^{68}Ga-RM2 PET/MRI in the Evaluation of Patients with Biochemical Recurrence of Prostate Cancer and Non-Contributory CT Scans

Principal Investigator:
Andrei Iagaru, MD
300 Pasteur Drive, Room H-2230
Stanford, CA 94305
Phone: 650-725-4711
Fax: 650-498-5047
Email: aiagaru@stanford.edu

Co-investigators:	
Bruce Daniel, MD, PhD 300 Pasteur Dr H1307 MC 5621 Stanford, CA 94305 Phone: 650-725-1812 Email: bdaniel@stanford.edu	Steven Hancock, MD 875 Blake Wilbur Dr, Clinic D Stanford, CA 94305 Phone: 650-723-6171 Email: shancock@stanford.edu
Andreas Loening, MD, PhD 300 Pasteur Dr, H1307 MC 5105 Stanford, CA 94305 Phone: 650-723-7816 Email: loaning@stanford.edu	Guido Davidzon, MD 300 Pasteur Drive, Room H-2230 Stanford, CA 94305 Phone: 650-725-4711 Email: gdavidzon@stanford.edu
Geoffrey Sonn, MD 875 Blake Wilbur Dr, Clinic E Stanford, CA 94305 Phone: 650-725-5544 Email: gsonn@stanford.edu	Sandy Srinivas, MD 875 Blake Wilbur Dr, Clinic E Stanford, CA 94305 Phone: 650-724-8372 Email: sandysri@stanford.edu
Shreyas Vasanawala, MD, PhD 725 Welch Rd, St 1679 MC 5913 Palo Alto, CA94304 Phone: 650-724-9824 Email: vasanawala@stanford.edu	
Biostatistician Jarrett Rosenberg, PhD 1201 Welch Road, Room P-280 Stanford, CA 94305 Phone: 650-724-3289 Email: Jarrett.rosenberg@stanford.edu	**Study Coordinator** Jordan Cisneros, BS 800 Welch Road Phone: 650-725-6409 Email: jordan.cisneros@stanford.edu

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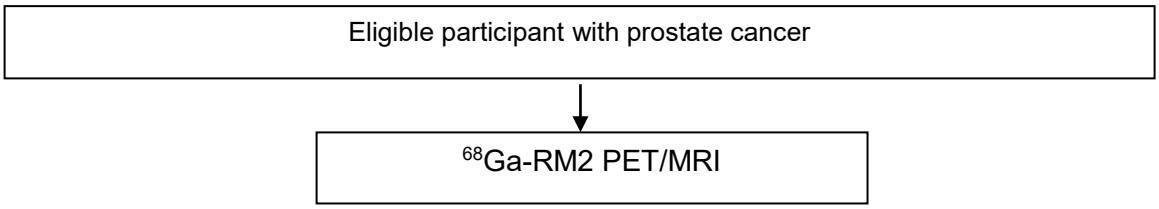
PROTOCOL SYNOPSIS

TITLE	^{68}Ga-RM2 PET/MRI in Patients with Biochemically Recurrent Prostate Cancer and Non-Contributory Conventional Imaging
STUDY PHASE	Phase 2-3
INDICATION	Prostate cancer
INVESTIGATIONAL PRODUCT OR PROCEDURE	^{68}Ga-RM2
PRIMARY OBJECTIVE(S)	To evaluate ^{68}Ga-RM2 (formerly known as ^{68}Ga Bombesin or BAY 86-7548) PET/MRI for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA and non-contributory computed tomography (CT).
SAMPLE SIZE	125 participants
STATISTICAL CONSIDERATIONS	Prospective single center, single-arm study. HYPOTHESES 1. At least 30% of patients will have one or more lesions detected on PET/MR. 2. PET/MR sensitivity will be higher than MR alone. STATISTICAL TEST McNemar tests of paired proportions for sensitivity and specificity. STATISTICAL POWER AND SAMPLE SIZE We expect that roughly 50% of patients will have lesions (as determined by biopsy or follow-up). Assuming a difference in sensitivity for PET/MRI and MRI of 20 percentage points (eg, 70% vs 50%), a sample of 60 diseased patients will provide 90% power at 5% error to detect such a difference. Assuming a difference in specificity for PET/MRI and MRI of 20 percentage points (eg, 70% vs 90%), a sample of 60 non-diseased patients will provide 98% power at 5% error to detect such a difference.

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

1. OBJECTIVE

Specific Aim

To evaluate ^{68}Ga-RM2 (formerly known as DOTA Bombesin or BAY 86-7548) PET/MRI for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA and non-contributory computed tomography (CT).

2. BACKGROUND

2.1 Preliminary information

Prostate cancer (PC) remains the most-common non-cutaneous cancer diagnosed in American males, accounting for an estimated 174,560 estimated new cases and 31,620 estimated deaths in 2019 (*1*). Subsequent treatment is multifaceted and may involve observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormonal therapy, chemotherapy, or a combination of these (*2-4*).

Up to 40% of the patients with prostate cancer develop biochemical recurrence within 10 years after initial treatment (*5*). Usually an increase of the PSA-level precedes a clinically detectable recurrence by months to years (*6*). However, it cannot differentiate between local, regional or systemic disease with the necessary precision that is essential for further disease management (*7*).

Morphological imaging methods exhibit considerable limitations: sensitivity ranges between 25% and 54% for the detection of local recurrence by transrectal ultrasound (TRUS) or contrast-enhanced CT and is moderately improved by using functional MRI techniques (*7-9*). The sensitivity for detection of lymph node metastases of CT or MRI is reported to be 30 to 80% (*10*). Ultra-small particles of iron oxides (USPIOs) proved to be very effective, but are yet to be approved by regulatory authorities (*11*). Bone metastases presenting as osteoblastic lesions can be effectively detected by bone scintigraphy, PET, CT and MRI (*12,13*).

Various targets have been addressed by molecular imaging to improve the detection of recurrent prostate cancer. PET tracers such as ^{18}F- or ^{11}C-labeled choline and ^{11}C-acetate have been investigated for the diagnosis of recurrent (*14-16*) prostate cancer. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes (*17,18*). In addition, fluorinated versions are not available in the United States, while ^{11}C-labeled tracers cannot be widely used due to the requirement for an on-site cyclotron due to the short half-life. ^{18}F-FACBC, a new synthetic amino acid, might be superior when compared to ^{11}C-choline PET/CT (*19*). owever, recent work indicates that ^{18}F-FACBC uptake in prostate cancer is similar to that in BPH nodules (*20*). Prostate-specific membrane antigen (PSMA) continues to elicit high interest. This cell surface protein is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands. It therefore provides a promising target for prostate cancer-specific imaging.

Recently methods have been developed to label PSMA ligands with ^{68}Ga and ^{18}F. Initial experience suggests that these novel tracers can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (*21,22*). However, these promising agents do not detect all recurrences.

Consequently, improved imaging of biochemically recurrent prostate cancer continues to be an area of unmet clinical need. ^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (^{68}Ga-DOTA-Bombesin or ^{68}Ga-RM2, formerly also known as BAY86-7548) is a synthetic bombesin receptor antagonist, which targets gastrin-releasing peptide

receptors (GRPr) (*23*). GRPr proteins are highly overexpressed in several human tumors, including prostate cancer (*24*). Because of their low expression in BPH and inflammatory prostatic tissues (*25,26*), 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 prostate cancer with high GRPr expression (*27*).

We conducted a pilot phase evaluation of ^{68}Ga-RM2 under an RDRC-approved protocol at Stanford University. Ten men (age range: 60 to 83 year-old; mean ± SD: 73.1 ± 6.9) with biochemical recurrence of prostate cancer (PSA range: 3.7 to 36.4; mean ± SD: 12.5 ± 9.8) were enrolled. PET/MRI images were acquired at 42-51 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. The uptake of ^{68}Ga-RM2 was identified as described in previously published studies referenced above. All participants had multiple standard of care imaging studies (CT, MRI, ^{18}F FDG PET/CT, ^{18}F-NaF PET/CT, ^{99m}Tc MDP bone scan) prior to enrollment that were non-contributory, despite rising PSA values. The time from conventional imaging to enrollment in the protocol ranged 10 to 107 days (mean ± SD: 43.3 ± 26.0). One participant also had ^{11}C Acetate and ^{11}C-Choline at other institutions in the setting of rising PSA (2.72 ng/mL and 3.63 ng/mL, respectively). Both scans were negative for recurrent prostate cancer lesions. The participants did not receive treatment in this interval as they were managed under a wait and watch strategy due to no identifiable disease. The interval from biochemical recurrence to the ^{68}Ga-RM2 PET/MRI scan ranged 5 to 75 months (mean ± SD: 30.8 ± 20.4). This pilot data (*28*) also showed **distinct biodistribution and lesion localization** between ^{68}Ga-RM2 and ^{68}Ga-PSMA11 due to non-overlapping underlying biology.

Biodistribution and localization of ^{68}Ga-RM2

All participants tolerated the procedure without immediate or delayed (up to 7 days) complaints or complications. Table 2 shows the ^{68}Ga-RM2 uptake (SUV_{max} and SUV_{mean}) in normal tissues. The areas with the highest ^{68}Ga-RM2 accumulation are the pancreas (mean SUV_{max}: 52.0 ± 16.7 [range: 36.8 to 93.8] and SUV_{mean}: 33.2 ± 17.5 [range: 8.8 to 66.1]) and bladder (mean SUV_{max}: 121.6 ± 67.5 [range: 32.6 to 220.7] and SUV_{mean}: 93.8 ± 59.7 [range: 29.8 to 195.7]), while moderate uptake was noted in the blood pool (mean SUV_{max}: 2.3 ± 0.7 [range: 1.8 to 4.0] and SUV_{mean}: 1.3 ± 0.7 [range: 0.7 to 2.7]), stomach (mean SUV_{max}: 2.5 ± 0.7 [range: 1.3 to 3.7] and SUV_{mean}: 1.3 ± 0.5 [range: 0.6 to 1.9]), small bowel (mean SUV_{max}: 2.4 ± 0.6 [range: 1.7 to 3.3] and SUV_{mean}: 1.4 ± 0.5 [range: 0.7 to 2.3])and colon (mean SUV_{max}: 2.0 ± 0.7 [range: 1.3 to 3.8] and SUV_{mean}: 1.0 ± 0.6 [range: 0.5 to 2.3]). The liver had low ^{68}Ga-RM2 uptake with SUV_{mean} of less than 1.0. There were no differences between the ^{68}Ga-RM2 biodistribution at 45 minutes post-injection among the 10 participants (Figure 1). The pattern of ^{68}Ga-RM2 uptake is similar to previous reports (*29,30*).

^{68}Ga-RM2 uptake outside the expected physiologic biodistribution

One case had no focal ^{68}Ga-RM2 uptake outside the expected physiologic biodistribution. The remaining 9 participants had 28 areas of high ^{68}Ga-RM2 uptake (up to 10 areas were recorded per participant) that corresponded to retroperitoneal lymph nodes (n = 10), bone marrow (n = 7), mediastinal lymph nodes (n = 3), pelvic lymph nodes (n = 2), seminal vesicle (n = 2), subclavian lymph node (n = 1), mesenteric lymph node (n = 1) and prostate bed (n = 1) on the MRI images. These areas of high ^{68}Ga-RM2 uptake had SUV_{max} of 13.4 ± 8.3 (range: 2.6 to 33.5) and SUV_{mean} of 6.7 ± 3.9 (range: 1.7 to 16.1), above the background and easily identifiable given the lack of hepato-biliary clearance.

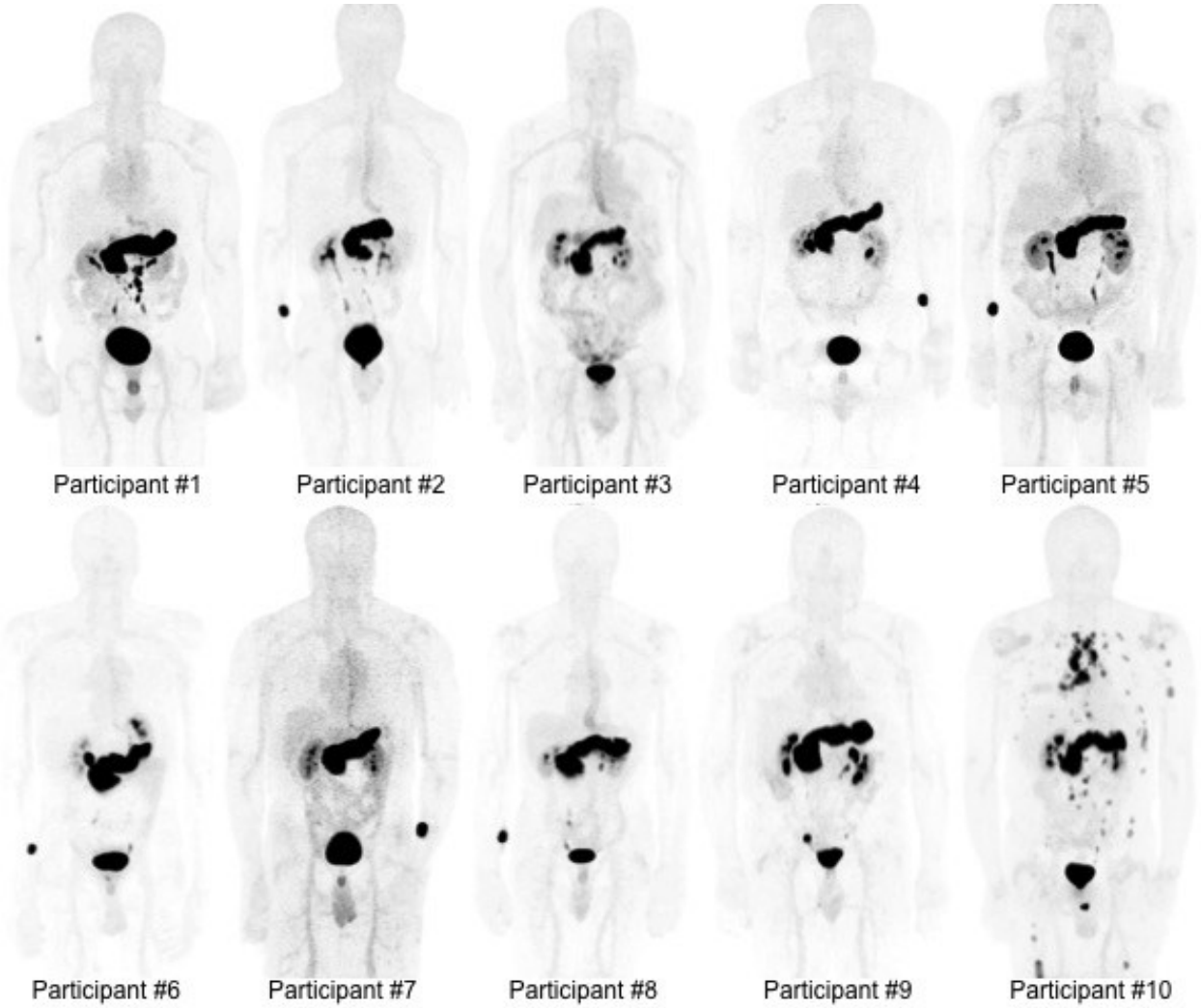


Figure 1: Maximum intensity projection (MIP) images from 5 participants in the pilot study conducted at Stanford University. Arrows mark suspected recurrent prostate cancer; high uptake in the pancreas is due to known over-expression of GRPr.

The mean diameter of lymph nodes with high ^{68}Ga-RM2 uptake was 1.3 ± 0.8 cm (range: 0.4 to 2.9 cm). PSA was 6.7 ng/mL in the patient with no focal ^{68}Ga-RM2 uptake outside the expected physiologic biodistribution and ranged 3.7 to 36.4 (mean ± SD: 13.1 ± 10.2) for the other patients.

We recently published our results using ^{68}Ga-RM2 PET/MRI in 32 patients with biochemical recurrence of PC and negative conventional imaging (bone scintigraphy and CT or MRI) (*31*). These participants will not be evaluated in the current analysis.

2.2 Study Agent

We will use ^{68}Ga-RM2, formerly also known as ^{68}Ga-DOTA Bombesin or BAY86-7548 as the PET radiopharmaceutical. This is not an FDA-approved product, but we have a FDA-approved IND (127137) allowing the use of this tracer in this proposed clinical indication.

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 bombesin receptor antagonist, ^{68}Ga-RM2, which has high affinity for gastrin-releasing peptide

receptors. GRPr proteins are highly overexpressed in several human tumors, including prostate cancer (*24*). Because of their low expression in BPH and inflammatory prostatic tissues (*25,26*), imaging of GRPr has the potential to improve the lesion detection in prostate cancer. Therefore, we propose the following aim:

- To evaluate ^{68}Ga-RM2 (^{68}Ga-DOTA-Bombesin) PET/MRI for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA (> 2 ng/mL) and non-contributory computed tomography (CT).

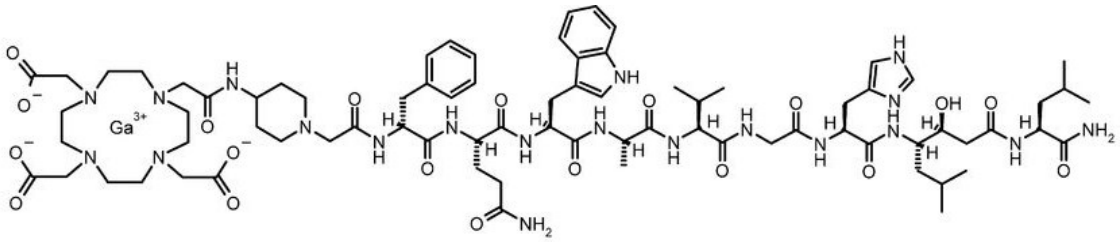


Figure 2. Chemical structure of ^{68}Ga-DOTA-Bombesin

The first-in-human study investigated the safety, tolerability, metabolism, pharmacokinetics, biodistribution, and radiation dosimetry of ^{68}Ga-RM2. Five healthy men underwent dynamic whole-body PET/CT after an intravenous injection of ^{68}Ga-RM2 (138 ± 5 MBq). Besides total radioactivity, plasma samples were analyzed by radio–high-performance liquid chromatography for metabolism of the tracer. Dosimetry was calculated using the OLINDA/EXM software. The organs with the highest absorbed doses were the urinary bladder wall (0.62 mSv/MBq) and the pancreas (0.51 mSv/MBq). The mean effective dose was 0.051 mSv/MBq. ^{68}Ga-RM2 was well tolerated by all subjects. The authors concluded that the intravenously injected ^{68}Ga-RM2 is safe, and rapid metabolism is demonstrated. A 150-MBq injection of ^{68}Ga-RM2 results in an effective dose of 7.7 mSv, which could be reduced to 5.7 mSv with frequent bladder voids (*29*).

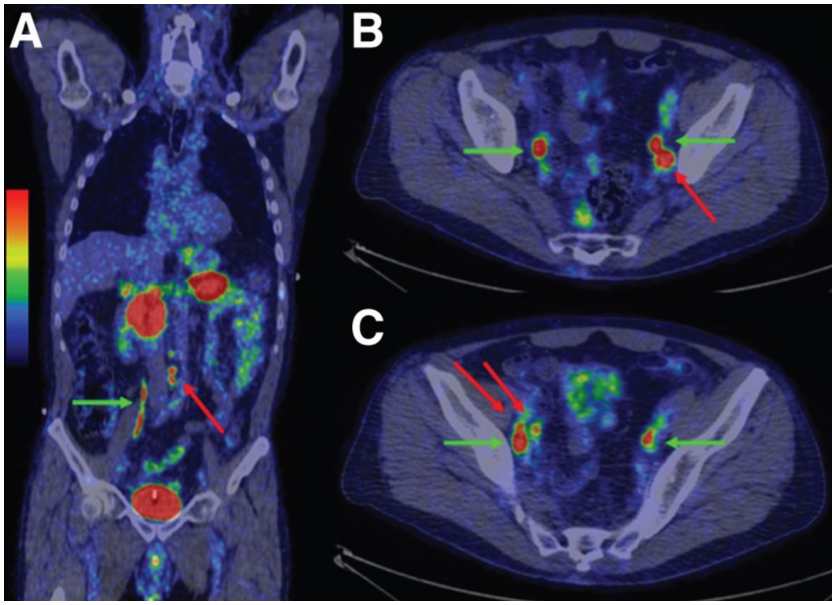


Figure 3: Coronal (A) and axial views (B and C) of ^{68}Ga-RM2 PET/CT in patient no. 8 with prostate cancer metastasis to multiple lymph nodes. Two normal-sized (less than 10 mm) nodes above the aortic bifurcation indicated with red arrow showed increased uptake of tracer, SUVmax 6.2 and 6.3. In addition, one left parailiac node, SUVmax 12.7, (B) and two right parailiac nodes, SUVmax 6.1 and 4.7, (C) showed

increased uptake of ^{68}Ga-RM2. These five lymph nodes were histologically confirmed as metastases at surgery. Green arrows point to ureters, which can be easily distinguished on anatomic CT.

In the first study with ^{68}Ga-RM2 in patients with prostate cancer, 14 men scheduled for radical prostatectomy (n = 11) or with biochemical recurrence after surgery or hormonal therapy (n = 3) were enrolled. The patients received an intravenous injection of ^{68}Ga-RM2 followed by over 60-minute dynamic imaging of prostate gland (n = 10) and/or subsequent whole-body imaging (n = 14). The visual assessment of PET/CT images included evaluation of intraprostatic (12 subsextants) and pelvic nodal uptake of ^{68}Ga-RM2 in 11 surgical patients and detection of potential metastatic foci in all patients. In patients with biochemical recurrence, results were compared with those of either ^{11}C-acetate (n = 2) or ^{18}F-fluoromethylcholine (n = 1) PET/CT. The authors reported a sensitivity, specificity, and accuracy of 88%, 81% and 83%, respectively, for detection of primary prostate cancer and sensitivity of 70% for metastatic lymph nodes using histology as gold standard (*30*).

2.5 Study Design

This is a prospective, single center, single-arm study enrolling 125 participants with prostate cancer. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive ^{68}Ga-RM2 and undergo a PET/MRI scan. All patients will first be seen by a Stanford Cancer Institute physician and then referred if appropriate on clinical grounds to Dr. Iagaru or his colleagues for this study. The following steps will take place.

1. Participant will be asked to drink 1 to 2 glasses of water before arrival at the clinic
2. Participants will be weighed and vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) will be recorded
3. Participant will be injected i.v. with 140 MBq of ^{68}Ga-RM2
4. Participant will void immediately prior to the scan
5. Approximately 45 minutes after the radiopharmaceutical i.v. 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 3–5 table positions at a 4-min acquisition time per table position.
6. Participants will be given a copy of the consent form s/he signed and will be dismissed.
7. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) will be recorded again at the completion of the study.
8. Participants will be contacted at 24 to 48 hours following the scan in order to capture potential late occurring Adverse Events.

The ^{68}Ga-RM2 PET/MRI may be repeated at the completion of treatment to evaluate response to therapy, if requested by the treating physician.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

1. Biopsy proven prostate adenocarcinoma
2. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy)
    a. Post radical prostatectomy (RP) – AUA recommendation (*32*)

i. PSA greater than 0.2 ng/mL measured after at least 6 weeks from radical prostatectomy

ii. Confirmatory persistent PSA greater than 0.2 ng/mL (total of two PSA measurements greater than 0.2 ng/mL)

b. Post-radiation therapy –ASTRO-Phoenix consensus definition (*33*)

A rise of PSA measurement

3. No evidence of metastatic disease on conventional imaging, including a negative bone scan for skeletal metastasis and negative CT scan, with or without contrast. NaF PET CT can substitute for separate bone scan and CT. CT in Axumin® (also known as ^{18}F FACBC or ^{18}F Fluciclovine) can substitute for separate CT.
4. Able to provide written consent
5. Karnofsky performance status of ≥50 (or ECOG/WHO equivalent)

3.2 Exclusion Criteria

1. Less than 18 years-old at the time of radiotracer administration
2. Unable to provide informed consent
3. Inability to lie still for the entire imaging time
4. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
5. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance
6. 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 36 months from the time the study opens to accrual.

3.4.2. Study Completion:

The study will reach study completion 48 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agent

We will use ^{68}Ga-RM2 as the PET radiopharmaceutical. The administered dosage is 140 MBq i.v. Effective Doses (ED) of [^{68}Ga]-DOTA Bombesin as calculated using OLINDA for the hermaphroditic male model, ranged between 0.028mSv/MBq and 0.051mSv/MBq depending on the bladder-voiding interval (0.75h, 1h or 2h). Consequently, the **urinary bladder wall was the main contributor to the ED** followed by the lower large intestinal wall, the gonads and the

stomach wall. Based on the fact that human pancreas expresses only low levels of GRPr in contrast to mouse and rat pancreas, which demonstrate extremely high expression levels, pancreas data of the biodistribution were not taken into account (but contributed to the remainder of the body).

Table 1: Effective Doses and whole body doses for a 140 MBq ^{68}Ga-DOTA-RM2 or 300 MBq ^{18}F FDG PET scan

Tracer	ED (mSv/ MBq)	Whole Body Dose PET scan	Whole Body Dose PET/ CT scan *
[^{68}Ga]DOTA-RM2 (0.75h-void.)	0.028	3.92 mSv (140 MBq)	6.92 mSv
[^{68}Ga]DOTA-RM2 (1h-void.)	**0.034**	**4.76 mSv (140 MBq)**	**7.76 mSv**
[^{68}Ga]DOTA-RM2 (2h-void.)	0.051	7.14 mSv (140 MBq)	10.14 mSv
[^{18}F]-FDG	0.019**	5.70 mSv (300 MBq)	8.70 mSv

* Low dose CT yields a dose of appr. *3 mSv (Brix et al.*)
** ICRP-80

Measured human dosimetry data are available from published data (*30*) and presented below.

^{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 estimations of the absorbed doses are reported in Table 2. 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).

Table 2: Dose Equivalent estimates (mSv/MBq) after injection of ^{68}Ga-RM2 (n = 5)

Organ	Mean	SD	Minimum	Maximum
Adrenals	0.011	0.00080	0.010	0.012
Brain	0.0056	0.00051	0.0049	0.0061
Breasts	0.0060	0.00048	0.0053	0.0064
Gallbladder wall	0.011	0.00054	0.0099	0.011
Lower large intestine wall	0.014	0.00036	0.013	0.014
Small intestine	0.010	0.00032	0.0096	0.010
Stomach wall	0.038	0.0090	0.027	0.045
Upper large intestine wall	0.0094	0.00037	0.0089	0.0098
Heart wall	0.028	0.0030	0.023	0.031
Kidneys	0.081	0.011	0.067	0.096
Liver	0.023	0.0035	0.019	0.028
Lungs	0.0071	0.00048	0.0064	0.0076
Muscle	0.0082	0.00038	0.0077	0.0086
Pancreas	0.51	0.16	0.32	0.73
Red marrow	0.013	0.0087	0.0068	0.026
Osteogenic cells	0.013	0.0051	0.0092	0.021

Table 2: Dose Equivalent estimates (mSv/MBq) after injection of ^{68}Ga-RM2 (n = 5)				
Organ	**Mean**	**SD**	**Minimum**	**Maximum**
Salivary glands	0.022	0.0022	0.020	0.026
Skin	0.0060	0.00044	0.0055	0.0065
Spleen	0.023	0.0036	0.017	0.026
Testes	0.010	0.00045	0.0097	0.011
Thymus	0.0070	0.00055	0.0064	0.0076
Thyroid	0.027	0.011	0.014	0.039
Urinary bladder wall	0.61	0.057	0.54	0.68
Total body	0.010	0.00031	0.0098	0.011
Effective dose	**0.051**	**0.0072**	**0.044**	**0.063**

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) (*34-37*).

4.2 Specify the source of the study agent.

Molecular Imaging Program at Stanford
Satellite Radiochemistry Facility
300 Pasteur Dr, C21
Stanford, CA 94305

4.3 Describe how the agent will be requested and provide mailing address and phone number.

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 (i.e. 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 to define the table positions. After correct positioning of the spatial acquisition windows is ensured, the combined PET/MRI acquisition will be initiated with 3–5 table positions at a 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.

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

5.3 Details of processing/analysis

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

6. STUDY PROCEDURES

6.1 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.

6.2 Alternatives

The alternative is to not participate in the study.

7. STUDY CALENDAR

	Pre-Study	Scan Date	24 - 48 Hours Post-Study	12 Months
Informed consent	X			
Demographics	X			
Medical history	X			
Follow-up Call to Participant			X	
^{68}Ga-RM2		X		
Data analysis				X

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

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

This research study involves exposure to radiation. This radiation exposure is for research purposes only. The amount of radiation from one ^{68}Ga-RM2 PET/MR is 4.76 mSv, approximately

equal to 10% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, standard of care procedures will be in place for verification of correct radiopharmaceutical dose and route of administration. The study Principal Investigator (PI) or his designee will report unanticipated AEs related to the Stanford CCTO Safety Coordinator within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death) using the Adverse Events Communication Form. If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible, but no later than 5 working days after the PI makes the determination and no later than 15 working days after first receiving notification of the effect.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review of Protocol

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

9.2 Data Management Plan

The CRFs will be stored in a locked office in the Cancer Clinical Trials Office. 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.

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.

The Research Monitor, Carina Mari Aparici, MD, in the Division of Nuclear Medicine and Molecular Imaging is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

10. MEASUREMENTS

10.1 Primary outcome measure

The principal goal of this study is to compare the diagnostic performance of ^{68}Ga-RM2 PET/MRI to that of MR alone for detecting recurrent prostate cancer in clinically (PSA) recurrent but CT negative cases. The number and location of lesions will be recorded for each modality in each patient. Gold standard will be based on either biopsy or one-year follow-up.

Specifically, it is hypothesized that:

1. At least 30% of these patients will have one or more lesions detected on ^{68}Ga-RM2 PET/MRI.
2. The proportion of patients with detected lesions will be higher for ^{68}Ga-RM2 PET/MRI than for MR alone.

10.2 Measurement Methods

PET images will be interpreted using dedicated software and the location of uptake will be recorded for each patient, blinded to the results of other studies. MR images will be evaluated for detection of areas of abnormal signal or anatomical structures, blinded to the results of PET or other studies.

10.3 Measurement Time Points

Uptake will be evaluated after the scan completion.

11. STATISTICAL CONSIDERATIONS

11.1 Statistical Design

Prospective single center, single-arm study. Patients will be scanned with ^{68}Ga-RM2 PET/MRI after the CT scan. MRI and PET/MRI scans will each be evaluated separately by two readers.

11.2 Randomization

No randomization will be done.

11.3 Interim analyses

No interim analyses are planned.

11.4 Key variables

Reference standard: disease status of a lesion will be defined by conventional imaging followed by biopsy of suspicious lesions, when clinically feasible. 12-months clinical follow-up will be gold standard if biopsy cannot be done.

Test to be evaluated: ^{68}Ga-RM2 positivity will be determined by the operator as uptake more than the liver (malignant) or less (benign). Visual conspicuity against background on the diffusion weighted images and presence of an anatomically corresponding abnormality on the T1w and T2w images are the criteria for detecting a lesion on MRI.

11.4.1 Analysis Population

All lesions identified by ^{68}Ga-RM2 PET/MRI.

11.4.2 Analysis Plan

Sensitivity and specificity of PET/MRI and MR alone will be compared by McNemar tests of paired proportions.

11.5 Sample Size

We used the "paired proportions" power analysis procedure in Stata Release 14 to determine the sample size (36). We expect that roughly 50% of patients will have lesions (as determined by biopsy or follow-up). Assuming a difference in sensitivity for PET/MRI and MRI of 20 percentage points (eg, 70% vs 50%), a sample of 60 diseased patients will provide 90% power at 5% error to detect such a difference. Assuming a difference in specificity for PET/MRI and MRI of 20 percentage points (eg, 70% vs 90%), a sample of 60 non-diseased patients will provide 98% power at 5% error to detect such a difference.

--11.6 Accrual estimates

We expect to accrue a total of 125 participants for this study. The 10 patients included in the pilot study were enrolled in less than 2 months. The participants evaluated in published data will not be included in the analysis. There are approximately 10 prostate cancer patients scanned each week using in Nuclear Medicine to evaluate for metastatic disease. Our enrollment plan is achievable given our experience with other protocols and the expected support from the referring physicians, Drs. Hancock, Sonn and Srinivas.

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Inclusion/Exclusion Criteria Checklist

Protocol Title:	^{68}Ga RM2 PET/MRI in Patients with Biochemically Recurrent Prostate Cancer and Non-Contributory Conventional Imaging
Protocol Number:	35155
Principal Investigator:	Andrei Iagaru, MD

Inclusion Criteria – Yes must be checked to be eligible (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Biopsy proven prostate adenocarcinoma	☐	☐	☐
2. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy) a. Post radical prostatectomy (RP) ii. PSA greater than 0.2 ng/mL measured after at least 6 weeks from radical prostatectomy ii. Confirmatory persistent PSA greater than 0.2 ng/mL (total of two PSA measurements greater than 0.2 ng/mL) b. Post-radiation therapy c. i. A rise of PSA measurement of 2 or more ng/mL over the nadir	☐	☐	☐
3. No evidence of metastatic disease on conventional imaging, including a negative bone scan for skeletal metastasis and negative CT scan, with or without contrast. NaF PET CT can substitute for separate bone scan and CT. CT in Axumin® (also known as ^{18}F FACBC or ^{18}F Fluciclovine) can substitute for separate CT.	☐	☐	☐
4. Able to provide written informed consent	☐	☐	☐
5. Karnofsky performance status of ≥50 (or ECOG/WHO equivalent)	☐	☐	☐

Exclusion Criteria –No must be checked to be eligible (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Patient is < 18 years old at the time of the drug administration	☐	☐	☐
2. Unable to provide informed consent	☐	☐	☐
3. Inability to lie still for the entire imaging time	☐	☐	☐
4. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia radiation phobia, etc.)	☐	☐	☐
5. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance.	☐	☐	☐
6. 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.

Signature:	Date:
Printed Name:	

Signature:	Date:
Printed Name:	

Signature:	Date:
Printed Name:	