Evaluation of Patients With Low-Risk and Intermediate-Risk Prostate Cancer Scheduled for High-Dose Rate Brachytherapy Using 68-Ga-RM2 PET, 68Ga-PSMA-11 PET and Multi Parametric MRI

Study Protocol and Statistical Analysis Plan

NCT04264208

July 12, 2019

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Protocol IRB-51987 // SRC-TBD // NCT-TBD

Protocol version // 12 July 2019

SRC Approval Date –

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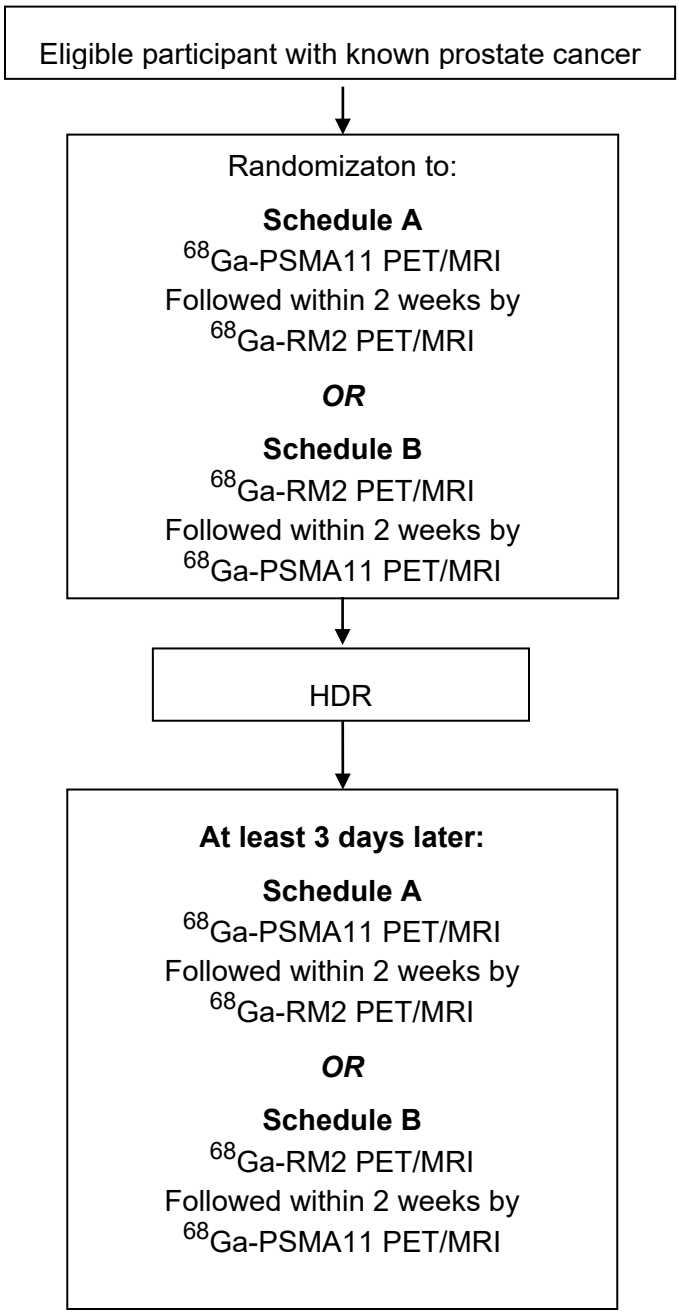
PROTOCOL SYNOPSIS

TITLE	Evaluation of Patients with Low-Risk and Intermediate-Risk Prostate Cancer Scheduled for High-Dose Rate Brachytherapy Using ^{68}Ga-RM2 PET, ^{68}Ga-PSMA-11 PET and Multi Parametric MRI
STUDY PHASE	Phase 2 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	100 participants
PRIMARY OBJECTIVES	To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can detect additional cancers over mpMRI To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can assess changes in response to treatment and predict PFS at 24 months

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
HDR
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
HDR	High-dose rate

1. OBJECTIVE

Specific Aims

Aim 1: ^{68}Ga-RM2 PET/MRI and ^{68}Ga PSMA-11 PET/MRI detection of PC. We will investigate the performance of the new GRPr-binding PET radiopharmaceutical, ^{68}Ga-RM2, and compare it to the currently most widely investigated (but not FDA-approved) PC PET radiopharmaceutical, ^{68}Ga PSMA-11, as well as to mpMRI acquired during PET/MRI for the localization and staging of low-risk and intermediate-risk PC. New lesions identified on PET/MRI and not known from prior systematic prostate biopsy will be confirmed by targeted biopsy and GRPr and PSMA status will be evaluated with specific immunohistochemical stains [1, 2].

Aim 2: ^{68}Ga-RM2 PET/MRI and ^{68}Ga PSMA-11 PET/MRI prediction of PFS after local targeted therapy for PC. We will investigate if the combination of the GRPr-binding PET imaging agent, ^{68}Ga-RM2, and the most widely investigated (but not FDA-approved) PSMA-binding PET imaging agent, ^{68}Ga PSMA-11, together with mpMRI can predict PFS after local targeted therapy. We will determine if ^{68}Ga-RM2 PET/MRI and ^{68}Ga-PSMA-11 PET/MRI assessment at 6-months follow-up will predict PFS at 24 months based on standard clinical follow-up (PSA, imaging, tissue diagnosis).

2. BACKGROUND

2.1 Preliminary information

Prostate cancer (PC) remains the most-common non-cutaneous cancer diagnosed in American males, accounting for an estimated 164,690 estimated new cases and 29,430 estimated deaths in 2018 [3]. Historically, PC 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 PC-specific mortality dropped to 20 per 100,000 by 2012 [4]. While improvements in therapy likely play some role, independent groups in the CISNet consortium have shown through modeling that 45% - 70% of the decline in PC mortality can be plausibly attributed to PSA screening [5].

Meanwhile, PSA screening also dramatically increased detection and treatment of slow-growing, low-grade PC 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 PC mortality in the PSA era, the US Preventive Services Task Force (USPTF) recommended in 2011 against routine screening with PSA [6] because it deemed that the harms of screening outweighed the benefits. Accordingly, PSA use and early diagnosis PC have decreased dramatically [7]. The dilemma for patients and treating 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, less invasive and fundamentally less risky** treatments for localized PC.

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 to identify metastases. However many cancers are diagnosed before this stage and are candidates for targeted local therapy.

Changing paradigms in management of localized PC. Not all localized PC 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 [8]. Low-risk PC (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 PC [9, 10]. 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 [11]. Newer less invasive local therapies seek to offer 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 localized therapies are 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 PC is most often multifocal, the highest grade, index lesion drives clinical outcomes [12, 13]. Conventional trans-rectal ultrasound (TRUS)-guided systematic prostate biopsy consisting of 6-12 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 [14]. MRI-guided biopsies find more clinically significant tumors (≥G7) and less insignificant (G6) tumor than conventional systematic biopsies. MRI is increasingly used for the following:

- Prior to biopsy, MRI can be used to determine if biopsy is necessary and can enable image-targeted biopsy if an abnormality is seen on MRI [14]
- Men contemplating active surveillance: a normal mpMRI adds confidence that this is a safe management option. An abnormal mpMRI prompts a conventional MRI-transrectal ultrasound (MRI-TRUS) fusion biopsy that often reveals clinically significant cancer that warrants treatment [15].
- 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 *[16]*, the size of high-grade cancers is underestimated *[17]*, **and ~40% of men with a normal MRI have PC on biopsy** *[18]*.

Positron emission tomography (PET) and PC. PET tracers, such as ^{18}F- or ^{11}C-labeled choline and [^{11}C]-acetate, are used mainly for the diagnosis of recurrent [19-21] or metastatic [22] PC. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes [23, 24]. Although choline based PET/CT is widely used outside the US for imaging PC, there have been numerous studies reporting a low sensitivity and specificity, especially at low PSA levels [25, 26]. Consequently, improved molecular imaging of PC is necessary. One novel method is PET imaging with ^{18}F-FACBC, a synthetic amino acid. Nanni et al. indicate that this tracer might be superior when compared to choline PET/CT [27]. However, others shown that ^{18}F-FACBC uptake in PC is similar to that in BPH nodules [28]. Prostate-specific membrane antigen (PSMA) is a transmembrane protein of high interest in PC. This cell surface protein is significantly overexpressed in PC cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands. PSMA is highly overexpressed on almost all PC [29-31]. Only 5-10% of primary PC lesions have been shown to be PSMA-negative [32, 33], making this class of radiopharmaceuticals suitable for diagnosis of primary PC and for initial staging [34-39]. Non-invasive tumor grading has also been reported [40]. PSMA ligands can be labeled with ^{68}Ga for PET imaging [41]. Experience with PET/CT using Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)] (^{68}Ga-PSMA-11) indicates that this compound can detect PC relapses and metastases with high contrast by binding to the extracellular domain of PSMA,

followed by internalization [42]. 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 [43, 44] and other cancers also express PSMA [45-47]. False positive findings have also been reported using PSMA agents [48-51].

Consequently, improved imaging of PC 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 [52, 53]. 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 [52, 53]. Studies show that GRPr is expressed at very low levels in normal prostate glands but is increased in 45-100% of human PCa [54, 55]. ^{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 [56]. GRPr proteins are highly overexpressed in several human tumors, including PC [57]. Because of their low expression in BPH and inflammatory prostatic tissues [58, 59], 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 PC with high GRPr expression [60]. 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 [61] and mean effective doses comparable to other radiopharmaceuticals [62, 63]. Published data indicate encouraging results for use at initial diagnosis of PC [61-65] or at biochemical recurrence [66].

While the PSMA is over-expressed in prostate cancer, this is not universal; there are lesions undetected by PSMA-targeted imaging in different risk classes or stages of disease. The influence of GRPr expression on cancer grade and stage has been evaluated by several groups. Nagasaki et al. found that GRPr expression is correlated with higher Gleason score [67]. Most recently, Michaud et al. showed that ***GRPr expression in PC is independent from PSMA expression***. In some cases GRPr expression occurred in the absence of detectable PSMA expression on IHC [2].

Evolution of Radiotherapy. Localized PC is effectively treated with external beam radiation therapy (EBRT) to 78 to 80 Gy, a non-invasive, outpatient treatment regimen. It requires approximately 40 fractions, or treatments, delivered 5 days/week over 2 months, necessitating a significant time commitment from patients. Potential side effects include urinary urgency, dysuria, hematuria, urinary retention, impotence, and GI toxicity. Biochemical failure (rising PSA after treatment) may occur in as many as 20-30% of men after EBRT for intermediate risk PC [68]. Low dose rate (LDR) brachytherapy with trans-perineal radioactive seed implantation can deliver potentially higher local doses which is important for local tumor control. However, seed placement is challenging with real-time planning and seed placement resulting in variable dosimetry, and the radioactive seeds mandate contact restrictions for patients. Recently, high dose rate (HDR) brachytherapy has been utilized as an alternative. Although usually done under general anesthesia, HDR is minimally invasive, enables real time treatment planning, the ability to preferentially boost dominant tumor locations, and has favorable dosimetry [69]. Local control after HDR is excellent [70], the treatment is more convenient for patients and side effects are less common than after EBRT as the radiation is delivered with a sharp fall-off minimizing dose to surrounding pelvic structures. At Stanford, we have an active, well-established HDR brachytherapy program led by Dr. Mark Buyyounouski who consistently treats at least 6 patients per week with this technique. Since initiation of the program approximately 3 years ago, we have treated over 500 patients with this modality either as part of a boost treatment in addition to EBRT (325 patients) or as HDR monotherapy (175 patients) for definitive treatment of their PC. These include 45 patients to date in 2018 with low or intermediate

risk PC.

Efficacy assessment: a major unsolved question. Unlike after prostatectomy, where PSA levels fall to zero soon after successful surgery, after local targeted therapy (HDR) 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 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%, respectively, for clinical recurrence [71]. 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 [72]. 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. After brachytherapy, local recurrence can potentially be retreated with more brachytherapy. This 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 [73]. For example, after radiation therapy, decreased exocrine function, and fibrosis can cause low signal on T2-weighted images and variable diffusion restriction that mimic tumor [74]. Similarly, after ablation, resolving hemorrhage and proteinaceous necrosis can cause variable diffusion restriction, and inflammation can cause contrast enhancement [75].

Simultaneous PET/MRI: PET/MRI is an advanced hybrid imaging 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 [76]. PET/MRI is particularly important for accurate localization and assessment of the pelvic extent of disease at the initial staging of PC. 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 [77]. In addition, the silicon photomultipliers (SiPM) based PET detectors in SIGNA PET/MRI or digital PET/CT scanners are more sensitive than photomultiplier tubes (PMT) based PET detectors in standard PET/CT [78-80]. The knowledge we propose to acquire can be generalized to separately acquired PET/CT and mpMRI, although motion artefacts and other factors may prevent accurate fusion of the data.

In summary, 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 128379.

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 goals:

1. To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can detect additional cancers over mpMRI.

2. To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can assess changes in response to treatment and predict PFS at 24 months.

^{68}Ga-RM2 at Stanford University: Under an FDA-approved IND (# [redacted]) our group currently uses ^{68}Ga-RM2 in 2 clinical scenarios, either prior to prostatectomy in patients with intermediate or high-risk PC or at biochemical recurrence after definitive treatment (prostatectomy or radiation therapy).

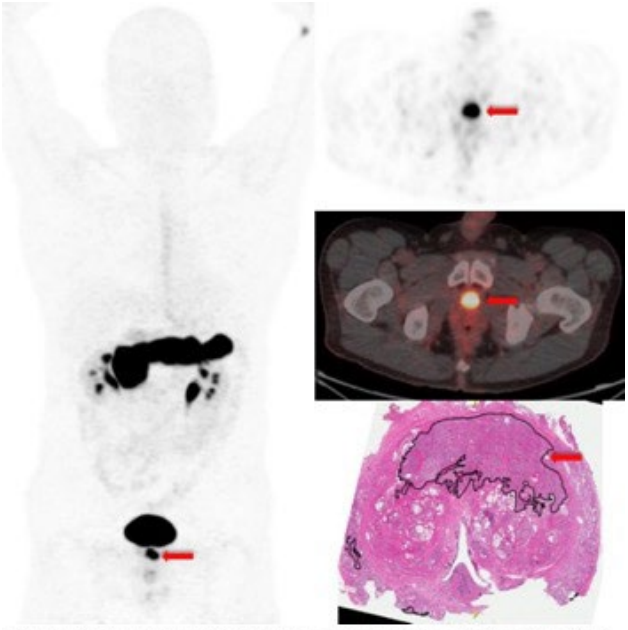


Figure 1. The uptake of ^{68}Ga-RM2 in a representative patient was localized in the anterior aspect of the prostate gland (arrows). This area correlated with PC (outlined in black) on corresponding prostatectomy sections.

^{68}Ga-RM2 identified primary PC lesions in all 15 patients scheduled for prostatectomy included in our pilot study [81]. An example is shown in **Figure 1**.

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) [66]. Currently, we have 80 participants scanned at BCR and our data indicates a 70% detection rate in this population with a mean PSA of 8.0 ng/dl and negative conventional imaging. The lowest PSA in a patient with positive ^{68}Ga-RM2 PET was 0.24. ***One third of the lesions found on ^{68}Ga-RM2 PET were biopsied; all results were true positive***. Examples are shown in **Figure 2**. More importantly in our opinion, ***PSA velocity values were 0.32±0.59 ng/ml/year (range: 0.04-1.9) in patients with negative PET scans and 2.51±2.16 ng/ml/year (range: 0.13-8.68) in patients with positive PET scans (P=0.006), suggesting the ability to detect more aggressive PC***.

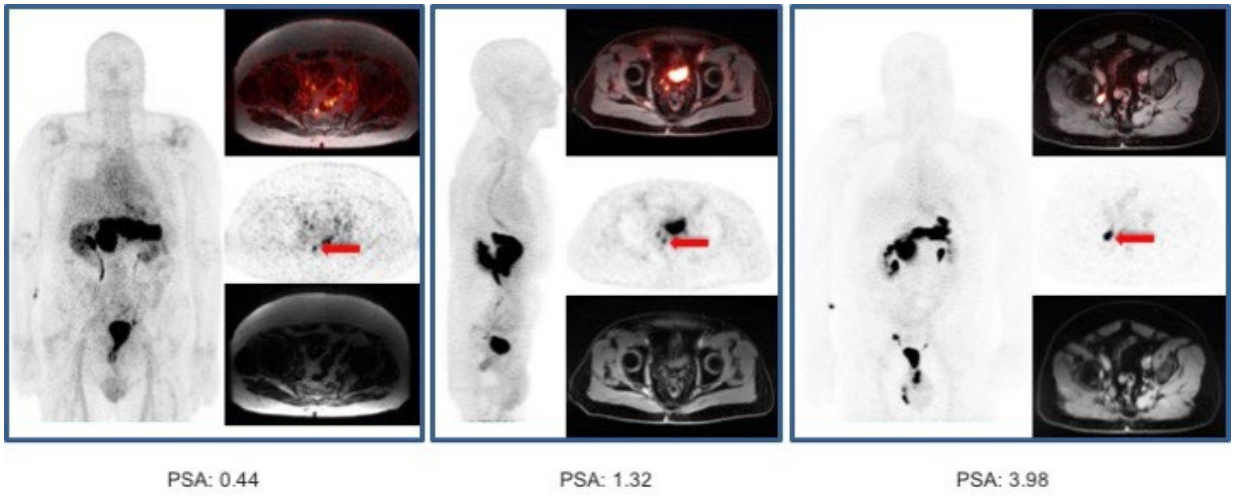


Figure 2. ^{68}Ga-RM2 uptake in pelvic nodal metastases in representative patients at BCR with various PSA levels. ^{68}Ga-RM2 lesion detection rate is 47.6% at PSA<1, 70% at PSA 1-2, 72.2% at PSA 2-5 and 90.3% at PSA>5 in our experience.

^{68}Ga PSMA-11 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 are currently conducting prospective studies under IND #128379 in the same indications as for ^{68}Ga-RM2 (prior to prostatectomy in patients with intermediate or high-risk PC or at biochemical recurrence after definitive treatment).

To date we enrolled 49 men with intermediate and high risk newly diagnosed PC, scheduled to undergo prostatectomy and pelvic nodal dissection [82]. ^{68}Ga PSMA-11 PET identified intraprostatic cancer in all 49 patients, while mpMRI alone identified PIRADS 4 or 5 lesions in ¾ of patients. ^{68}Ga PSMA-11 PET showed focal uptake in pelvic lymph nodes in 9 patients. Final pathology confirmed cancer in the prostate of all patients. No patient with normal pelvic nodes on PET/MRI had metastases on pathology. An example is shown in **Figure 3**.

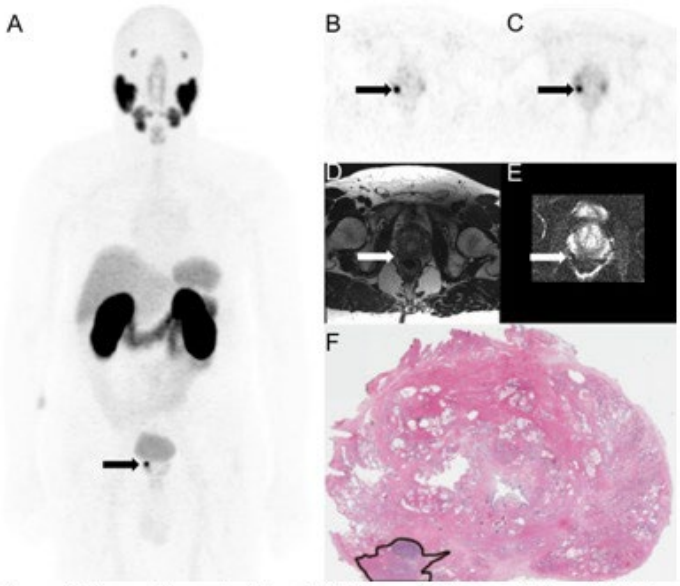


Figure 3: 74 year-old man (participant #4) with recently diagnosed intermediate risk, T1c, Gleason 4+4 prostate cancer presenting with PSA of 4.12 ng/ml. Maximum intensity projection (MIP) PET image (A), early transaxial PET (B) and delayed transaxial PET (C) showed focal ^{68}Ga-PSMA-11 uptake in histopathological proven prostate cancer (F, circled in black). The milder focal uptake in the left lobe was likewise proved to be prostate cancer. Transaxial T2-weighted MRI (D) and DWI (B=800) MRI (E) are also shown

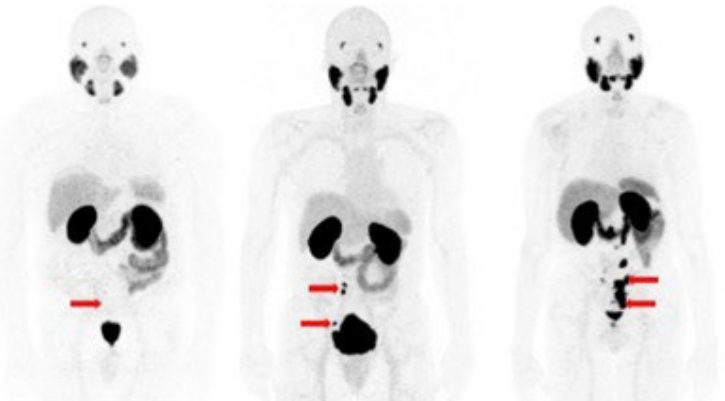


Figure 4. ^{68}Ga-PSMA-11 uptake in nodal metastases (arrows) in representative patients at BCR.

In addition, we now have data from 62 patients with BCR PC who had ^{68}Ga PSMA-11 PET/CT at our institution [83]. ^{68}Ga PSMA-11 detected sites of recurrence in 73% of patients, with the lowest PSA and a positive scan

at 0.05 ng/mL. Examples are shown in **Figure 4**.

^{68}Ga-RM2 vs. ^{68}Ga PSMA-11 at Stanford University: We first published a pilot comparison of ^{68}Ga-PSMA-11 with ^{68}Ga-RM2 at BCR [84]. 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. ^{68}Ga-RM2 shows similar sensitivity to ^{68}Ga-PSMA and provides higher lesion conspicuity in selected patients due to no significant hepatobiliary clearance (**Figure 5**).

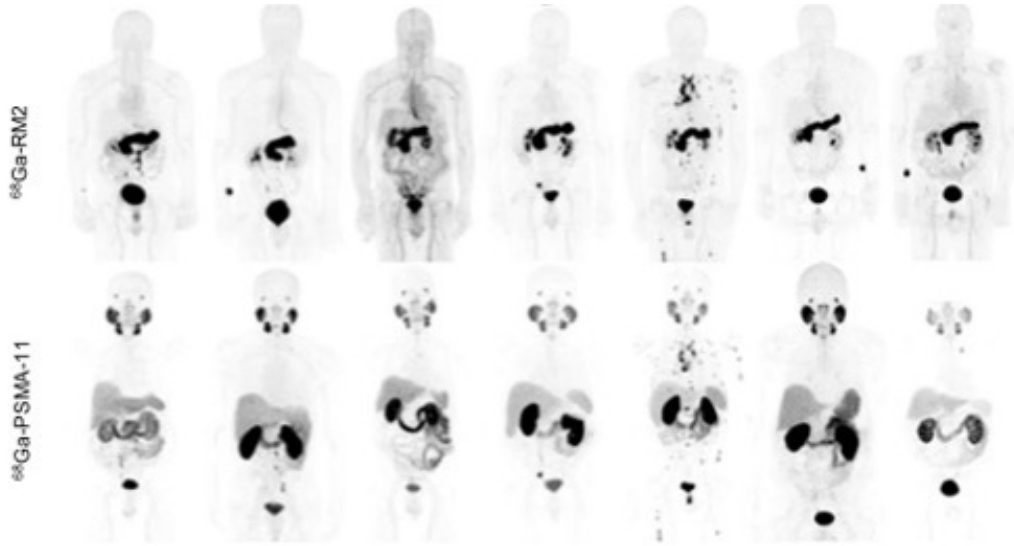


Figure 5: ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 have distinct biodistribution and lesion detection in the first prospective head-to-head comparison conducted at Stanford University [77].

At this time, we enrolled 9 patients with intermediate and high risk newly diagnosed PC, scheduled to undergo prostatectomy and pelvic nodal dissection, in a prospective comparison of ^{68}Ga-RM2 and ^{68}Ga-PSMA-11. At least one lesion in the prostate was identified by each radiopharmaceutical in every participant, but the results did not overlap, as shown in **Figure 6**.

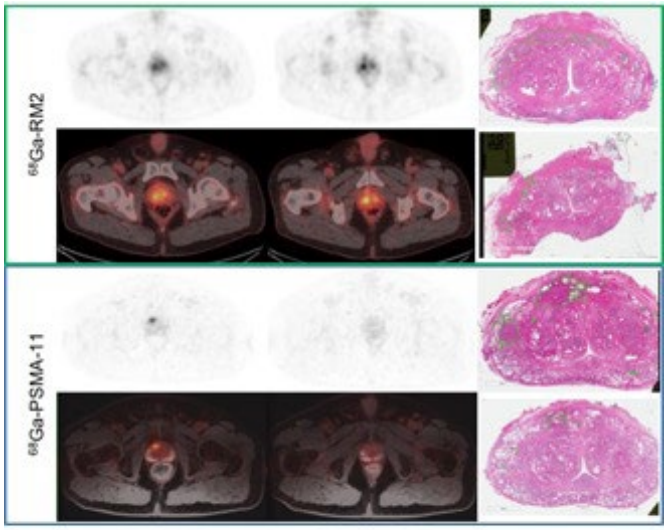


Figure 6: 73 year-old man with bilateral prostate adenocarcinoma, Gleason score 3+4. Both the lesion seen on ^{68}Ga-RM2 and the lesion seen on ^{68}Ga-PSMA-11 were positive for PC.

Another study at our institution enrolled 29 patients with BCR PC in a direct comparison of ^{68}Ga-RM2 and ^{68}Ga-PSMA-11. ***^{68}Ga-PSMA found sites of disease in 22/29 patients and ^{68}Ga-RM2 identified recurrent prostate cancer in 20/29 patients. ^{68}Ga-PSMA-11 was positive and ^{68}Ga-RM2 was negative in 3 patients; ^{68}Ga-PSMA-11 was negative and ^{68}Ga-RM2 was positive in 2 patients. More lesions were seen on ^{68}Ga-PSMA-11 than on ^{68}Ga-RM2 in 4 patients, while ^{68}Ga-RM2 identified more lesions than ^{68}Ga-PSMA-11 in 3 patients.*** PSA was 0.4-36.4 ng/mL; mean±SD: 8.3±8.8) in patients with positive ^{68}Ga-PSMA-11 and 0.3-36.4 ng/mL; mean±SD:

8.8±9.1) in patients with positive ^{68}Ga- RM2 (*P:* 0.86). PSA was 0.2-8.2 ng/mL; mean±SD: 2.5±3.2) in patients with negative ^{68}Ga-PSMA-11 and 0.2-8.2 ng/mL; mean±SD: 2.7±2.9) in patients with negative ^{68}Ga- RM2 (*P:* 0.90). Examples are shown in **Figure 7**.

PSMA is over-expressed in many but not all PC; some lesions will not be detected by PSMA-targeted imaging in different risk classes or stages of disease. The influence of GRPr expression on PC grade and stage has been evaluated by several groups. Nagasaki et al. found that GRPr expression is correlated with higher Gleason score [67]. ***GRPr expression in PC is independent from PSMA expression*** and GRPr expression can occurr in the absence of detectable PSMA expression on IHC [2]. Therefore, GRPr PET is complementary to PSMA PET for detection of PC. ***The use of both PET radiopharmaceuticals will ensure appropriate evaluation of PC patients.***

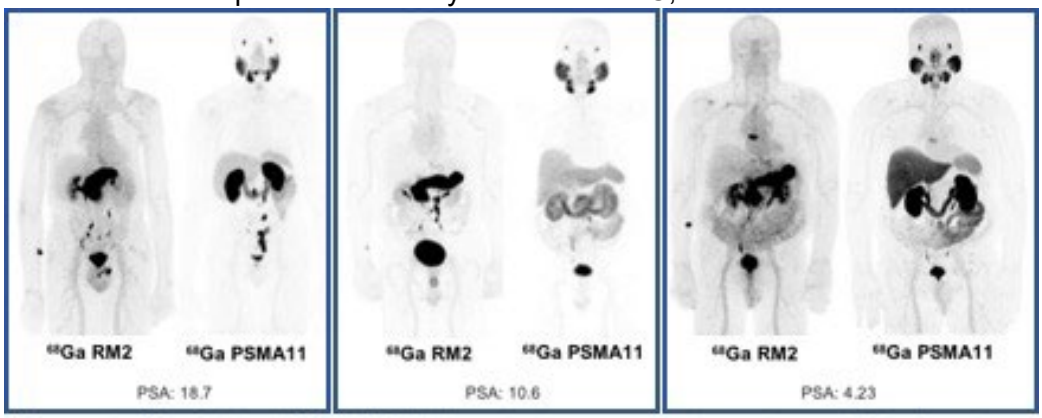


Figure 7. ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 uptake in representative patients at BCR. Note how different lesions are better seen on one vs. the other radiopharmaceutical.

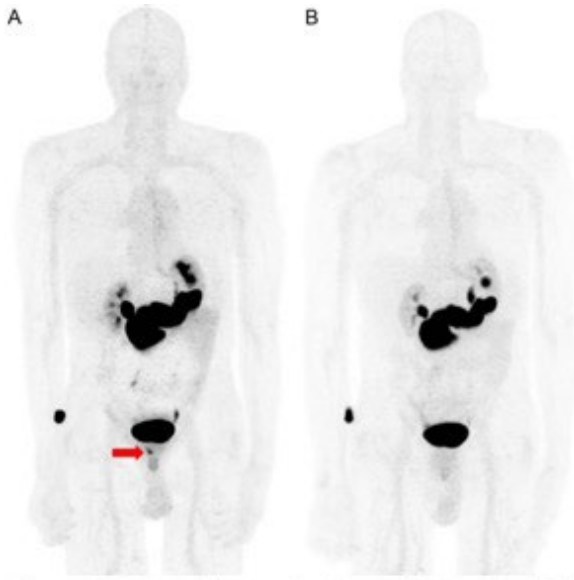


Figure 8: 72 year-old man with history of Gleason 3+4 PC treated with radiation and hormonal therapy, presenting with PSA of 3.7 ng/ml. Maximum intensity projection (MIP) ^{68}Ga-RM2 PET image before (A) and after (B) radiation treatment demonstrate resolution of prostate bed uptake (arrow).

Figure 8 shows a patient with local recurrence of PC identified with ^{68}Ga-RM2 and subsequently treated with HDR brachytherapy, showing resolution of ^{68}Ga-RM2 uptake in the prostate bed.

In summary, GRPr and PSMA expression is increased in PC, due to different underlying biological processes. 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 PC and we will attempt to predict PFS after targeted therapy.

We **hypothesize** *that the use of ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI will permit accurate localization of PC at initial diagnosis and allow for evaluation of response to treatment and prediction of PFS at 24 months after local targeted therapy*. We will use a state-of-the-art simultaneous PET/MRI scanner with time of flight capability that was first-ever installed system at Stanford University in December 2013. There are now more than 200 simultaneous PET/MRI systems world-wide and we collaborate with many of these sites.

2.5 Study Design

This is a NCI-funded phase II study with a total of 100 participants with known prostate cancer, scheduled to undergo HDR 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 ± 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 ± 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 or HDR local treatment, prior to standard of care biopsy to evaluate for residual disease in the prostate.

Objectives of the Study

Primary Objectives

- To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can detect additional cancers over mpMRI.
- To demonstrate that ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can assess changes in response to treatment and predict PFS at 24 months.

Secondary Objective

- None

Endpoints

Primary Endpoints

- Number of participants with assessable additional prostate cancedr lesions over mpMRI
- Number of participants with assessable pre- and post-treatment uptake in response to HIFU or HDR local therapy

Secondary Endpoint

- None

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- Patients must be at least 18 years of age;
- Patients must be able to provide informed consent;
- Histologically proven low-grade or intermediate-grade PC;
- Scheduled to undergo targeted local therapy (HDR brachytherapy).

3.2 Exclusion Criteria

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

3.3 Informed Consent Process

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

3.4 Study Timeline

3.4.1 Primary Completion:

The study will reach primary completion 24 months from the time the the last subject completes the first scan.

3.4.2 Study Completion:

The study will reach study completion 84 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) [85-88].

^{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 [89]. ^{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) [85-88].

4.2 Source of the Study Agent

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

4.3 Ordering

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

4.4 Agent Accountability

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 HDR local treatment.

5.3 Image interpretation

The PET/MRI scans will be interpreted by ABNM certified Nuclear Medicine physicians and 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 tracer will be conducted.

The study team will communicate the results of the scans to the referring (treating) physicians.

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 HDR 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 24 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 Aim 1

Participants: 100 patients with low- or intermediate-risk prostate cancer, as described in the inclusion/exclusion criteria.

Design: Patients will have both ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI, including mpMRI. mpMRI and PET images will each be evaluated separately. For each of the 12 prostate regions, between 1-3 imaging-positive samples will be taken, and 1 sample will be taken from each imaging-negative region.

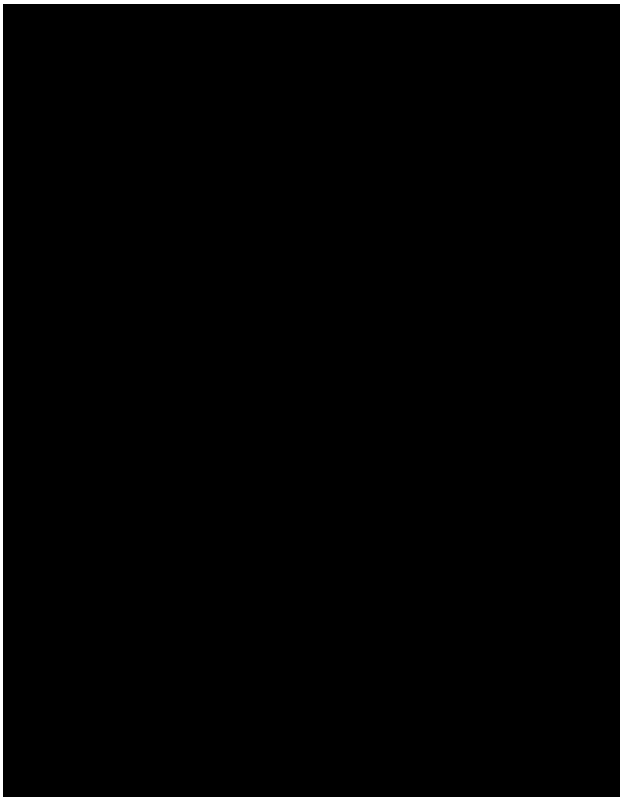
Outcome measures: Number and location of lesions will be recorded for each modality in each patient. Gold standard will be based on the biopsy of lesions found on ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET and prior systematic prostate biopsy, including IHC stains for GRPr and PSMA.

Hypothesis: ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI sensitivity, either alone or in combination, will be higher than that of mpMRI alone.

Reference standard: disease status of a lesion will be defined by biopsy of lesions found on ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET and from prior saturation prostate biopsy. Tissue samples will be evaluated for GRPr and PSMA expression as previously reported [1, 2] and results will be compared to imaging findings. For GRPr staining, immunohistochemistry will be performed using standard protocols with primary rabbit polyclonal antibody (OPA1-15619, 1:200 dilution; Affinity Bioreagents, Golden, Colorado). For PSMA, a rabbit polyclonal anti-PSMA antibody (D7I8E; Cell Signaling technology, #12815, 1:100 dilution) we be used following the manufacturer's immunohistochemistry protocol. We already successfully used [redacted]

these, as shown on page 11.

Drs. Kunder (clinical pathologist), Stoyanova and Dalm will perform all histopathological analyses. Clinical follow-up will be gold standard if biopsy cannot be done.



Test to be evaluated: All T1w, T2w, DWI and DCE MR images will first be analyzed and graded by two-board certified abdominal radiologists with subspecialty training in body MRI and extensive clinical experience in prostate MRI (Drs. Loening and Vasanawala) using the PI-RADS version 2 scoring system, blinded to the clinical information and pathology. The PET images will be corrected using the attenuation data from the MRI scan, and Drs. Iagaru and Davizon who already have extensive experience with ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 from our clinical trials, will perform blinded and random interpretation of the PET scans. Areas of focally increased ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 uptake above surrounding background will be considered positive for PC (**Figures 9 and 10**). This approach is based on recently published guidelines for standard image interpretation developed for ^{68}Ga-PSMA-11 image interpretation [90]. In addition, semi-quantitative measurements of tracer uptake (SUV_{max}) will be recorded for each lesion.

Statistical Analysis: The following statistical considerations have the full support of a biostatistician (Dr. Jarrett Rosenberg) within the Department of Radiology, who has been specifically assigned to the project and can provide continuous support throughout the data collection and data analysis process. He has also carefully reviewed the study design and was fully involved in the writing of this grant proposal.

Because there may be multiple lesions per-patient and an indefinite number of non-lesions, the primary analysis will be per-region. Each of the 12 regions will have gold-standard positive or negative information, as well as imaging positive or negative assessments. Predictive accuracy of PI-RADS composite score (mpMRI) and SUV_{max} PET uptake values will be assessed by ROC analysis using univariable logistic regression for the presence of PC. Areas under the entire ROC curve, and partial area at fixed 90% specificity will be compared. Additional benefit of the other modalities over mpMRI alone will be tested by a multivariable logistic regression. All analyses will be adjusted for clustering within patient.

Statistical Power and Sample Size: Based on our clinical experience at Stanford, we expect an average of 2 PC-positive regions and 10 PC-negative regions per patient. Assuming mpMRI has sensitivity of 80% and specificity of 80-90% [91], a sample size of 1200 regions with 20% prevalence will provide 90% power at 5% error to demonstrate non-inferiority of a PET sensitivity of 90% at 80-90% specificity [62, 92, 93].

The per-lesion analysis will depend on the number of lesions found but will be similar. We will also explore whether specific imaging findings are especially accurate in detection of specific subtypes of PC or prostate regions (i.e., peripheral versus transitional zones). It may also be the case that

predictive failures in imaging may be associated with a particular subtype. Given the small sample, we acknowledge that this analysis will be exploratory.

10.2 Aim 2

Participants: Those enrolled in Aim 1.

Design: Patients will be scanned with both ^{68}Ga-RM2 PET/MRI and ^{68}Ga-PSMA-11 PET/MRI at six months after initiation of therapy. MRI and PET images will each be evaluated separately.

Outcome measures: Changes in MRI features and/or changes in radiopharmaceutical uptake in lesions will be recorded for each modality in each patient. Gold standard of response to treatment and of PFS will be based on standard clinical follow-up (PSA, imaging, tissue diagnosis including IHC stains for GRPr and PSMA)

Test to be evaluated: All T1w, T2w, DWI and DCE MR images will first be analyzed and graded by two-board certified abdominal radiologists with subspecialty training in body MRI and extensive clinical experience in prostate MRI (Drs. Loening and Vasanawala), before and after treatment. Areas of focally increased ^{68}Ga-RM2 or ^{68}Ga-PSMA-11 uptake above surrounding background on pre-therapy scans will be evaluated for changes in uptake by Drs. Davidzon and Iagaru.

Hypotheses

Primary: Change in ^{68}Ga-RM2 or ^{68}Ga-PSMA-11 uptake from baseline (T0) to 6 months after start of treatment (T1) will predict treatment response better than T0-T1 changes in MRI.

Secondary: T0-T1 change in ^{68}Ga-RM2 or ^{68}Ga-PSMA-11 uptake will predict progression-free survival (PFS) better than MRI.

Statistical Analysis:

Primary: (a) logistic regression of response/non-response at T6 on T1-T0 change in PET/MRI measures; (b) McNemar tests of MRI and PET predictions of T6 response.

Secondary: (a) log-rank tests of PFS time (length of drug response) on patients dichotomized as above/below the median change in PET/MRI measures; (b) Cox proportional-hazards regressions of PFS on amount of T1-T0 change in PET/MRI measures.

Statistical Power and Sample Size: We expect a 70-80% response rate to treatment, and 20% of responders progressing by two years.

A sample size of ~75 responders and ~25 non-responders will provide 90% power at one-sided 5% error to detect sensitivity low as 80% at fixed 90% specificity, and to demonstrate a difference in sensitivities of 10 percentage points (e.g., 80% vs 90%).

Median-change groups of ~40 each among the responders will provide 90% power at one-sided 5% error to detect differences in PFS hazard ratios as small as 2.5.

10.3 Study Outcomes (ClinicalTrials.gov)

Primary Outcomes

Title: ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can detect additional cancers over mpMRI

Description: Detection of PC lesions will be assessed by ^{68}Ga-PSMA-11 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 PC lesions is successfully obtained.

Timeframe: 60 months

Safety outcome: No

Title: ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET/MRI can assess changes in response to treatment and predict PFS at 24 months

Description: Therapeutic response to HDR will be assessed by ^{68}Ga-PSMA-11 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 HDR is successfully obtained.

Timeframe: 84 months

Safety outcome: No

Secondary Outcome

None.

10.4 Accrual estimates

We expect the accrual of 20 patients each year for 5 years. This is achievable given our experience with other protocols and the support from the referring physicians, Drs Buyyounouski, Bagshaw and Hancock who run the HDR Brachytherapy Clinic at the Stanford Cancer Institute.

Potential difficulties and limitations: All patients will first be seen by a Stanford Cancer Institute physician and then referred if appropriate on clinical grounds for this study. SCI has a substantial volume of men with PC. We do not anticipate any difficulty in recruiting 100 men at Stanford with PC over the period of the grant since referring physicians from Radiation Oncology are supporting the study. We previously enrolled 10 patients included in a prior PET/MRI pilot study in less than 2 months.

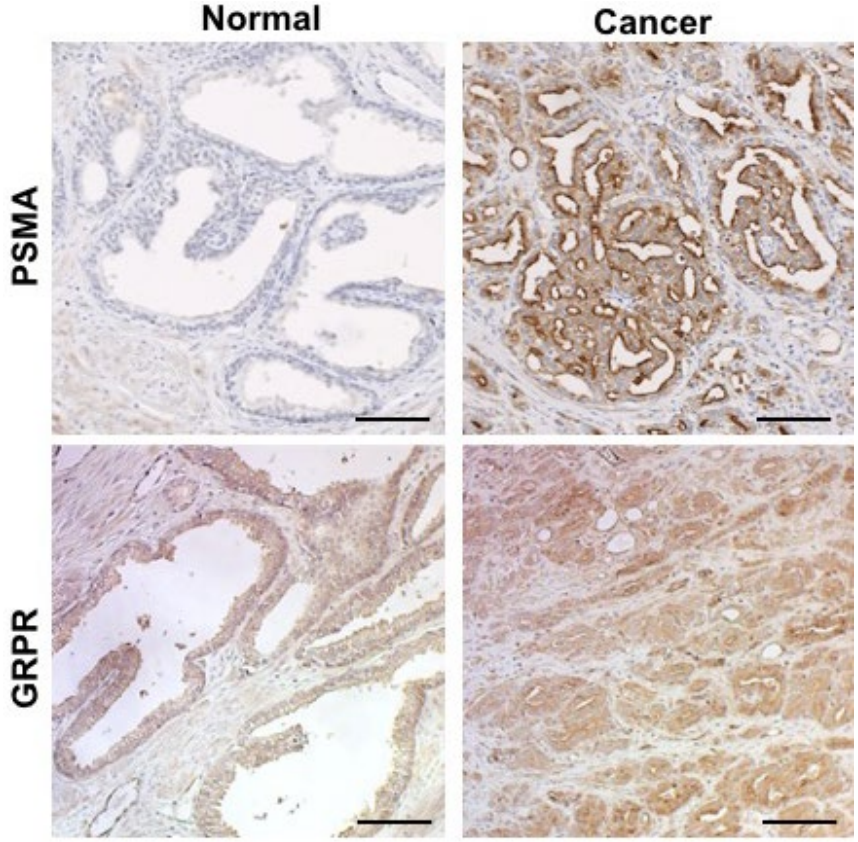


Figure 11: Benign human prostate and high-grade human prostate cancer (Gleason 4+4) were stained with anti-PSMA (Santa Cruz, sc-514444, 1:100 dilution) and anti-GRPR (Abcam, #39883, 1:100 dilution) antibody. Scale bar represents 100 microns

Based on our preliminary experience in patients with PC we do not expect any technical problems. We already hold FDA-approved INDs for ^{68}Ga-RM2 PET imaging (IND # [redacted]) and ^{68}Ga-PSMA-11 PET imaging (IND # 128379). We have already imaged 38 PC patients at initial diagnosis

(*n*=9) or BCR (*n*=29) with both ^{68}Ga-RM2 PET and ^{68}Ga-PSMA-11 PET. Therefore, we do not anticipate problems enrolling participants in this study.

Lastly, we successfully tested in-house the PSMA and GRPr IHC stains both in benign prostate tissue and PC, as shown in **Figure 11**. Therefore, we do not anticipate issues with the IHC analyses of tissue samples from the enrolled participants.

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Inclusion/Exclusion Criteria Checklist

Protocol Title:	Evaluation of Patients with Low-Risk and Intermediate-Risk Prostate Cancer Scheduled for High-Dose Rate Brachytherapy Using ^{68}Ga-RM2 PET, ^{68}Ga-PSMA-11 PET and Multi Parametric MRI
Protocol Number:	IRB-51987 / SRC-TBD
Principal Investigator:	Andrei Iagaru, MD

3.1 Inclusion Criteria

Inclusion Criteria Yes must be checked to be eligible	Yes	No	Supporting Documentation
1. Patients must be at least 18 years of age	☐	☐	
2. Patients must be able to provide informed consent	☐	☐	
3. Histologically proven low-grade or intermediate-grade PC	☐	☐	
4. Scheduled to undergo targeted local therapy (HDR brachytherapy)	☐	☐	

3.2 Exclusion Criteria

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

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

Statement of Eligibility

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

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	