expression in normal tissues.

MSTP2109A has been used in humans as the targeting moiety of an antibody drug conjugate (ADC DSPT3086S) that is being used in a Phase 1 trial at MSKCC.. The Anti-STEAP1 intact antibody MSTP2109A has not been used in humans. Safety data in non-human primates and rodent are available for both the antibody MSTP2109A and the antibody drug conjugate DSPT3086S. Anti-STEAP1 antibody MSTP2109A was included in non-GLP toxicity studies in both Sprague-Dawley rats and in cynomolgus monkeys. Single doses of 60 mg/kg MSTP2109A in rats and 2 doses every 3 weeks of 24 mg/kg MSTP2109A exhibited no toxicologically significant changes compared to vehicle control.

The primary safety signal identified for the anti-STEAP1 ADC DSTP3086S in cynomolgus monkeys and rats was bone marrow toxicity, specifically dose-dependent, reversible neutropenia. The toxicity findings with the ADC were consistent with the mechanism of action (microtubule inhibition) of the cytotoxic component (MMAE) of DSTP3086S, and were considered to be MMAE specific and independent of STEAP1 target.

A toxicity study in mice using our DFO-MSTP2109A formulation at 50 mg/kg did not show toxicity (no observable effect level).

The drug conjugate DSTP3086S has been used in 26 patients as of 08/22/2012 as part of an ongoing Phase I multi-center clinical trial - MSKCC protocol 11-016. Currently, enrollment is occurring at 2.8 mg/kg. Only two DLT have been observed consisting of transaminitis at the 2.25 mg/kg, and elevated liver enzymes in a patient treated at a dose level of 2.8 mg/kg. Reversible liver toxicity was observed in pre-clinical assessments with DSTP3086A and likely represents toxicity attributable to the drug conjugate Otherwise, treatments have been very well tolerated with very mild side effects possibly related to treatment such as Gr1 hypotension constipation or diarrhea. Other ^{89}Zr-labeled antibodies have been used in patients with good tumor localization and tolerated well (Borjesson, Jauw et al. 2006; Borjesson, Jauw et al. 2009; Dijkers, Munnink et al. 2010). As of date, the protocol continues to accrue.

3.2.2.1 ^{89}Zirconium

^{89}Zr is an attractive metallo-radionuclide for use in immuno-PET due to favorable decay characteristics. It has a 78.4h half life and a 22.7% positron yield.

Standardized methods for the routine production and isolation of high-purity and high-specific-activity ^{89}Zr using a small cyclotron are reported. Optimized cyclotron conditions reveal high average yields of 1.52 ± 0.11 mCi/muA*h at a proton beam energy of 15 MeV and current of 15 muA using a solid, commercially available ^{89}Y-foil target (0.1 mm, 100% natural abundance). ^{89}Zr was isolated in high radionuclidic and radiochemical purity (>99.99%) as (^{89}Zr)Zr-oxalate by using a solid-phase hydroxamate resin with >99.5% recovery of the radioactivity. The effective specific activity of ^{89}Zr was found to be in the range of 5.28–13.43 mCi/microg (470–1195 Ci/mmol) of zirconium.

New methods for the facile production of (^{89}Zr) Zr-chloride are reported. Radiolabeling studies using the trihydroxamate ligand desferrioxamine B (DFO) gave 100% radiochemical yields in <15 min at room temperature, and *in vitro* stability measurements confirmed that (^{89}Zr) Zr-DFO is stable with respect to ligand dissociation in human serum for >7 days. Small-animal PET imaging studies have demonstrated that free ^{89}Zr (IV) ions administered as (^{89}Zr) Zr-chloride accumulate in the liver, whilst (^{89}Zr) Zr-DFO is excreted rapidly via the kidneys within <20 min.

These results have important implications for the analysis of immuno-PET imaging of ^{89}Zr-labeled monoclonal antibodies. The detailed methods described can be easily translated to other radiochemistry facilities and will facilitate the use of ^{89}Zr in both basic science and clinical investigations (Holland, Sheh et al. 2009; Holland, Caldas-Lopes et al. 2010; Holland, Divilov et al. 2010; Holland, Divilov et al. 2010).

3.2.3 Pharmacokinetic and biodistribution of chimeric or humanized monoclonal antibodies.

We have based our antibody mass dose selection on the lack of cross reactivity of the STEAP1 antigen in normal human tissues. Furthermore we have drawn on the experience with various other antibodies to select our initial mass of DFO-MSTP2109A. The pharmacokinetics of a variety of radiolabeled antibodies has been determined in humans. Some antibodies have cross reactivity with normal antigens in vivo and thus require a certain mass amount in order to optimize pharmacokinetics and biodistribution. As an example clinical trials with ^{89}Zr trastuzumab have shown that mass of about 50 mg is necessary in trastuzumab naïve patients. In contrast, studies with the chimeric ^{89}Zr-cmAb U36 found adequate targeting when using 10 mg of the IgG. We have utilized PET imaging of I-124 anti huA33 antibody to target A33 antigen, a transmembrane glycoprotein with homology to tight junction-associated proteins that is present in normal colon and small bowel epithelium as well as in over 95% of human colon adenocarcinoma and approximately 50% of gastric and pancreatic cancers, while absent in most other human tissues and tumors (Sakamoto, Kojima et al. 2000). Our studies utilizing 10 mg of I-124 A33 have shown excellent targeting and have demonstrated Vd close to that of plasma 3,257 ± 631 mL, T1/2 of ~ 65 h and Co of ~31.9%ID/L (Carrasquillo, Pandit-Taskar et al. 2011). In our experience the use of 10 mg of I-124 chimeric antibody cG250 resulted in excellent imaging of renal cell tumors

(Divgi, Pandit-Taskar et al. 2007). The pharmacokinetic analysis in a clinical trial that used 2, 5, 10, 25 and 50 mg of I-131 cG250 showed that at the 2 mg dose levels there was faster clearance but at all other levels there was no dose response with a median T1/2 of 68.5 h. When doses of 25 and 50 mg of cG250 were administered there was less tumor uptake than at the 10 mg dose (Steffens, Boerman et al. 1997). Humanized antibody hPAM4 specifically binds a mucin glycoprotein expressed in pancreatic adenocarcinomas. A clinical trial using In-111 hPAM4 showed good targeting and similar pharmacokinetics of doses ranging from < 10 mg compared to 100 mg (Gulec, Cohen et al. 2011) with T1/2 of 91.2h. An ongoing clinical trial using I-124 GC33 humanized antibody in patients with hepatocellular carcinoma, being performed at MSKCC by Ghassan Abou-Alfa and Jorge A. Carrasquillo has shown good targeting at doses of 10 mg (unpublished observation). In contrast, at considerably higher doses of GC33 (390 mg) tumor uptake was significantly blocked, down to 1/3 of that seen with the 10 mg dose (SUV 21versus 7). Therefore it is expected that antibodies that have little cross reactivity with normal tissue will exhibit favorable pharmacokinetic for tumor imaging with mass amount of approximately 10 mg.

3.2.4 Rationale for ^{89}Zr-DFO-MSTP2109A PET use in prostate cancer

Various radionuclides are available to label monoclonal antibody for imaging, pharmacokinetics and biodistribution. Antibodies labeled with positron emitters have significant advantage compared to single photon emitters. These include the higher sensitivity, spatial resolution of PET and its quantitative ability. At MSKCC we have used various positron emitters for labeling antibodies. I-124 has been used by our group and is a good isotope for labeling non internalizing antibodies. Other groups have pioneered the use of ^{89}Zr labeled antibodies and its successful use in patients has been reported (Borjesson, Jauw et al. 2006; Dijkers, Munnink et al. 2010). It is well known that for antibodies that internalize there is significant improved retention of radio metals compared to Iodinated antibodies (Naruki, Carrasquillo et al. 1990). ^{89}Zr has an ideal half-life that is well matched to the half life of intact IgG. Correlating STEAP1 tumor targeting with the response to DSTP3086S may allow for optimal patient selection. Furthermore from this study we will determine the ability of ^{89}Zr-DFO-MSTP2109A to identify metastatic castrate resistant prostate cancer. This may allow us to perform future studies to phenotype the cancer (FDG, PSMA, STEAP1 and androgen receptor status) and may have a potential role in other drug development.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Patients with progressive castrate resistant metastatic prostate cancer are eligible to register for this study, providing all other eligibility criteria are met. Patients can be co-registered to therapeutic clinical trials, but may not receive any therapeutic treatments associated with those trials within 4 weeks prior to our imaging study.

We have based our selection of a 10 mg starting dose on the lack of cross reactivity of the STEAP1 antigen in normal human tissues and work with other antibodies reported in the literature. Cross-reactivity of MSTP2109A antibody with normal and binding affinity was similar between cynomolgus monkey and human, the cynomolgus monkey serves as a pharmacologically relevant model to predict human pharmacokinetics. DSTP3086A demonstrated pharmacokinetic linearity in cynomolgus monkey over the tested dose range of 0.3-5.0 mg/kg. Therefore it is expected that there will be no antibody sink to

rapidly clear the antibody injected. An amount of 10 mg is expected to be adequate for tumor imaging. The rationale for 10 mg is based on the fact that this is an amount that has been used successfully with other antibodies that have minimal or minor cross reactivity with normal tissues in vivo (Divgi, Pandit-Taskar et al. 2007; Carrasquillo, Pandit-Taskar et al. 2011). Nonetheless, since no pharmacokinetic or imaging studies have been performed with ^{89}Zr-DFO-MSTP2109A, initial studies must determine an acceptable mass for imaging. In order to streamline antibody mass selection, initial Cohort 1A patients (up to 6 in cohort) will receive 10 mg of ^{89}Zr -DFO-MSTP2109A and will undergo pharmacokinetics and serial imaging. Decision of whether to study a second cohort, Cohort 1B, at a higher dose (20 mg) will be based predominantly on the basis of whether adequate tumor targeting is observed (tumor detection in >75% of STEAP1 positive patients). As secondary measure we will evaluate for unexpected normal organ accumulation, based on PET imaging and evidence of rapid plasma clearance based on pharmacokinetic parameters and tumor targeting. If adequate tumor targeting is achieved we will use the starting dose of 10 mg in patients enrolled in Cohort 2. The absence of antigen sink may be confirmed if pharmacokinetics show Vd of less than 3 times plasma volume, T1/2 is greater than 50 h and if visually there is no binding to normal tissues above that expected from blood pool. If there is suggestion of antigen sink, and inadequate tumor targeting, we will evaluate an additional 6 patients who will receive total dose of 20 mg (Cohort 1B). The patients in Cohort 1B also will undergo pharmacokinetics, imaging and whole body measurements as outlined for the 10 mg cohort in section 9.0. Once the milligram dose to be administered is selected, a second group of patients (Cohort 2) consisting of up to 15 patients will be enrolled, that will have only 1 whole-body scan, at a time point to be determined based on the results of Cohort 1A or 1B patients.

Because ^{89}Zr-DFO-MSTP2109A has not been evaluated in patients, toxicity assessment will be performed using Common Terminology Criteria for Adverse Events (CTCAE) v4.

4.3 Intervention

The intervention is the administration of a single dose of the ^{89}Zr-DFO-MSTP2109A tracer for imaging purposes. In Cohort 1A or 1B, after administration of the experimental tracer, the patient will undergo up to four PET scans during the 7 days post injection, whole body probe measurements and pharmacokinetics. In Cohort 2, patients will undergo injection of ^{89}Zr-DFO-MSTP2109A, and they will undergo one PET scan from top of skull to mid thigh (this may be adjusted based on known extent of disease) and no pharmacokinetics will be performed. The primary population will be those who are planning to enroll in the therapeutic trial using DSTP3086S (11-016), although for Cohort 1A, 1B and potentially Cohort 2 patients that meet the inclusion criteria may be enrolled even if not considered for DSTP3086S therapy. No clinical management decisions will be made based on ^{89}Zr DFO- MSTP2109A imaging. Patients may not be re-imaged on this trial.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

MSTP2109A is a humanized antibody that targets STEAP1 that will be labeled with ^{89}Zr. We will use ^{89}Zr, a positron-emitting radionuclide, labeled to MSTP2109A via DFO. This protocol will explore the feasibility of ^{89}Zr-DFO-MSTP2109A PET imaging; the tracer's pharmacokinetic (PK) and biodistribution properties; its ability to detect disease relative to standard imaging modalities.

Drug Accountability

The investigator is obliged to keep sufficient documentation of the delivery and use of the investigational product. The documentation will include administration date/ time, calibration date/time, quantity, patient code, lot number and date of destruction. The investigator should maintain records that document adequately that the patients were provided the dose specified in the protocol and reconcile the medication received for the study. The label of each vial will contain the patient code and lot number, patient and radiopharmaceutical information will be entered in the radiopharmacy drug accountability forms. The investigator may assign some or all of the investigator's duties for drug accountability to an appropriate individual such as pharmacist or nuclear medicine technician who is under the supervision of the investigator.

^{89}Zr-DFO-MSTP2109A

Radiolabeling of ^{89}Zr-DFO-MSTP2109A: The **DFO-MSTP2109A** will be labeled in accordance with the MSKCC investigator sponsored IND. The study will be performed under an FDA approved IND for ^{89}Zr-DFO-MSTP2109A, no studies will be performed until the IND is approved. The final product will contain up to 5 mCi and will have been brought up to desired total antibody quantity (e.g. 10 or 20 mg) of DFO-MSTP2109A by adding cold carrier dfo-MSTP2109A as outlined in the design section. The product will have met the release criteria specified in the IND. Immunoreactivity and sterility assays will be performed post release.

The investigational product label will include the patient name, MRN and the calibration date and time. The investigational product is to be used within 8 hours of manufacturing.

Package Labeling and Formulation

Each vial will contain the following information on the label: ^{89}Zr-DFO-MSTP2109A
1 vial (10 mL) contains: up to 5 mCi / ~10 ML
Calibration date: <insert time>(EST)_on <insert date>_
Must use within 8 hours of manufacturing!
Excipients: Human serum albumin; sodium phosphate
Lot : <insert lot number>
Patient Name: <insert patient code>
Clinical study MSKCC IRB #:<insert IRB#>
PI: <insert PI name >
Caution: New Drug Limited to Investigational Use by Qualified Investigator Only
STORE AT 2°C-8°C IN A REFRIGERATOR or up to 4h at room temperature.
DO NOT USE IF CLOUDY OR CONTAINS PARTICULATE MATTER
Manufactured by: Radiohemistry Core MSKCC

Images will be corrected for attenuation and scatter and adjusted for system sensitivity and providing parametric images in terms of standardized uptake values (SUV) (= µCi found/gm tissue / (µCi injected/gm body mass).

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

To be included in this study, patients should be eligible for enrollment into protocol 11-016 (therapy with the DSTP3086S ADC) or meet all of the following criteria:

- Patients meeting the criteria for enrollment on research protocol 11-016 to receive

DSTP3086S ADC (therapeutic ADC based on MSTP2109A) will be the preferred patients for this study. Patients that are to receive DSTP3086S will not be injected with DSTP2086S until imaging with ^{89}Zr-DFO-MSTP2109A is finished, approximately 1 week.

- Adult male >21years of age
- Visible lesions by either CT, bone scan or MRI consistent with metastatic disease
    - Metastatic progressive disease
    - Imaging modalities:
      Bone scan: new osseous lesion and/or
      MRI or CT: An increase in measurable soft tissue disease or the appearance of new sites of disease.

Or

PSA Changes	Minimum No. of determinations	Interval	Percentage increase over range of values
Androgen independent	3 2	≥ 1Week ≥ 2Week	25%

- Patients with histologically confirmed prostate cancer at MSKCC
- STEAP1 antigen positive tissue known from prior IHC testing or if STEAP1 status is not known archival sample will be sent to Genentech for IHC. Samples need to be positive, when feasible metastatic lesions will be tested preferentially rather than the primary.
- Performance status of 60 or higher (Karnofsky scale) (Appendix A)
- Ability to understand and willingness to sign a written informed consent document
- PSA levels to be taken within 2 weeks of antibody administration.

6.3 Subject Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be eligible for study entry:

- Previous anaphylactic reaction to human, humanized or chimeric antibody
- Hematologic
    - Platelets <75K/mcL
    - ANC <1.0 K/mcL
- Hepatic laboratory values
    - Bilirubin >1.5 x ULN (institutional upper limits of normal)
    - AST/ALT >2.5 x ULN
- Renal laboratory values
    - eGFR < 30mL/min/1.73m2
- Patients with history of hypersensitivity reaction to any component of ^{89}Zr-DFO-MSTP2109A, including DFO.

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited Waiver of Authorization)

A member of the 11-016 clinical trial or the patient's treatment team at MSKCC will identify potential study participants. Men of all races and ethnic groups will be considered for study participation. Candidates must conform to all inclusion and exclusion criteria to be accepted into the study.

If the investigator is a member of the treatment team, s/he will screen their patients' 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.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/ research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/ research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted by either the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal protected health information (PHI) will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Estimated breakdown of target population

% Native American/Alaskan	0%
% Asian/Pacific Islander	1%
%Black Non Hispanic	3%
% Hispanic	1%
% White Non-Hispanic	94%
% Other	1%

8.1 PRETREATMENT EVALUATION

- History and physical examination
- Laboratory studies (within 2 weeks before study entry):
  - Complete blood count
  - PSA

  - Serum BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, and albumin
  - eGFR assessment
- Standard clinically indicated imaging studies (within 4 weeks before study entry or up to 2 weeks after entry, provided the patient has not received treatment). No intervening new therapy is allowed between conventional imaging studies and the ^{89}Zr-DFO-MSTP2109A
  - Bone scintigraphy
  - CT of chest, abdomen, and pelvis with contrast, unless contraindicated on clinical grounds (allergy or renal insufficiency). MRI is acceptable if CT is clinically contraindicated
  - Modified MRI of the pelvis, if clinically indicated

- If STEAP1 status is not known from prior testing patient archival tissue will be sent to Genentech to determine presence of STEAP1 antigen..

9.1 TREATMENT/INTERVENTION PLAN

9.2 Pharmacokinetics

Patients are not required to fast before ^{89}Zr-DFO-MSTP2109A injection or imaging.

Catheter insertion and Pharmacokinetics

If feasible, 2 intravenous catheters (Hep-Lock) will be placed by staff in the Nuclear Medicine department for radiopharmaceutical administration and blood sampling, or alternatively a central line may be used for injection or sampling. The intravenous catheter will be removed at the conclusion of the imaging session. If two lines are not feasible, one line will be used for both injection and PK sampling with intervening 10 cc saline flush and change of catheter hub. Patients in Cohort 2 (no pharmacokinetics, will not require a second catheter).

^{89}Zr-DFO-MSTP2109A**:** To determine clearance and for metabolite analysis of the drug, Cohort 1A and 1B patients (up to 6 patients per cohort) receiving ^{89}Zr-DFO-MSTP2109A will have serial blood samples drawn. Blood samples will be obtained in green top tube:

- Just prior to injection of ^{89}Zr-DFO-MSTP2109A (baseline)
- Approximately 5 ± 2, 15 ± 5, 30 ± 9, 60 ± 19, and 120 to 240 minutes after injection of the tracer.
- One sample at the time of each subsequent day of imaging (24 ± 8h, ~48-96h and ~120-168h post injection).

These data are used to determine the time-activity curves for plasma (% injected dose/liter). Blood is centrifuged, and the plasma pipetted and counted. Samples may be tested for breakdown products by TCA or HPLC. Blood will also be aliquoted for sampling, if in the first 3 patients no binding is observed to blood elements only plasma sampling will be counted in subsequent patients.

For each blood sample, 4-6 mL of blood will be drawn in green top tubes.

Patients in Cohort 2 will undergo injection and 1 imaging session, but no pharmacokinetics will be performed.

9.3 Imaging

^{89}Zr-DFO-MSTP2109A

Radiolabeling of ^{89}Zr-DFO-MSTP2109A: The **DFO-MSTP2109A** will be labeled in accordance with the MSKCC investigator sponsored IND. The study will be performed under an FDA approved IND for ^{89}Zr-DFO-MSTP2109A, no studies will be performed until the IND is approved. The final product will contain up to 5 mCi and will have been brought up to desired total antibody quantity (e.g. 10 or 20 mg) of DFO-MSTP2109A by adding cold carrier dfo-MSTP2109A as outlined in the design section. The product will have met the release criteria specified in the IND. Immunoreactivity and sterility assays will be performed post release.

The investigational product label will include the patient name, MRN and the calibration date and time. The investigational product is to be used within 8 hours of manufacturing.

PET scanning: In order to provide reproducible clinical data, we will acquire all ^{89}Zr-DFO-MSTP2109A PET scans on the GE PET-CT scanner DSTE at MSKCC or the same or a newer generation scanner. Once a study is begun in one scanner, it will be continued on the same scanner unless malfunction/emergency issues prevent this. Intravenous injection of ^{89}Zr-DFO-MSTP2109A (maximum of 5 mCi ± 10%) will be given over 5-15 minutes. Initially we will start with ~ 5 mCi of ^{89}Zr-DFO-MSTP2109A; the activity may be adjusted downward based on visual review of image quality. A PET-CT scan extending from top of skull to mid thighs will be performed to determine the biodistribution. The low dose CT portion of the ^{89}Zr-DFO-MSTP2109A on the first day will utilize 80 mA (low mA) and on subsequent days, we will use 10 mA in order to minimize radiation exposure. In order to minimize imaging time, lower limbs will be included only for patients with known lesions in lower limbs on previous imaging and if at least 5 other lesions are not identified in the torso.

Active lesions will be identified (Nuclear Medicine investigator and MM) based on conventional images and those thought to represent active disease based on review of the patients conventional images and treatment history (ie external radiation) will be considered as lesions for determination of antibody localization. A lesion will be considered present if there is greater localization than that expected based on blood pool distribution of the tracer. Given that at present we do not know the heterogeneity of the antigen between lesions or between primary and metastatic disease a patient will be considered positive if any of the active lesions are identified with the ^{89}Zr-DFO-MSTP2109A . We will, nonetheless tabulate the number of lesions and their status based on ^{89}Zr-DFO-MSTP2109A. When pathologic material that has been evaluated for the presence of STEAP1 is available for any specific lesion, we will correlate the presence of STEAP1 with imaging results.

Patients in Cohort 1A (and if performed Cohort 1B) will also have imaging at 4 time points post-injection to allow for selection of optimal imaging time and dosimetry determination. For these patients, top of skull to mid thigh scans will be acquired:

- Within one to four hours following injection of tracer on Day 1
- ~24 ± 8hours post-injection (Day 2)
- ~48–96 hours post-injection (once during Days 3–5)
- ~120–168 hours post injection (once during Days 6–8)

Images will be analyzed with ROI and SUVmean and max measurements will be obtained. The serial quantitative data obtained over the various organs of interest (heart, liver, spleen, kidney, lung and any other organ that exhibits uptake will be collected. These data can then be utilized to determine organ time activity curves and the dosimetry can be calculated. Uptake and clearance values will be summarized using descriptive statistics (mean, median standard deviation. Once the biodistribution and pharmacokinetics have been characterized, subsequent patients will not require serial imaging and pharmacokinetics, but rather will have a single scan at an optimal time point determined based on the patients in cohort 1A and or cohort 1B. We will determine the time at which the greatest number of lesions are seen. This is likely to be between 3-8 days, but choice will be based on the first Cohort 1 patients' data, using the most frequent day at which the most lesions are seen and/or at times at which best contrast is observed determined visually. Thus, for the remainder of the patients in Cohort 2, PET scan will be performed once. The timing of this scan will be determined based on findings from Cohort 1A and/or 1B, as described above.

Infusion reactions with MSTP2109A intact IgG have not been evaluated. Infusion reaction to the ADC DSTP3086S antibody drug conjugate in 18 patient treated thus far have been minor and not clinically significant (i.e. none or Gr1).In the event of fever, rigors, shortness of breath, or other evidence of infusion reaction, patients may receive diphenhydramine 25-50 mg IV and Tylenol 650 mg PO as felt to be clinically appropriate by the treating physician. The emission data are typically acquired for 3–10 minutes per bed position depending upon the time post-injection and visual quality of the images. Index lesions will be identified based on the patient's conventional diagnostic imaging.

Images will be stored as Digital Imaging and Communications in Medicine (DICOM) on the PACS and HERMES. Images to be sent out to Genentech will be burned on a CD or equivalent by patient. All images will be anonymized according to institutional policy with the patients code used as identifiers.

No decision on the patients' health care management will be made on the basis of Imaging with ^{89}Zr-DFO-MSTP2109A.

9.4 Whole body probe measurements (Cohort 1)

Patients in Cohort 1 will undergo whole body dose measurement using a NaI probe placed at ~3 meters from the patient. These measurements will be performed the day of injection of ^{89}Zr-DFO-MSTP2109A before voiding and after first void, and at each time the patient returns for imaging (typically less than 5 minutes).

9.5 Assessment for Toxicity

Safety Outcome Measures (CTCAE v4)

Infusion Reaction

Patients will be monitored during and after ^{89}Zr-DFO-MSTP2109A infusion for 90 minutes after the infusion. Patients who experience infusion-related symptoms should be managed as directed in Table 1.

The safety and tolerability of ^{89}Zr-DFO-MSTP2109A will be assessed using the following primary safety outcome measure:

- Incidence, nature, and severity of adverse events up to 1 week following antibody administration.
- Change in vital signs during administration

Table 1
Management of Infusion-Related Symptoms

Infusion-Related Symptoms	Guidance
Grade 1	• Slow or hold infusion • Give supportive treatment • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion
Grade 2	• Slow or hold infusion • Give supportive treatment • Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion
Grade 3 or Grade 4	• Discontinue infusion • Give supportive treatment Patient may be imaged if sufficient tracer has been administered and the patient is stable, at the discretion of the administering investigator.

Given that this is a humanized antibody and the antibody will be administered only once under this protocol the likelyhood of development of human anti human antibody is low. Patients enrolled, who are being treated with the ADC under protocol 11-016 will be monitored for the presence of anti-ADC antibodies as is currently stated in that study. Thus the presence, if any, of anti MSTP2109A, that would potentially interfere with ADC targeting will be evaluated in those patient on protocol 11-016. Baseline serum and 4-6 wk post infusion serum (serum separator or red top tube) will be collected and banked for future determination of HAHA response as requested by the FDA (Dr. Carrasquillo lab, storage approximately -70^{o}C).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Laboratory Safety Assessments

Blood testing:
Hematology and blood chemistry assessments (CBC, PSA, serum BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, albumin, blood glucose levels, and serum testosterone level) will be done at the time points described in Table 2. Additional blood tests may also be performed at the discretion of the investigator for the purposes of planning treatment administration, dose modification, or investigation and follow-up of adverse events. These additional tests will not be documented in the CRF.
Serum samples collected from baseline and 4-6 weeks after administration of DFO-MSTP2109A will be stored to assay for immune response to ^{89}Zr-DFO-MSTP2109A (assay to be developed).This assay may be done in house or shipped to Genentech for processing.

Physical examination:
A physical examination including, but not limited to, general appearance, skin, neck, eyes, ears,

throat, lungs, heart, abdomen, lymph nodes, extremities, and nervous system will be performed. The physical examination will include examination of known and suspected sites of disease. Physical examination results, height and weight will be recorded at baseline .

Performance Status

Performance status will be assessed using the Karnofsky Performance Status scale (Appendix A).

Vital Signs

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

Table 2
Schedule of Assessments

Cohort 1 (A and B):

	Screening[a]						
	Within 4 weeks	**Within 14 days**	**Day 1**	**Day 2**	**Days 3-5**	**Days 6-8**	**4-6 wks post dose**
Informed consent	X						
Demographics	X						
Medical history	X						
Concomitant medications	X						
Physical exam	X						
Performance status	X						
Vital signs[b]	X		X	X	X	X	
Laboratory studies[c]		X				X	
Serum sample for banking		X					X
Radiographic studies[d]	X						
IHC for STEAP[e]	Prior to enrollment						
^{89}Zr-DFO-MSTP2109A tracer administration			**X**				

Adverse events on day of imaging			X	X	X	X	
Serial whole-body scans (Cohort 1A and 1B)[f]			X	X	X	X	
Serial whole-body probe[g]			X	X	X	X	
Serial blood samples[h](Cohort 1A and 1B)			X	X	X	X	

[a] Screening evaluation should be performed following informed consent and within 4 weeks before study entry, except when noted otherwise. Evaluations performed as standard of care before informed consent but within the 4-week window need not be repeated.

[b] Vital signs will be monitored prior to infusion and every 30 minutes for at least 2 h or later if the patient is still in the department for imaging.

[c] Within 14 days laboratory studies include CBC, PSA, serum BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, albumin, blood glucose levels, and serum testosterone level. All laboratory studies are to be performed up to 2 weeks before study entry (serum testosterone level may be up to 4 weeks before study entry). At Days 6 to 8 CBC and comprehensive labs will be obtained.

[d] Radiographic evaluations include bone scintigraphy, CT of chest, abdomen and pelvis (MRI is acceptable if CT is clinically contraindicated), and modified MRI of the pelvis, if clinically indicated. All radiographic studies are to be performed within 4 weeks before, or up to 2 weeks after study entry, provided the patient has not received treatment.

[e] sample sent out to Genentech

[f] Following injection with the ^{89}Zr-DFO-MSTP2109A tracer, the patients enrolled in the study (Patients Cohort 1 A and or 1B) will have serial whole-body PET-CT scans (WBS) performed to determine the biodistribution of the tracer. PET scans will be acquired: 1–4 hours following injection of the tracer, ~24 h ± 8 h post-injection, ~48–96 hours post injection, and ~120–168 hours post injection. Slight variations in times due to scheduling or technical difficulties will not be considered violations

[g] Whole body counts (WBC) using a probe will be performed during the imaging in the first 12 patients and the exact time recorded:

- Within 0.1 to four hours following injection of tracer on Day 1 (prior to voiding) and post voiding
- 24 ± 8 hours post-injection (Day 2)
- ~48–96 hours post-injection (once during Days 3–5)
- ~120–168 hours post injection (once during Days 6–8)

[h] For the first 12 patients enrolled, serial blood samples will be obtained for biodistribution, metabolite analysis of the ^{89}Zr-DFO-MSTP2109A compound will be performed on selected samples. Samples will be obtained just prior to injection of the ^{89}Zr-DFO-MSTP2109A tracer, and at 5 ± 2 minutes, 15 ± 5, 30 ± 9, 60 ± 19 minutes, and 120 – 240 minutes after the injection of the tracer on 24±8, and at the time of each subsequent day of imaging , ~48-96, ~120-168, slight variations in times due to scheduling or technical difficulties will not be considered violations.

Cohort 2:

	Screening[a]		**Day 1**	**Day TBD**	**Follow up**	
	Within 4 weeks	**Within 14 days**			**~1 weeks post dose (Day6-8)**	**4-6 weeks post dose**
Informed consent	X					
Demographics	X					
Medical history	X					
Concomitant medications	X					
Physical exam	X					
Performance status	X					
Vital signs[b]	X		X	X		
Laboratory studies[c]		X		X		
Serum sample for banking		X				X
Radiographic studies[d]	X					

^{89}Zr-DFO-MSTP2109A tracer administration			**X**			
Adverse events **Phone assessment[e]** **Torso PET scan[f](Cohort 2)**			X	X X	X X	

[a] Screening evaluation should be performed following informed consent and within 4 weeks before study entry, except when noted otherwise. Evaluations performed as standard of care before informed consent but within the 4-week window need not be repeated.

[b] Vital signs will be monitored prior to infusion and every 30 minutes for at least 2 h or later if the patient is still in the department for imaging.

[c] Laboratory studies include CBC, PSA, serum BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, albumin, blood glucose levels, and serum testosterone level. All laboratory studies are to be performed up to 2 weeks before study entry (serum testosterone level may be up to 4 weeks before study entry). Second set of laboratory on TBD will consist of CBC and comprehensive. At TBD CBC and comprehensive will be repeated.

[d] Radiographic evaluations include bone scintigraphy, CT of chest, abdomen and pelvis (MRI is acceptable if CT is clinically contraindicated), and modified MRI of the pelvis, if clinically indicated. All radiographic studies are to be performed within 4 weeks before, or up to 2 weeks after study entry, provided the patient has not received treatment.

[e] A phone call will be used to assess for changes in concomitant medications and any adverse events after all scans have been completed if the scanning time is less than 6-8 days.

[f] For the 13th through 27th patients enrolled, only 1 PET scan will be performed, at a time point to be determined based on data from the first 12 patients.

11.0 TOXICITIES/SIDE EFFECTS

Risks

^{89}Zr-DFO-MSTP2109A 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. Although any exposure to ionizing radiation has the potential to cause some harm to tissue, the radiation exposures in this study are comparable to the low-level exposures associated with common diagnostic procedures such as CT scanning. There remains 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. This risk is much smaller that the clinical risks posed by the patient's current cancer.

DFO-MSTP2109A

Potential risks associated with DFO-MSTP2109A are similar to those of other humanized antibody and include allergic reactions, characterized by fever, chills, and sometimes rashes or hives. Less likely shortness of breath can occur. Rare allergic reactions can present as shock or death or swelling of the throat. 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.

Radiation Dosimetry

Normal-organ radiation absorbed doses and the effective dose for ^{89}Zr-DFO-MSTP2109A in human were estimated based on measured time-activity data in mice. The time-activity data (percent of the injected dose per gram (%ID/gm) versus time (t) post-administration) for each organ were fit to an exponential functions and the resulting function were analytically integrated (incorporating the radioactive decay of ^{89}Zr) to yield the residence time (cumulated activity) of ^{89}Zr in each organ. The mouse organ ^{89}Zr residence times were converted to ^{89}Zr residence times in human organs (for the 70-kg Standard Man anatomic model) by adjusting for the difference in fractional organ masses between mice and humans. The resulting human residence times were then entered into the OLINDA/EXM radionuclide dosimetry program, which implements the MIRD (Medical Internal Radionuclide Dosimetry) algorithm, to yield the normal-organ radiation absorbed doses (in rad) and effective dose (in rem) for ^{89}Zr-DFO-MSTP2109A in man. Assuming a 5-mCi administered activity of ^{89}Zr-DFO-MSTP2109A and a low-dose (80 mA) and three very-low-dose (10-mA) CT scans are to be performed, with approximate CT effective doses of 0.90 rem and 0.11 rem the radiation dosimetry is tabulated below.

Table 3. ^{89}Zr-DFO-MSTP2109A Absorbed Doses in 70-kg Standard Man per MIRD (OLINDA) Formalism Based on Biodistribution Data in Mice[1]

^{89}Zr-DFO-MSTP2109A AP Antibody Radiation Doses in the 70-kg Standard Man

^{89}Zr Administered Activity:	**5**	**mCi**
# of 80-mA CT scans:	**1**	
Organ dose per 80-mA CT scan:	**0.90**	**rem**
# of 10-mA CT scans:	**3**	
Organ dose per 10-mA CT scan:	**0.10**	**rem**
Total CT organ dose:	**1.20**	**rem**

	Absorbed Doses			
	^{89}Zr-DFO-MSTP2			P2109A
	rad/mCi	rad/5 mCi	(rad)	
Adrenals	**1.56**	**7.80**	**9.00**	
Brain	**0.68**	**3.42**	**4.62**	
Gallbladder Wall	**1.32**	**6.60**	**7.80**	
LLI Wall	**1.52**	**7.60**	**8.80**	
Small Intestine	**1.25**	**6.25**	**7.45**	
Stomach Wall	**1.39**	**6.95**	**8.15**	
ULI Wall	**1.34**	**6.70**	**7.90**	
Heart Wall	**1.50**	**7.50**	**8.70**	
Kidneys	**2.33**	**11.7**	**12.9**	
Liver	**1.81**	**9.05**	**10.25**	
Lungs	**2.82**	**14.10**	**15.30**	

Muscle	**1.21**	**6.05**	**7.25**
Pancreas	**1.42**	**7.10**	**8.30**
Red Marrow	**3.26**	**16.3**	**17.5**
Osteogenic Cells	**4.59**	**23.0**	**24.2**
Skin	**0.71**	**3.55**	**4.75**
Spleen	**1.98**	**9.90**	**11.10**
Testes	**0.82**	**4.09**	**5.29**
Thymus	**1.11**	**5.55**	**6.75**
Thyroid	**1.03**	**5.15**	**6.35**
Urinary Bladder Wall	**1.04**	**5.20**	**6.40**
Total Body	**1.31**	**6.55**	**7.75**
Effective Dose Equivalent	**1.87**	**9.35**	**10.55**
Effective Dose	**1.68**	**8.40**	**9.60**

[1]mouse data obtained with ^{89}Zr-DFO-MSTP2109A, conjugate generated at MSKCC. .

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Positive lesions on ^{89}Zr-DFO-MSTP2109A will be defined visually as a focus of accumulation of radioactivity that is deemed to not be physiologic and is higher than adjacent or contralateral background. Antibody scan will be read blinded from clinical history and conventional imaging modalities. Two different experienced, blinded readers will visually analyze the ^{89}Zr-DFO-MSTP2109A scans, and SUVmax/mean will be determined in lesions identified and in normal organs and blood pool. To study the accumulation and biodistribution of ^{89}Zr-DFO-MSTP2109A in patients with progressive prostate cancer, the accumulation of ^{89}Zr-DFO-MSTP2109A will be assessed for each site and compared with the baseline radionuclide bone scan, FDG PET/CT, CT, and/or MRI imaging. The definition of a positive lesion will be a lesion identified by an experienced reader on conventional imaging CT/MRI, bone scan, and/or FDG scan consistent with metastatic disease, as is currently done clinically. Lesions on ^{89}Zr-DFO-MSTP2109A or conventional imaging will be read in a scale of 1 to 5, 1= negative, 2 = probably negative, 3= not sure, 4= probably positive and 5= definitively positive. Once this is done, a consensus master list of lesions will be created that compares all imaging conventional imaging modalities(CT/MRI, FDG PET, bone scan), only those lesions that are conspicuously positive (i.e., “4 or 5”) by imaging will be considered as a positive site of disease. Discrepant findings between findings on conventional imaging and ^{89}Zr-DFO-MSTP2109A modalities will be considered false positive or false negative. Although it would be ideal to biopsy any site that is considered abnormal this is not logistically feasible or ethically acceptable. Successful imaging will be considered a sensitivity of detection of $\geq$ 75% of patients that are STEAP1 positive. One or 2 non-blinded readers (access to clinical, laboratory and imaging data) will identify “positive lesions” .

As a first level, we will compare site by site. Since the individual modalities are based on different mechanisms of uptake, they may not have exact correspondence in space, since bone scan is a 2D modality and looks at bone reaction and ^{89}Zr looks at tumor antigen expression and is a 3D modality.

For this purpose, we have made a list of standardized anatomic sites, to make sure that a positive

lesion would have a positive ^{89}Zr-DFO-MSTP2109A uptake. As a second level, we will compare lesion by lesion. Sensitivity and specificity of the imaging modalities will be compared in those patients receiving the better/"adequate" antibody mass. The "better/adequate" dose is defined as that which will allow us to visualize the targeted number of lesions defined and will consist of either 10 or 20 mg of DFO-MSTP2109A antibody.

12.1 Bone Scan

Each lesion will be evaluated using the same 5-point scale. These findings will be compared with that of ^{89}Zr-DFO-MSTP2109A PET scanning.

Any discrepant reading of the antibody images or conventional images will require review of the images by both readers who will discuss and reach a consensus, if a consensus cannot be reached the finding shall be considered "not sure" and categorized as negative.

12.2 CT and MRI

Available CT and/or MRI imaging done clinically will be used as a correlative diagnostic imaging tool to compare to results of ^{89}Zr-DFO-MSTP2109A PET scanning. Sensitivity of ^{89}Zr-DFO-MSTP2109A PET scanning to detect lesions will be compared with routine imaging including CT, MRI, FDG PET, and bone scans. Furthermore soft tissue lesions greater than 2 cm on CT or MRI will also be compared to ^{89}Zr -DFO-MSTP2109A in order to overcome the issues of partial volume.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Participation in the study is strictly 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.

14.1 BIOSTATISTICS

14.2 Primary Objective

The primary objective of this protocol is to determine the feasibility, safety and tolerability of single dose administration of ^{89}Zr-DFO-MSTP2109A antibody.

A patient with STEAP1 positive tumor will be considered antibody-imaging-positive if 20% or more of the active lesions are detectable (STEAP1 positivity is an eligibility criterion for protocol 11-016 which forms the basis of eligibility for this protocol; see section 6 for details). Active lesion means any lesion that was identified by conventional imaging methods and clinical data at baseline. We have selected a low threshold of 20% for this first imaging study for 3 reasons: 1) we do not know what the heterogeneity of antigen expression is within a number of lesions in the same patient; 2) we will consider positive any lesion based on conventional clinical imaging criteria, in which case some lesions considered positive may be false positive and more importantly 3) our main emphasis is to evaluate whether patients whose tumor images are positive with ^{89}Zr-DFO-MSTP2109A are more likely to have a response to the antibody based drug conjugate used under

protocol 11-016. Thus, we do not want to discard this agent if we can use it as a **theranostic** (defined as an agent that is integrated into the drug development process so as to guide patient selection and drug development) for the development of the antibody base drug conjugate being used under protocol 11-016. Nonethe less, we intend to evaluate treatment response of all available lesions in this way we will maximize our ability to determine the relationship between uptake of antibody and response.

If, for any patient, there is evidence of an "antigen sink" based on rapid clearance < 50 h or Vd>3 times plasma volume, we will consider a patient antibody-imaging-positive if 20% or more of the active lesions are visualized. The presence of an "antigen sink" may bind a significant amount of antibody and make less available for binding to tumor.

Antibody imaging will be considered feasible if 75% of the patients are antibody-imaging-positive as defined above..We will enroll 6 patients (cohort 1A) at the 10mg dose level for an initial decision on feasibility. If 4 or more of these patients have 20% or more of their active lesions detectable by ^{89}Zr-DFO-MSTP2109A then we will consider the agent feasible for imaging, otherwise we will proceed to cohort 1B. If the true feasibility rate is 40%, this rule will affords more than 82% chance that cohort 1B will be opened for enrollment; this probability is less than 17% if the true feasibility is 75%. We will also require that none of these patients experience dose severe toxicity attributable to the initial 10 mg dose before cohort 1B is opened for enrollment.

If severe adverse effect (grade 3 or 4 CTCAE) is observed in any cohort we will review with MSKCC-DSMC and IRB before continuing with accrual. If 3 patients in cohort 1A do no not show acceptable imaging, as described above, we will proceed to cohort 1B.

In cohort 1B, 6 more patients will be enrolled at a higher dose (20mg) for safety and pharmacokinetic evaluation. Serial blood draws will be used to estimate the pharmacokinetic profile of the 10 and 20mg ^{89}Zr-DFO-MSTP2109A in this patient population. Pharmacokinetic analysis will be performed using a non-compartmental analysis; standard parameters such as AUC, clearance, volume of distribution, and Co will be reported. Descriptive statistics will be tabulated. If 3 patients in Cohort 1B have antibody negative imaging accrual will stop. If 4 patients in cohort 1B have positive imaging we will move to cohort 2 using the best imaging dose from cohort IA or 1B..

Based on pharmacokinetic analysis from cohorts 1A and 1B an optimal time point (based visually on optimal image quality for tumor detection and clinically/logistically feasible) will be determined for imaging and cohort 2 will enroll up to 15 patients at the dose also determined from cohorts 1A or 1B. These patients will undergo a single whole-body scan at the optimal time point. The ability of ^{89}Zr-DFO-MSTP2109A to detect tumors will be estimated from this cohort using the proportion of antibody-imaging-positive patients (within +/-22% if the true detection rate is 75%).

This study does not intend to find the maximal tolerated dose of DFO-MSTP2109A. This is a diagnostic agent that is expected to have low incidence of adverse events. Patients will be monitored closely looking for evidence of adverse events. Because patients will likely start new therapies within 2 weeks of receiving ^{89}Zr-DFO-MSTP2109A only short term toxicity will be evaluated. The safety and tolerability of ^{89}Zr-DFO-MSTP2109A will be assessed using the following primary safety outcome measures: Incidence and nature of incidence, nature, and severity of adverse events; and change in vital signs and clinical laboratory results. Incidence and

severity of adverse events will be summarized with descriptive statistics.

Dosimetry: SUVmax/mean (that can easily be converted to %ID/g) in normal organs of patients from Cohort 1A and Cohort 1B will be determined and this data over time will be used to determine the residence time in each visualized organ (liver, spleen, kidney and lung), other organ will be evaluated if clinically appropriate. The median residence time value will be used in OLINDA software to calculate the dosimetry.

14.3 Secondary objectives

One of our secondary exploratory objectives is to estimate the uptake in tumors. We will present lesion-based summary statistics for the uptake adjusted for clustering. Another secondary objective is to correlate ^{89}Zr-DFO-MSTP2109A imaging to response to treatment in those patients recruited to protocol 11-016 DSTP3086S ADC. Outcome measures to be correlated include those that are outlined in the parent protocol 11-016 and include PSA response, RECIST response, presence or absence of new bone scan lesion and progression free survival. We will use Kaplan-Meier estimates and 95% confidence intervals to correlate these outcomes with imaging response.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 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.

15.3 Randomization

This research study does not require randomization procedures.

16.1 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. Records will be retained and securely stored for a minimum of 2 years after the completion of all study activities.

Data will be entered throughout the duration of the trial as patients are enrolled. Accrual is expected to last 2 years.

16.2 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.
Random-sample data quality and protocol compliance audits will be conducted by the study team at least once a year, more frequently if indicated.

16.3 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 serial vital signs will be monitored every half hour for at least 2 h or later if the patient remains in the department. Patients will be queried for adverse events up to 6-8 days after infusion.

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

17.1 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).

A limited waiver of authorization will be utilized to effectively screen and track patients in screening, however the recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal protected health information (PHI) will be maintained as part of a screening log.

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-DFO-MSTP2109A PET scans, whole body probe counts, radiotracer drugs, extra blood draws (to measure radiotracer activity), and optional biopsies.

17.2 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).

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- 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
- 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.

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

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

SAE Reporting To Genentech:

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

- Serious AE reports that are related to the ^{89}Zr-MSTP2109A will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the ^{89}Zr-MSTP2109A will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Investigators must report all SAEs to Genentech within the timelines described above. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

17.4 SAE Recording and Grading

17.3.1 Recording

The investigator must assess each event to determine if it meets the criteria for classification as a serious adverse event (SAE) or serious adverse drug reaction (ADR). An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- Results in death
- Is life-threatening
- Results in inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is medically significant in the opinion of the investigator

All SAEs that occur any time a patient is on study (i.e., as soon as the informed consent has been signed) or within 30 days of the ^{89}Zr-DFO-MSTP2109A scan must be reported, regardless of the suspected relationship to ^{89}Zr-DFO-MSTP2109A. Any SAE occurring more than 30 days after the ^{89}Zr-DFO-MSTP2109A scan must be reported if a causal relationship to ^{89}Zr-DFO-MSTP2109A is suspected.

Because the subjects enrolled in this clinical investigation will be exclusively patients with advanced prostate cancer, these patients will typically have received extensive medical care before and at the time of enrollment in the study. Such medical care includes extensive diagnostic radiological studies, such as x-rays, CT scans, and nuclear medicine studies (e.g., bone scans) and, in at least some cases, external beam radiation therapy, brachytherapy, or both. The additional radiation doses associated with the ^{89}Zr-

DFO-MSTP2109A study will typically represent a small increment in their "lifetime" exposures, given the number of clinical studies (CT, bone scan, FDG scan) and that many of these patients will have had primary radiation to their prostate or external beam radiation to bone.

When accounting for many tests per year, the radiation doses (on the order of 10 rem) lie well within the "low-dose" range—well below the threshold doses (typically on the order of 100 rem or greater) for any known deterministic effects. A detailed description of the expected dosimetry from the ^{89}Zr-DFO-MSTP2109A is included (Table 3). The dose of ^{89}Zr-DFO-MSTP2109A per administration (~5mCi) gives the lowest amount that would be consistent with the research goal, namely, biodistribution, metabolism, and pharmacokinetics of the compound.

17.3.2 Grading Severity

All adverse events will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the CTCAE v4.0.

17.3.3 Attributing Causality

The investigator will evaluate the potential relationship between all clinical AEs, abnormal laboratory values, and the ^{89}Zr-DFO-MSTP2109A, and categorize the relationship according to the descriptions in Table 5. Abnormal laboratory values of clinical significance that were present at baseline and did not change in either severity or frequency during the experimental therapy or intervention and/or that can obviously be attributed to the underlying disease will be evaluated by the investigator and recorded in the "unrelated" category.

Table 6. Relationship of Adverse Event to ^{89}Zr-DFO-MSTP2109A

Relationship	Description
Unrelated	AE is clearly not related to the ^{89}Zr-DFO-MSTP2109A
Unlikely	AE is unlikely related to the ^{89}Zr-DFO-MSTP2109A
Possible	AE may be related to the ^{89}Zr-DFO-MSTP2109A
Probable	AE is likely related to the ^{89}Zr-DFO-MSTP2109A
Definite	AE is clearly related to the ^{89}Zr-DFO-MSTP2109A

Adverse events will be defined graded using CTCAE V4.0.

18.1 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

Appendix A

ADC	Antibody drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Asparagine aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood count
cG250	Chimeric G250 antibody
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
DFO	Desferrioxamine B
18F	Fluor-18
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IgG1	Immunoglobulin G1 subclass
IHC	Immunohistochemistry
124I	Iodine-124
IND	Investigational New Drug
IRB/ PB	Institutional Review Board/ Privacy Board
IV	Intravenous
KPS	Karnofsky Performance Scale
mCi	milliCurie
mg	milligram
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PHI	Protected Health Information
PK	Pharmacokinetics
PO	Per os (by mouth)
PSA	Prostate-specific antigen
PSMA	Prostate Specific Membrane Antigen
rad	Radiation absorbed dose
RECIST	Response Evaluation Criteria in Solid Tumors
rem	Roentgen equivalent man
ROI	Region of interest
SAE	Serious adverse event
STEAP1	Six-transmembrane epithelial antigen of the prostate-1
SUV	Standardized uptake value
WBC	Whole Body Count
WBS	Whole Body Scan
^{89}Zr	Zirconium-89

APPENDIX B: Karnofsky Performance Status

Karnofsky Performance Scale

Condition	%	Comments
Able to carry on normal activity and to work; no special care needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead