First-in-human imaging of multiple myeloma using ^{89}Zr-DFO-daratumumab, a CD38-targeting monoclonal antibody

PROTOCOL FACE PAGE FOR MSK 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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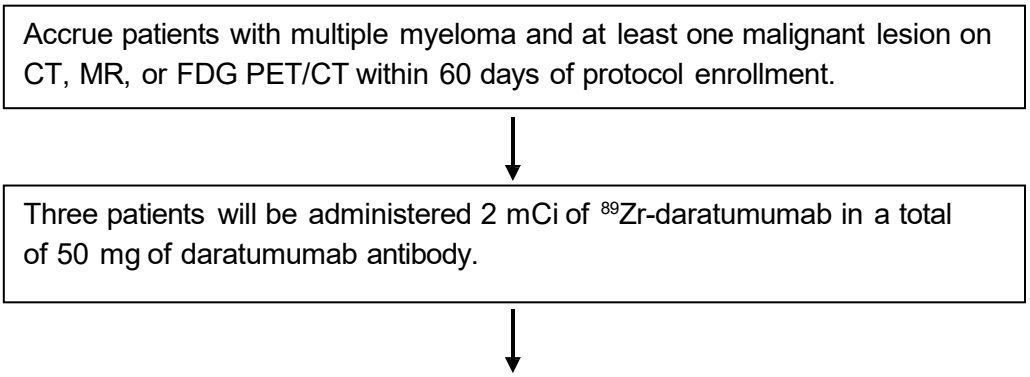
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase I/II study with the goal to assess the feasibility of using the anti-CD38 monoclonal antibody daratumumab, labeled with Zirconium-89 (^{89}Zr) through deferoxamine (DFO), known as ^{89}Zr-DFO-daratumumab, for PET imaging of multiple myeloma. CD38 is an established therapeutic target in multiple myeloma that is expressed at high density by almost all myeloma cells. Daratumumab binds directly to CD38. Imaging with ^{89}Zr-DFO-daratumumab may therefore provide a sensitive and specific way to detect and stage multiple myeloma. In addition, the degree of uptake of ^{89}Zr-DFO-daratumumab may predict the effectiveness of daratumumab therapy. Finally, daratumumab labeled with a beta or alpha emitter may eventually be used to treat multiple myeloma.

The study has two phases: a short phase 1 to confirm the safety of the imaging agent, identify the suitable antibody mass for imaging, and identify the most appropriate time for imaging; and a subsequent phase 2 to correlate tumor uptake on ^{89}Zr-DFO-daratumumab PET serum M protein concentration, percentage plasma cells on bone marrow biopsy, and patient response to daratumumab/lenalidomide therapy.The total patient population is up to 30 (6-12 evaluable patients in phase 1 and 18-24 evaluable patients in phase 2). The study outline is as follows:

Phase I (total of 6-12 evaluable patients). At least 6 and up to 12 evaluable patients will be needed to determine pharmacokinetics and radiation dosimetry for ^{89}Zr-DFO-daratumumab. Only the number of patients needed to determine pharmacokinetics and radiation dosimetry will be enrolled in phase I.



Administered activity (1 to 5 mCi) of radioactivity and total amount of administered antibody (3 to 50 mg) will be adjusted in subsequent patients in order to maximize image quality.

Patients in phase I will have up to 4 PET/CT scans, multiple blood draws, whole-body counts, and safety monitoring to determine pharmacokinetics, radiation dosimetry, and safety of ^{89}Zr-DFO-daratumumab for PET/CT imaging.

Phase II (total of 18-24 evaluable patients). After pharmacokinetics and radiation dosimetry are determined in phase I, additional patients will be enrolled in phase II.

Accrue patients with multiple myeloma and at least one malignant lesion on CT, MR, or FDG PET/CT within 60 days of protocol enrollment.

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Administer ^{89}Zr-daratumumab at a dose and antibody amount, as optimized in phase I. Obtain PET/CT imaging at the time point optimized in phase I.

Correlate ^{89}Zr-daratumumab PET uptake with serum M protein concentration, percentage plasma cells on bone marrow biopsy, and patient response to daratumumab/lenalidomide therapy.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Phase I objectives

- Determine the safety, pharmacokinetics, and radiation dosimetry of ^{89}Zr-DFO-daratumumab PET/CT imaging of CD38 expression in multiple myeloma.

- Determine the optimal parameters for imaging with ^{89}Zr-DFO-daratumumab, including antibody mass and time post-administration imaging.

Phase II objective

- Obtain data on the correlation between tumor uptake of ^{89}Zr-DFO-daratumumab with patient serum M protein concentration, percentage of plasma cells on bone marrow biopsy, and patient response to daratumumab/lenalidomidetherapy

Patients who are inevaluable will be replaced until 30 evaluable patients have been accrued to both Phase I and Phase II of this study.

3.0 BACKGROUND AND RATIONALE

Multiple myeloma

Multiple myeloma is a plasma cell neoplasm and the second most common hematologic malignancy in adults (1). Large independent studies have shown that the genetic and molecular landscape underlying multiple myeloma pathogenesis is massively heterogeneous, including several recurrent mutations in *KRAS*, *NRAS*, *TP53*, and other genes (2-4). However, no single mutation is seen in all or most patients with multiple myeloma. Prospective studies have demonstrated that multiple myeloma is consistently preceded by a precursor state—monoclonal gammopathy of undetermined significance and smoldering myeloma (5, 6). Smoldering myeloma is an earlier, asymptomatic stage of myeloma and is defined based on clinical and laboratory characteristics. It carries an increased risk of progression to multiple myeloma (7). Only limited information is available regarding the genetic profiles of smoldering myeloma and preliminary studies have suggested comparable mutational load and copy number profiles of myeloma cells in smoldering myeloma and multiple myeloma patients (8, 9).

Previously we reported results from two prospective studies including patients with high-risk smoldering myeloma and newly diagnosed multiple myeloma (10). In both cohorts, all patients were treated uniformly with 8 cycles of combination therapy including carfilzomib, lenalidomide, and dexamethasone (KRd) followed by two years of lenalidomide maintenance (KRd-R). We recently expanded our early results (10) by enrolling additional patients with high-risk smoldering myeloma and capturing a longer median follow-up of almost four years. Our promising early results of high overall response rate and minimal residual disease (MRD) negativity among high-risk smoldering myeloma patients treated with modern KRd-R combination therapy (10) prompted us to prospectively investigate the baseline genetic landscape and patterns of mutations in our cohort of patients. As a reference group, we included 40 patients with newly diagnosed multiple myeloma who received the same KRd-R therapy (10). In brief; the overall response rate was 100%. With median potential follow-up of 43.3 months, 10 (63%) remain in MRD negativity and the estimated 4-year progression-free and overall survival is 71% and 100%, respectively (*in press*). Importantly, we report differences in mutational patterns in patients with high-risk smoldering myeloma and newly diagnosed multiple myeloma, reflected in a lower frequency of mutations in significant myeloma genes (6.6% vs. 45%) and *NF-KB* pathway genes (6.6% vs. 25%) (*in press*). Based on these data, important differences are evident in the genetic landscape of high-risk smoldering

myeloma and newly diagnosed multiple myeloma patients, suggestive of a more treatment-responsive biology in early disease.

As mentioned above, we have pioneered the development of modern therapy in early disease, which has resulted in unprecedented high rates of MRD negativity (10). However, we still see MRD-positive disease in many patients (10). Also, many patients convert back from MRD-negative to MRD-positive status. A major clinical limitation with current MRD assays is the fact that they are based on blind bone marrow biopsies/aspirates (11). It is clinically well known that myeloma can grow in a patchy manner in the bone marrow, particularly at stages with lower-level disease burden. Therefore, current bone marrow biopsy/aspirate-MRD assays are inherently limited by potential sampling error (i.e., false MRD negativity) (11). Furthermore, current standard PET/CT assessment using FDG as a tracer is limited for the assessment of myeloma. It is based on glucose uptake and cell proliferation. Because myeloma cells typically have low cell proliferation, FDG is only positive in about 70% of patients with established myeloma bone disease. In addition, there is a high rate of false positivity due to inflammatory and degenerative causes (12). Clearly, myeloma-specific PET tracers are currently lacking.

Current monitoring of treated multiple myeloma patients is based on blood tests focusing on secreted abnormal immunoglobulins (monoclonal proteins and free light chains). Based on current guidelines, therapy is not initiated until the patient develops symptoms or the biomarkers are elevated (13). Similar to multiple myeloma patients, in patients with smoldering myeloma the current monitoring is based on blood tests focusing on secreted abnormal immunoglobulins. This remains the current standard although is it well established that all myeloma cells do not secrete proteins (14-16).

Design of a targeted PET tracer for multiple myeloma

To overcome the inherent dilemmas with blind bone marrow biopsies/aspirates and the limitations of blood-based protein markers, we have developed a targeted immuno-PET imaging agent to rule out MRD in multiple myeloma and its precursors. Specifically, we have developed a PET tracer based upon daratumumab for tracking CD38 expression. CD38 is expressed on the surface of virtually every multiple myeloma cell. Daratumumab (Darzalex®, Janssen Biotech) is a clinically approved antibody targeting CD38 for the treatment of multiple myeloma. In our laboratory, Daratumumab has been prepared for radiolabeling with ^{89}Zr ($t_{1/2}$ = 78.4 h) through conjugation with desferrioxamine (DFO). Western blot, flow cytometry, saturation binding assays, and internalization assays have been utilized to characterize CD38 expression and binding of daratumumab in an OPM2 myeloma cell line. A murine xenograft model of the OPM2 cell line has been generated for further *in vivo* studies. Longitudinal PET imaging is being performed following injection of 5-10 MBq ^{89}Zr-DFO-daratumumab out to 120 h post-injection. Based on our successful preclinical results, this project is designed as a first-in-human trial of our CD38-targeted immuno-PET imaging agent. Primary objectives are to determine the safety, pharmacokinetics, and radiation dosimetry of ^{89}Zr-DFO-daratumumab PET/CT imaging of CD38

expression in multiple myeloma. In addition, we will determine the optimal timing and mass of antibody for imaging and acquire preliminary data on the sensitivity and specificity of ^{89}Zr-DFO-daratumumab to visualize multiple myeloma lesions in patients. These are the first steps to develop a more sensitive and specific imaging test to assess MRD in multiple myeloma.

^{89}Zirconium (^{89}Zr) was chosen as the radionuclide for immuno-PET due to favorable decay characteristics. It has a 78.4 h half life, allowing for multiple-day circulation times for antibodies, which are needed to increase target-to-background uptake. Standardized methods for the routine production and isolation of high-purity and high-specific-activity ^{89}Zr using a small cyclotron are currently used at MSK and other institutions. 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). 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. 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 more than 7 days.

Preclinical data on ^{89}Zr-DFO-daratumumab PET/CT

Before animal studies were conducted, the expression of CD38 on OPM2 cells was determined by flow cytometry. After conjugation of daratumumab to the DFO chelate, preservation of the immunoreactivity (>90%) of the antibody was determined by Lindmo assay in OPM2 cells.

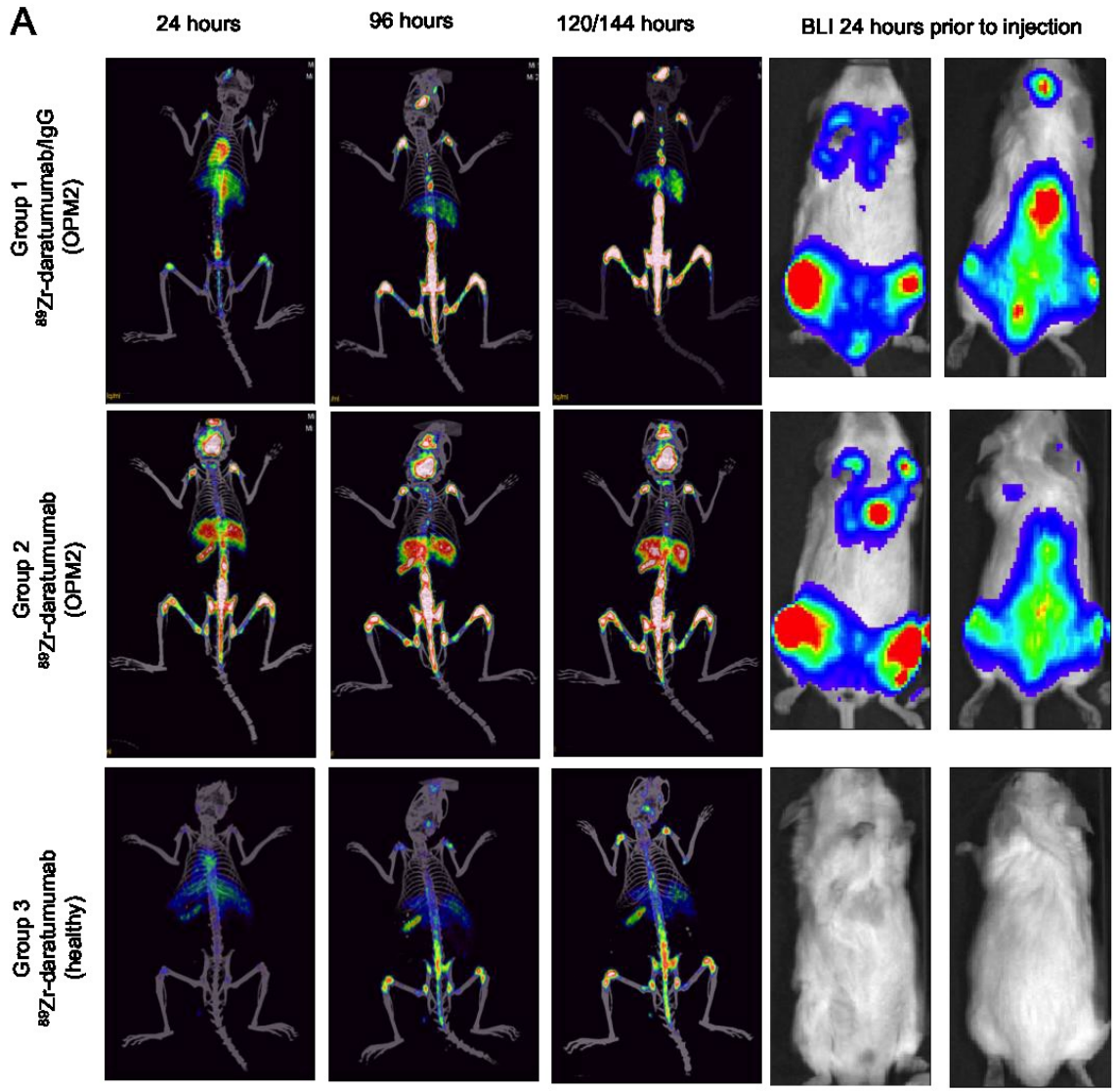
For the preliminary study, NSG mice were injected with a human multiple myeloma (MM) tumor cell line (OPM2) intravenously approximately four weeks before administration of the radiolabeled antibody. The intravenous injection of 1×10^6 OPM2s in NSG miceis a well-validated model to study MM bone disease (4). Myeloma cells accumulate in the bone marrow of the femurs and sternum primarily. We used OPM2 cells that were stably transduced with firefly luciferase to allow for *in vivo* imaging.

Due to the NSG background of the mice used in this study, one group of mice received a coinjection with an excess of human IgG. It has been shown that the biodistribution of radiolabeled antibodies is affected by the lack of endogenous IgG in mouse strains bearing a SCID mutation (Sharma, SK, et al. Cancer Res; 78(7) April 2018). This manifests itself in reduced tumor uptake in these mice, along with higher nonspecific spleen and bone uptake. This uncharacteristic distribution can be blocked by coninjection of an isotype IgG.

Mice were separated into three groups (**Figure 1A**) (n=5). Groups 1 and 2 were injected with OPM2 cells; Group 3 consisted of healthy mice. Each mouse was injected with approximately 200µCi (70 µg) of ^{89}Zr-DFO-daratumumab via the tail vein. Group 1 was co-injected with cold IgG (400 µg) to block nontarget uptake in the spleen. PET/CT imaging was conducted at 24, 96, and 144 hours post-injection. Images are coronal maximum intensity projections. Biodistribution was performed at

120 hours post-injection for Group 2 and at 144 hours post-injection for Groups 1 and 3 (**Figure 1B**).

Approximately 24 hours prior to PET/CT imaging, mice were imaged by BLI so as to correlate the antibody distribution to the actual distribution of OPM2 cells. Free 89Zr which is not chelated to DFO *in vivo* is osteophilic and will become incorporated into bone due to its high affinity for phosphate. Because the OPM2 cells reside in the bone marrow in this model, it was necessary to extract the bone marrow from the bone for a more accurate view of the biodistribution. Both hindlimbs from each mouse were collected and the bone marrow was extracted by centrifugation. With this technique, about 30 milligrams of bone marrow per mouse can be reproducibly obtained.


A
24 hours
96 hours
120/144 hours
BLI 24 hours prior to injection
Group 1
89Zr-daratumumab/IgG
(OPM2)
Group 2
89Zr-daratumumab
(OPM2)
Group 3
89Zr-daratumumab
(healthy)

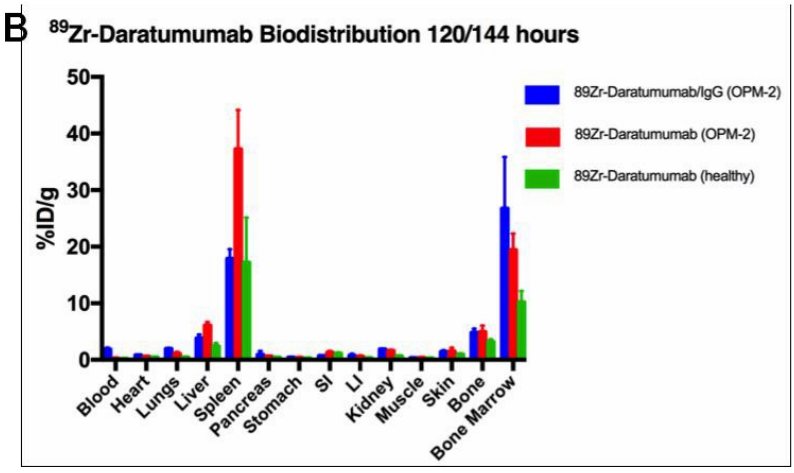

B
89Zr-Daratumumab Biodistribution 120/144 hours
%ID/g
50
40
30
20
10
0
89Zr-Daratumumab/IgG (OPM-2)
89Zr-Daratumumab (OPM-2)
89Zr-Daratumumab (healthy)
Blood
Heart
Lungs
Liver
Spleen
Pancreas
Stomach
SI
LI
Kidney
Muscle
Skin
Bone
Bone Marrow

Figure 1: (A) Group 1 was co-injected with cold IgG (400 µg) to block nontarget uptake in the spleen. PET/CT imaging was conducted at 24, 96, and 144 hours post-injection. Images are coronal maximum intensity projections. **(B)** Biodistribution was performed at 120 hours post-injection for Group 2 and at 144 hours post-injection for Groups 1 and 3.

At 24 hours post-injection, Group 1 mice showed a significant amount of ^{89}Zr-dartumamab in the blood circulation. Group 2 mice show earlier uptake in the bones of the hind limbs and pelvic region, but also increased accumulation in the liver and spleen as compared to Group 1. At later time points, Group 1 mice show increasing accumulation in the hind limbs, pelvic region, and sternum. Group 2 mice also show higher accumulation in the hind limb region, but the sternum cannot be resolved due to significant uptake in the liver and spleen. The uptake in these bones is consistent targeted imaging of multiple myeloma in this cancer model and confirmed by the bioluminescence data. Importantly, the healthy control mice show significantly lower uptake in the bone as seen by imaging. (Data from the laboratory of Dr. Jason Lewis, unpublished data.)

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This protocol will perform first-in-human imaging of patients with ^{89}Zr-DFO-daratumumab. Patients with known CD38-positive malignancy will be recruited.

For phase I patients:

- Biodistribution of ^{89}Zr-DFO-daratumumab will be obtained from the serial PET/CT images.
- Blood pharmacokinetics of ^{89}Zr-DFO-daratumumab will be obtained from serial blood draws.
- Radiation dosimetry will be determined from whole-body counts, blood counts, and PET/CT images.
- Safety of the imaging dose of ^{89}Zr-DFO-daratumumab will be documented through assessment of symptoms and physical examinations.
- The optimal antibody mass of non-radiolabeled (cold) daratumumab to be added to radiolabeled ^{89}Zr-DFO-daratumumab will be determined by administration of varying amounts of “cold” (i.e., non-radioactive) daratumumab.
- The optimal timing of ^{89}Zr-DFO-daratumumab PET/CT imaging will be determined by sequential scanning of patients over 1-8 days post-administration.

For phase II patients we will correlate tumor uptake of ^{89}Zr-DFO-daratumumab with:

- Serum M protein concentration;
- Percentage of plasma cells on bone marrow biopsy; and
- Patient response to daratumumab/lenalidomidetherapy.

Serum M protein concentration and bone marrow biopsy will be required for all phase II patients. As all myeloma patients will have clinically standard serum M protein concentration and bone marrow biopsy results, this should not impede patient recruitment.

4.3 Intervention

^{89}Zr-DFO-daratumumab PET/CT and PET/CT interpretation: ^{89}Zr-DFO-daratumumab PET/CT studies will be performed as hybrid PET/CT examinations for attenuation correction, lesion localization, and availability of additional findings on CT images. The patient will be positioned on a GE PET/CT scanner. The CT component will be obtained utilizing a low mA (80 mA) to minimize radiation exposure. 3D imaging will be obtained from skull apex to feet (approximately 10 bed positions). ^{89}Zr-DFO-daratumumab PET/CT images will be reconstructed using iterative reconstruction and displayed in a multiplanar format. All routinely applied corrections will be implemented and the reconstructed images parameterized in terms of standard uptake values (SUVs).

^{89}Zr-DFO-daratumumab PET/CT scans will be interpreted by a nuclear medicine physician experienced in the use of routine and novel research PET radiotracers. Physiologic ^{89}Zr-DFO-daratumumab uptake will be determined from the images. Physiologic ^{89}Zr-DFO-daratumumab may be expected in the blood pool, liver, spleen, and kidneys, similar to other radiolabeled antibodies. Radiotracer uptake in areas that are not physiologic will be graded both qualitatively and semiquantitatively. For qualitative scoring, we will use a scale of one to five where 1 = definitely normal, 2 = probably normal, 3 = equivocal, 4 = probably abnormal, and 5 = definitely abnormal. Semiquantitative analysis of tracer uptake will be performed for all lesions receiving a score of 4 or 5, as well as for apparently normal background blood pool. Three-dimensional regions of interest (ROIs) will be placed over grade 4 and 5 lesions and the mediastinal blood pool and tracer uptake will be quantified using maximum SUV = decay-corrected maximum ROI activity (µCi/ml) / (injected dose (µCi) / body weight (g)). ^{89}Zr-DFO-daratumumab PET/CT images are for research purposes only, and will not be used to influence patient care. This approach was recently utilized for first-in-human work with ^{89}Zr-DFO-pertuzumab, MSK IRB 17-059.

For patients in phase I, the following will be performed to determine ^{89}Zr-DFO-daratumumab tissue distribution, pharmacokinetics, and radiation dosimetry:

1. ^{89}Zr-DFO-daratumumab kinetic measurements: Blood and serum samples will be weighed and counted in a scintillation well counter calibrated for ^{89}Zr. Immediately before or after each PET/CT imaging session, whole-body activities will be measured using a scintillation detector probe, with whole-body net count rates converted to the percent of the administered activity by normalization to the first whole-body net count rate (i.e., the count rate measured shortly after administration of the ^{89}Zr-DFO-daratumumab).

2. Timing of ^{89}Zr-DFO-daratumumab PET/CT: Radiolabeled antibodies normally require several days to clear blood pool, accumulate in targets, and yield reliable tumor images (17). ^{89}Zr-DFO-daratumumab will be administered on day 0. PET/CT images will be obtained on post-administration days 1, 2-4, 5-6, and/or 7-8 following administration of ^{89}Zr-DFO-daratumumab to determine the optimal time point for imaging. (At least three PET/CT images at different time points are required to calculate dosimetry—i.e., the radiation dose received throughout the body—for the novel radiotracer. We will obtain three or four sets of images at the time points described above.)

For patients in phase II, a single PET/CT scan will be performed using the dose of ^{89}Zr-DFO-daratumumab, antibody mass of daratumumab, and timing determined from phase I patients. No blood samples for dosimetry or whole-body counts will be performed. The research PET/CT will be performed to correlate ^{89}Zr-DFO-daratumumab PET uptake with serum M protein concentration (measured prior to ^{89}Zr-DFO-daratumumab PET/CT), percentage plasma cells on bone marrow biopsy (measured prior to ^{89}Zr-DFO-daratumumab PET/CT), and patient response to daratumumab/lenalidomide therapy. The radiologist evaluated the ^{89}Zr-DFO-daratumumab PET/CT will be blinded to patient serum M protein concentration and percentage of plasma cells on bone marrow biopsy. As patient response to daratumumab/lenalidomide therapy will be subsequently determined, that information will not be avialable at the time of ^{89}Zr-DFO-daratumumab PET/CT. Combined daratumumab/lenalidomide therapy is a standard-of-care combination for treatment of myeloma, with response rates of up to 90%. Single agent daratumumab therapy has lower response rates, and thus the combination therapy is the current appropriate standard of care. Please see section 14.0 for statistical details.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

^{89}Zr-DFO-daratumumab: ^{89}Zr-DFO-daratumumab is an investigational new drug (not FDA approved) produced on demand by the Cyclotron-Radiochemistry Core at MSK (under the direction of Dr. Jason Lewis), under GMP conditions adequate for clinical trials. ^{89}Zr-DFO-daratumumab is composed of the native CD38 targeting drug daratumumab labeled with the positron-emitting radionuclide zirconium 89 (^{89}Zr) through the linker DFO. Daratumumab is an FDA-approved monoclonal antibody. ^{89}Zr is a metallo-radionuclide with a half-life of 78 hours, long enough to allow favorable biodistribution of radiolabeled antibodies. The final product will be radiolabeled and tested for sterility, endotoxin, identity, purity, and potency as described in the chemistry, manufacturing, and controls section of the IND application. ^{89}Zr-DFO-daratumumab will be administered intravenously over a 30-60 minute period.

No patient will receive ^{89}Zr-DFO-daratumumab until the FDA approves the IND.

Administered activity of ^{89}Zr-DFO-daratumumab: For phase 1 patients, the administered activity of ^{89}Zr-DFO-daratumumab will be between 1 and 5 mCi in 3 mg radiolabeled ("hot") antibody. Successful imaging of other ^{89}Zr-labeled antibodies will be performed with 1-5 mCi (17, 18). Changes in administered activity alter counts of radioactivity detected by the PET/CT camera and may affect image quality. The administered activity of ^{89}Zr-DFO-daratumumab will start at 2 mCi, as this is an administered activity which has resulted in successful imaging in past radio-antibody imaging trials, including the principle investigator's trial of 89Zr-DFO-pertuzumab (IRB 17-059). If 2 mCi does not provide sufficient radioactive counts for successful imaging, then we will increase the administered dose to 5 mCi. If 2 mCi provides more radioactive counts than is needed for successful imaging, then we will attempt imaging with 1 mCi, to see if successful imaging can be obtained with a lower exposure to radiation dose. This approach was recently utilized for first-in-human work with ^{89}Zr-DFO-pertuzumab, MSK IRB 17-059.

For phase 2 patients, the optimal dose of ^{89}Zr-DFO-daratumumab determined in phase I will be utilized.

Antibody mass of ^{89}Zr-DFO-daratumumab: Radiolabeled PET antibodies have been shown to demonstrate superior imaging when administered together with cold antibody to block non-specific binding (17). For phase I patients, to determine the optimal antibody mass for imaging, 0, 17, or 47 mg of unlabelled ("cold") antibody will be added to the radiolabeled antibody to produce total administered antibody masses of 3, 20, and 50 mg. Antibody masses between 20 and 50 mg per dose have provided the best image contrast in several prior studies with radiolabeled antibodies at MSK (18-20). Changes in total amount of administered antibody alter distribution of specific and non-specific binding of antibody and may affect image quality. The first three patients will be imaged with a total antibody mass of 50 mg based on MSK's prior experience with Zr-labeled antibodies, as higher antibody mass usually results in better imaging due to cold antibody occupying non-specific in vivo binding sites. Antibody mass will be reduced to 20 mg in the next three patients to evaluate the effect on image quality. The choice of total antibody mass for each group of three patients will depend on the quality of images already obtained from prior patients. Thus, in this trial the first three patients will receive an antibody mass of 50 mg, and the fourth through sixth patients will receive an antibody mass of 20 mg. If an improvement in image quality is observed at 20 mg, or if image quality at 50 mg and 20 mg is comparable, then any subsequent patients will receive an antibody mass of 3 mg. If image quality worsens at 20 mg, then the antibody mass will be increased back to 50 mg for the remaining patients. The means of determining whether one antibody mass is superior to another is described in section 14.0, Biostatistics.

In summary, the antibody mass received by patients will be:

- Patients 1, 2 and 3: 50 mg
- Patients 4, 5, 6: 20 mg
- Any subsequent patients: 50 mg, 20 mg, or 3 mg, depending on imaging results of the prior 6 patients.

For any further patients, antibody mass will be determined based on imaging results from prior patients. This approach was recently utilized for first-in-human work with ^{89}Zr-DFO-pertuzumab, MSK IRB 17-059.

For phase 2 patients, the optimal daratumumab antibody mass determined in phase I will be utilized.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Age 21 years or greater
- Histologically/Immunohistochemistry confirmed CD38-positive multiple myeloma
- At least one tumor lesion on CT, MRI, or FDG PET/CT within 60 days of protocol enrollment
- ECOG performance status 0 to 2
- For Phase II patients only: plan for initiation of standard-of-care daratumumab/lenalidomide therapy.

6.3 Subject Exclusion Criteria

- Life expectancy < 3 months
- Pregnancy or lactation
- Patients who cannot undergo PET/CT scanning because of weight limits. PET/CT scanners may not be able to function with patients over 450 pounds.
- History of anaphylactic reaction to humanized or human antibodies or a Grade 3 or 4 administration reaction during a daratumumab administration.

7.0 RECRUITMENT PLAN

Patients who meet the above inclusion and exclusion criteria will be invited to participate in the study by their primary oncologist. We will invite men and women of all races/ethnicities on an equal basis.

Consenting professionals will meet with the patients and obtain informed consent in either the oncologist's clinic or the Molecular Imaging and Therapy Service clinic. As patients in Phase I will require multiple visits, a small honorarium ($400) will be provided to patients that complete the trial, in order to compensate them for their time and expenses. No payments will be offered to patients in phase II.

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).

We anticipate an accrual rate of 1-2 patients per month. We may accrue multiple patients at the same time however, in phase I, tracer administration for the next patient will wait until the prior patient has completed all anticipated scans.

8.1 PRETREATMENT EVALUATION

Prior to enrollment in the protocol, the following will be available:

- History and physical exam
- Histology demonstrating CD38-positive multiple myeloma.
- Clinically standard imaging scans (CT, MR, FDG PET/CT) demonstrating at least one focus of suspected malignancy within 60 days of protocol enrollment
- Negative blood pregnancy test for women of childbearing potential

9.1 TREATMENT/INTERVENTION PLAN

For women of childbearing age, pregnancy will be excluded before ^{89}Zr-DFO-daratumumab administration. This will be accomplished by the use of a serum pregnancy test within two weeks of ^{89}Zr-DFO-daratumumab administration or a urine pregnancy test on the day of ^{89}Zr-DFO-daratumumab administration.

^{89}Zr-DFO-daratumumab administration: ^{89}Zr-DFO-daratumumab will be administered intravenously on day 0.

Prior to ^{89}Zr-DFO-daratumumab administration, the patient will be premedicated with Acetaminophen 650 mg orally, Diphenhydramine 25mg intravenously, and Dexamethasone 20 mg intravenously.

Physical exam and vital signs will be obtained prior to the ^{89}Zr-DFO-daratumumab administration, as well as 30-60 minutes post-administration to document the absence of any acute toxicity from the low imaging dose of ^{89}Zr-DFO-daratumumab.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

For Phase I patients: Patients in phase I will have up to 4 PET/CT scans, multiple blood draws, whole-body counts, and safety monitoring to determine pharmacokinetics, radiation dosimetry, and safety of ^{89}Zr-DFO-daratumumab for PET/CT imaging.

^{89}Zr-DFO-daratumumab PET/CT: Patients will undergo up to 4 serial ^{89}Zr-DFO-daratumumab PET/CT scans. PET/CT images will be obtained on days 1, 2-4, 5-6, and/or 7-8 following administration of ^{89}Zr-DFO-daratumumab. All CT scans will be acquired as low-dose CT scans to minimize radiation exposure. PET/CT images will be obtained from skull apex to feet (approximately 10 bed positions) and reconstructed using our standard iterative reconstruction algorithm.

Radiation dosimetry of ^{89}Zr-DFO-daratumumab: The measured time-dependent blood, whole-body, and PET-derived organ activities will be fit to exponential functions and the corresponding ^{89}Zr residence times calculated by integration of the respective exponential functions, accounting for the physical decay of the ^{89}Zr. The resulting residence times will then be entered into the *OLINDA* radiation dosimetry program and mean organ-absorbed doses (in rad and rad/mCi) and the effective dose (in rem and rem/mCi) calculated.

Whole-body count measurements: Patients will undergo whole-body count rate measurements using a sodium iodide (NaI) probe placed approximately 3 meters from the patient. Pre- and post-first-void measurements will be performed within 6 hours of administration of ^{89}Zr-DFO-daratumumab, as well as each time the patient returns for PET/CT scanning.

Blood samples for determination of pharmacokinetics of ^{89}Zr-DFO-daratumumab: Approximately 3-5 ml of blood will be drawn at each of the following time points. Drawn blood will be collected in lavender-top tubes (to prevent coagulation).

- Day 0: Pre-dose
- Day 0: Within 30 minutes of completion of dose administration
- Day 0: 30-60 minutes of completion of dose administration
- Day 0: 60-120 minutes of completion of dose administration
- On each return visit for PET/CT imaging

After all samples have been collected, weighed blood and serum aliquots will be counted in a scintillation well counter calibrated for ^{89}Zr and counts will be corrected for time of decay.

For Phase II patients: ^{89}Zr-DFO-daratumumab will be administered at a dose and antibody amount as optimized in phase 1. PET/CT imaging will be obtained at the time point optimized in phase I. ^{89}Zr-DFO-daratumumab PET ue will be correlated with serum M protein, percent plasma cells on bone marrow biopsy, and patient response to daratumumab therapy as described in section 4.2.

11.0 TOXICITIES/SIDE EFFECTS

^{89}Zr-DFO-daratumumab: ^{89}Zr-DFO-daratumumab is a diagnostic (not therapeutic) agent, and the doses of ^{89}Zr-DFO-daratumumab used for PET/CT are very low compared to approved therapeutic daratumumab doses, and are expected to have a very low incidence of adverse events. Prior results from patients who received ^{89}Zr-DFO-trastuzumab as part of protocol #14-156 demonstrated no grade 3 or 4 toxicities, with one patient reporting chills the night of antibody administration, which is a recognized side effect of antibody administration. Nevertheless, patients will be monitored closely for evidence of adverse events, including vital signs before and after tracer administration. Phase I patients will be scheduled for a brief visit to the nuclear medicine clinic the day after tracer administration to confirm that there have been no side effects requiring treatment. If a severe adverse effect (Common Terminology Criteria for Adverse Events grade 3 or 4) attributable to ^{89}Zr-DFO-daratumumab occurs in any patient, then further use of ^{89}Zr-DFO-daratumumab will be suspended and the protocol will be reviewed with the MSK Data Safety Monitoring Committee.

Less Likely: Infusion or allergic reactions, which may include fevers, chills, tiredness, rashes, hives, tachycardia, or shortness of breath.

Radiation risk: The effective dose from 2 mCi of ^{89}Zr-DFO-daratumumab is estimated to be between 1.74 and 1.90 centiGray (see Appendix 1). A low milliampere CT scan, performed as part of the hybrid ^{89}Zr-DFO-daratumumab PET/CT, contributes an additional effective dose of 0.9 rem. The effective dose from an experimental ^{89}Zr-DFO-daratumumab PET and up to 4 CT examinations is in the range of 7.1 to 7.4 centiGray, which is comparable to the dose from other ^{89}Zr-labeled radiolabeled antibodies received by oncology patients in MSK clinical trials. A table of projected radiation doses to normal tissues based on extrapolation from animal biodistribution, including contribution from CT scans, is shown in Appendix 1. No specific patient instructions are required for the low level of radioactivity encountered from the doses of ^{89}Zr administered in this protocol (21).

Pregnancy risk: Even low diagnostic levels of radiation, such as those that will be received in this protocol from the investigational ^{89}Zr-DFO-daratumumab PET/CT studies, have been associated with a risk of inducing childhood cancer. A negative pregnancy test will be required before a patient is accrued to this protocol. Patients on this protocol will be advised not to become pregnant for at least one month following administration of ^{89}Zr-DFO-daratumumab.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

There is no therapy arm or measurement of response to the imaging agent. This is a diagnostic imaging study; therefore, no criteria for therapeutic response are included. The doses of ^{89}Zr-DFO-daratumumab used for imaging are very low compared to therapeutic daratumumab doses, and we do not expect a significant therapeutic effect from the diagnostic (not therapeutic) dose of this agent. This protocol will be a first-in-human CD38-targeted imaging study with ^{89}Zr-DFO-daratumumab PET/CT.

Flow chart for phase 1 patients

	Screening	On study				
	Within 60 days	Day 0	Day 1	Day 2-4	Day 5-6	Day 7-8
Informed consent	X					
Medical history	X					
Physical exam	X					
Prior radiographic studies (CT, MR, FDG PET/CT) reviewed	X					
Histology/Immunohistochemistry proof of CD38-positive myeloma	X					
Vital signs		X				
^{89}Zr-DFO-daratumumab administration		X				
Adverse events monitored		X	X	X	X	X
Whole-body counts		X	X	X	X	X
Blood samples for pharmacokinetics		X	X	X	X	X
PET/CT scan			X	X	X	X

Flow chart for phase 2 patients

	Screening	On study		
	Within 60 days	Day 0	Day TBD[1]	Up to 2 years
Informed consent	**X**			
Medical history	**X**			
Physical exam	**X**			
Prior radiographic studies (CT, MR, FDG PET/CT) reviewed	**X**			
Histology/Immunohistochemistryproof of CD38-positive myeloma	**X**			
Pregnancy test for women with active menstrual cycles	**x**			
Vital signs		**X**		
^{89}Zr-DFO-daratumumab injection		**X**		
Adverse events monitored		**X**	**X**	
PET/CT scan			**X**	
Standard-of-care daratumumab therapy and monitoring of disease response				**X**

[1] The day of the PET/CT scan will be determined bythe results from the phase I patients.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Patients may withdraw from the protocol voluntarily at any time.
- Development of unacceptable toxicity.
- The patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis).

14.0 BIOSTATISTICS

This is a pilot first-in-human trial of ^{89}Zr-DFO-daratumumab in patients with multiple myeloma.

In phase I, we will determine the tissue distribution, pharmacokinetics, radiation dosimetry, and safety of ^{89}Zr-DFO-daratumumab for PET/CT imaging.

The organ/tissue uptake and dosimetry following IV injection of ^{89}Zr-DFO-daratumumab will be determined. Standardized uptake value (SUV) in various organs will be estimated from VOI analysis of clinical images and converted to activity-time curves. The areas under the activity-time curves will be derived by integration, converted to residence times, and used as input to the OLINDA/EXM dosimetry program to obtain absorbed dose estimates for normal tissues. Additionally, SUVmean, max and peak for lesions will be summarized with descriptive statistics.

Pharmacokinetic analysis will be performed using a compartmental analysis (SAAM or GraphPad V5); standard parameters such as AUC, clearance, volume of distribution of central compartment, and Co will be reported. Descriptive statistics will be tabulated.

There are three scan parameteers that will be optimized in phase I: administered radioactivity, antibody mass, and time of scan. The primarily method of determining these variables will be quantitative, based of the proportion of lesions identified of the research ^{89}Zr-DFO-daratumumab scans. The number of lesions in the patient will be determined from the lesions seen on CT, MR, and FDG PET/CT studies perfromed within the last 60 days. Then the number of ^{89}Zr-DFO-daratumumab avid lesions will be counted on the ^{89}Zr-DFO-daratumumab PET/CT. The greatest proportion of lesion lesions detected on ^{89}Zr-DFO-daratumumab PET will be the primary method of determining optimal scan parameters. Since it is possible that the same proportion of lesions may be identified using different scan parameters and that contrast may vary between the different imaging days, a consensus visual assessment of a group of experienced Molecular Imaging and Therapy investigator who will grade the studies separately (GU, CR, and JO), will be used to make the final decision. This qualitative assesement will be a secondary method, after using the primary quantitative comparison of number of lesions visualized. It is possible that these three scan parameters will interact to effect optimal scan parameters. By sequential modification of administered activity and antibody mass and obtaining imaging at multiple time points for each combination of activity and antibody mass, we will obtain adequate comparisons with which to make quantitative and qualitative comparisons. This approach has been successfully used in prior radio-antibody imaging trials, including the principle investigator's trial of 89Zr-DFO-pertuzumab (IRB 17-059).

^{89}Zr-DFO-daratumumab is a diagnostic (not therapeutic) agent, and the doses of ^{89}Zr-DFO-daratumumab used for PET/CT are very low compared to approved therapeutic daratumumab doses. We expected to have a very low incidence of adverse events. Prior results from patients who received ^{89}Zr-DFO-trastuzumab as part of protocol #14-156 demonstrated no grade 3 or 4 toxicities, with one patient reporting chills the night of antibody administration, which is a recognized side effect of antibody administration. Nevertheless, phase I patients will be monitored closely for evidence of adverse events, including vital signs before and after tracer administration and a brief visit to the Nuclear Medicine Clinic the day after tracer administration to confirm that there are no side effects requiring treatment. This diagnostic agent is not expected to result in significant adverse effects, but the number and propotion of patients with any adverse effect from tracer administration will be deermined.

In the phase II portion, we will correlate tumor uptake of ^{89}Zr-DFO-daratumumab with serum M protein concentration, percentage plasma cells on bone marrow biopsy and patient response to daratumumab/lenalidomidetherapy. The total planned sample size for both phases is 30 evaluable patients; hence Phase II component will enroll 18-24 evaluable patients, depending on how many patients were needed for the Phase I. The total sample size was chosen given budgetary concerns.

Phase II patients will be monitored for adverse effects, including vital signs before and after tracer administration. This disagnostic agent is not expected to result in significant adverse effects, but the number and propotion of patients with any adverse effect from tracer administration will be deermined.

Serum M protein concentration: Serum M protein concentration (including heavy-chains and serum free light-chains) is a standard of care laboratory measurement and reported as a continuous metric. High serum M protein concentration represents high tumor burden in the blood. We will explore the correlation between ^{89}Zr-DFO-daratumumab PET SUVmax and serum M protein concentration using scatterplots and Spearman's rank correlation.

Percentage plasma cells on bone marrow biopsy: Percentage plasma cells on bone marrow biopsy is a standard of care pathology measurement and reported as a continuous metric. High percentage plasma cells on bone marrow biopsy represents a high tumor burden. We will explore the correlation between ^{89}Zr-DFO-daratumumab PET SUVmax and percentage plasma cells on bone marrow biopsy by scatterplots and Spearman's rank correlation.

Patient response to daratumumab/lenalidomidetherapy: We will evaluate response by one dichotomous and one continuous method. Dichotomous evaluation will categorize patients as complete/partial response vs. stable disease/progressive disease, as defined by International Myeloma Working Group consensus criteria for response (IMWG). Continuous evaluation will assess best anti-tumor response as a percentage of change from baseline by IMWG, and will be graphed as a waterfall plot. We will explore the correlation between ^{89}Zr-DFO-daratumumab PET SUVmax and anti-tumor efficacy of daratumumab using a Wilcoxon test and an ROC curve in the case of IMWG response and scatterplots with Spearman rank correlation in the case of percent change from baseline.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

N/A

16.1 DATA MANAGEMENT ISSUES

16.2 Quality Assurance

Accrual rates and 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 study team for discussion and action.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new 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/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Clinical Research Administration. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at:https://one.mskcc.org/sites/pub/clinresearch/Pages/protocol-review-committees/data-and- safety-monitoring-committee.aspx

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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 QA) and departmental procedures for quality control, plus 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 Center's 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.

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Confidentiality: All patient records will be kept as confidential as is possible under the law. No individual identifiers will be used in any reports or publication resulting from this study, but the data will be used in the interest of the ongoing research.

Benefits: There is no guarantee of any benefits.

Incentives: $400 will be provided to patients/subjects for participation in Phase I of the study. No incentive will be provided to patients in phase II.

Costs: The research ^{89}Zr-DFO-daratumumab radiotracer and ^{89}Zr-DFO-daratumumab PET/CT scan(s) will be performed without charge. Patients in phase II requiring a bone marrow biopsy will be performed without charge. The patient will be responsible for the costs of standard medical care.

Alternatives: The patient can choose not to be on this study and follow the treatment outlined by his or her treating physician.

Treatment and Compensation: If the patient is injured as a result of participating in this study, emergency care, hospitalization, and outpatient care will be made available by the hospital and billed to the patient and his insurance company as part of his medical expenses. If the patient desires additional information about the consent process, research patient's rights, or research-related injury, he/she may call the Patient Representative's office at (212) 639-8254

17.2 Privacy

MSK'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

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

Any additional SAE reporting information required by the sponsor or drug supplier should be included in this section.

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 1: ^{89}Zr-DFO-daratumumab Radiation Dosimetry

A primary objective of this study is to quantify the biodistribution and pharmacokinetics of ^{89}Zr-DFO-daratumumab in human patients and thereby generate absorbed radiation dose estimates. Absorbed dose projections for humans, based on animal biodistribution data from the lab of Dr Jason Lewis, are provided below.

^{89}Zr-DFO-daratumumab: Absorbed Radiation Dose estimates for 70-kg Standard Man
Includes X-ray CT (for anatomic fusion and attenuation correction)
Fields in blue must have values entered

			# of Injections/CT scans
Activity of ^{89}Zr-DFO-daratumumab	2	mCi	1
low dose CT scan (80mA)	0.9	cGy	4
ultra-low dose CT scan (10mA)	0.11	cGy	0

Absorbed Dose

	^{89}Zr-DFO-daratumumab [1]		total ^{89}Zr-DFO-daratumumab + CT
Target Organ	cGy/mCi	cGy per inj	cGy
Adrenals	1.78	3.6	**7.2**
Brain	1.11	2.2	**5.8**
Breasts	0.91	1.8	**5.4**
Gallbladder Wall	1.45	2.9	**6.5**
LLI Wall	1.39	2.8	**6.4**
Small Intestine	1.46	2.9	**6.5**
Stomach Wall	1.35	2.7	**6.3**
ULI Wall	1.38	2.8	**6.4**
Heart Wall	3.27	6.5	**10.1**
Kidneys	2.21	4.4	**8.0**
Liver	2.16	4.3	**7.9**
Lungs	2.86	5.7	**9.3**
Muscle	1.30	2.6	**6.2**
Ovaries	1.28	2.6	**6.2**
Pancreas	1.56	3.1	**6.7**
Red Marrow	3.28	6.6	**10.2**
Osteogenic Cells	6.59	13.2	**16.8**
Skin	0.82	1.6	**5.2**
Spleen	2.16	4.3	**7.9**
Testes	0.87	1.7	**5.3**
Thymus	1.39	2.8	**6.4**
Thyroid	1.15	2.3	**5.9**
Urinary Bladder Wall [2]	1.08	2.2	**5.8**
Uterus	1.18	2.4	**6.0**
Total Body	1.52	3.0	**6.6**
Effective Dose (rem/mCi; rem)	1.74	3.5	**7.1**

[1] Based on biodistribution of Zr-89-DFO-daratumumab in nude mice
(data from Nicholas Sobol, Lewis Lab)
OLINDA/EXM-based absorbed dose estimates by J O'Donoghue
[2] (assumed 3-hr voiding interval)

The following table indicates human dose projections in cases where a large multiple myeloma load is present in bone and bone marrow. This is based on data derived from a mouse model of multiple myeloma in comparison with normal healthy mice.

^{89}Zr-DFO-daratumumab: Absorbed Radiation Dose estimates for 70-kg Standard Man
Includes X-ray CT (for anatomic fusion and attenuation correction)
Fields in blue must have values entered

			# of Injections/CT scans
Activity of ^{89}Zr-DFO-daratumumab	2	mCi	1
low dose CT scan (80mA)	0.9	cGy	4
ultra-low dose CT scan (10mA)	0.11	cGy	0

	Absorbed Dose		
	^{89}Zr-DFO-daratumumab [1]		total ^{89}Zr-DFO-daratumumab + CT
Target Organ	cGy/mCi	cGy per inj	cGy
Adrenals	1.90	3.8	**7.4**
Brain	1.14	2.3	**5.9**
Breasts	0.79	1.6	**5.2**
Gallbladder Wall	1.30	2.6	**6.2**
LLI Wall	1.34	2.7	**6.3**
Small Intestine	1.31	2.6	**6.2**
Stomach Wall	1.20	2.4	**6.0**
ULI Wall	1.24	2.5	**6.1**
Heart Wall	3.31	6.6	**10.2**
Kidneys	2.29	4.6	**8.2**
Liver	2.20	4.4	**8.0**
Lungs	2.94	5.9	**9.5**
Muscle	1.34	2.7	**6.3**
Ovaries	1.19	2.4	**6.0**
Pancreas	1.47	2.9	**6.5**
Red Marrow	4.85	9.7	**13.3**
Osteogenic Cells	9.40	18.8	**22.4**
Skin	0.80	1.6	**5.2**
Spleen	2.16	4.3	**7.9**
Testes	0.69	1.4	**5.0**
Thymus	1.28	2.6	**6.2**
Thyroid	1.09	2.2	**5.8**
Urinary Bladder Wall [2]	0.81	1.6	**5.2**
Uterus	0.98	2.0	**5.6**
Total Body	1.65	3.3	**6.9**
Effective Dose (rem/mCi; rem)	1.90	3.8	**7.4**

[1] Based on biodistribution of Zr-89-DFO-daratumumab in normal and MM mice
(data from Nicholas Sobol, Lewis Lab)
OLINDA/EXM-based absorbed dose estimates by J O'Donoghue
[2] (assumed 3-hr voiding interval)

Absorbed Dose Projections for Phase 2

In phase 2, a single PET/CT scan will be acquired following administration of 1-5 mCi of ^{89}Zr-DFO-daratumumab at the mass dose and time deemed optimal from phase 1 Absorbed dose projections for low and high disease burdens for the minimum and maximum activities envisaged are provided below:

^{89}Zr-DFO-daratumumab Phase 2:
Absorbed Radiation Dose estimates for 70-kg Standard Man including X-ray CT

	min	max	# of Injections/CT scans
Activity of ^{89}Zr-DFO-daratumumab (mCi)	**1**	**5**	**1**
low dose CT scan (80mA)	0.9	cGy	1
ultra-low dose CT scan (10mA)	0.11	cGy	0

	Absorbed dose for ^{89}Zr-DFO-daratumumab + CT (cGy)			
	Low disease burden		High disease burden	
Target Organ	min	max	min	max
Adrenals	**2.7**	**9.8**	**2.8**	**10.4**
Brain	**2.0**	**6.5**	**2.0**	**6.6**
Breasts	**1.8**	**5.5**	**1.7**	**4.8**
Gallbladder Wall	**2.3**	**8.1**	**2.2**	**7.4**
LLI Wall	**2.3**	**7.8**	**2.2**	**7.6**
Small Intestine	**2.4**	**8.2**	**2.2**	**7.4**
Stomach Wall	**2.3**	**7.7**	**2.1**	**6.9**
ULI Wall	**2.3**	**7.8**	**2.1**	**7.1**
Heart Wall	**4.2**	**17.3**	**4.2**	**17.5**
Kidneys	**3.1**	**11.9**	**3.2**	**12.3**
Liver	**3.1**	**11.7**	**3.1**	**11.9**
Lungs	**3.8**	**15.2**	**3.8**	**15.6**
Muscle	**2.2**	**7.4**	**2.2**	**7.6**
Ovaries	**2.2**	**7.3**	**2.1**	**6.9**
Pancreas	**2.5**	**8.7**	**2.4**	**8.2**
Red Marrow	**4.2**	**17.3**	**5.7**	**25.1**
Osteogenic Cells	**7.5**	**33.8**	**10.3**	**47.9**
Skin	**1.7**	**5.0**	**1.7**	**4.9**
Spleen	**3.1**	**11.7**	**3.1**	**11.7**
Testes	**1.8**	**5.2**	**1.6**	**4.4**
Thymus	**2.3**	**7.8**	**2.2**	**7.3**
Thyroid	**2.1**	**6.7**	**2.0**	**6.4**
Urinary Bladder Wall [2]	**2.0**	**6.3**	**1.7**	**4.9**
Uterus	**2.1**	**6.8**	**1.9**	**5.8**
Total Body	**2.4**	**8.5**	**2.5**	**9.1**
Effective Dose (rem/mCi; rem)	**2.6**	**9.6**	**2.8**	**10.4**

[1] Based on biodistribution of Zr-89-DFO-daratumumab in nude mice (Nicholas Sobol, Lewis Lab)
OLINDA/EXM-based absorbed dose estimates by J O'Donoghue

[2] (assumed 3-hr voiding interval)