A Pilot Study of ^{68}Ga-RM2 PET/MRI in the Evaluation of Patients with Estrogen Receptor-positive Breast Cancer

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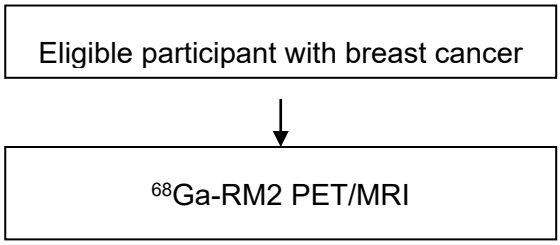
PROTOCOL SYNOPSIS

TITLE	A Pilot Study of ^{68}Ga-RM2 PET/MRI in the Evaluation of Patients with Estrogen Receptor-positive Breast Cancer
STUDY PHASE	Pilot study
INDICATION	Breast cancer
INVESTIGATIONAL PRODUCTS	^{68}Ga-RM2; also known as: • Bombesin • BAY86-7548
SAMPLE SIZE	20 participants
PRIMARY OBJECTIVE	To evaluate the feasibility of ^{68}Ga-RM2 PET/MRI for identification of estrogen receptor positive primary breast cancer and metastases

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ga-68; ^{68}Ga	Gallium-68
IRB	Institutional Review Board
IV	Intravenous
PET/MRI	Positron emission tomography – magnetic resonance imaging
SUV	Standardized Uptake Value
GRPr	Gastrin releasing peptide receptor
ER	Estrogen receptor

1. OBJECTIVE

Specific Aim

To evaluate the feasibility of ^{68}Ga-RM2 PET/MRI for identification of estrogen receptor positive primary breast cancer and metastases.

2. BACKGROUND

2.1 Preliminary information

Breast cancer is a leading cause of cancer-related death found in women worldwide, with a steadily increasing incidence in many countries over the past 30 years (1). Thus, early detection and thorough evaluation of primary breast cancer and its metastases may lead to a higher rate of successful treatment and extend the patient's life span. Currently, the diagnosis of breast cancer is usually determined using anatomical imaging, such as x-ray mammography, ultrasound, and MRI, and is confirmed via biopsy.

With the advent of molecular imaging, nuclear medicine techniques are considered to hold promise for the early detection of tumors through a functional perspective, providing information on molecular characteristics.

GRPR is known as a G-protein-coupled receptor that is expressed in a series of cancer types, including breast cancer, small cell lung cancer, prostate cancer, glioma, and neuroblastoma. According to literature, 62% to 96% of estrogen receptor positive (ER+) breast cancers express GRPR (2). Gastrin-releasing peptide receptor is heterogeneously expressed in neoplastic epithelial mammary cells, ductal carcinomas in situ, and invasive carcinoma. GRPR is also expressed in metastatic lymph nodes from breast cancer, whereas the level of GRPR expression in normal lymph node tissue is very low.

^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (^{68}Ga-DOTA-Bombesin or ^{68}Ga-RM2, formerly also known as BAY86-7548) is a synthetic bombesin receptor antagonist, which targets gastrin-releasing peptide receptors (GRPR) (3). Stoykow and colleagues reported the use of ^{68}Ga-RM2 in 15 patients with breast cancer. A total of 13 of 18 tumors demonstrated strongly increased ^{68}Ga-RM2 uptake compared to normal breast tissue (defined as PET-positive). All PET-positive primary tumors were ER- and PR-positive (13 of /13) in contrast to only 1 of 5 PET-negative tumors. Mean SUV_{max} of ER-positive tumors was 10.6 ± 6.0 compared to 2.3 ± 1.0 in ER-negative tumors (P = 0.016). In a multivariate analysis including ER, PR, HER2/neu and MIB-1, only ER expression predicted ^{68}Ga-RM2 uptake (model: r2 = 0.55, p = 0.025). Normal breast tissue showed inter- and intraindividually variable, moderate GRPR binding (SUV_{max} 2.3 ± 1.0), while physiological uptake of other organs was considerably less except pancreas. Of note, ^{68}Ga-RM2-PET/CT detected internal mammary lymph nodes with high ^{68}Ga-RM2 uptake (n = 8), a contralateral axillary lymph node metastasis (verified by biopsy) and bone metastases (n = 1; not detected by bone scan and CT). This study demonstrated that ^{68}Ga-RM2-PET/CT is a promising imaging method in ER-positive breast cancer. *In vivo* GRPR binding assessed by ^{68}Ga-RM2-PET/CT correlated with ER expression in primary tumors of untreated patients (4).

We conducted a pilot phase evaluation of ^{68}Ga-RM2 in prostate cancer patients under an RDRC-approved protocol at Stanford University. Ten men (age range: 60 to 83 year-old; mean ± SD: 73.1 ± 6.9) with biochemical recurrence of prostate cancer (PSA range: 3.7 to 36.4; mean ± SD: 12.5 ± 9.8) were enrolled. PET/MRI images were acquired at

42 to 51 minutes (mean ± SD: 47.2 ± 3.2) after injection of 3.6 to 4.1 mCi (mean±SD: 3.7 ± 0.2) of ^{68}Ga-RM2.

Biodistribution and localization of ^{68}Ga-RM2

All participants tolerated the procedure without immediate or delayed (up to 7 days) complaints or complications. Table 2 shows the ^{68}Ga-RM2 uptake (SUV_{max} and SUV_{mean}) in normal tissues. The areas with the highest ^{68}Ga-RM2 accumulation are the pancreas (mean SUV_{max}: 52.0 ± 16.7 [range: 36.8 to 93.8] and SUV_{mean}: 33.2 ± 17.5 [range: 8.8 to 66.1]) and bladder (mean SUV_{max}: 121.6 ± 67.5 [range: 32.6 to 220.7] and SUV_{mean}: 93.8 ± 59.7 [range: 29.8 to 195.7]), while moderate uptake was noted in the blood pool (mean SUV_{max}: 2.3 ± 0.7 [range: 1.8 to 4.0] and SUV_{mean}: 1.3 ± 0.7 [range: 0.7 to 2.7]), stomach (mean SUV_{max}: 2.5 ± 0.7 [range: 1.3 to 3.7] and SUV_{mean}: 1.3 ± 0.5 [range: 0.6 to 1.9]), small bowel (mean SUV_{max}: 2.4 ± 0.6 [range: 1.7 to 3.3] and SUV_{mean}: 1.4 ± 0.5 [range: 0.7 to 2.3]) and colon (mean SUV_{max}: 2.0 ± 0.7 [range: 1.3 to 3.8] and SUV_{mean}: 1.0 ± 0.6 [range: 0.5 to 2.3]). The liver had low ^{68}Ga-RM2 uptake with SUV_{mean} of less than 1.0. There were no differences between the ^{68}Ga-RM2 biodistribution at 45 minutes post-injection among the 10 participants (Figure 1). The pattern of ^{68}Ga-RM2 uptake is similar to previous reports (5).

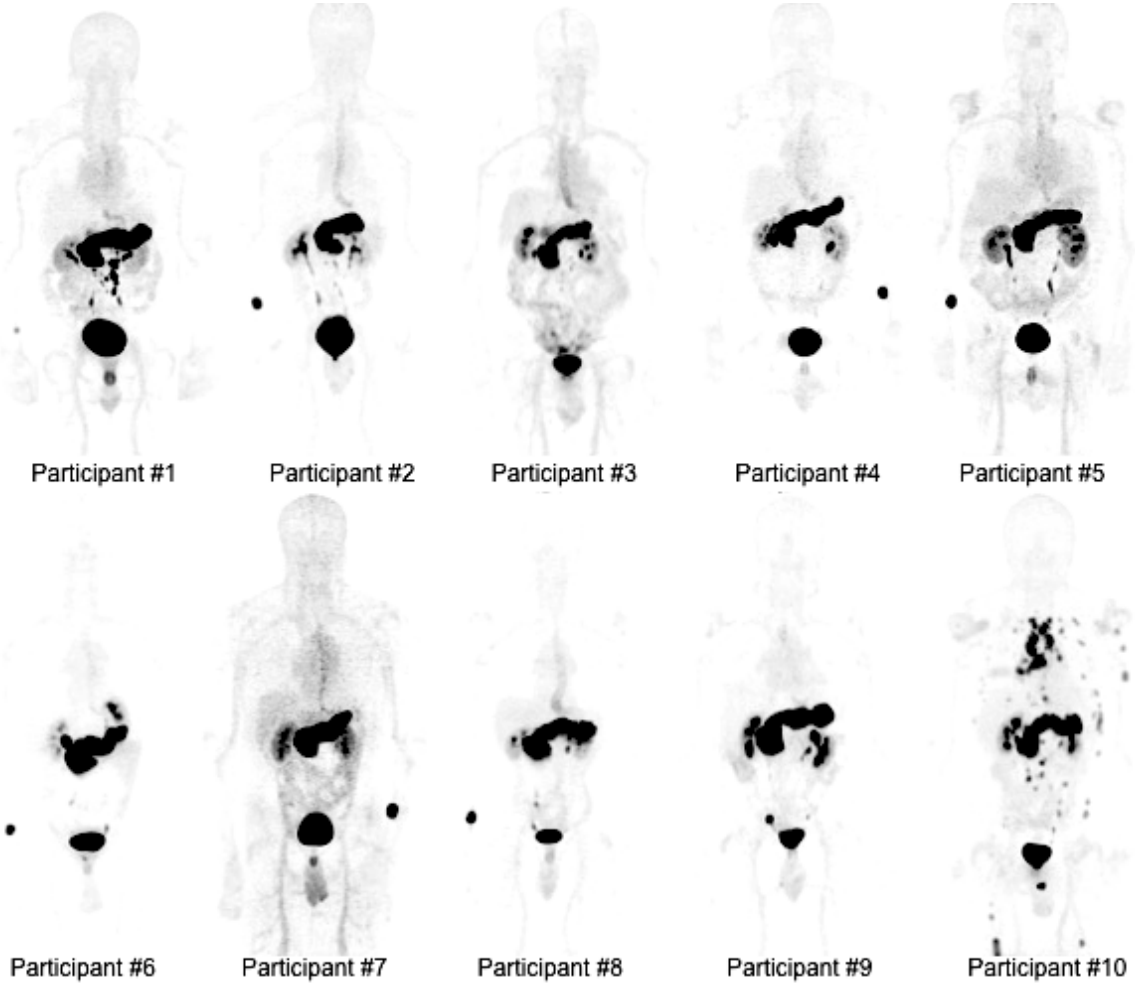


Figure 1: Maximum intensity projection (MIP) images from 10 participants in the prostate cancer pilot study conducted at Stanford University.

The sponsor-investigator Dr Iagaru holds an Investigational New Drug application (IND) for ^{68}Ga-RM2 (IND 127137), and the group has significant experience using the tracer in currently ongoing clinical studies in prostate cancer at our institution, including 81 patients with biochemically recurrent prostate cancer and 16 patients with newly diagnosed prostate cancer. We propose to extend the use in patients with estrogen receptor positive (ER+) breast cancer.

2.2 Clinicaltrials.gov

This protocol will be registered on Clinicaltrials.Gov. ClinicalTrials.gov outcomes are described at Section 2.4.3.

2.3 Rationale

In this study, we propose to use a well-established PET isotope, Gallium-68 (^{68}Ga), bound to a bombesin receptor antagonist, ^{68}Ga-RM2, which has high affinity for gastrin-releasing peptide receptors. GRPR proteins are highly overexpressed in several human tumors, including breast cancer (2). The following aim is proposed:

> To evaluate the feasibility of ^{68}Ga-RM2 PET/MRI for identification of ER+ primary breast cancer and metastases.

The first-in-human study investigated the safety, tolerability, metabolism, pharmacokinetics, biodistribution, and radiation dosimetry of ^{68}Ga-RM2. Five healthy men underwent dynamic whole-body PET/CT after an intravenous injection of ^{68}Ga-RM2 (138 ± 5 mBq). Besides total radioactivity, plasma samples were analyzed by radio–high-performance liquid chromatography for metabolism of the tracer. Dosimetry was calculated using the OLINDA/EXM software. The organs with the highest absorbed doses were the urinary bladder wall (0.62 mSv/MBq) and the pancreas (0.51 mSv/MBq). The mean effective dose was 0.051 mSv/MBq. ^{68}Ga-RM2 was well tolerated by all subjects. The authors concluded that the intravenously injected ^{68}Ga-RM2 is safe, and rapid metabolism is demonstrated. A 150-MBq injection of ^{68}Ga-RM2 results in an effective dose of 7.7 mSv, which could be reduced to 5.7 mSv with frequent bladder voids (5).

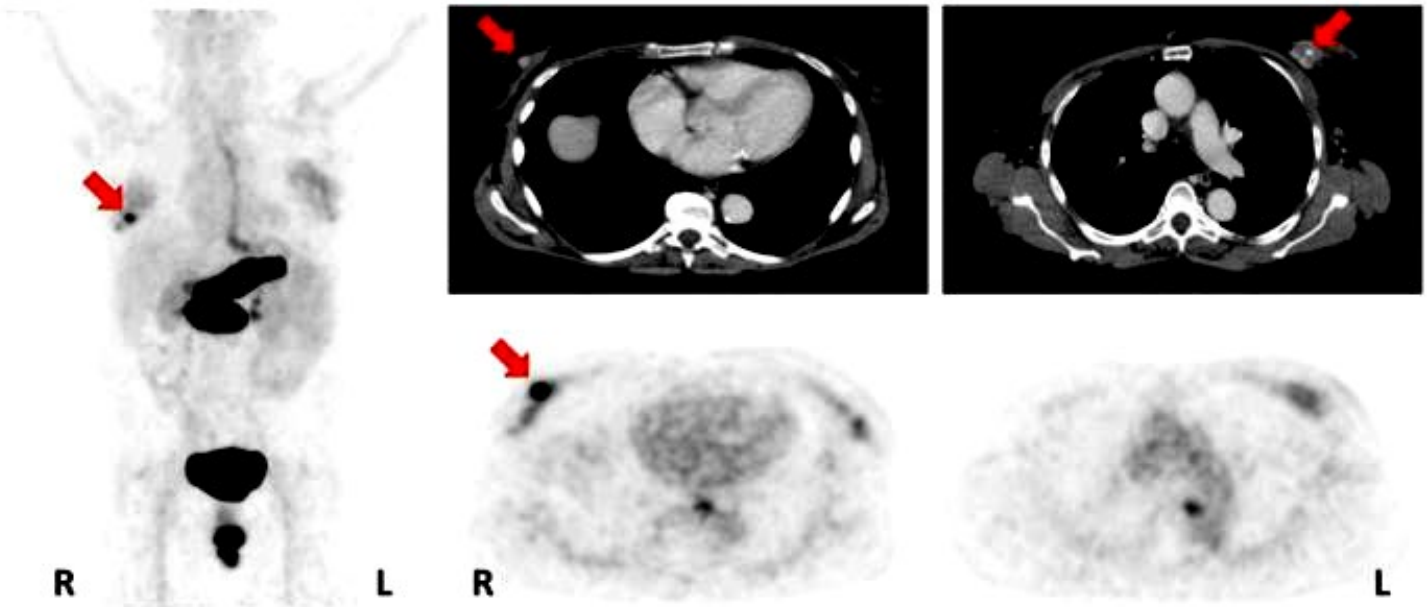


Figure 2: 74-year-old patient with a bilateral tumor with an ER/PR-positive tumor on the right side (PET-positive) and an ER/PR-negative tumor on the left side (PET-negative). Maximum intensity projection (left); CT (upper row); ^{68}Ga-RM2-PET (lower row); primary tumors indicated by red arrows (4).

2.4 Study Design

This is a pilot study enrolling up to 20 participants with ER+ breast cancer, either at initial diagnosis prior to surgery or at suspected recurrence. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive ^{68}Ga-RM2 and undergo a PET/MRI scan. All patients will first be seen by a Stanford Cancer Institute physician and then referred if appropriate on clinical grounds to Dr Iagaru or his colleagues for this study. The following steps will take place.

1. Participants will be given a copy of the consent form s/he signed.
2. Participant will be asked to drink 1 to 2 glasses of water before arrival at the clinic
3. Vital signs (heart rate, blood pressure) will be recorded
4. Participant will be injected IV with 140 $\pm$ 20% mBq of ^{68}Ga-RM2
5. Participant will void immediately prior to the scan
6. Data acquisition will begin with a dedicated scan of the breasts, followed by a vertex to mid-thighs scan. First, localizer MRI scans will be performed to define the table positions and then MR structural imaging and diffiusion weigted imaging will be performed simultaneousely with PET imaging. After the dedicated scan of the breasts, a whole-body combined PET/MRI acquisition will be initiated with 3 to 5 table positions at a 2 to 4 minute acquisition time per table position.
7. Vital signs (heart rate, blood pressure) will be recorded again at the completion of the study, and the patient will be dismissed.
8. Participants will be contacted at 24 to 72 hours following the scan in order to collect record any adverse events.

2.4.1 Objectives of the Study

Primary Objective

- To evaluate the feasibility ^{68}Ga-RM2 PET/MRI for identification of estrogen receptor positive primary breast cancer and metastases

2.4.2 Endpoints

Primary Endpoints

- Number of lesions identified on ^{68}Ga-RM2 PET/MRI
- Correlation of ^{68}Ga-RM2 uptake and ER positivity on biopsy (when done as clinically indicated)

2.4.3 ClinicalTrials.gov Outcomes

Primary Outcome

Title: Number of lesions identified on ^{68}Ga-RM2 PET/MRI

Description: Findings deemed as compatible with breast cancer

The outcome will be reported as the number of participants with successful PET-based detection of ER-positive breast cancer and metastases

Timeframe: 12 months

Safety outcome: No

Secondary Outcome

None

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

1. ≥ 18 years-old
2. Biopsy proven ER+ breast cancer, either at initial diagnosis prior to surgery or at suspected recurrence.
3. Able to provide written consent
4. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)
5. Females must be not be pregnant per urine pregnancy test

3.2 Exclusion Criteria

1. Inability to lie still for the entire imaging time Inability to lie still for the entire imaging time
2. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
3. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance
4. Metallic implants (contraindicated for MRI)

3.3 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

3.4.1 Primary Completion:

The study will reach primary completion 24 months from the time the study opens to accrual.

3.4.2. Study Completion:

The study will reach study completion 36 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agent ^{68}Ga-RM2

The PET radiopharmaceutical ^{68}Ga-RM2 has previously been identified as 68Ga-DOTA Bombesin or BAY86-7548. This is not an FDA-approved product,and is described within IND 127137, the IND to which this protocol is submitted. The structure of ^{68}Ga-RM2 is represented in Figure 3.

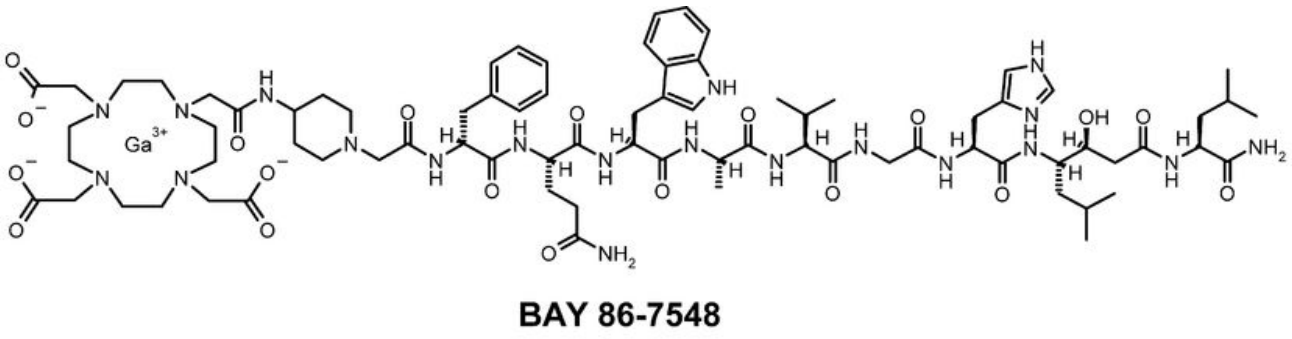


Figure 3: Chemical structure of ^{68}Ga-RM2

The administered dosage of ^{68}Ga-RM2 will be 140 mBq ± 20%, administered IV. The administered dosage is 140 mBq i.v. Measured human dosimetry data are available from published data (5). ^{68}Ga-RM2 is rapidly excreted through the kidneys to the urinary bladder and accumulated predominantly in the pancreas and liver. Maximum peak uptake of the total injected radioactivity was seen in the urinary bladder contents and the liver, with approximately 36% and 14%, respectively.

The organ with the highest absorbed dose was the urinary bladder wall at 0.61 mSv/MBq, followed by the pancreas at 0.51 mSv/MBq. The mean effective dose (14) was 0.051 mSv/MBq. Thus, the effective dose from a 140 MBq injected radioactivity is 7.7 mSv, which could be reduced to roughly 4.76 mSv with frequent bladder voiding (1-h voids).

To summarize the results of the published human dosimetry study, there were no observed adverse events to the radiopharmaceutical. The measured dosimetry showed that the critical organ with ^{68}Ga-RM2 is the urinary bladder, followed by the pancreas. The effective dose of ^{68}Ga-RM2 reported (0.051 mSv/MBq) is approximately twice as much as those of ^{68}Ga-DOTA-TOC (0.023 mSv/MBq), ^{68}Ga-DOTA-NOC (0.025 mSv/MBq), ^{68}Ga-DOTA-TATE (0.021 mSv/MBq) and ^{68}Ga-NOTA-RGD (0.022 mSv/MBq) (6-9).

4.2 Source of the Study Agent

Molecular Imaging Program at Stanford (MIPS)
Satellite Radiochemistry Facility
300 Pasteur Dr, [redacted]
Stanford, CA 94305

4.3 Ordering

Ordered in Radiology Information System (RIS), address per above.

4.4 Agent Accountability

The RIS is password-protected and part of the electronic medical records.

5. IMAGING SPECIFICS

5.1 Modality or Modalities to be used

PET/MRI

5.2 Details of Imaging (ie, dynamic, static, number of scans, etc)

First a standard breast MRI will be done, at the discretion of the investigator. After correct positioning of the spatial acquisition windows is ensured, the combined PET/MRI acquisition will be initiated with 3 to 5 table positions at a 2 to 4 min acquisition time per table position. A volumetric T1 acquisition with fat-water separation and motion correction to enable free-breathing will be obtained at each table position and used for the generation of attenuation maps and for anatomic allocation of the PET results. Simultaneously with the start of the T1 MRI sequence, the PET acquisition will start at the same table position, thus ensuring optimal temporal and regional correspondence between MRI and PET data. The PET acquisition time will be 4 min per table position, taking delayed acquisition times and radioactive decay into account. As the T1 will take less than 4 minutes, a rapid diffusion weighted MRI will also be performed. After completion of the PET acquisition, the table will be moved to the next table position and the procedure will be repeated. Upon completion of the PET acquisition for all stations, volumetric T1- and T2-weighted MR images may be obtained at multiple stations as needed.

The PET emission scan is corrected using segmented attenuation data of the MRI scan. The PET images are reconstructed with a standard iterative algorithm. All images are reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (AW, GE Medical Systems).

5.3 Image interpretation

The PET/MRI scans will be interpreted by ABNM certified Nuclear Medicine physicians and ABR certified Radiologists. Drs Iagaru, Daniel, Loening and Mari have significant clinical experience and will be blinded to the participants' medical history and the results of other imaging modalities. Consensus read will be obtained for each scan. Each lesion will be tabulated and a comparison of lesion detection by each scanner will be conducted.

6. STUDY PROCEDURES

6.1 Pre-Study

Potential subjects will be referred by treating physicians for participation in this imaging study. The following procedures will occur pre-study:

- Review of eligibility criteria
- Obtain informed consent
- Collect demographics
- Review medical history, including any concomitant medication.

6.2 Imaging Days

Subjects will undergo one clinic visit for imaging. Subjects will receive an intravenous (IV) injection of investigational imaging agent (^{68}Ga-RM2) and undergo PET/MRI image collection as described above.

6.3 Follow-up

Active subject participation ends after the 24 to 72 hour post-scan Safety Follow-up. Investigators will follow subjects by chart review for 12 months post-scan (chart review of medical records at approximately 6 months post scan and 12 months post scan) to record any

standard of care biopsies or imaging results. The investigators will assist with identification of lesions that can be biopsied, based on ^{68}Ga-RM2 findings, if requested by treating physicians.

If a subject transfers clinical care outside of Stanford Healthcare during the chart review clinical follow-up period, investigators will request permission to contact the treating physician

6.4 Criteria for Removal from Study

The Protocol Director may withdraw subjects from the study for one or more of the following reasons: failure to follow the instructions of the Protocol Director and/or study staff; determination that continuing the participation could be harmful to the subject; the study is cancelled or other administrative reasons.

6.5 Alternatives

The alternative is to not participate in the study.

7. STUDY CALENDAR

	Pre-Study	Scan Date	24 to 72 Hours Post-Scan	12 Months
Informed consent	X			
Demographics	X			
Medical history	X			
^{68}Ga-RM2		X		
Safety Follow-up Call to Participant			X	
Data analysis				X

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick when given by i.v. injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body.

This research study involves exposure to radiation. This radiation exposure is for research purposes only. The amount of radiation from one ^{68}Ga-RM2 PET/MR is 4.76 mSv, approximately equal to 10% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in 1 year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, standard of care procedures will be in place for verification of correct radiopharmaceutical dose and route of administration. The study Principal Investigator (PI) or his designee will report all serious adverse events (per 21CFR§312.32) to the Stanford CCTO Safety Coordinator within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted

in death) using the Adverse Events Communication Form. If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible, but no later than 5 working days after the PI makes the determination and no later than 15 working days after first receiving notification of the effect.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

9.2 Data Management Plan

The study charts will be stored in a locked office in the Cancer Clinical Trials Office. Demographic information will be kept using OnCore.

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will audit study related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC audits will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

10. Statistical Considerations and Evaluation of Results

10.1 Study Endpoints

Primary endpoint:

- Number of participants with successful PET-based detection of ER-positive breast cancer and metastases

Other endpoints:

None

10.2. Accrual estimates

We anticipate enrolling 20 patients in total.

10.3 Analyses Plans

As this is an initial feasibility pilot, and we have no control over the biopsy process, we will only estimate the per-lesion sensitivity of ^{68}Ga-RM2 PET-based in detecting the known ER+ lesions.

There will be at least 20 ER+ lesions, and we expect that the PET sensitivity will be at least 80%. A sample of 20 will provide 90% power at one-sided 5% error to demonstrate that a sensitivity of 80% is greater than chance performance. A sample of 25 will provide 80% power to demonstrate sensitivity of 75%, which we believe is the minimum that would justify further study.

10.4 Accrual estimates

We expect the accrual of 10 patients each year for 2 years. This is achievable given our experience with other protocols and the support from the referring physicians, Drs Masarweh and Telli.

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Inclusion/Exclusion Criteria Checklist

Protocol Title:	A Pilot Study of ^{68}Ga-RM2 PET/MRI in the Evaluation of Patients with Estrogen Receptor-positive Breast Cancer
Protocol Number:	**IRB-48150 / BRS0098**
Principal Investigator:	Andrei Iagaru, MD

3.1 Inclusion Criteria

Inclusion Criteria Yes must be checked to be eligible	Yes	No	Supporting Documentation
1. ≥ 18 years-old	☐	☐	
2. Biopsy proven ER+ breast cancer, either at initial diagnosis prior to surgery or at suspected recurrence.	☐	☐	
3. Able to provide written consent	☐	☐	
4. Karnofsky performance status of ≥50 (or ECOG/WHO equivalent)	☐	☐	
5. Females must be not be pregnant per urine pregnancy test			

3.2 Exclusion Criteria

Exclusion Criteria No must be checked to be eligible	Yes	No	Supporting Documentation
1. Inability to lie still for the entire imaging time	☐	☐	
2. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc)	☐	☐	
3. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance.	☐	☐	
4. Metallic implants (contraindicated for MRI)	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Principal Investigator or Sub-Investigator:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	