# Can HER2 targeted PET/CT imaging identify u nsuspected HER2 positive breast cancer metastases, which are am enable to HER2 targeted therapy?

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTO COL

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|---|---|---|
| Principal Investigator/Department: | Gary Ulaner MD, PhD | Radiology/Molecular Imaging |
| Co-Principal Investigator(s)/Department: | Jorge Carrasquillo, MD | Radiology/Molecular Imaging |
| Investigator(s)/Department: | Steven Larson, MD | Radiology/Molecular Imaging |
| | Mark Dunphy, DO | Radiology/Molecular Imaging |
| | Christopher Riedl, MD, PhD | Radiology/Molecular Imaging |
| | Josef Fox, MD | Radiology/Molecular Imaging |
| | Lisa Bodei, MD, PhD | Radiology/Molecular Imaging |
| | Randy Yeh, MD | Radiology |
| | Jason Lewis, PhD | Radiology/Radiochemistry |
| | Joe Erinjeri, MD | Radiology/Interventional |
| | Maxine Jochelson, MD | Radiology/Breast Imaging |
| | Larry Norton, MD | Medicine/Breast Oncology |
| | Shanu Modi, MD | Medicine/Breast Oncology |
| | Maura Dickler, MD | Medicine/Breast Oncology |
| | Cliff Hudis, MD | Medicine/Breast Oncology |
| | Gabriella D'Andrea, MD | Medicine/Breast Oncology |
| | Chau Dang, MD | Medicine/Breast Oncology |
| | Komal Jhaveri, MD | Medicine/Breast Oncology |
| | Devika Gajria, MD | Medicine/Breast Oncology |
| | Mithat Gonen, PhD | Epidemiology and Biostatistics |
| Consenting Professional(s)/Department: | Gary Ulaner, MD, PhD | Radiology/Molecular Imaging |
| | Jorge Carrasquillo, MD | Radiology/Molecular Imaging |
| | Mark Dunphy, DO | Radiology/Molecular Imaging |
| | Christopher Riedl, MD, PhD | Radiology/Molecular Imaging |
| | Josef Fox, MD | Radiology/Molecular Imaging |
| | Lisa Bodei, MD, PhD | Radiology/Molecular Imaging |
| | Randy Yeh, MD | Radiology |
| | Larry Norton, MD | Medicine/Breast Oncology |
| | Jose Baselga, MD | Medicine/Breast Oncology |
| | Shanu Modi, MD | Medicine/Breast Oncology |
| | Maura Dickler, MD | Medicine/Breast Oncology |
| | Clifford Hudis, MD | Medicine/Breast Oncology |
| | Chau Dang, MD | Medicine/Breast Oncology |
| | Gabriella D'Andrea, MD | Medicine/Breast Oncology |
| | Komal Jhaveri, MD | Medicine/Breast Oncology |
| | Devika Gajria, MD | Medicine/Breast Oncology |

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

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

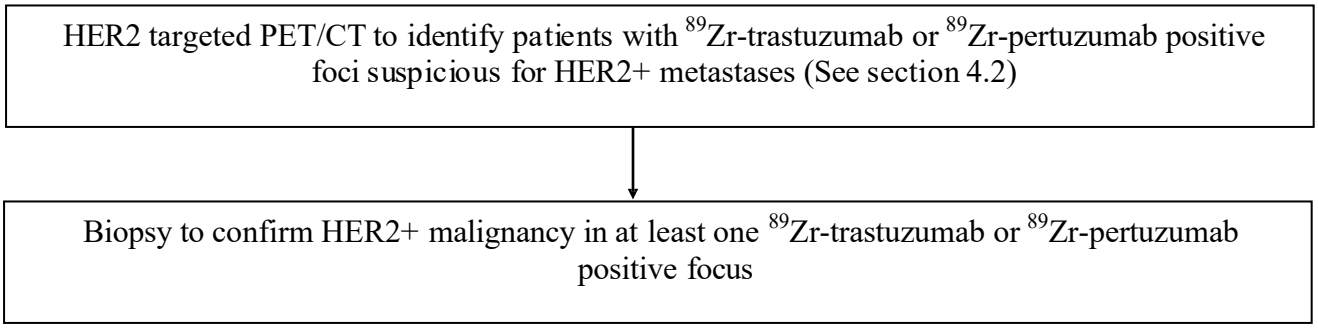
Human epidermal growth factor receptor 2 (HER2) is a highly valuable biomarker in breast cancer, and its expression or gene amplification directly influences treatment. Patients with HER2 positive (HER2+) breast cancer (overexpressed and/or gene-amplified) receive targeted HER2 therapies that reduce the risk of death by up to 1/3$^{rd}$, while patient with HER2 negative ("normal") (HER2-) breast cancer do not receive them. However, 10-15% of patients with HER2- primary malignancies on repeat central testing (after an initial test was positive) appear to benefit from HER2 targeted adjuvant treatment. This lack of central confirmation of positive HER2 status has led to the hypothesis that some patients without overexpression/amplification may nonetheless benefit from anti-HER2 therapies. On the other hand, prospective randomized trials that included patients with metastases known to only test negative for HER2 have never demonstrated benefit for anti-HER2 therapies. Change in HER2 status over time and site is a potential confounder and some studies suggest that a minority of patients with HER2- primary malignancies develop HER2+ metastases, which would then presumably respond to HER2 targeted therapy. Indeed, there is evidence that up to 10-15% of HER2- primary breast cancer patients develop HER2+ metastases. Identifying such patients non-invasively would be an example of targeted imaging guiding the choice of targeted therapy.

We hypothesize that imaging with a targeted HER2 radiotracer will allow us to identify patients with HER2- primary breast cancers who develop HER2+ metastases, and who may benefit from the addition of HER2 targeted therapy.

The following schema will be used to test this central hypothesis:

Pre-protocol evaluation & recruitment: Identify patients with HER2- primary breast cancer and metastases demonstrable on CT, MR, and FDG PET

Protocol: Determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer.



## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

The aim of this study is to determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer.

## 3.0 BACKGROUND AND RATIONALE

HER2

The HER2 receptor is a 185-kDa transmembrane receptor tyrosine kinase that is expressed in a wide variety of human epithelial cancers including breast, bladder, ovarian, endometrial, cervical, lung, stomach, prostate as well as head and neck and pancreatic cancers [1]. In preclinical studies, HER2 over-expression has been found to contribute to oncogenic transformation, tumorigenesis, and metastatic potential [2, 3]. In human breast cancers, HER2 is overexpressed in 20-30% of cases, and this has been correlated with resistance to therapy, shorter disease-free and overall survival in patients with this disease [4, 5]. The ErbB2/HER2 oncogene encodes a transmembrane tyrosine kinase receptor that belongs to the epidermal growth factor receptor (EGFR) family and plays an essential role in promoting cell growth, migration, differentiation, proliferation, and survival. The family is comprised of ErbB1 (EGFR/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). Each receptor has an extracellular domain, a lipophilic transmembrane domain, and an intracellular tyrosine kinase domain. Activation of the kinase occurs with ligand binding and hetero- or homodimerization of these receptors. Ligand-independent activation of HER2 may occur due to mutations in HER2 or receptor overexpression [6]. Activation plays a pivotal role in cell proliferation and survival [7]. Therefore, HER2 has become a very important target of anticancer drug development.

Trastuzamab and Pertuzumab

Trastuzumab and pertuzumabare humanized anti-HER2 monoclonal antibodies (Herceptin; Genentech, South San Francisco, CA and Perjeta; Genentech, South San Francisco), that inhibit the growth of breast cancer cells with HER2 over-expression [8]. In a landmark randomized clinical trial, the addition of trastuzumab to chemotherapy improved response rates and prolonged survival for patients with HER2-overexpressing metastatic breast cancer [9]. Large, multicenter randomized adjuvant trials have shown a 50% reduction in the risk of recurrence for women with HER2+ early stage breast cancer treated with trastuzumab plus chemotherapy versus chemotherapy alone [10, 11].

Experience with trastuzumab and pertuzumab administration has shown that the drug is relatively safe. The most significant safety signal observed during clinical trials was cardiac dysfunction (principally clinically significant heart failure [CHF]), particularly when trastuzumab was given in combination with an anthracycline-containing regimen. Much of the cardiac dysfunction was reversible on discontinuation of drug.

In addition, during the first infusion with trastuzumab and pertuzumab, a symptom complex most commonly consisting of fever and/or chills was observed in approximately 40% of patients. The symptoms were usually mild to moderate in severity and controlled with acetaminophen, diphenhydramine, or meperidine. These symptoms were uncommon with subsequent infusions. However, in the postapproval setting, more severe adverse reactions to trastuzumab have been reported. These have been categorized as hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these severe reactions culminated in a fatal outcome.

There are no adequate or well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response. Therefore, these agents should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. In the postmarketing setting, oligohydramnios (decreased amniotic fluid) has been reported in women who received trastuzumab during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between trastuzumab and oligohydramnios has not been established. Advise women of childbearing potential to use effective contraceptive methods during treatment and for seven months after last dose of trastuzumab.

Trastuzumab appears to be relatively nonimmunogenic. Only 1 of 903 patients evaluated developed neutralizing antibodies to trastuzumab. The development of anti-trastuzumab antibodies in this patient was not associated with clinical signs or symptoms.

HER2 Heterogeneity in Breast Cancer and its Significance

There is growing evidence that HER2 expression may change between the primary breast malignancy and metastases.[12-14] Thus, knowledge of HER2 status in the primary breast malignancy may not be representative of the metastases. This is an example of tumor heterogeneity. Inaccurate knowledge of HER2 status in metastases, due to tumor heterogeneity, may lead to suboptimal treatment of metastatic breast cancer.

Tumor heterogeneity has specific important implications for HER2 negative (HER2-) primary breast cancer. Patients with HER2 positive (HER2+) breast cancer (overexpressed and/or gene-amplified) receive targeted HER2 therapies that reduce the risk of death by up to 1/3rd, [9, 10] while patient with HER2 negative ("normal") (HER2-) breast cancer do not receive them. However, 10-15% of patients with HER2- primary malignancies on repeat central testing (after an initial test was positive) appear to benefit from HER2 targeted adjuvant treatment. [15] This lack of central confirmation of positive HER2 status has led to the hypothesis that some patients without overexpression/amplification may nonetheless benefit from anti-HER2 therapies. On the other hand, prospective randomized trials that included patients with metastases known to only test negative for HER2 have never demonstrated benefit for anti-HER2 therapies. Change in HER2 status over time and site is a potential confounder and some studies suggest that a minority of patients with HER2- primary malignancies develop

HER2+ metastases, which would then presumably respond to HER2 targeted therapy. Indeed, there is evidence that up to 10-15% of HER2- primary breast cancer patients develop HER2+ metastases. [14]

There are over 900,000 women currently living with metastatic breast cancer, with more than 50,000 diagnosed each year.[16] 80% of these women have HER2- primary malignancies. If 10% of these patients could respond to HER2 therapy, that represents a current population of over 72,000 women. Identifying the patients with HER2- primary breast cancer who could benefit from the addition of HER2 targeted therapy may reduce breast cancer mortality in tens of thousands of breast cancer patients.

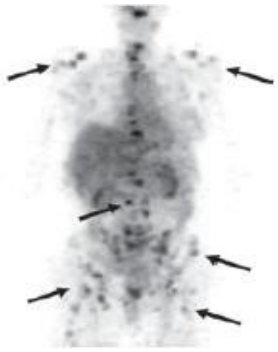


**Figure 1**: Maximum Intensity Projection image from an $^{89}$Zr-trastuzumab PET in a HER2+ breast cancer patient (Reference #8). Background avidity is demonstrated in the blood pool, liver, spleen, and kidneys. Several $^{89}$Zr-trastuzumab avid foci, that correspond to osseous metastases, have been labeled with arrows.

Rationale for HER2-targeted PET/CT imaging in HER2 negative Breast Cancer

As HER2 is a critical protein in many malignancies, there has been significant interest in targeted HER2 imaging. Several radionuclide agents have been developed, such as 68Galium-DOTA-F(ab‟)2-trastuzumab [17] and 64Cu-DOTA-trastuzumab [18], but their use has been limited due to the unique properties of antibody distribution of radiotracer half- lives. $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab overcome these limitations by combining the highly specific monoclonal antibody trastuzumab with a PET radiotracer ($^{89}$Zr , half-life 78 hours) that matches the pharmacokinetics of the antibody. The half-life of $^{89}$Zr is long enough to allow optimal antibody biodistribution. This results in PET/CT images with excellent visualization of HER2+ lesions in patients with HER2+ metastatic breast cancer (Figure 1). [19] Memorial Sloan-Kettering Cancer Center (MSKCC) is one of the few institutions in the world with experience in $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab production and pre-clinical imaging.[20] MSKCC has approved Investigational New Drug from the FDA for human $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab imaging . If HER2-targeted PET/CT could identify HER2- primary breast cancer patients who develop HER2+ metastases, then HER2 targeted systemic therapy becomes a new treatment option in these patients.

## 4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.2 Design

The aim of this study is to determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer. Determining this proportion will help ascertain if there is value translating HER2-targeted PET/CT from a research study to a clinical study.

Patients presenting to the clinic with metastatic HER2- primary breast cancer will have their prior pathology and imaging studies reviewed by the PI or another investigator to determine patients with a) biopsy proven metastatic disease and b) 5 or more metastases demonstrable on the most recent CT, MR, or FDG PET/CT. At least one biopsy proven site of metastasis in the medical record will be required to provide proof of metastatic breast cancer for each patient. The most recent body CT, body MR, and FDG PET/CT studies will be reviewed to determine the number of demonstrable metastases. Demonstrable metastases will be defined as lytic or blastic osseous metastases on CT, osseous metastases on MR, liver metastases greater than 1.5cm in long axis on CT or MR, lymph nodes greater than 1.5 cm in short axis on CT or MR, lung metastases greater than 1.0 cm in long axis on CT or MR, and FDG-avid foci that cannot be explained as physiologic or inflammatory. Preference will be given to selecting patients with increasing metastatic burden on recent sequential imaging studies, in order maximize the likelihood of patients with active metastases. Patients must have an ECOG performance score of 0-2.[24] 50 Patients with HER2- primary breast cancer, biopsy proof of metastatic disease, and at least 5 foci of demonstrable metastases on recent clinical imaging modalities will be considered for the protocol.

HER2 status will be defined according to recently published ASCO guidelines, as described in "Step 1" of Section 9.0 "Treatment/Intervention Plan". In brief, only patients that are IHC 0, IHC 1+, or IHC 2+ and FISH < 2.0 on the repeat testing or reexamination will be considered HER2- and will proceed to HER2-targeted PET/CT. Patients with repeat testing results of IHC 3+ or IHC 2+ and FISH ≥2.0, will be removed from the protocol.

Patients with confirmed HER2- breast cancer will then undergo HER2-targeted PET/CT. $^{89}$Zr-trastuzumab is a novel radiotracer which allows excellent visualization of HER2+ lesions.[19] $^{89}$Zr-pertuzumab is a novel radiotracer which may allow for specific visualization of HER2+ lesions. PET/CT imaging with these novel radiotracers will allow evaluation of all identifiable malignant lesions, rather than evaluation of only single lesions by biopsy. Avid lesions will be considered suspicious for HER2+ malignancy. Following amendment 9, we will use $^{89}$Zr-pertuzumab preferentially, unless unavailable for a successful imaging study.

Patients with at least one $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab avid lesion will be biopsied to confirm HER2+ pathology. From these 50 patients, we will determine the proportion of HER2- primary breast cancer patients that express HER2+ malignancy imagable by HER2-targeted PET/CT. Patients who are recruited to the protocol, but then drop out prior to HER2-targeted PET/CT, will be replaced with newly recruited patients.

### 4.3 Intervention

HER2-targeted PET/CT will be performed in HER2- primary breast cancer patients to identify patients with positive foci suspicious for HER2+ metastases.

Timing of $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab PET/CT imaging: Optimal time between tracer injection and PET scanning of $^{89}$Zr-trastuzumab depends on both clearance of the antibody from the blood pool and counting statistics. The optimum time between tracer injection and $^{89}$Zr-trastuzumab

PET scanning in patients with metastatic breast cancer has been shown to be 4-6 days.[19] We will perform PET/CT 4-6 days after radiotracer administration.

$^{89}$Zr-trastuzumab PET/CT imaging: $^{89}$Zr-trastuzumab PET studies will be performed as hybrid PET/CT examinations for attenuation correction, lesion localization, and availability of additional CT data. 4 to 6 days following radiotracer administration, the patient will be positioned on a GE PET/CT scanner, dedicated for research scans at MSKCC. The CT component will be obtained utilizing a low mA (80 mA) to minimize radiation exposure. 3D imaging will be obtained from the mid skull to proximal thighs (approximately 6-7 bed positions). $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab PET/CT images will be reconstructed using iterative reconstruction, and displayed in multiplanar reconstruction.

$^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab PET/CT interpretation: HER2-targeted PET/CT scans will be interpreted by two different nuclear medicine experts, both experienced in the use novel research PET radiotracers. Physiologic $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab uptake will be expected in the blood pool, liver, spleen, and kidneys. Radiotracer uptake in areas which are not physiologic will be graded both qualitatively and semiquantitatively. For qualitative scoring, we will use a score of 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 grade 4 and 5 lesions, as well as for apparently normal background liver and background blood pool. Three-dimensional regions of interest (ROIs) will be placed over grade 4 and 5 lesions, the liver, and the mediastinal blood pool, and tracer uptake will be quantified using standardized uptake value (SUV), calculated as: SUV = decay corrected mean ROI activity (μCi/ml) / (injected dose (μCi)/ body weight (g)). Both SUVmax and SUVpeak will be recorded for lesions, and SUVmax and SUVaverage will be recorded for background measurements. Only those foci qualitatively scored conspicuously positive by both readers (scores of 4 or 5) will be considered as "positive".

## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

$^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab

$^{89}$Zr-trastuzumab is composed of the native HER2 targeting drug trastuzumab conjugated with desferrioxamine (DFO) and labelled with the positron emitting radionuclide zirconium 89 ($^{89}$Zr). $^{89}$Zr-pertuzumab is composed of the native HER2 targeting drug trastuzumab conjugated with desferrioxamine (DFO) and labelled with the positron emitting radionuclide zirconium 89 ($^{89}$Zr). Trastuzumab and pertuzumab are FDA approved monoclonal antibodies that disrupt HER2 receptor signaling. $^{89}$Zr is a metallo-radionuclide with a half-life of 78 hours, long enough to allow favorable biodistribution of radiolabeled antibodies. Memorial Sloan-Kettering Cancer Center is one of the few institutions in the world with experience in $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab production and imaging.[20] MSKCC has approved Investigational New Drug from the FDA for human $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab imaging .

$^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab will be produced on demand by the Cyclotron-Radiochemistry Core at MSKCC (under the direction of Dr. Jason Lewis), which has experience in the production of these PET radiopharmaceuticals. $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab will be manufactured

according to the MSKCC IND. The final product is tested for sterility, pyrogenicity, as well as other quality control determinants, including radionuclide and radiochemical purity, prior to release and administration.

Dose of $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab: Patients will receive between 37 and 203 Mbq (1.0 and 5.5 mCi) of $^{89}$Zr-trastuzumab given IV over 5-10 min, depending on radiotracer production capacity. The initial injected activity is expected to be 185Mbq (5 mCi) +/- 10% with full radiotracer production capacity. The activity may be adjusted downward in later patients if imaging quality can be maintained at a lower level of activtiy. In order to optimize tumor targeting radiolabeled $^{89}$Zr-trastuzumab will be brought up to a final mass dose of 50mg by adding non-radiolabeled trastuzumab (For example: 185MBq in 3mg $^{89}$Zr -trastuzumab added to 47 mg of non-radiolabeled trastuzumab). Data in the literature has shown that the optimal mass of trastuzumab is ~50 mg, in trastuzumab naïve breast cancer patients.[19] Non-radiolabeled trastuzumab and pertuzumab will be obtained from the MSKCC pharmacy.

Please see section 11.0 for a discussion of $^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab side effects and radiation safety.

## 6.1 CRITERIA FOR SUBJECT ELIGIBILITY

### 6.2 Subject Inclusion Criteria

- Women age > 18
- Biopsy proven HER2 negative primary breast cancer and biopsy proven metastatic disease.
- 5 or more foci of demonstrable metastases on recent imaging modalities (CT, MR, FDG PET/CT)
- ECOG performance score of 0-2

### 6.3 Subject Exclusion Criteria

- Life expectancy < 3 months
- Pregnancy or lactation
- Patients who cannot undergo PET/CT scanning because of weight limits
- CNS only disease on recent imaging

## 7.0 RECRUITMENT PLAN

The recruitment plan will identify HER2- primary breast cancer patients with multiple metastases demonstrable on recent clinical imaging modalities (CT, MR, and FDG PET/CT). All patients recruited to the protocol will be women, as breast cancer is primarily a disease of women and the

initial cohort size of 50 will be too small to generalize meaningful results in a small number of men. Eligible patients will be approached to enroll in the protocol and provide written informed consent.

Potential research subjects will be identified by a member of the patient‟s treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is amember of the treatment team, s/he will screen their patient‟s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

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 either by 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 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).

## 8.0 PRETREATMENT EVALUATION

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

- History and physical exam
- Biopsy demonstrating HER2- primary breast malignancy
- Biopsy demonstrating metastatic disease
- Clinically standard imaging scans (CT, MR, FDG PET/CT) demonstrating at least 5 foci of suspected metastatic disease within 12 weeks of protocol enrollment (As clinically indicated)
- Serum pregnancy test for women of childbearing age

## 9.0 TREATMENT/INTERVENTION PLAN

The aim of this study is to determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer. Once a patient is confirmed eligible for protocol participation, the following will occur:

Step 1. HER2-targeted PET/CT to identify patients with $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab positive foci suspicious for HER2+ metastases.

Patients with confirmed HER2- malignancy from archived pathology samples will undergo HER2-targeted PET/CT to determine if the patient demonstrates $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab positive lesions suspicious for HER2+ metastases. Please see section 4.2 for a discussion of HER2-targeted PET/CT imaging and interpretation.

Step 2. Biopsy to confirm HER2+ status of at least one $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab metastasis

$^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab positive foci will be suspected of being HER2+ metastases. At least one of these foci will be biopsied to confirm a HER2+ breast cancer metastasis at the suspected site.

Selection of biopsy target and performance of biopsy: Biopsies will be performed by a fellowship trained oncologic interventional radiologist, experienced in ultrasound, CT, and PET/CT guided biopsies. In order to minimize risk to the patient, site selection will be performed with consultation between the study PI and the interventional radiologist. PET and CT images will be reviewed to determine the most accessible and least invasive site of suspected $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab avid metastatic disease. If the avid lesion is believed to be amenable to ultrasound guided biopsy (lymph nodes, soft tissue lesions), then ultrasound guided biopsy will be performed. Next, CT guided biopsy will be considered for lesions determined to be inaccessible to ultrasound, but visible on CT (lytic and sclerotic osseous lesions, liver lesions, lung nodules). In cases where the focus cannot be localized by ultrasound or CT, then a PET/CT guided biopsy will be utilized. MSKCC has substantial experience with PET/CT guided biopsy of radiotracer avid foci which are occult on CT. One-to-three 18-20 gauge core specimens will be obtained for pathologic analysis and placed in formalin. If the avid foci are not amenable to biopsy, due to the risk of the biopsy or any other risk, then biopsy will not be performed. The fellowship trained oncologic interventional radiologist will determine if PT/INR or other laboratory tests shall be performed prior to biopsy. In most cases this will result in PT/INR measurement.

If a biopsy is not performed because no avid foci are deemed amenable to biopsy, then the patient‟s participation in the protocol will end at this point. They will be counted as 1 of the 50 patients to undergo the HER2-targeted PET/CT as part of this study.

Pathologic analysis of biopsy samples: Pathologic analysis will be performed by a board-certified breast pathology specialist with more than 5 years experience. Standard Hematoxylin and Eosin slides will be prepared and evaluated to confirm the presence of breast cancer metastasis at the biopsied site. Biopsy proven breast cancer metastases will then undergo evaluation for HER2 expression by immunohistochemistry, as described above. The immunohistochemical results will be as follows: 0, 1+ = negative result; 2+ = equivocal result; and 3+ = positive result. Tissues with 2+ staining (equivocal) will go on to analysis with fluorescent in situ hybridization (FISH) for HER2 amplification as per ASCO guidelines. [26] FISH is performed from paraffin embedded tissue using FDA-approved ERBB2 (HER2/NEU) PathVysion assay probes and procedure. Green fluorescence represents CEP17, while red fluorescence represents Her2. A HER2/CEP17 ratio of > 2.0 HER2 will be considered positive. Only tissues with 3+ immunohistochemical staining or tissues with 2+ immunohistochemical staining AND positive HER2 FISH will be considered "HER2 positive". These criteria for HER2+ breast cancer are equivalent to the recently published ASCO guidelines[25]. If the pathologic analysis of a $^{89}$Zr-trastuzumab avid focus yields inconclusive tissue or results, then the possibility of an additional biopsy will be discussed with the patient and the interventional radiologist.

Only patients with HER2+ metastases on pathology will be considered to have proven HER2+ disease .

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

$^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab PET/CT scans will be interpreted by two different nuclear medicine experts, both experienced in the use novel research PET radiotracers. Physiologic $^{89}$Zr-trastuzumab uptake will be expected in the blood pool, liver, spleen, and kidneys. Radiotracer uptake in areas which are not physiologic will be graded both qualitatively and semiquantitatively. For qualitative scoring, we will use a score of 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 grade 4 and 5 lesions, as well as for apparently normal background liver and background blood pool. Three-dimensional regions of interest (ROIs) will be placed in these areas and tracer uptake will be quantified using standardized uptake value (SUV), calculated as: SUV = decay corrected mean ROI activity (μCi/ml) / (injected dose (μCi)/ body weight (g)). Both SUVmax and SUVpeak will be recorded for lesions, and SUVmax and SUVaverage will be recorded for background measurements. Only those foci qualitatively scored conspicuously positive by both readers (scores of 4 or 5) will be considered as "positive".

## 11.0 TOXICITIES/SIDE EFFECTS

$^{89}$Zr-trastuzumab and $^{89}$Zr-pertuzumab: These diagnostic agents are expected to have a very low incidence of adverse events. Nevertheless, patients will be monitored closely for evidence of adverse event, including vital signs and followup patient reporting. If a severe adverse effect (Common

Terminology Criteria for Adverse Events grade 3 or 4) attributable to $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab occurs in any patient, then further use will be suspended and the protocol reviewed with the MSKCC Data Safety Monitoring Committee.

Less Likely: Infusion or allergic reactions, which may include fevers

- Chills
- Tiredness
- Rashes
- Hives

Radiation risk: We will image with 37 and 203 Mbq (1.0 and 5.5 mCi) of $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab. The effective dose from 185MBq of $^{89}$Zr-trastuzumab is estimated to be 7.4 cGy (see Appendix 1).[29] A low milliampere CT scan, performed as part of the hybrid $^{89}$Zr-trastuzumab PET/CT, has an effective dose of 0.9 rem. The effective dose from the experimental $^{89}$Zr-trastuzumab PET/CT examination is 8.3 rem, which is comparable to the dose from other radiolabeled antibodies received by oncology patients in MSKCC clinical trials.

Pregnancy risk: Even low diagnostic levels of radiation, such as those that will be received in this protocol from the investigational PET/CT studies, are associated with a risk of inducing childhood cancer. HER2 targeted systemic therapy could have additional pregnancy risks. A negative pregnancy test will be required before patient accrual to this protocol. Patients on this protocol will be advised not to become pregnant during the time period of the protocol.

Biopsy risks: Minimally invasive biopsy procedures are selected to minimize the risk to patients; however, risks cannot be eliminated. Risks from biopsies include pain, bleeding, infection, and need for additional procedures. Risks may vary based on site of biopsy. Most biopsies will be of lymph nodes or bones.

## 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

There are no criteria for therapeutic response. This protocol will identify previously unknown HER2+ metastases in presumed HER2- breast cancer 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.

## 14.0 BIOSTATISTICS

50 patients with HER2- primary breast cancer will undergo $^{89}$Zr-trastuzumab or $^{89}$Zr-pertuzumab targeted scanning, with an expected accrual rate of 2-3 patients per month. All lesions with uptake will be noted and, among patients with uptake, at least one lesion per patient will be biopsied to confirm HER2+ pathology. We expect 5-10 patients will have at least one such lesion, based on a previous study that estimated this proportion as 12% in biopsy samples, which is limited compared with our whole body imaging. We will report the proportion of patients with at least one pathologically verified HER2+ lesion along with its 95% exact binomial confidence interval with an anticipated half-width of 14%. We note that this is a lower bound to the proportion of patients with HER2+ metastases from a HER2- primary. To prevent unnecessary imaging, we will perform an interim analysis after 23 patients are imaged. If none of the 23 patients has a pathologically verified HER2 positive metastasis, then we will stop the trial. The probabilities of stopping the trial are 5% and 63% if the proportions of patients with pathology verified HER2 positive lesions are 12% and 2%. To precent unnecessary biopsies we will perform separate interim analyses using the data from patients who had a biopsy following positive imaging. This is especially a concern if there are more patients with uptake than expected. Since the number of biopsied patients is not known at this stage we implement this decision rule in a rolling fashion: if 5 or more of the first 8 biopsied patients have no pathologically confirmed HER2+ disease, then HER2-targeted imaging will be deemed insufficiently specific and the study will stop to prevent unnecessary biopsies. If the study continues beyond the first 8 biopsied patients, then a second interim look will take place at 15 biopsied patients (if reached). If 7 or more of these 15 patients have no pathologically confirmed HER2+ disease, then we will stop the study. Based on this rule the probability of stopping the study is 90% if the true proportion of HER2+ disease in biopsied patients is 50%. The probability of stopping decreases to 20% if the true proportion of HER2+ disease in biopsied patients is 75%.

## 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

This protocol does not involve randomization.

## 16.1 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to this study. The responsibilities of the RSA include project compliance, data collection, and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of activities of the protocol study team. The data collected from this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

### 16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. 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 MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm.

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.

The protocol will be conducted in accordance with the protocol submitted to and approved by the United States Army Medical Research and Materiel Command‟s (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

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

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

**Reporting Requirements and Responsibilities of the Principal Investigator to the USAMRMC ORP HRPO**

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

(1) Substantive modifications to the research protocol and nay modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a changes in the Principle Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory (e.g., adding children, adding active duty population, etc), significant change in study design (i.e., would prompt additional scientific review) or a change that could potentially increase risk to subjects.

(2) All unanticipated problems involving risk to subjects or others must be promptly reported by phone (301-619-2165), by email (HRPO@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

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

(4) A copy of the approved continuing review approval notification by the IRB of Record will be submitted to the ORP as soon as possible after receipt. Please note that the ORP also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time.

(5) The final study report, including any acknowledgment documentation and supporting documents, must be submitted to the ORP when available.

(6) The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Research Protections (OHRP), or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported promptly to the ORP.

***Guidance for the Requirement of a Research Monitor***

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

***Responsibilities of the Research Monitor***

The research monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event.

**Research Monitor: David Hyman, MD**

Dr. Hyman will serve as an independent clinical monitor of the research trial and oversee the conduct and expectations of fulfilling its research goals and obligations. He will be meeting with the Principal Investigator to review any relevant toxicities incurred by patients and to determine whether the study accrual is being conducted in a timely and efficient manner. Dr. Hyman is a qualified physician, other than the Principal Investigator, not associated with this particular study, able to provide medical care to research subjects for conditions that may arise during the conduct of this study, and will monitor the subjects during the conduct of the study. As the research monitor, Dr. Hyman:

- May discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- Shall have authority to stop the research protocol in progress, remove individual human subjects from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor‟s report;
- Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

## 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: HER2 targeted therapy reduces the risk of death by 1/3$^{rd}$ in appropriately selected HER2+ breast cancer patients. This protocol attempts to identify breast cancer patients with HER2- primary tumors that develop HER2+ metastases. Patients with newly identified HER2+ metastases may

benefit from the addition of HER2 target therapies to their treatment regimen. There is no guarantee of any benefit.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Costs: The research $^{89}$Zr-trastuzumab radiotracer and $^{89}$Zr-trastuzumab PET/CT scan will be performed without charge. Biopsies resulting from the $^{89}$Zr-trastuzumab PET/CT scan will be performed without charge. Pathological examinations performed as part of this protocol will be performed without charge. If HER2+ metastases are discovered as part of this protocol, then HER2 targeted therapy will be performed according to current standards of care for HER2+ breast cancer and the patient will be charged for this therapy. 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

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

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-dau period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per SOP RR-408 „Reporting of Serioues 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 containg 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
    - An 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 Reporting to Genentech

Any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of trastuzumab should be reported to Genentech within 7 calendar days of first learning of the event. IND safety reports are to be submitted to Genentech within 15 calendar days of first learning of the event.

Genentech Drug Safety fax: (650) 225-4682 or (650) 225-5288

Any study report submitted to the FDA should be sent to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be emailed to the assigned Clinical Operations contact for the study:

**Herceptin Protocols**

Email : herceptin-gsur@gene.com

Fax : 650-360-6908

Please see Appendix 2 for Genentech Safety Reporting Fax Cover Sheet.

## 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- trastuzumab Radiation Dosimetry

| | | |
|---|---|---|
| Activity of $^{89}$Zr-DFO-trastuzumab | 5 | mCi |
| low dose CT scan (80mA) | 0.9 | cGy |

| | Absorbed Dose | | |
|---|---|---|---|
| | $^{89}$Zr-DFO-trastuzumab [1] | | Dose from $^{89}$Zr-trastuzumab + CT |
| Target Organ | cGy/mCi | cGy per inj | cGy |
| Adrenals | 1.47 | 7.4 | 8.3 |
| Bone Surfaces | 3.36 | 16.8 | 17.7 |
| Brain | 0.64 | 3.2 | 4.1 |
| Heart Wall | 1.32 | 6.6 | 7.5 |
| Kidneys | 2.45 | 12.3 | 13.2 |
| Large Intestine - Lower Wall | 1.08 | 5.4 | 6.3 |
| Large Intestine - Upper Wall | 1.06 | 5.3 | 6.2 |
| Liver | 2.96 | 14.8 | 15.7 |
| Lungs | 2.07 | 10.4 | 11.3 |
| Ovaries | 1.00 | 5.0 | 5.9 |
| Pancreas | 1.33 | 6.7 | 7.6 |
| Red Marrow | 2.76 | 13.8 | 14.7 |
| Small Intestine | 1.08 | 5.4 | 6.3 |
| Spleen | 2.30 | 11.5 | 12.4 |
| Stomach Wall | 1.33 | 6.7 | 7.6 |
| Testes | 0.62 | 3.1 | 4.0 |
| Thyroid | 0.75 | 3.8 | 4.7 |
| Urinary Bladder Wall [2] | 1.83 | 9.2 | 10.1 |
| Uterus | 0.98 | 4.9 | 5.8 |
| Total Body | 1.06 | 5.3 | 6.2 |
| **Effective Dose (rem)** | **1.48** | **7.4** | **8.3** |

[1] Based on biodistribution of $^{89}$Zr-89-DFO-trastuzumab in nude mice (Holland et al, PLoS ONE 5(1): e8859. doi:10.1371/journal.pone.0008859)
OLINDA/EXM-based absorbed dose estimates by Pat Zanzonico
[2] assumed 3-hr voiding interval

**Appendix 2:** $^{89}$Zr-pertuzumab Radiation Dosimetry

| | | |
|---|---|---|
| Activity of $^{89}$Zr-DFO-pertuzumab | 2 | mCi |
| low dose CT scan (80mA) | 0.9 | cGy |

| | Absorbed Dose | | |
|---|---|---|---|
| | $^{89}$Zr-DFO-pertuzumab [1] | | Dose from $^{89}$Zr-pertuzumab + CT |
| Target Organ | cGy/mCi | cGy per inj | cGy |
| Adrenals | 2.37 | 4.75 | 5.65 |
| Bone Surfaces | 2.04 | 4.08 | 4.98 |
| Brain | 0.91 | 1.81 | 2.71 |
| Heart Wall | 4.50 | 9.00 | 9.90 |
| Kidneys | 4.70 | 9.40 | 10.30 |
| Large Intestine - Lower Wall | 1.57 | 3.13 | 4.03 |
| Large Intestine - Upper Wall | 1.69 | 3.39 | 4.29 |
| Liver | 6.49 | 12.97 | 13.87 |
| Lungs | 3.98 | 7.95 | 8.85 |
| Ovaries | 1.40 | 2.80 | 3.70 |
| Pancreas | 2.28 | 4.56 | 5.46 |
| Red Marrow | 1.78 | 3.57 | 4.47 |
| Small Intestine | 1.44 | 2.88 | 3.78 |
| Spleen | 3.84 | 7.69 | 8.59 |
| Stomach Wall | 1.70 | 3.40 | 4.30 |
| Thyroid | 1.07 | 2.14 | 3.04 |
| Urinary Bladder Wall [2] | 1.01 | 2.03 | 2.93 |
| Uterus | 1.36 | 2.71 | 3.61 |
| Total Body | 1.47 | 2.93 | 3.83 |
| **Effective Dose (rem)** | **1.99** | **3.98** | **4.88** |

[1] Based on MSKCC biodistribution of 89Zr-DFO-pertuzumab in 6 patients
OLINDA/EXM-based absorbed dose estimates by Joe O'Donoghue

**Appendix 3:** Genentech Safety Reporting Fax Cover Sheet

**Genentech**

*A J\>fc:111bc:rof1/teRo<he Group*

**SAFETY REPORTING FAX COVER SHEET**

**GENENTECH SUPPORTED RESEARCH**

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

| |
|---|
| Genentech Study Number |
| PrincipalInvestigator |
| Site Name |
| Repor er rtctrrie |
| Reporter Telephone # |
| Reporter Fax # |

| | |
|---|---|
| Initial Report Date | [QQJ /[MQNJ /['il] |
| Follow-up Report Date | [QQJ / [MQ!i] / [aJ |

| | |
|---|---|
| Subject Initials<br>(Enter a dash if patient has no middle name) | D-0-!J |

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET