A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Evaluation of Prostate Cancer Response to HIFU Therapy

Principal Investigator / Protocol Director

Andrei Iagaru, MD
300 Pasteur Drive, [redacted]
Stanford, CA 94305
Phone: 650-725-4711
Fax: 650-498-5047
Email: aiagaru@stanford.edu

Co-investigators	
Geoffrey Sonn, MD 875 Blake Wilbur Dr; [redacted] Stanford, CA 94305 Phone: [redacted]; Fax: [redacted] Email: gsonn@stanford.edu	Pejman Ghanouni, MD, PhD 1201 Welch Road, [redacted] Stanford, CA 94305 Phone: 650-498-4485; [redacted] Email: ghanouni@stanford.edu
Carina Mari Aparici, MD 300 Pasteur Dr, [redacted] Stanford, CA 94305 Phone: 650-725-4711; Fax: 650-498-5047 Email: drmari@stanford.edu	Guido Davidzon, MD 300 Pasteur Dr, [redacted] Stanford, CA 94305 Phone: 650-725-4711; Fax: 650-498-5047 Email: gdavidzon@stanford.edu
Biostatistician [redacted], PhD Department of Radiology Lucas MRS Imaging Center 1201 Welch Road, [redacted] Stanford, CA 94305-[redacted]	**Study Coordinator** [redacted] 800 Welch Rd Palo Alto, CA 94304 Phone: [redacted]; Fax: [redacted] Email: [redacted]

Protocol IRB-48213 // PROS0093 // NCT- NCT03949517

Protocol version // 05 January 2021

SRC Approval Date – 5 March 2019

TABLE OF CONTENTS

PROTOCOL SYNOPSIS **4**

SCHEMA **5**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **6**

1. OBJECTIVE **7**

Specific Aim 7

2. BACKGROUND **7**

2.1 Preliminary information 7

2.2 Study Agent 10

2.3 Clinicaltrials.gov 10

2.4 Rationale 10

2.5 Study Design 14

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES **16**

3.1 Inclusion Criteria 16

3.2 Exclusion Criteria 16

3.3 Informed Consent Process 16

3.4 Study Timeline 16

4. IMAGING AGENT INFORMATION **16**

4.1 Study Agents ^{68}Ga-PSMA-11 and ^{68}Ga-RM2 16

4.2 Source of the Study Agent 17

4.3 Ordering 17

4.4 Agent Accountability 17

5. IMAGING SPECIFICS **17**

5.1 Modality or Modalities to be used 17

5.2 Details of Imaging (ie, dynamic, static, number of scans, etc) 17

5.3 Image interpretation 18

6. STUDY PROCEDURES **18**

6.1 Pre-Study 18

6.2 Imaging Days 18

6.3 Follow-up 19

6.4 Criteria for Removal from Study 19

6.5 Alternatives 19

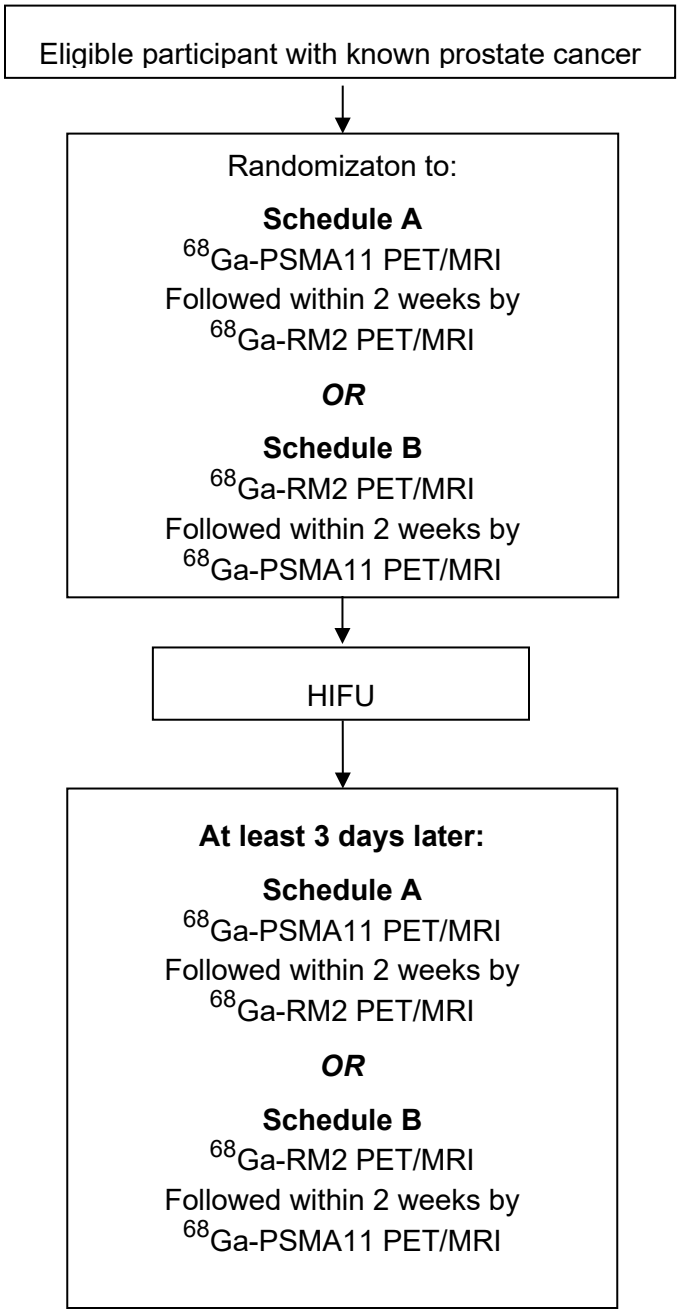
7. STUDY CALENDAR **19**

8. ADVERSE EVENTS AND REPORTING PROCEDURES 20
8.1 Potential Adverse Events 20
8.2 Adverse Event Reporting 20
9. REGULATORY CONSIDERATIONS 20
9.1 Institutional Review of Protocol 20
9.2 Data Management Plan 20
10. Statistical Considerations and Evaluation of Results 21
10.1 Study Endpoints 21
10.2 Accrual estimates 22
10.3 Study Outcomes (ClinicalTrials.gov) 22
10.4 Analyses Plans 22
10.5 Accrual estimates 22
11. REFERENCES: 23
3.1 Inclusion Criteria 28
3.2 Exclusion Criteria 28

PROTOCOL SYNOPSIS

TITLE	A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Evaluation of Prostate Cancer Response to HIFU Therapy
STUDY PHASE	Phase 1-2 study (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 determine feasibility of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for evaluation of HIFU local therapy in patients with known prostate cancer
EXPLORATORY ENDPOINTS	• Comparison of ^{68}Ga-PSMA-11 post-treatment uptake and pre-post change in uptake in response to HIFU local therapy • Comparison of ^{68}Ga-RM2 post-treatment uptake and pre-post change in uptake in response to HIFU local therapy

SCHEMA


Eligible participant with known prostate cancer
Randomizaton to:
Schedule A
68Ga-PSMA11 PET/MRI
Followed within 2 weeks by
68Ga-RM2 PET/MRI
OR
Schedule B
68Ga-RM2 PET/MRI
Followed within 2 weeks by
68Ga-PSMA11 PET/MRI
HIFU
At least 3 days later:
Schedule A
68Ga-PSMA11 PET/MRI
Followed within 2 weeks by
68Ga-RM2 PET/MRI
OR
Schedule B
68Ga-RM2 PET/MRI
Followed within 2 weeks by
68Ga-PSMA11 PET/MRI

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
HIFU	High-intensity focused ultrasound

1. OBJECTIVE

Specific Aim

To determine the feasibility of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for evaluation of high-intensity focused ultrasound (HIFU) local therapy in patients with known prostate cancer.

2. BACKGROUND

2.1 Preliminary information

Prostate cancer (PCa) remains the most-common non-cutaneous cancer diagnosed in American males, accounting for an estimated 161,360 new cases and 26,730 deaths in 2017 (1). Historically, PCa often presented as painful metastatic disease, and killed up to 40 per 100,000 men annually in the US between 1991 and 1993. The introduction of widespread PSA screening in the early 1990's led to a profound stage migration with most cancers detected while localized to the prostate. Subsequently PCa-specific mortality dropped to 20 per 100,000 by 2012 (2). While improvements in therapy likely play some role, independent groups in the CISNet consortium have shown through modeling that 45% to 70% of the decline in PCa mortality can be plausibly attributed to PSA screening (3).

Meanwhile, PSA screening also dramatically increased detection and treatment of slow-growing, low-grade PCa that would have otherwise remained asymptomatic. Treating all these cancers with radical prostatectomy or external beam radiotherapy (EBRT) is expensive to the healthcare system and led to significant short and long-term side effects in hundreds of thousands of men. As a result, despite the ~50% reduction in age-specific PCa mortality in the PSA era, the US Preventive Services Task Force (USPTF) recommended in 2011 against routine screening with PSA (4) because it deemed that the harms of screening outweighed the benefits. Accordingly, PSA use and early diagnosis PCa have decreased dramatically (5). The dilemma for patients and physicians is: either continue screening despite the problem of overtreatment and treatment-related side effects, or do not screen and miss the opportunity for early diagnosis and cure. To reduce the harms of screening while maintaining the benefits, **there is a clear need for faster, cheaper, less invasive and fundamentally less risky** treatments for localized PCa.

Standard treatment options include observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), and/or hormonal therapy, depending on the initial stage, the patient's age, co-morbidities, and preferences. If T-stage is greater than 2 or if the PSA > 20 ng/mL or if Gleason score is > 8, there is an increased risk of metastatic disease and cross-sectional imaging and bone scans are performed identify metastases. However most tumors present before this stage and are candidates for targeted local therapy.

Changing paradigms in management of localized PCa. Not all localized PCa have the same biologic potential; most men with small, non-aggressive (Gleason 3+3) cancers can be safely followed by 'active surveillance' – a strategy that has gained acceptance in the last 5 years (6). Low-risk PCa (Gleason score ≤ 6, pretreatment PSA level < 10 ng/mL, and clinical stage T1–T2a) is a group that accounts for 35% to 70% of all patients with prostate cancer (7, 8). But, for the remaining patients with higher grade, *clinically significant* cancers still merit treatment. They face a difficult choice: aggressive whole-gland treatment that risks life-altering side effects, vs no treatment and the risk of cancer progression, metastasis and potential death (9). Newer less invasive local therapies seek to offer a treatment options that are faster, less invasive, less risky and potentially cheaper than surgery or EBRT. These include ablation with heating (high-intensity

focused ultrasound - HIFU, microwaves, or lasers), freezing (with needle cryoprobes), electroporation, stereotactic radiation therapy and brachytherapy. Such local therapy is becoming popular despite limited long-term evidence of tumor control, especially for ablation modalities.

The role of multi-parametric MRI (mpMRI) for guiding care. While PCa is most often multifocal, the highest grade, index lesion drives clinical outcomes (10, 11). Conventional trans-rectal ultrasound (TRUS)-guided systematic prostate biopsy consisting of 6 to 12 biopsy cores is limited by under-diagnosis of index lesions and over-diagnosis of small, non-aggressive tumors that pose little threat to a man's life. Use of mpMRI is increasing rapidly due to its ability to improve detection of clinically significant index tumors using MRI-guided biopsy (12). MRI-guided biopsies find more clinically significant tumor (≥ G7) and less insignificant (G6) tumor than conventional systematic biopsies. MRI use is increasing for:

- MRI prior to biopsy is sometimes used to determine if biopsy is necessary and can enable image-targeted biopsy if an abnormality is seen on MRI (12)
- Men contemplating active surveillance: a normal mpMRI adds confidence that this is a safe management option. An abnormal mpMRI prompts MRI-TRUS fusion biopsy that often reveals clinically significant cancer that warrants treatment (13).
- Men deciding between whole-gland treatment (surgery or radiation) and partial-gland focal ablation. Finding a single tumor on MRI prompts consideration of focal ablation. Finding multiple and/or bilateral tumors prompts consideration of whole-gland treatment (surgery or radiation). Finding extracapsular disease (T3 / T4) prompts workup for potential metastatic cancer.

It should be noted that mpMRI has limitations: ~20% of all index lesions are missed *(14)*, the size of high grade cancers is underestimated *(15)*, and ~40% of men with a normal MRI have PCa on biopsy *(16)*.

Positron emission tomography (PET) and PCa. PET tracers, such as ^{18}F- or ^{11}C-labeled choline and [^{11}C]-acetate, are used mainly for the diagnosis of recurrent (17-19) or metastatic (20) PCa. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes (21, 22). Although choline based PET/CT is widely used outside the US for imaging PCa, there have been numerous studies reporting a low sensitivity and specificity, especially at low PSA levels (23, 24). Consequently, improved molecular imaging of PCa is necessary. One novel method is PET imaging with ^{18}F-FACBC, a synthetic amino acid. Recent evaluations by Nanni et al. indicate that this tracer might be superior when compared to choline PET/CT (25). However, recent work indicates that ^{18}F-FACBC uptake in PCa is similar to that in BPH nodules (26). Prostate-specific membrane antigen (PSMA) is a transmembrane protein that elicits high interest. This cell surface protein is significantly overexpressed in PCa cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands. PSMA is highly overexpressed on almost all PCa (27-29). Only 5-10% of primary PCa lesions have been shown to be PSMA-negative (30, 31), making this class of radiopharmaceuticals suitable for diagnosis of primary PCa and for initial staging (32-37). Non-invasive tumor grading has also been reported (38). Recently methods have been developed to label PSMA ligands with ^{68}Ga enabling their use for PET imaging and therapy (39). Initial experience with PET/CT using Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)] (^{68}Ga-PSMA-11) suggests that it can detect PCa relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (40). Better localization of cancer within

the prostate itself would also have a clinical impact by guiding image-targeted biopsy and patient selection for local targeted therapy. However, these promising agents do not detect all recurrences (41, 42) and other cancers also express PSMA (43-45). False positive findings have also been reported using PSMA agents (46-49).

Consequently, improved imaging of PCa continues to be an area of unmet clinical need. Gastrin-releasing peptide (GRP) is a 27-amino acid neuropeptide that is the mammalian homologue of the linear tetradecapeptide bombesin. It shares homology with bombesin at the C-terminal amidation sequence in the final 7 amino acids(50, 51). The GRP receptor (GRPr) is the only well characterized receptor to which GRP and bombesin bind with a high affinity. GRPr belongs to a family of G-coupled protein receptors, and the GRP binds selectively to the GRPr(50, 51). Studies show that GRPr is expressed at very low levels in normal prostate glands but is increased in 45-100% of human PCa (52, 53). ^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (^{68}Ga-RM2, formerly also known as BAY86-7548 or ^{68}Ga-DOTA-Bombesin) is a synthetic bombesin receptor antagonist, which targets GRPr (54). GRPr proteins are highly overexpressed in several human tumors, including PCa (55). Because of their low expression in BPH and inflammatory prostatic tissues (56, 57), imaging of GRPr has potential advantages over current choline- and acetate-based radiotracers. Indeed, preclinical studies using BAY86-7548 have shown a high and persistent tracer uptake in mice bearing PC-3 tumor xenografts, which represent androgen-independent human PCa with high GRPr expression (58). Clinically translated GRPr antagonists PET radiopharmaceuticals include ^{68}Ga-RM2, ^{68}Ga-SB3, ^{68}Ga-NeoBOMB1, ^{18}F-BAY-864367 and ^{64}Cu-CB-TE2A-AR06. They have been shown to have stable biodistribution in healthy volunteers (59) and mean effective doses comparable with other radiopharmaceuticals (60, 61). Preliminary data indicate encouraging potential for their future use at initial diagnosis of PCa (59-63).

Efficacy assessment: a major unsolved question. Unlike after prostatectomy, where PSA levels fall to zero soon after successful surgery, after local targeted therapy (HIFU) PSA levels are poor measures of efficacy. PSA falls to a variable nadir due to continued production by residual prostate tissue as well as potential occult non-index tumor that was outside the ablation or boost region. Even the Phoenix criterion for radiation failures (2 ng/mL rise above nadir), now a *de facto* standard, has a sensitivity and specificity of only ~65% and ~77% for clinical recurrence, respectively (64). False negatives may occur early because it takes time for tumor to grow back fast enough to generate 2 ng/mL of PSA. False positives may be due to residual BPH, regeneration of normal prostate tissue, and prostatitis. PSA is especially problematic for ablation because some portions of the gland are left entirely untreated. The potential for residual under-treated target tumor, or occult non-target tumor to progress, and potentially become clinically significant, highlights the unmet need for sensitive surveillance methods after local targeted therapy.

Therapeutic options after local treatment. Evidence from salvage treatment for post-prostatectomy recurrence reveals that success is more likely when treatment is initiated early (65). One theoretical advantage of local treatments is that tissue damage is restricted to the prostate. This enables options for local retreatment and second line therapy after failure. Cancer recurrence after focal ablation can be managed with repeat ablation or whole-gland treatment with surgery or radiation. This potential ability to retreat further highlights the need for sensitive surveillance methods after initial treatment.

Can mpMRI also help find recurrence or residual tumor *after* local targeted therapy? It is much more difficult to interpret mrMRI after treatment (66). For example, after ablation, resolving hemorrhage and proteinaceous necrosis can cause variable diffusion restriction, and inflammation can cause contrast enhancement (67).

Simultaneous PET/MRI: PET/MRI is an advanced hybrid technology that can provide both biological and morphological information of various biological pathways, as discussed in more details in "Approach". Compared to PET/CT, simultaneous PET/MRI has advantages resulting from reduced radiation exposure and higher soft tissue contrast (68). PET/MRI is particularly important for accurate localization and assessment of the extent of disease in the pelvis in the initial staging of PCa. In fact, the majority of pathologic findings leading to up-staging are microscopic, requiring the high resolution of intraprostatic anatomy and adjacent structures afforded by co-registration with MRI rather than CT (69).

In summary, without ways to answer: *"Was my cancer adequately treated?"*, some men could undergo ineffective local treatment and miss the chance for effective local salvage treatment before metastasis occurs.

2.2 Study Agent

This study will use ^{68}Ga-RM2. This PET radiopharmaceutical has previously been identified as ^{68}Ga-DOTA Bombesin or BAY86-7548. This is not an FDA-approved product. This protocol is submitted to IND [redacted], the IND to which this protocol is submitted.

This study will also use ^{68}Ga-PSMA11. This PET radiopharmaceutical has previously been identified as DFKZ-11; HBED-CC PSMA; or the "Heidelberg compound." This is not an FDA-approved product, and is described in detail in IND [redacted].

2.3 Clinicaltrials.gov

This study will be registered on ClinicalTrials.gov.

2.4 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 evaluation of HIFU local therapy in patients with known prostate cancer.

^{68}Ga-RM2 PET/MRI at Stanford University: Under an FDA-approved IND (IND [redacted]) our group completed the evaluation of ^{68}Ga-RM2 PET/MRI in 32 patients with biochemical recurrence of PCa and negative conventional imaging (bone scintigraphy and CT or MRI) (70). PET/MRI images were acquired at 42-51 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. ^{68}Ga-RM2 PET findings were compatible with recurrent PCa in 23 of the 32 participants (including in the prostate). Conventional MRI identified findings compatible with recurrent PCa in only 11 of the 32 participants. PET findings were confirmed by biopsy in (7 of 23, 30.4%) or clinical follow-up (16 of 23, 69.6%). The duration of follow-up was 3 to 25 months (mean ± SD: 17 ± 5.2). PSA velocity values were 0.32 ± 0.59 ng/mL/year (range: 0.04 to 1.9) in patients with negative PET scans and 2.51 ± 2.16 ng/mL/year (range: 0.13 to 8.68) in patients with positive PET scans (P = 0.006).

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.

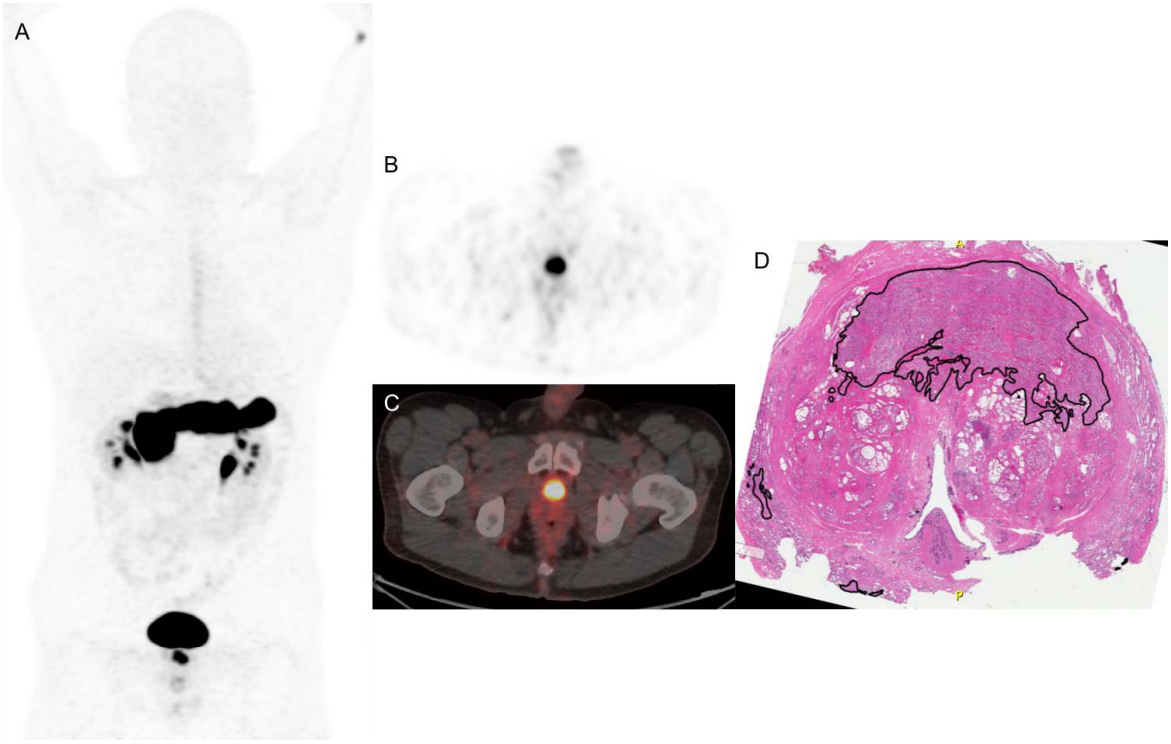


Figure 1: 68 year-old man (participant #2) with recently diagnosed intermediate risk, T1c, Gleason 3+4 prostate cancer presenting with PSA of 4.53 ng/mL. Maximum intensity projection (MIP) RM2 PET image (A), transaxial PET (B) and fused transaxial PET (C) showed focal uptake in histopathological proven prostate cancer (D).

^{68}Ga PSMA-11 PET/MRI at Stanford University: ^{68}Ga PSMA-11 is under clinical investigation in the US, although it is widely-used elsewhere despite lack of regulatory approval. We conducted a prospective study under IND 128379 and enrolled 33 men with intermediate and high risk newly diagnosed PCa, scheduled to undergo prostatectomy and pelvic nodal dissection (71). ^{68}Ga PSMA-11 PET identified intraprostatic cancer foci in all 33 patients, whereas mpMRI alone identified PIRADS 4 or 5 lesions in 26 patients and PIRADS 3 lesions in 4 patients. ^{68}Ga PSMA-11 PET showed focal uptake in pelvic lymph nodes in five patients. Final pathology confirmed cancer in the prostate of all patients, as well as nodal metastasis in three. No patient with normal pelvic nodes on PET/MRI had metastases on pathology. An example is shown in Figure 3.

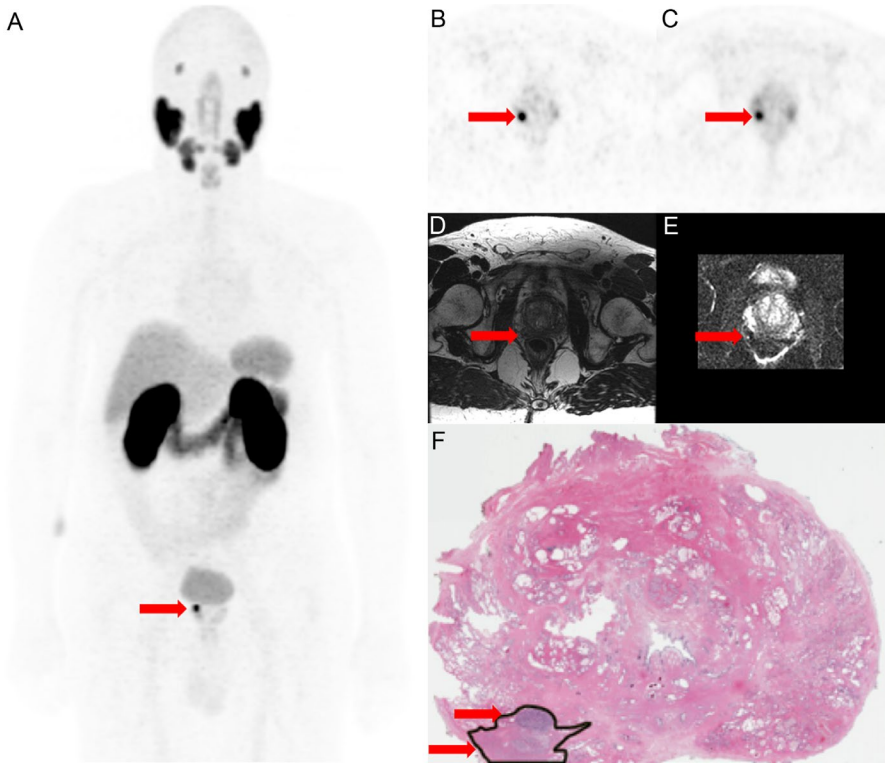


Figure 2: 74 year-old man (participant #4) with recently diagnosed intermediate risk, T1c, Gleason 4+4 prostate cancer presenting with PSA of 4.12 ng/mL. Maximum intensity projection (MIP) PSMA PET image (A), early transaxial PET (B) and delayed transaxial PET (C) showed focal uptake in histopathological 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.

^{68}Ga-RM2 vs ^{68}Ga PSMA-11 at Stanford University: We completed a pilot comparison of ^{68}Ga-PSMA-11 (IND [redacted]) with ^{68}Ga-RM2 (72). There were 45 areas of high ^{68}Ga-PSMA uptake that corresponded to metastases shown on the CT images in the bone marrow (*n* = 13), retroperitoneal lymph nodes (*n* = 12), mediastinal lymph nodes (*n* = 8), pelvic lymph nodes (*n* = 9), seminal vesicle (*n* = 2), and subclavian lymph node (*n* = 1). ^{68}Ga-RM2 uptake was high in all these areas, except for one pelvic lymph node and seminal vesicle in the same patient. ^{68}Ga PSMA-11 uptake and/or clearance in the bowel made assessment of small retroperitoneal lymph nodes more difficult compared to ^{68}Ga-RM2 in 2 participants. The fact that ^{68}Ga-RM2 shows similar sensitivity to ^{68}Ga-PSMA, and provides higher lesion conspicuity due to the lack of significant hepatobiliary clearance is a promising result for a radiopharmaceutical that is complementary to ^{68}Ga-PSMA (Figure 3).

While the over-expression of PSMA is ubiquitous in prostate cancer, it is not universal and there will be lesions not detected by PSMA-targeted imaging in different risk classes or stages of disease. The influence of GRPr expression on cancer grade and stage is not clear. Nagasaki et al. (73) found that GRPr expression was correlated with higher Gleason score, but another study found that it was inversely correlated with Gleason score, preoperative PSA concentration, and tumor size (57). Therefore, the indication (ie, low- vs intermediate- vs high-risk, early- vs late-stage of disease) to use PSMA- vs GRPR-targeted imaging or both is an active focus of research. Until more data is

available, scanning using both PET radiopharmaceuticals will ensure appropriate evaluation of PCa patients.

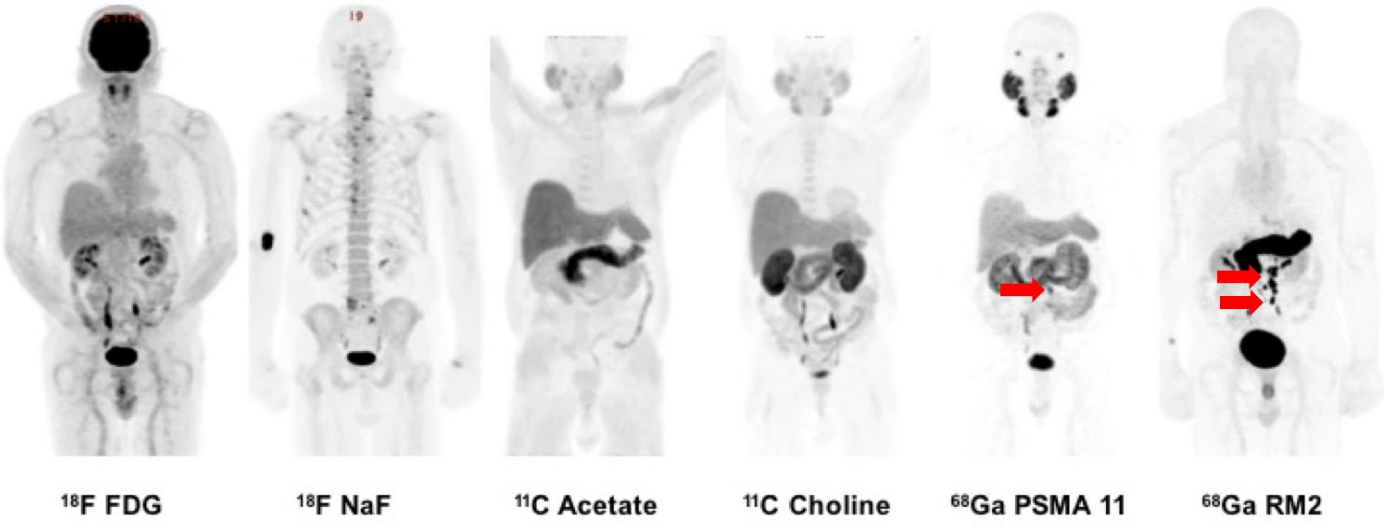


Figure 3: 83-year-old man presenting with confirmed Gleason 5+4 PCa and treated with intensity-modulated radiotherapy and androgen blockade. Follow up at 40 months showed positive ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 (both showing retroperitoneal lymph nodes) while all other studies were negative).

We also have an example of a patient with local recurrence of PCa treated with brachytherapy showing resolution of ^{68}Ga-RM2 uptake in the prostate bed (Figure 4).

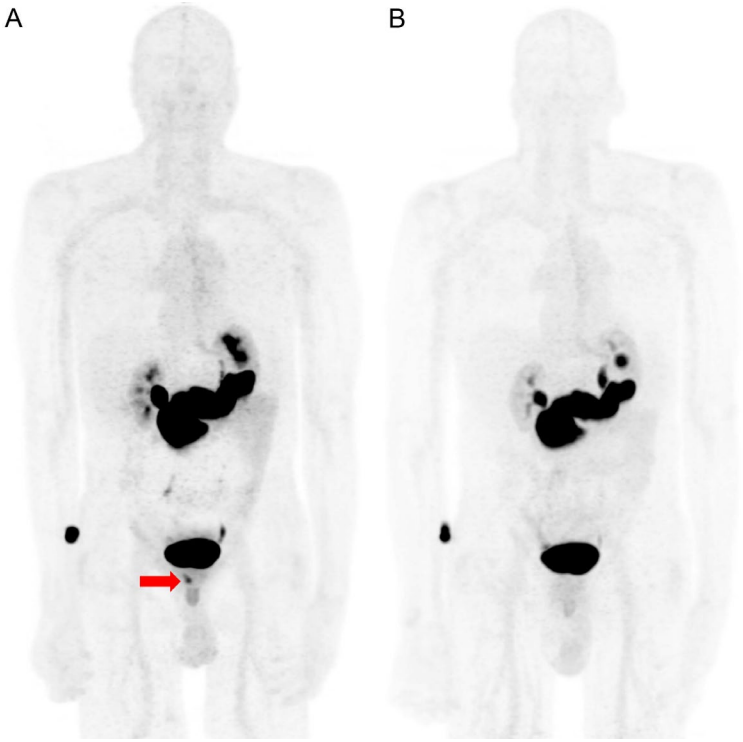


Figure 4: 72 year-old man with history of Gleason 3+4 PCa treated with radiation and hormonal therapy, presenting with PSA of 3.7 ng/mL. Maximum intensity projection (MIP) ^{68}Ga-RM2 PET image before (A) and after (B) radiation treatment demonstrate resolution of prostate bed uptake (arrow).

In summary, GRPr and PSMA expression is increased in PCa. By using a novel approach combining both ^{68}Ga-RM2 and ^{68}Ga-PMSA-11 PET/MRI within each patient, we will be able to accurately identify PCa and we will attempt to evaluate response to targeted local therapy.

Our **hypothesis** is that the use of ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI will permit accurate localization of PCa at initial diagnosis and allow for evaluation of response to treatment. We will use a state of the art simultaneous PET/MRI scanner with time of flight ability whose first world-wide installation was at Stanford University in December 2013.

2.5 Study Design

This is a pilot study with a total of 20 participants with known prostate cancer, scheduled to undergo HIFU local therapy. 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]). After the 1st scan, the 2nd scan will only occur after the follow-up with the patient for the 1st scan, and after a minimum of 3 days have elapsed.

Scan 1

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 **OR** 3 to 7 mCi of ^{68}Ga-PSMA11.
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-min acquisition time per table position.
7. Participants will be dismissed.
8. Vital signs (heart rate, blood pressure) will be recorded again at the completion of the study
9. Participants will be contacted at 24 to 72 hours following the scan in order to capture potential occurring Adverse Events.

Scan 2

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 **OR** 140 $\pm$ 20% mBq of ^{68}Ga-RM2 (ie, the radiopharmaceutical not administered for Scan 1)

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 capture potential occurring Adverse Events.

The above will be repeated approximately 6 months after HIFU local treatment, prior to standard of care biopsy to evaluate for residual disease in the prostate.

Objectives of the Study

Primary Objective

- To determine feasibility of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for evaluation of HIFU local therapy in patients with known prostate cancer.

Secondary Objective

- None

ExploratoryObjectives

- Comparison of ^{68}Ga-PSMA-11 post-treatment uptake and pre-post change in uptake in response to HIFU local therapy
- Comparison of ^{68}Ga-RM2 post-treatment uptake and pre-post change in uptake in response to HIFU local therapy

Endpoints

Primary Endpoints

- Number of participants with assessable pre- and post-treatment uptake in response to HIFU local therapy

Secondary Endpoint

- None

Exploratory Endpoints

- Pre- and post-treatment ^{68}Ga-PSMA-11 SUV_{max} and pre-post change in SUV_{max} after HIFU local therapy
- Pre- and post-treatment ^{68}Ga-RM2 SUV_{max} and pre-post change in SUV_{max} after HIFU local therapy

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- ≥ 18 years-old
- Known prostate cancer
- Planned HIFU local therapy
- 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 12 months from the time the the last subject completes the first scan.

3.4.2 Study Completion:

The study will reach study completion 66 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agents ^{68}Ga-PSMA-11 and ^{68}Ga-RM2

^{68}Ga-PSMA-11

This study will use ^{68}Ga-PSMA-11 as the PET radiopharmaceutical. This agent has previously been identified as DFKZ-11; HBED-CC PSMA; or the “Heidelberg compound.”

The administered dosage of ^{68}Ga-PSMA-11 is 111 to 259 mBq (3 to 7 mCi) IV. We will use ^{68}Ga-PSMA-11 as the PET radiopharmaceutical. 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) (74-77).

^{68}Ga-RM2

This study will also use ^{68}Ga-RM2 as the PET radiopharmaceutical. The administered dosage is 140 ± 20% mBq IV. Measured human dosimetry data are available from published data (78). ^{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) (74-77).

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

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 ± 20% 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 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 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 to 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 min 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).

The above will be repeated approximately 6 months after HIFU local treatment, prior to standard of care biopsy to evaluate for residual disease in the prostate.

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.

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 not less than 3 days apart for imaging before therapy and two separate clinic visits for imaging after therapy. After the 1st scan, the 2nd scan will only occur after the follow-up with the patient for the 1st scan, and after a minimum of 3 days have elapsed. 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 Safety Follow-up after the 2nd post-therapy scan. 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 (≥ 3 days and ≤ 2 weeks)		**X** [a]		
Follow-up call to participant (24 to 72 hours)			**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 ^{68}Ga-PMSA11 PET/MRI followed within 2 weeks by ^{68}Ga-RM2 PET/MRI. After the 1st scan, the 2nd scan will only occur after the follow-up with the patient for the 1st scan, and after a minimum of 3 days have elapsed. This will be repeated approximately 6 months after HIFU local treatment, prior to standard of care biopsy to evaluate for residual disease in the prostate.

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 two (before and after treatment) ^{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 two ^{68}Ga-PSMA-11 PET/MRI is 13.36 mSv, approximately equal to 26% of the limit that radiation workers (eg, a hospital X-ray technician) are allowed to receive in one year.

This research study also involves exposure to radiation from two (before and after treatment) ^{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 two ^{68}Ga-RM2 PET/MRI is 9.52 mSv, approximately equal to 20% of the limit that radiation workers (for example, a 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 the 20 participants with assessable pre- and post-treatment uptake (on either type) in response to HIFU local therapy.

"Assessable uptake" on a scan is defined as being successfully able to:

1. Appreciate the presence/absence of localized uptake (a "lesion"), and
2. Produce an SUV_{max} measurement for that ROI.

The rationale is that if both pre- and post-treatment uptake are assessable, then (presumably) changes in (1) and (2) have the potential to be used to evaluate treatment response in future trials. A patient may be assessable on the ^{68}Ga-PSMA-11 scan but not the ^{68}Ga-RM2-11 scan, and vice-versa.

Thus we will tabulate findings as below:

SCAN TYPE

	------- ^{68}Ga-PSMA-11 ---------				-------- ^{68}Ga-RM2-11 --------			
	--- Pre-TX --		--- Post-Tx ---		--- Pre-TX --		-- Post-Tx ---	
Patient #	Seen?	SUV_{max}?	Seen?	SUV_{max}?	Seen?	SUV_{max}?	Seen?	SUV_{max}?
1								
2								
3								
.								
.								
.								
20								

The number of patients assessable on either (or both) types of scan is the primary endpoint; if at least 10 of the 20 patients are assessable on at least one type of scan, then the study will be deemed a success.

Secondary endpoint:

- None

Exploratory endpoints:

- Pre- and post-treatment ^{68}Ga--PSMA--11 SUV_{max} and pre-post change in SUV_{max} after HIFU local therapy
- Pre- and post-treatment ^{68}Ga-RM2 SUV_{max} and pre-post change in SUV_{max} - after HIFU local therapy

10.2 Accrual estimates

We anticipate enrolling 20 patients in total. We expect 1 to 2 patients to have residual tumor after HIFU.

10.3 Study Outcomes (ClinicalTrials.gov)

Primary Outcome

Title: Successful PET-based of Assessment of Local Theraeputic Response

Description: Therapeutic response to high-intensity focused ultrasound (HIFU) will be assessed by ^{68}Ga-PSMA11 and ^{68}Ga-RM2 PET scans. The outcome is the number of participants without dispersion, by randomization schedule, for which an assessment of PET--based therapeutic response to HIFU is successfully obtained.

Timeframe: 12 months

Safety outcome: No

Secondary Outcome

None.

10.4 Analyses Plans

This is a pilot study that will not have pre--defined analyses plans, other than the described assessment for the number of participants for which a PET--based therapeutic response to HIFU successfully obtained. We will compare the changes in SUV_{max} after HIFU local thearpy with results of biopsy done as standard of care at 6 months post-treatment, as well as with PSA values done every 3 months afterwards (ie, a decrease in uptake is expected to predict response, while stable or increased uptake is expected to indicate no response to HIFU local therapy). Data from 2 arms (^{68}Ga-PSMA11 done first or ^{68}Ga-RM2 done first) will be aggregated. In the case that the treatment has worked to extent that the primary tumor is no longer visible, the disappearance will be detectable because of the correspondence between pre and post ROIs. In that case, we will consider the tumor assessable, and record the SUV_{max} as the ROI background.

There is no analysis beyond noting whether the total number of assessable patients meets or exceeds the threshold for success (10 of 20).

10.5 Accrual estimates

We expect the accrual of 5 patients each year for 4 years. This is achievable given our experience with other protocols and the support from the referring physicians, Drs Buyyounouski, Ghanouni, and Sonn.

11. REFERENCES:

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

2. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220-41.

3. Berg CD. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: the prostate cancer screening results in context. Acta Oncol. 2011;50 Suppl 1(sup1):12-7.

4. Moyer VA, Force USPST. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157(2):120-34.

5. Penson DF. The Pendulum of Prostate Cancer Screening. JAMA. 2015;314(19):2031-3.

6. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. JAMA. 2015;314(1):80-2.

7. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst. 2009;101(18):1280-3.

8. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA. 2010;304(21):2373-80.

9. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England Journal of Medicine. 2016;375(15):1415-24.

10. Ahmed HU, Arya M, Freeman A, Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? The Lancet Oncology. 2012;13(11):e509-e17.

11. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009;361(17):1704-6.

12. Puech P, Rouviere O, Renard-Penna R, et al. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy--prospective multicenter study. Radiology. 2013;268(2):461-9.

13. Hoeks CM, Schouten MG, Bomers JG, et al. Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. Eur Urol. 2012;62(5):902-9.

14. Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol. 2015;67(3):569-76.

15. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. J Urol. 2017;197(2):320-6.

16. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol. 2014;65(4):809-15.

17. Sandblom G, Sorensen J, Lundin N, Haggman M, Malmstrom PU. Positron emission tomography with C11-acetate for tumor detection and localization in patients with prostate-specific antigen relapse after radical prostatectomy. Urology. 2006;67(5):996-1000.

18. Oyama N, Miller TR, Dehdashti F, et al. 11C-Acetate PET Imaging of Prostate Cancer: Detection of Recurrent Disease at PSA Relapse. Journal of Nuclear Medicine. 2003;44(4):549-55.

19. Wachter S, Tomek S, Kurtaran A, et al. 11C-acetate positron emission tomography imaging and image fusion with computed tomography and magnetic resonance imaging in patients with recurrent prostate cancer. J Clin Oncol. 2006;24(16):2513-9.

20. Kotzerke J, Volkmer BG, Glatting G, et al. Intraindividual comparison of [11C]acetate and [11C]choline PET for detection of metastases of prostate cancer. Nuklearmedizin. 2003;42(1):25-30.

21. Souvatzoglou M, Weirich G, Schwarzenboeck S, et al. The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration. Clin Cancer Res. 2011;17(11):3751-9.

22. Rietbergen DD, van der Hiel B, Vogel W, Stokkel MP. Mediastinal lymph node uptake in patients with prostate carcinoma on F18-choline PET/CT. Nucl Med Commun. 2011;32(12):1143-7.

23. Heinisch M, Dirisamer A, Loidl W, et al. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA < 5 ng/ml?

24. Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy.

25. Nanni C, Schiavina R, Boschi S, et al. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. Eur J Nucl Med Mol Imaging. 2013;40 Suppl 1:S11-7.

26. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with 18F FACBC PET/CT: comparison with MR imaging and histopathologic analysis. Radiology. 2014;270(3):849-56.

27. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3(1):81-5.

28. Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009;15(2):167-72.

29. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82(11):2256-61.

30. Budaus L, Leyh-Bannurah SR, Salomon G, et al. Initial Experience of (68)Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. Eur Urol. 2016;69(3):393-6.

31. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. J Urol. 2016;195(5):1436-43.

32. Koerber SA, Utzinger MT, Kratochwil C, et al. 68Ga-PSMA11-PET/CT in newly diagnosed carcinoma of the prostate: correlation of intraprostatic PSMA uptake with several clinical parameters. J Nucl Med. 2017.

33. Schmuck S, Mamach M, Wilke F, et al. Multiple Time-Point 68Ga-PSMA I&T PET/CT for Characterization of Primary Prostate Cancer: Value of Early Dynamic and Delayed Imaging. Clin Nucl Med. 2017;42(6):e286-e93.

34. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA PET/CT Detects the Location and Extent of Primary Prostate Cancer. J Nucl Med. 2016;57(11):1720-5.

35. Giesel FL, Sterzing F, Schlemmer HP, et al. Intra-individual comparison of (68)Ga-PSMA-11-PET/CT and multi-parametric MR for imaging of primary prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(8):1400-6.

36. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. Eur Urol. 2016;70(5):829-36.

37. Sachpekidis C, Kopka K, Eder M, et al. 68Ga-PSMA-11 Dynamic PET/CT Imaging in Primary Prostate Cancer. Clin Nucl Med. 2016;41(11):e473-e9.

38. Koerber SA, Utzinger MT, Kratochwil C, et al. 68Ga-PSMA11-PET/CT in newly diagnosed carcinoma of the prostate: correlation of intraprostatic PSMA uptake with several clinical parameters. Journal of Nuclear Medicine. 2017.

39. Hillier SM, Maresca KP, Femia FJ, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17):6932-40.

40. Afshar Oromieh A, Malcher A, Eder M, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions.

41. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid (6)(8)Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med. 2015;56(5):668-74.

42. Rowe SP, Gage KL, Faraj SF, et al. (1)(8)F-DCFBC PET/CT for PSMA-Based Detection and Characterization of Primary Prostate Cancer. J Nucl Med. 2015;56(7):1003-10.

43. Sathekge M, Lengana T, Modiselle M, et al. 68Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients. Eur J Nucl Med Mol Imaging. 2017;44(4):689-94.

44. Rhee H, Blazak J, Tham CM, et al. Pilot study: use of gallium-68 PSMA PET for detection of metastatic lesions in patients with renal tumour. EJNMMI Res. 2016;6(1):76.

45. Patel D, Loh H, Le K, Stevanovic A, Mansberg R. Incidental Detection of Hepatocellular Carcinoma on 68Ga-Labeled Prostate-Specific Membrane Antigen PET/CT. Clin Nucl Med. 2017.

46. Hermann RM, Djannatian M, Czech N, Nitsche M. Prostate-Specific Membrane Antigen PET/CT: False-Positive Results due to Sarcoidosis? Case Rep Oncol. 2016;9(2):457-63.

47. Sasikumar A, Joy A, Nanabala R, Pillai MR, T AH. 68Ga-PSMA PET/CT False-Positive Tracer Uptake in Paget Disease. Clin Nucl Med. 2016;41(10):e454-5.

48. Noto B, Vrachimis A, Schafers M, Stegger L, Rahbar K. Subacute Stroke Mimicking Cerebral Metastasis in 68Ga-PSMA-HBED-CC PET/CT. Clin Nucl Med. 2016;41(10):e449-51.

49. Demirkol MOMD, Kiremit MCMD, Acar OMD, Sag AAMD, Kapran YMD. False-Positive Pancreatic Uptake Detected on 68Ga-PSMA PET/CT: A Priority Changing Incidental Finding While Assessing the Need for a Prostate Biopsy. Clinical Nuclear Medicine.

50. Erspamer V, Erspamer GF, Inselvin.M. Some Pharmacological Actions of Alytesin and Bombesin. J Pharm Pharmacol. 1970;22(11):875-&.

51. Ischia J, Patel O, Shulkes A, Baldwin GS. Gastrin-releasing peptide: different forms, different functions. BioFactors. 2009;35(1):69-75.

52. Ischia J, Patel O, Bolton D, Shulkes A, Baldwin GS. Expression and function of gastrin-releasing peptide (GRP) in normal and cancerous urological tissues. BJU international. 2014;113 Suppl 2:40-7.

53. Korner M, Waser B, Rehmann R, Reubi JC. Early over-expression of GRP receptors in prostatic carcinogenesis. The Prostate. 2014;74(2):217-24.

54. Jensen RT, Battey JF, Spindel ER, Benya RV. International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling, and functions in normal and disease states. Pharmacol Rev. 2008;60(1):1-42.

55. Reubi JC, Wenger S, Schmuckli-Maurer J, Schaer J-C, Gugger M. Bombesin Receptor Subtypes in Human Cancers: Detection with the Universal Radioligand 125I-[d-TYR6, β-ALA11, PHE13, NLE14] Bombesin(6–14). Clinical Cancer Research. 2002;8(4):1139-46.

56. Markwalder R, Reubi JC. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer Res. 1999;59(5):1152-9.

57. Beer M, Montani M, Gerhardt J, et al. Profiling gastrin-releasing peptide receptor in prostate tissues: clinical implications and molecular correlates. The Prostate. 2012;72(3):318-25.

58. Mansi R, Wang X, Forrer F, et al. Development of a potent DOTA-conjugated bombesin antagonist for targeting GRPr-positive tumours. Eur J Nucl Med Mol Imaging. 2011;38(1):97-107.

59. Roivainen A, Kahkonen E, Luoto P, et al. Plasma pharmacokinetics, whole-body distribution, metabolism, and radiation dosimetry of 68Ga bombesin antagonist BAY 86-7548 in healthy men. J Nucl Med. 2013;54(6):867-72.

60. Kahkonen E, Jambor I, Kemppainen J, et al. In vivo imaging of prostate cancer using [68Ga]-labeled bombesin analog BAY86-7548. Clin Cancer Res. 2013;19(19):5434-43.

61. Wieser G, Mansi R, Grosu AL, et al. Positron emission tomography (PET) imaging of prostate cancer with a gastrin releasing peptide receptor antagonist--from mice to men. Theranostics. 2014;4(4):412-9.

62. Nock BA, Kaloudi A, Lymperis E, et al. Theranostic Perspectives in Prostate Cancer with the Gastrin-Releasing Peptide Receptor Antagonist NeoBOMB1: Preclinical and First Clinical Results. J Nucl Med. 2017;58(1):75-80.

63. Sah BR, Burger IA, Schibli R, et al. Dosimetry and first clinical evaluation of the new 18F-radiolabeled bombesin analogue BAY 864367 in patients with prostate cancer. J Nucl Med. 2015;56(3):372-8.

64. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. International journal of radiation oncology, biology, physics. 2006;65(4):965-74.

65. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006;7(6):472-9.

66. Kirkham AP, Emberton M, Hoh IM, Illing RO, Freeman AA, Allen C. MR imaging of prostate after treatment with high-intensity focused ultrasound. Radiology. 2008;246(3):833-44.

67. Kim CK, Park BK, Lee HM, Kim SS, Kim E. MRI techniques for prediction of local tumor progression after high-intensity focused ultrasonic ablation of prostate cancer. AJR Am J Roentgenol. 2008;190(5):1180-6.

68. Antoch G, Bockisch A. Combined PET/MRI: a new dimension in whole-body oncology imaging? Eur J Nucl Med Mol Imaging. 2009;36 Suppl 1(1):S113-20.

69. Engeler CE, Wasserman NF, Zhang G. Preoperative assessment of prostatic carcinoma by computerized tomography. Weaknesses and new perspectives. Urology. 1992;40(4):346-50.

70. Harrison C, Sonni I, Loening A, Vasanawala S, Iagaru A. Detection of Recurrent Prostate Cancer Using 68Ga-RM2 PET/MRI in Patients with Negative Conventional Imaging. Journal of Nuclear Medicine. 2017;58(supplement 1):711.

71. Zacharias C, Harrison C, Ghanouni P, Sonn G, Iagaru A. Ga-68 PSMA 11 PET/MRI in Patients with Newly Diagnosed Intermediate and High-Risk Prostate Cancers. Journal of Nuclear Medicine. 2017;58(supplement 1):537.

72. Minamimoto R, Hancock S, Schneider B, et al. Pilot Comparison of (6)(8)Ga-RM2 PET and (6)(8)Ga-PSMA-11 PET in Patients with Biochemically Recurrent Prostate Cancer. J Nucl Med. 2016;57(4):557-62.

73. Nagasaki S, Nakamura Y, Maekawa T, et al. Immunohistochemical analysis of gastrin-releasing peptide receptor (GRPR) and possible regulation by estrogen receptor betacx in human prostate carcinoma. Neoplasma. 2012;59(2):224-32.

74. Hartmann H, Zophel K, Freudenberg R, et al. [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. Nuklearmedizin. 2009;48(5):201-7.

75. Pettinato C, Sarnelli A, Di Donna M, et al. 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2008;35(1):72-9.

76. SandstrÃƒm M, Velikyan I, Garske-RomÃƒn U, et al. Comparative Biodistribution and Radiation Dosimetry of 68Ga-DOTATOC and 68Ga-DOTATATE in Patients with Neuroendocrine Tumors. The Journal of nuclear medicine. 2013;54(10):1755-9.

77. Kim JH, Lee JS, Kang KW, et al. Whole-body distribution and radiation dosimetry of (68)Ga-NOTA-RGD, a positron emission tomography agent for angiogenesis imaging. Cancer Biother Radiopharm. 2012;27(1):65-71.

78. Kähkönen E, Jambor I, Kemppainen J, et al. In Vivo Imaging of Prostate Cancer Using [68Ga]-Labeled Bombesin Analog BAY86-7548. Clinical Cancer Research. 2013;19(19):5434-43.

Inclusion/Exclusion Criteria Checklist

Protocol Title:	A Pilot Study of ^{68}Ga-PSMA-11 PET/MRI and ^{68}Ga-RM2 PET/MRI for Evaluation of Prostate Cancer Response to HIFU Therapy
Protocol Number:	IRB-48213 / PROS0093
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. Known prostate cancer	☐	☐	
3. Planned HIFU local therapy	☐	☐	
4. Able to provide written consent	☐	☐	
5. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)	☐	☐	

3.2 Exclusion Criteria

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:	