A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Biopsy Guidance in Patients with Suspected Prostate Cancer

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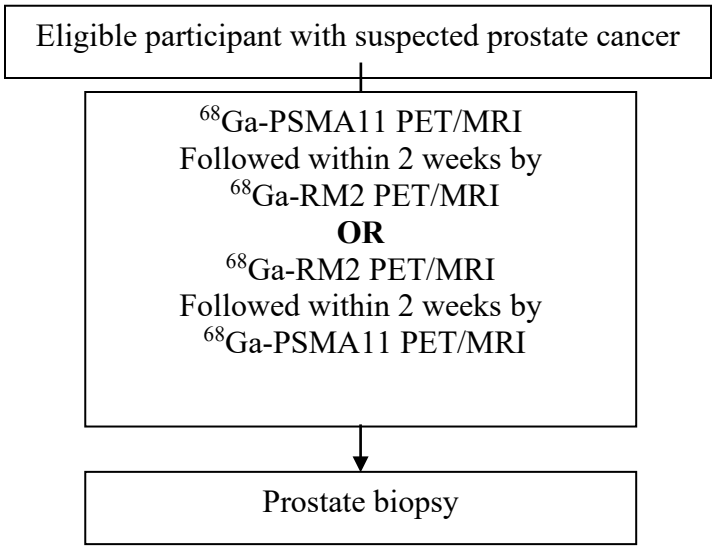
PROTOCOL SYNOPSIS

TITLE	A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Biopsy Guidance in Patients with Suspected Prostate Cancer
STUDY PHASE	Phase 2 pilot study
INDICATION	Prostate cancer
INVESTIGATIONAL PRODUCTS	^{68}Ga-PSMA-11; also known as: • DFKZ-11 • HBED-CC PSMA • The "Heidelberg compound" ^{68}Ga-RM2; also known as: • Bombesin • BAY86-7548
SAMPLE SIZE	20 participants
PRIMARY OBJECTIVE	To evaluate ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for biopsy guidance in patients with suspected prostate cancer.
EXPLORATORY ENDPOINTS	• Correlation of ^{68}Ga-PSMA-11 uptake and Gleason score at biopsy • Correlation of ^{68}Ga-RM2 and Gleason score at biopsy

SCHEMA


Eligible participant with suspected prostate cancer
^{68}Ga-PSMA11 PET/MRI
Followed within 2 weeks by
^{68}Ga-RM2 PET/MRI
OR
^{68}Ga-RM2 PET/MRI
Followed within 2 weeks by
^{68}Ga-PSMA11 PET/MRI
Prostate biopsy

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ga-68; ^{68}Ga	Gallium-68
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
PET	Positron emission tomography
SUV	Standardized Uptake Value
PSMA	Prostate-specific membrane antigen
GRPR	Gastrin releasing peptide receptor
PRCA	Prostate cancer

1. OBJECTIVE

Specific Aim

To evaluate ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for biopsy guidance in patients with suspected prostate cancer.

2. BACKGROUND

2.1 Preliminary information

Prostate cancer (PRCA) kills ~29,000 American men each year (1). However, most of the ~180,000 new cases diagnosed each year are not deadly. While the 50% drop in PRCA specific mortality in the US occurred concurrently with systematic PSA screening starting in the 1980s, the PLCO randomized trial of PSA screening showed no survival benefit, and ERSPC in Europe showed a small but positive benefit to PSA screening (2, 3). Two significant limitations of PSA testing contribute to the poor results of these trials and form the basis of this proposal:

The 1st limitation is that PSA has poor sensitivity and specificity with ~15% of men with PRCA having a normal PSA (4) while 60-80% of men who are biopsied are found to have no cancer, either because there is none and the PSA test was falsely positive or the cancer is missed by the biopsy (5). Until recently, transrectal ultrasound (TRUS) has been the only widely available used imaging modality. Because of the major limitations of TRUS for PRCA detection, diagnosis is most commonly accomplished by systematically sampling the entire prostate using 12 needles passed through the rectum under TRUS guidance, rather than directing biopsy to any particular target seen in the gland on TRUS images. This biopsy procedure can be painful and is associated with significant and increasing rates of infectious complications (6, 7). Since autopsy studies show that many men have small, indolent cancers that are not likely to be life threatening (8), PSA driven biopsy leads to overdiagnosis of indolent cancers (9) that are not clinically significant. The ideal approach would be to eliminate unnecessary biopsies in men with no cancer or indolent cancer, and selectively biopsy men with aggressive cancers who are more likely to benefit from therapy.

The 2nd limitation is that PSA screening and biopsies miss a significant number of aggressive cancers, either by under-sampling high grade cancers, or by underestimating of tumor volume (10-12). The ideal approach would be to direct biopsies towards the areas of most aggressive tumor, so that biopsy accurately reflects the severity of their disease.

In response to these shortcomings of PSA screening as well as the significant treatment associated side effects (13), the management of localized PRCA has changed dramatically in the past 5 years to directly address the problem of over-treatment (5). One of the greatest changes has been the increased use of Active Surveillance (AS) in men with low grade, low risk PRCA (14). In the US, rates of AS have increased from 5-9% in 1990-2010 to 40%, while in Europe, rates are 80 to 90% (15-17). Gleason scoring is an established marker of outcome and is the most important factor used in selecting patients for AS (5). Low grade cancers (Grade group 1 or Gleason score 3 + 3 + 6) are recommended for AS, while cases > 3 + 4 (or in some cases > 4 + 3) are recommend for definitive therapy (18). Therefore, accurate identification of cases with grade > 3 + 4 is critical for determining initial treatment vs AS. Second, ancillary tests, such as the urinary test PCA3 (a lncRNA over-expressed in PRCA), as well as the

Prostate Health Index and 4Kscore have emerged (both assessing molecular forms of PSA) (19-21). These tests have been calibrated to identify men who do not need biopsy, and can decrease biopsy rates by 10-20%. However, many unnecessary biopsies continue to occur, and none of these tests effectively identifies aggressive PRCA. For example, neither the PCA3 or 4K score provide clinically meaningful prediction of outcomes in men on AS and cannot be used in clinical decision-making in this large and growing cohort of men (22, 23). New technologies are critically needed to eliminate unnecessary biopsies in men with no cancer or indolent cancer, and to better identify men with aggressive forms (≥ 3 + 4) of PRCA.

Recently, novel PET tracers that target PRCA cells have emerged as promising methods to improve PRCA imaging. PET tracers such as ^{18}F- or ^{11}C-labeled choline and ^{11}C-acetate are used at selected institutions in the USA (24, 25) but uptake in benign prostatic hyperplasia (BPH) or inflammatory lymph nodes (26, 27) limits their clinical utility. A new synthetic amino acid ^{18}F-FACBC suffers from limited specificity as its uptake in PRCA is reported to be similar to that in BPH (28). Prostate-specific membrane antigen (PSMA) is a cell surface protein significantly over-expressed in PRCA cells, and anti-PSMA antibodies labeled with ^{68}Ga and ^{18}F-labeled radiotracers can detect PRCA relapses and metastases by binding to the extracellular domain of PSMA. While PSMA appears to be a very promising molecular imaging target (29, 30), it does not detect all recurrences (31, 32) and is not specific to PRCA only (33, 34). False positives have also been reported (35-37). Gastrin releasing peptide receptor (GRPR) has emerged as a novel imaging target which is also highly expressed in PRCA and has much lower expression in benign prostate tissue including BPH and inflammation (38). This high specificity provides an advantage over current choline- and acetate-based radiotracers. GRPR can be targeted by its natural ligand GRP or other bombesin-like peptides. Compared to antibodies, peptides are usually cleared faster, penetrate tissue more rapidly, show lower antigenicity, and can be synthesized in large quantities relatively easily, making GRPR an attractive target (39). Also, a clear difference of RM2 expression level between Gleason patterns 3 and ≥ 4 has been shown with higher expression of RM2 antigen significantly associated with primary Gleason pattern ≥ 4, high Gleason score (≥ 8), larger tumor volume, and advanced tumor stage (40). Furthermore, 5-year PSA failure-free survival was significantly lower in the higher expression groups (40).

The sponsor-investigator Dr Iagaru holds Investigational New Drug applications (INDs) for both ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 (IND [redacted] and IND [redacted], respectively) and the group has significant experience using both tracers in currently ongoing clinical studies at our institution. To improve the performance of MRI imaging in the prostate, one possible solution could be to combine molecular imaging strategies. MRI provides excellent soft tissue contrast and mpMRI has significantly improved PRCA detection in the prostate. PET/MRI can increase the specificity of MRI alone when using PRCA specific PET tracers (41). We propose testing this multimodal imaging platform in patients with early stage PRCA to understand its performance characteristics for detection, particularly for aggressive disease (defined as high grade > 3 + 4).

2.2 Clinicaltrials.gov

This protocol will be registered on Clinicaltrials.Gov. ClinicalTrials.gov outcomes are described in 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 PSMA ligand (ie, ^{68}Ga-PSMA-11) and a GRPR ligand (ie, ^{68}Ga-RM2) that have high affinity for prostate specific membrane antigen and gastrin releasing peptide receptors, respectively.

Therefore, we propose the following aim: to evaluate ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for biopsy guidance in patients with suspected prostate cancer.

We have an ongoing protocol at Stanford University evaluating ^{68}Ga-PSMA-11 PET/MRI for evaluation of extent of disease in patients with intermediate or high-risk prostate cancer scheduled to undergo prostatectomy and nodal dissection. Our initial analysis of the first 33 participants showed that prostate cancer was seen using ^{68}Ga-PSMA-11 PET in all patients, whereas multiparametric MR imaging depicted Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 lesions in 26 patients and PI-RADS 3 lesions in four patients. Focal uptake was seen in the pelvic lymph nodes in five patients. Pathologic examination confirmed prostate cancer in all patients, as well as nodal metastasis in three. All patients with normal pelvic nodes in PET/MR imaging had no metastases at pathologic examination (42).

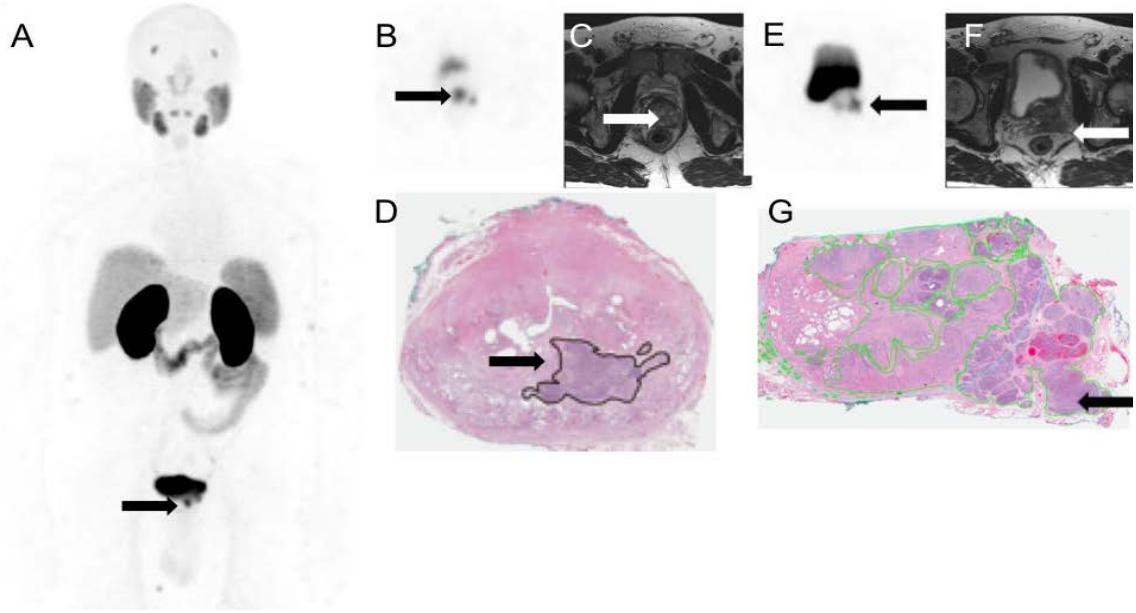


Figure 1: 74 year-old man (participant #4) with recently diagnosed intermediate risk, T1c, Gleason 4+4 prostate cancer presenting with PSA of 4.12 ng/mL. Maximum intensity projection (MIP) PSMA 11 PET image (A), early transaxial PET (B) and delayed transaxial PET (C) showed focal uptake in histopathological proven prostate cancer (F). The milder focal uptake in the left lobe was likewise proven to be prostate cancer. Transaxial T2-weighted MRI (D) and DWI (B = 800) MRI (E) are also shown. Only the right-side tumor was mpMRI positive (PI-RADS 5).

In addition, we now have pilot data from 12 participants with intermediate or high-risk prostate cancer scheduled to undergo prostatectomy and nodal dissection who had ^{68}Ga-RM2 PET/CT prior to surgery. Prostate cancer was identified in all 12 patients.

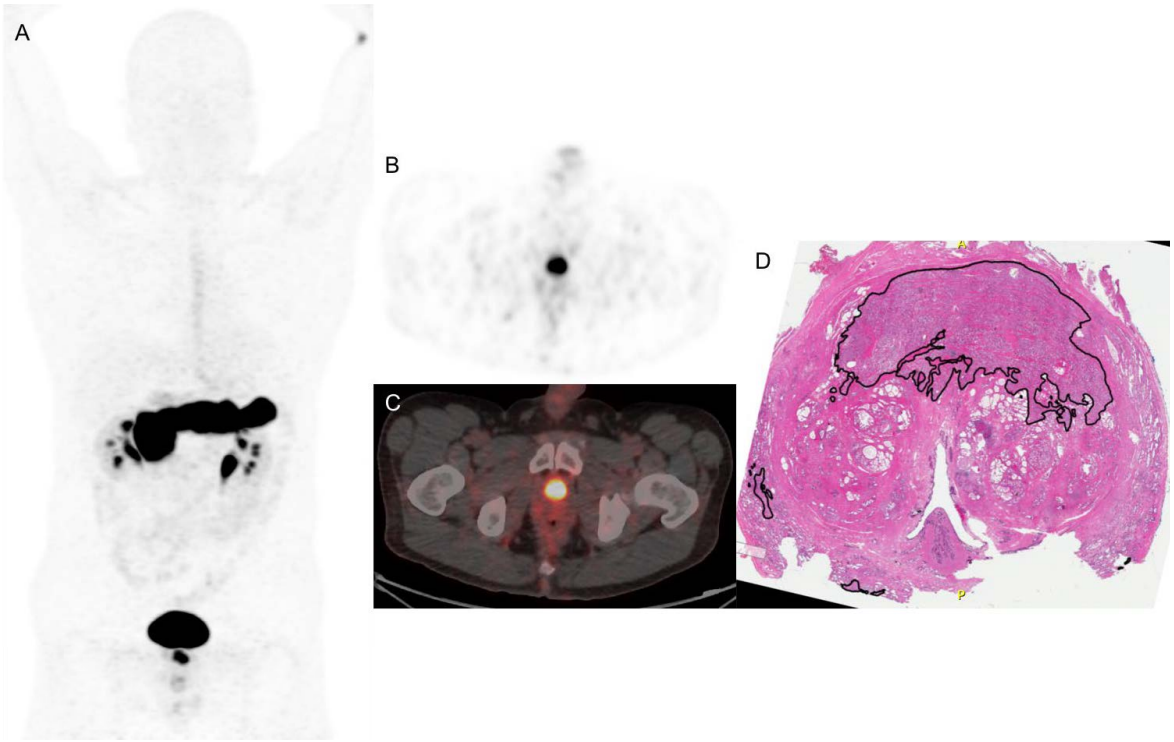


Figure 2: 68 year-old man (participant #2) with recently diagnosed intermediate risk, T1c, Gleason 3+4 prostate cancer presenting with PSA of 4.53 ng/mL. Maximum intensity projection (MIP) RM2 PET image (A), transaxial PET (B) and fused transaxial PET (C) showed focal uptake in histopathological proven prostate cancer (D).

2.4 Study Design

This is a pilot study with a total of 20 participants with suspected prostate cancer. 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. Eligible participants will undergo baseline assessments at enrollment. The following steps will take place after the participant has signed the written consent (participants will be randomized to have ^{68}Ga-RM2 first followed by ^{68}Ga-PSMA11 within 2 weeks or ^{68}Ga-PSMA11 first followed by ^{68}Ga-RM2 within 2 weeks [50/50 chance for each schedule]).

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. Approximately 45 minutes after the radiopharmaceutical IV administration, data acquisition will begin in the pelvic region and move toward the head. First, localizer MRI scans will be performed to define the table positions. 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 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 participant will be dismissed.

8. Participants will be contacted at 24 to 72 hours following the scan in order to collect any adverse events.

The same will be repeated for ^{68}Ga-PSMA11 (within 2 weeks of ^{68}Ga-RM2):

1. Participant will be asked to drink 1 to 2 glasses of water before arrival at the clinic
2. Vital signs (heart rate, blood pressure) will be recorded
3. Participant will be injected IV with 3 to 7 mCi of ^{68}Ga-PSMA11
4. Participant will void immediately prior to the scan
5. Approximately 45 to 60 minutes after the radiopharmaceutical IV administration, data acquisition will begin in the pelvic region and move toward the head. First, localizer MRI scans will be performed to define the table positions. 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 minute acquisition time per table position. Only MR sequences required for attenuation correction of PET data will be acquired.
6. Vital signs (heart rate, blood pressure) will be recorded again at the completion of the study.
7. Participants will be contacted at 24 to 72 hours following the scan in order to collect any adverse events.

2.4.1 Objectives of the Study

Primary

- To evaluate ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for biopsy guidance in patients with suspected prostate cancer.

Exploratory

- Correlation of ^{68}Ga-PSMA-11 uptake and Gleason score at biopsy
- Correlation of ^{68}Ga-RM2 and Gleason score at biopsy

2.4.2 Endpoints

Primary Endpoints

- Number of participants with successful PET-based biopsy guidance

Exploratory Endpoints

- Observation of SUV_{max} from ^{68}Ga-PSMA-11 uptake and Gleason score at biopsy
- Observation of SUV_{max} from ^{68}Ga-RM2 uptake and Gleason score at biopsy

2.4.3 ClinicalTrials.gov Outcomes

Primary Outcome

Title: Successful PET-based Biopsy Guidance

Description: Number of participants with biopsy results correlated with imaging findings (ie, prostate uptake on ^{68}Ga-PSMA-11 and ^{68}Ga-RM2 scans)

The outcome will be reported as the number of participants without dispersion for which PET-based biopsy guidance is successfully obtained.

Timeframe:

Safety outcome: No

Secondary Outcome

None.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- ≥ 18 years-old
- Suspected prostate cancer
- Planned prostate biopsy
- Able to provide written consent
- Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)

3.2 Exclusion Criteria

- Patients not capable of getting PET study due to weight, claustrophobia, or inability to lay still for the duration of the exam
- 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 Agents

This protocol will utilize ^{68}Ga-RM2 and ^{68}Ga-PSMA11 as radioimaging agents.

4.1.1 ^{68}Ga-RM2

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

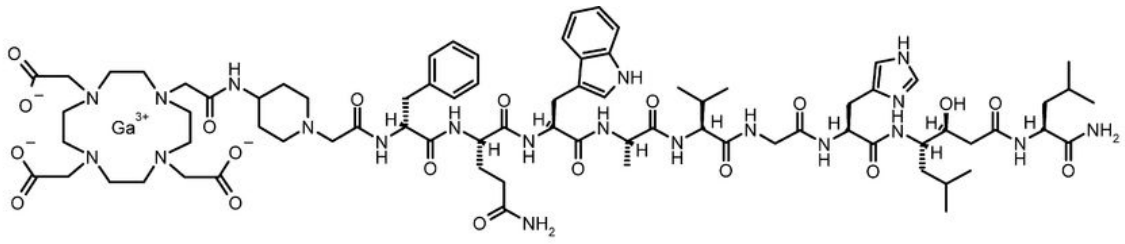


Figure 3: Chemical structure of ^{68}Ga-RM2

The administered dosage of ^{68}Ga-RM2 will be 140 mBq ± 20%, administered IV. Measured human dosimetry data are available from published data (47). ^{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-hr 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) (43-46).

4.1.2 ^{68}Ga-PSMA11

The PET radiopharmaceutical ^{68}Ga-PSMA11 will also be utilized, and has previously been identified as DFKZ-11; HBED-CC PSMA; or the "Heidelberg compound." This is not an FDA-approved product, and is described within IND [redacted], which is cross-referenced to IND [redacted]. The structure of ^{68}Ga-PSMA11 is represented in Figure 4.

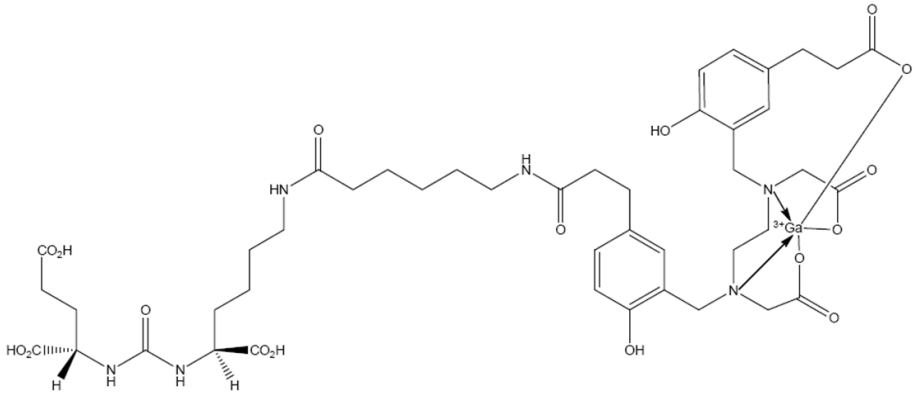


Figure 4: Chemical structure of ^{68}Ga-PSMA11.

The administered dosage of ^{68}Ga-PSMA-11 will be 111 to 259 mBq (3 to 7 mCi), administed IV. There are 2 publications on dosimetry for ^{68}Ga-PSMA-11 (PMID: 27260521; 28012435). The first lists 0.0236 mSv/MBq for the mean effective dose, while the other indicates 0.0258 mSv/MBq. We used the maximum potential administered activity of 7 mCi and the higher of the reported dosimetry values. Therefore, 259 mBq x 0.0258 mSv/MBq + 6.68 mSv.

To summarize the results of the published human studies, there were no observed adverse events to the radiopharmaceutical. The measured dosimetry showed that the critical organ with ^{68}Ga-PSMA-11 is the spleen, followed by the stomach wall; pancreas; and bladder wall. The effective dose of ^{68}Ga-PSMA-11 reported (0.0258 mSv/MBq) is similar to 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) (43-46).

4.2 Source of the Study Agent

Molecular Imaging Program at Stanford (MIPS)
Satellite Radiochemistry Facility
300 Pasteur Dr, C21
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)

A localizer MRI scan will be performed at 45 minutes after injection of 140 mBq of ^{68}Ga-RM2 (or 3 to 7 mCi of ^{68}Ga-PSMA11, depending on randomization) to define the table positions. 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 minute 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 minutes 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 post-contrast T1- and T2-weighted MR images may be obtained at multiple stations as needed.

A localizer MRI scan will be performed at 45 minutes after injection of 3-7 mCi of ^{68}Ga-PSMA11 (or ^{68}Ga-RM2, depending on randomization) to define the table positions. 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 minute acquisition time per table position. Only MR sequences required for attenuation correction of PET data will be acquired. Participants will be randomized to have ^{68}Ga-RM2 first followed by ^{68}Ga-PSMA11 within 2 weeks or ^{68}Ga-PSMA11 first followed by ^{68}Ga-RM2 within 2 weeks (50/50 chance for each schedule).

5.3 Image interpretation

The PET/MRI scans will be interpreted by ABNM certified Nuclear Medicine physicians and an ABR-certified radiologists. Drs Iagaru, Daniel, Davidzon, and Ghanouni 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 tracer will be conducted.

The study team will communicate the results of the scans to the referring (treating) physicians. Additional imaging/biopsy may be performed as a result of the research scan data.

PET and MRI data will be imported in the biopsy device to assist with lesion localization during the biopsy procedure.

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 2 separate clinic visits for imaging. On each imaging day, subjects will receive an intravenous (IV) injection of investigational imaging agent (^{68}Ga-RM2 or ^{68}Ga-PMSA11) 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 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 and/or ^{68}Ga-PMSA11 PET/MRI findings.

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** [a]		
^{68}Ga-PSMA11 (within 2 weeks)		**X** [a]		
Follow-up Call to Participant			**X**	
Chart review [b]				**X**

a. Subjects will undergo either ^{68}Ga-RM2 PET/MRI followed within 2 weeks by ^{68}Ga-PMSA11 PET/MRI, or 68Ga-PMSA11 PET/MRI followed within 2 weeks by 68Ga-RM2 PET/MRI
b. Subjects will be followed by chart review for 12 months from initial scan date. If a subject transfers clinical care from Stanford Healthcare, investigators may request records from the treating physician

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 IV 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 from one ^{68}Ga-PSMA-11 PET/MRI. There is no radiation exposure from MRI. The effective dose from one typical maximum of 259 mBq (range: 3 to 7 mCi) administration of ^{68}Ga-PSMA-11 is 6.68 mSv. Therefore, the effective dose from one ^{68}Ga-PSMA-11 PET/MRI is 6.68 mSv, approximately equal to 13% of the limit that radiation workers (eg, a hospital X-ray technician) are allowed to receive in 1 year.

This research study also involves exposure to radiation from one ^{68}Ga-RM2 PET/MRI. There is no radiation exposure from MRI. The amount of radiation from one administration of 140 mBq of ^{68}Ga-RM2 is 4.76 mSv. Therefore, the effective dose from one ^{68}Ga-RM2 PET/MRI is 4.76 mSv, approximately equal to 10% of the limit that radiation workers (eg, hospital x-ray technician) are allowed to receive in one year.

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 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 CRFs will be stored in a locked office in the Nuclear Medicine clinic. Records 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. Monitoring of the trial will occur every 8 weeks and a record of monitoring activities will be maintained by the study team.

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 biopsy guidance

Exploratory endpoints:

- Observation of SUV_{max} from ^{68}Ga-PSMA-11 uptake and Gleason score at biopsy
- Observation of SUV_{max} from ^{68}Ga-RM2 uptake and Gleason score at biopsy

10.2. Accrual estimates

We anticipate enrolling 20 patients in total.

10.3 Analyses Plans

This is a pilot study that will not have a pre-defined analysis plan.

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 Chung, Sonn, Brooks, and Gill.

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Inclusion/Exclusion Criteria Checklist

Protocol Title:	A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Biopsy Guidance in Patients with Suspected Prostate Cancer
Protocol Number:	**IRB-48151 / PROS0091**
Principal Investigator:	Andrei Iagaru, MD

Inclusion Criteria **Yes must be checked to be eligible**	**Yes**	**No**	**Supporting Documentation**
1. ≥ 18 years-old	☐	☐	
2. Suspected prostate cancer	☐	☐	
3. Planned prostate biopsy	☐	☐	
4. Able to provide written consent	☐	☐	
5. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)	☐	☐	

Exclusion Criteria **No must be checked to be eligible**	**Yes**	**No**	**Supporting Documentation**
1. Patients not capable of getting PET study due to weight, claustrophobia, or inability to lay still for the duration of the exam	☐	☐	
2. 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.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	