68Ga-NeoBOMB1 and 68Ga-PSMA R2 PET/MRI in the Evaluation of Patients With Biochemical Recurrence of Prostate Cancer

Study Protocol and Statistical Analysis Plan

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^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 PET/MRI in the Evaluation of Patients with Biochemical Recurrence of Prostate Cancer

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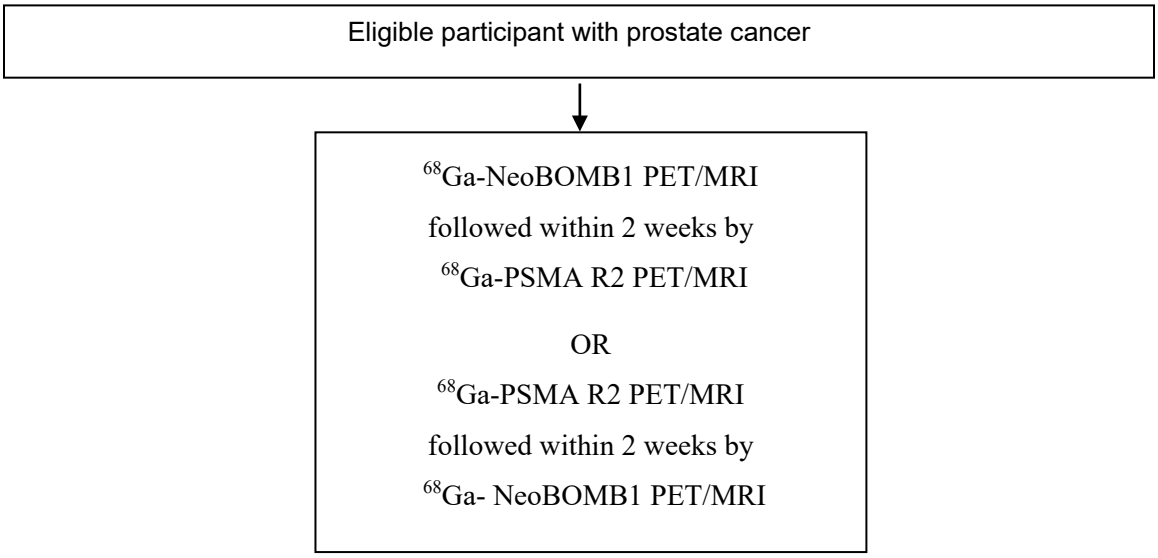
Summary of Changes

Version 2	Added new source for ^{68}Ga-NeoBOMB1

PROTOCOL SYNOPSIS

TITLE	^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 PET/MRI in Patients with Biochemically Recurrent Prostate Cancer and Non-Contributory Conventional Imaging
STUDY PHASE	Phase II
INDICATION	Prostate cancer
INVESTIGATIONAL PRODUCT OR PROCEDURE	^{68}Ga-NeoBOMB1 ^{68}Ga-PSMA R2
PRIMARY OBJECTIVE(S)	To evaluate ^{68}Ga-NeoBOMB1 PET/MRI and ^{68}Ga-PSMA R2 PET/MRI for detection of recurrent prostate cancer after initial therapy in patients with biochemical recurrence
SAMPLE SIZE	50 participants
STATISTICAL CONSIDERATIONS	Prospective single center, single-arm study.

SCHEMA


Eligible participant with prostate cancer
^{68}Ga-NeoBOMB1 PET/MRI
followed within 2 weeks by
^{68}Ga-PSMA R2 PET/MRI
OR
^{68}Ga-PSMA R2 PET/MRI
followed within 2 weeks by
^{68}Ga- NeoBOMB1 PET/MRI

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

BPH	Benign prostatic hyperplasia
Ga-68	Gallium-68
GRPR	Gastrin releasing peptide receptor
IRB	Institutional Review Board
IV	Intravenous
PC	Prostate cancer
PET/MRI	Positron emission tomography – magnetic resonance imaging
PSA	Prostate-specific antigen
PSMA	Prostate specific membrane antigen
SUV	Standardized Uptake Value
TRUS	Transrectal ultrasound

1. OBJECTIVE

Specific Aim

To evaluate ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 PET/MRI for detection of recurrent prostate cancer after initial therapy in patients meeting the criterion of biochemical recurrence.

2. BACKGROUND

2.1 Preliminary information

Data from the American Cancer Society suggests that prostate cancer (PC) will continue to be the leading non-cutaneous cancer diagnosis in males in 2016 in the US with 180,980 estimated new cases, and has the second highest mortality with 26,120 estimated deaths (*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 30-80% (*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 (BPH) 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*). However, 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.

Gastrin-releasing peptide receptors (GRPR) are highly overexpressed in several human tumors, including PC (*23*). GRP receptor was detected in 63-100 % of human prostate cancer tissue (*24,25*). Moreover, because of their low expression in BPH and inflammatory prostatic tissues (*25*), imaging of GRPR has potential advantages over current choline- and acetate-based radiotracers.

Maina and colleagues evaluated ^{68}Ga-SB3 in 8 patients with breast cancer and 9 patients with prostate cancer. All patients had disseminated disease and had received previous therapies (26). ^{68}Ga-SB3 did not produce adverse effects and identified cancer lesions in 4 out of 8 (50 %) with breast cancer and 5 out of 9 (55 %) with PC. An improved version of this radiopharmaceutical, ^{68}Ga-NeoBOMB1, is showing promising results in preliminary studies (27,28). ^{68}Ga-NeoBOMB1 has undergone extensive pre-clinical testing confirming specific and high affinity GRPR targeting (IC50: 1-2 nM), both in vitro and in vivo, as well as an appropriate pharmacokinetic profile compatible with a diagnostic use and a favorable safety profile. ^{68}Ga-NeoBOMB1 specifically and strongly bound on the cell-membrane of PC-3 cells displaying low internalization, as expected for receptor antagonists. During a translational study in prostate cancer patients ^{68}Ga-NeoBOMB1 rapidly localized in pathological lesions achieving high contrast imaging (29).

A phase 1-2 clinical study (MITIGATE trial) aimed to evaluate ^{68}Ga-NeoBOMB1 safety, tolerability, biodistribution, dosimetry and preliminary diagnostic performance is ongoing in GIST patients at Innsbruck University. The safety assessment on the first 6 patients enrolled in the study confirmed good tolerance, with no AEs reported. Uptake in tumors was fast with good visibility of the metastasis already at 1h after administration, associated with rapid renal and blood clearance (*30*).

PET/MRI is an advanced multimodality technology that can provide both biological and morphological information of various biological processes. Compared to PET/CT, simultaneous PET/MRI has advantages resulting from reduction in the radiation exposure and improvements in diagnostic ability due to better soft tissue contrast (*31*).

2.2 Study Agent

We will use ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 as the PET radiopharmaceuticals. These are not FDA-approved products, but we have letters of cross-reference for FDA-approved INDs allowing the use of these tracers in this proposed clinical indication under a Stanford investigator sponsored IND ([redacted]).

2.3 Clinicaltrials.gov

Since ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 are not FDA-approved products, we will register the study on clinicaltrials.gov once initial FDA, IRB and SRC approvals are in place.

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, NeoBOMB1, which has high affinity for gastrin-releasing peptide receptors (GRPR), and to PSMA R2 which has high affinity for prostate specific

membrane antigen (PSMA). GRPR proteins are highly overexpressed in several human tumors, including prostate cancer (*23*) and its overexpression has been demonstrated in patients with biochemically recurrent prostate cancer (*32,33*). Therefore, imaging GRPR has the potential to improve the lesion detection in prostate cancer.

^{68}Ga and ^{18}F labeled PSMA ligands can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (*21,22*).

Therefore, we propose the following aim:

- To evaluate ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 PET/MRI for detection of recurrent prostate cancer after initial therapy in patients with biochemical recurrence.

Imaging gastrin releasing peptide receptors using ^{68}Ga-NeoBOMB1

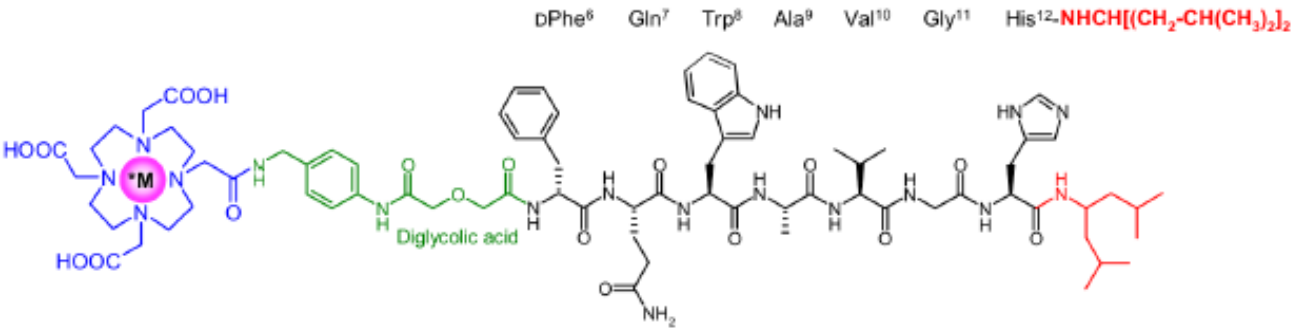


Figure 1. Chemical structure of ^{68}Ga-NeoBOMB1

Four prostate cancer patients were imaged with ^{68}Ga-NeoBOMB1 PET/CT by Nock et al (*28*). The tracer was well-tolerated by all participants and no side-effect was registered from the administration of ^{68}Ga-NeoBOMB1. Successful visualization of prostate cancer lesions in man was described by the authors for applying ^{68}Ga-NeoBOMB1PET/CT.

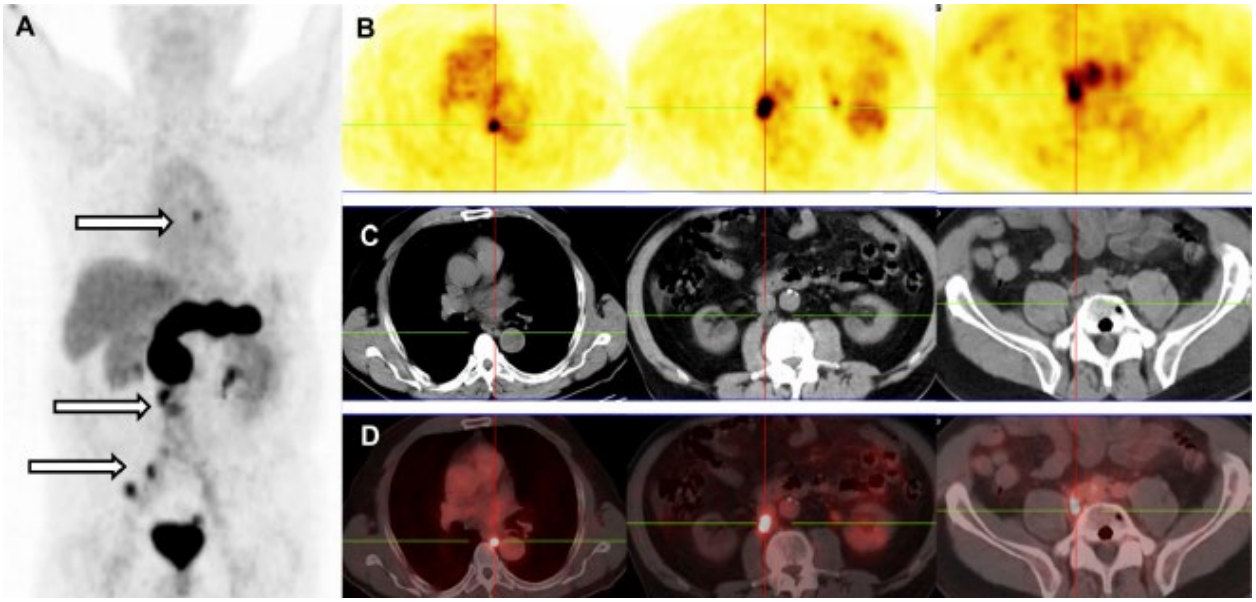


Figure 2: 65-year-old man with pT3b (G3) pN1c M0, Gleason score 7 prostate cancer. Multiple mediastinal, para-oesophageal, abdominal and pelvic lymph node metastases are strongly positive for ^{68}Ga-NeoBOMB1 uptake.

Preliminary results from MITIGATE trial after completion of phase-I part of the study (6 patients included) showed that ^{68}Ga-NeoBOMB1 presents a favorable safety and tolerability profile, with no adverse events (AEs) related with the compound. Overall, two subjects experienced adverse events, none of which were causally linked to the study drug. Uptake in tumor was fast with good imaging performance already at 1h after administration, associated with rapid renal and blood clearance (*30*).

Imaging prostate specific membrane antigen using ^{68}Ga-PSMA R2

Prostate specific membrane antigen (PSMA) is a type II integral membrane glycoprotein identified on human prostatic carcinoma cell lines. The PSMA protein has a unique 3-part structure consisting in a 19-amino-acid internal portion, a 24-amino-acid transmembrane portion, and a 707-amino-acid external portion. The PSMA gene is located on the short arm of chromosome 11 in a region that is not commonly deleted in prostate cancer. PSMA triggers a signal that allows internalization of the protein on the cell surface into an endosomal compartment. This characteristic seems to be useful for diagnostic and therapeutic (theragnostic) approach in which PSMA could be used as an antigenic target or as a specific docking-station for tailored small molecules (*34*).

Increased PSMA expression has been detected most notably in prostate cancer; though, it was also detected in the peritumoral and endotumoral capillaries of a variety of malignancies including renal cell carcinomas, transitional cell carcinomas, and colon carcinomas (*35*). Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in most primary and metastatic lesions (*36*). Immuno-histochemical studies have shown that PSMA expression increases in cases of de-differentiated, metastatic, or hormone-refractory disease (*37*) and its expression level is a significant prognosticator for disease outcome (*38*).

Several urea-based PSMA ligands have already been successfully tested in prostate cancer patients confirming good imaging performance and favorable safety profile. In line with existing guidelines, the diagnostic doses of the ^{68}Ga-PSMA ligands range 120-200 MBq/patient (approximately 2 to 3 MBq/kg). Considering the half-life of ^{68}Ga, as well as the foreseen imaging and blood sampling schedule in early phase trials (up to ¾ h for imaging acquisition or 6h for PK sampling), a dose of 3 MBq/kg, but not less than 150 MBq and not more than 250 MBq, is considered adequate to obtain good quality imaging using ^{68}Ga-PSMA R2. The proposed dose is also consistent with the one applied in the two marketed AAA diagnostic products Somakit and NETSpot.

The safety of the cold compound present in a single dose of ^{68}Ga-PSMA R2 is supported by the preclinical data obtained in GLP single and repeated dose toxicity studies performed in rats and mini-pigs showing good tolerability of the compound and no toxicity signs at the highest tested dose (in single dose studies: 8000 (rats) and 3500 (mini-pigs) times the maximum foreseen human dose; in repeated dose studies: 2600 (rats) and 1150 (mini-pigs) times the maximum foreseen human dose). Similarly, no adverse effects have been observed in the safety pharmacology studies performed in rats and mini-pigs at any of the tested doses which were 4000 (studies on effects on CNS and respiratory function in rats) or 1150 times higher (study on effects on cardiovascular function in mini-pigs) than the dose foreseen in human for the imaging drug product.

2.5 Study Design

This is a prospective, single center, single-arm phase II study enrolling 50 participants with biochemically recurrent prostate cancer. All patients will first be seen by a Stanford Cancer Institute physician and then referred if appropriate on clinical grounds to Dr Iagaru or his colleagues for this study. Eligible participants will undergo baseline assessments at enrollment. The following steps will take place after the participant has signed the written consent (participants will be randomized to have ^{68}Ga-NeoBOMB1 first followed by ^{68}Ga-PSMA R2 within 2 weeks or ^{68}Ga-PSMA R2 first followed by ^{68}Ga-NeoBOMB1 within 2 weeks [50/50 chance for each schedule]).

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 IV with 150 to 250 MBq of ^{68}Ga-NeoBOMB1
4. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) will be recorded after the injection
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 4-min acquisition time per table position.
7. Participants will be given a copy of the consent form s/he signed and will be dismissed.
8. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) 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.

The same will be repeated for ^{68}Ga-PSMA R2 (within 2 weeks of ^{68}Ga-NeoBOMB1):

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 IV with 150 to 250 MBq of ^{68}Ga-PSMA R2
4. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) will be recorded after the injection
5. Participant will void immediately prior to the scan
6. 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 4-min acquisition time per table position. Only MR sequences required for attenuation correction of PET data will be acquired.
7. Participants will be given a copy of the consent form s/he signed and will be dismissed.
8. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) 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.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- Biopsy proven prostate adenocarcinoma
- Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy)
    a. Post radical prostatectomy (RP) – AUA recommendation (*39*)
        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 (*40*)
        i. A rise of PSA measurement of 2 or more ng/mL over the nadir
- Able to provide written consent
- Karnofsky performance status of ≥50 (or ECOG/WHO equivalent)

3.2 Exclusion Criteria

- Less than 18 years old at the time of radiotracer administration
- 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
- Known allergy, hypersensitivity, or intolerance to the investigational product or its excipients
- 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 (all 50 participants enrolled) 24 months from the time the study opens to accrual.

3.4.2 Study Completion:

The protocol will reach study completion when all participants will have 12 months of clinical follow-up completed.

4. IMAGING AGENT INFORMATION

4.1 Study Agent

We will use ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 as the PET radiopharmaceuticals. These will be provided as ready-to-inject unit doses from a commercial radiopharmacy (Sofie Biosciences, previously dba Zevacor). No manufacturing will take place at Stanford University.

The administered dosage of ^{68}Ga-NeoBOMB1 is 150 to 250 MBq IV. The *in vivo* distribution of ^{68}Ga-NeoBOMB1 was studied by Dalm et al in Balb c nu/nu mice bearing the PC-3 tumor-xenograft, injected with ~13 MBq/250 pmol ^{68}Ga-NeoBOMB1 (specific activity ~ 50 MBq/nmol) (*41*). At 6 time-points (15 min; 30 min; 60 min; 2 h; 4 h; and 6 h) post-injection (p.i.), tumor and organ uptake was determined using a gamma counter. To assess receptor-specificity additional groups of animals were co-injected with an excess of unlabelled NeoBOMB1 (40 nmol). Results of the biodistribution studies were also used to determine pharmacokinetics parameters and to perform dosimetry calculations. The highest tumor uptake of 12.4 ± 2.3 %ID/g tissue was measured at 2 h p.i. At that time point, the uptake in the pancreas was 22.7 ± 3.3 %ID/g tissue. Uptake values in kidney and liver were 5.7 ± 2.4 and 8.3 ± 1.8 % ID/g tissue, respectively, indicating renal and hepatobiliary excretion. When receptors were blocked by co-injection with an excess of unlabelled NeoBOMB1, uptake in GRPR-expressing tissues decreased, as observed in tumor and pancreas, where relative uptake reached 1.0 ± 0.1 and 0.7 ± 0.1 %ID/g tissue, respectively. Pharmacokinetic calculations resulted in a tumor clearance half-life of 6.9 ± 2.8 h and a pancreas clearance half-life of 12.9 ± 4.0 h. Clearance from blood proceeded according to a bi-phasic pattern: 66 ± 9 % with half-life of 8±5 min and 34% with half-life of 50 ± 15 min.

Using the OLINDA/EXM for ^{68}Ga and assuming equal uptake per organ in human and mice, extrapolation to humans was performed obtaining an effective dose of 0.039 mSv/MBq. Estimated absorbed doses extrapolated from animal study showed that the critical organ is the pancreas (0.341 mGy/MBq). However, it is important to note that the contribution to the effective dose (calculated using the ICRP-60 weighting factors) for this organ is 0.002 mSv/MBq. Therefore, with an administered dose of 250 MBq (max dose), the resulting expected dose in the pancreas will be 0.43 mSv (50 mSv is the organ radiation dose limit for adults receiving a single administration, as per the Guidance for Industry and Researchers; “The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application”, August 2010).

The estimated effective dose for total human body, for an injected dose of 150 to 250 MBq is between 5.85 to 9.75 mSv, which is below the FDA limit of 30 mSv for adult research subjects receiving a single dose (Guidance for Industry and Researchers; “The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application”, August 2010).

Table 1: Absorbed dose estimates for ^{68}Ga-NeoBOMB1 in humans (mGy/MBq). Effective dose and contributions to the effective (ED Cont.) are also reported (mSv/MBq).

Target Organ	Beta	Photon	Total	ED Cont.
Adrenals	2.03E-03	6.43E-03	8.46E-03	4.23E-05
Brain	2.03E-03	1.27E-03	3.30E-03	1.65E-05
Breast	2.03E-03	1.64E-03	3.66E-03	1.83E-04
Gallbladder Wall	2.03E-03	9.28E-03	1.13E-02	0.00E+00
LLI Wall	1.45E-02	8.13E-03	2.27E-02	2.72E-03
Small Intestine	7.44E-03	6.08E-03	1.35E-02	6.76E-05
Stomach Wall	9.23E-03	5.83E-03	1.51E-02	1.81E-03
ULI Wall	3.17E-02	7.53E-03	3.92E-02	1.96E-04
Heart Wall	2.03E-03	3.57E-03	5.59E-03	0.00E+00
Kidneys	3.19E-02	7.37E-03	3.93E-02	1.96E-04
Liver	6.10E-02	1.48E-02	7.58E-02	3.79E-03
Lungs	2.05E-03	2.64E-03	4.69E-03	5.63E-04
Muscle	2.29E-05	3.25E-03	3.28E-03	1.64E-05
Ovaries	2.03E-03	7.80E-03	9.82E-03	1.96E-03
Pancreas	3.15E-01	2.65E-02	3.41E-01	1.71E-03
Red Marrow	1.41E-03	3.34E-03	4.75E-03	5.70E-04
Osteogenic cells	3.15E-03	2.61E-03	5.76E-03	5.76E-05
Skin	2.03E-03	1.59E-03	3.62E-03	3.62E-05
Spleen	5.24E-03	4.94E-03	1.02E-02	5.09E-05
Testes	2.03E-03	4.77E-03	6.80E-03	0.00E+00
Thymus	2.03E-03	1.68E-03	3.70E-03	1.85E-05
Thyroid	2.03E-03	1.18E-03	3.21E-03	1.61E-04
Urinary Bladder Wall	4.29E-01	5.88E-02	4.88E-01	2.44E-02
Uterus	2.03E-03	1.42E-02	1.62E-02	8.10E-05
Total Body	4.67E-03	3.45E-03	8.12E-03	0.00E+00
Effective Dose			**3.86E-02**	

The administered dosage of ^{68}Ga-PSMA R2 is 150 to 250 MBq IV. The effective dose is expected to be similar to that from ^{68}Ga-PSMA-617.

Within healthy organs, the kidneys and salivary glands showed the highest ^{68}Ga-PSMA-617 uptake. The average radiation exposure (effective dose) was approximately 0.021 mSv/MBq.

Table 3: Absorbed Organ Doses of ^{68}Ga-PSMA-617 PET:

	Absorbed organ dose (mGy/MBq) for patient			
Target organ	16	17	18	19
Adrenals	0.015	0.014	0.015	0.015
Brain	0.010	0.011	0.010	0.011
Breasts	0.010	0.011	0.010	0.010
Gallbladder	0.015	0.014	0.016	0.015
Lower colon	0.013	0.014	0.013	0.013
Small intestine	0.019	0.015	0.024	0.015
Stomach	0.013	0.013	0.013	0.013
Upper colon	0.053	0.045	0.064	0.017
Heart	0.012	0.012	0.012	0.012
Kidneys	0.239	0.085	0.305	0.196
Liver	0.033	0.022	0.032	0.028
Lungs	0.011	0.012	0.011	0.012
Muscle	0.011	0.012	0.011	0.012
Pancreas	0.014	0.014	0.015	0.015
Red marrow	0.010	0.010	0.010	0.010
Osteogenic cells	0.015	0.017	0.015	0.016
Skin	0.009	0.010	0.009	0.010
Spleen	0.040	0.020	0.015	0.039
Testes	0.011	0.012	0.011	0.012
Thymus	0.011	0.012	0.011	0.012
Thyroid	0.011	0.012	0.011	0.011
Urinary bladder	0.098	0.121	0.062	0.080
Total body	0.013	0.013	0.013	0.013
Effective dose (mSv/MBq)	0.023	0.018	0.022	0.020

The estimated effective dose for total human body, for an injected dose of 150 – 250 MBq is between 3.15-5.25 mSv, which is below the FDA limit of 30 mSv for adult research subjects receiving a single dose (Guidance for Industry and Researchers; "The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application", August 2010). The effective dosage from ^{68}Ga-PSMA-617 (and the expected effective dose from ^{68}Ga-PSMA-R2) 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) (*42-45*).

4.2 Source of the study agent

^{68}Ga-PSMA-R2

Sofie Biosciences (local manufacturer for Advanced Accelerator Applications)

Attn: [redacted]
5900B Obata Way

Gilroy, CA, 95020
Phone: 408-842-0520

^{68}Ga-NeoBOMB1

Cardinal Health (local manufacturer for Advanced Accelerator Applications)

254 E. Gish Rd.
San Jose, CA, 95112
Phone: 408-573-7819

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

Ordered in Radiology Information System (RIS).

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 150 to 250 MBq of ^{68}Ga-NeoBOMB1 (or ^{68}Ga-PSMA R2, 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 3–5 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.

A localizer MRI scan will be performed at 45 minutes after injection of 150 – 250 MBq of ^{68}Ga-PSMA R2 (or ^{68}Ga-NeoBOMB1, 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 3–5 table positions at a 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-NeoBOMB1 first followed by ^{68}Ga-PSMA R2 within 2 weeks or ^{68}Ga-PSMA R2 first followed by ^{68}Ga-NeoBOMB1 within 2 weeks (50/50 chance for each schedule).

5.3 Details of image 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.

The study team will communicate the results of the scans to the referring (treating) physicians who can decide what to do with the findings, including making treatment decisions.

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. Record past prostate cancer diagnosis and treatment details.

6.2. Imaging Days

Subjects will undergo two separate clinic visits for imaging. On each imaging day, subjects will receive an intravenous (IV) injection of investigational imaging agent (^{68}Ga-NeoBOMB1 or ^{68}Ga-PMSA-R2) and undergo PET/MRI image collection as described in Section 2.5.

6.3. Follow-up

Active subject participation ends after the 24 to 72 hour post-scan Safety Follow-up. Investigators will follow subjects by chart review for 12 months post-scan to record any standard of care biopsies or imaging results. If required by treating physicians for standard of care biopsies, the investigators will assist with identification of lesions that can be biopsied, based on ^{68}Ga-NeoBOMB1 and/or ^{68}Ga-PMSA-R2 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 to review medical records.

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 - 72 Hours Post-Scan	12 Months
Informed consent	**X**			
Demographics	**X**			
Medical history	**X**			
^{68}Ga-NeoBOMB1		**X** [a]		
^{68}Ga-PSMA R2 (within 2 weeks)		**X** [a]		
Follow-up Call to Participant			**X**	
Chart review[b]				**X**

a: Subjects will undergo either ^{68}Ga-NeoBOMB1 PET/MRI followed within 2 weeks by ^{68}Ga-PMSA-R2 PET/MRI, or ^{68}Ga-PMSA-R2 PET/MRI followed within 2 weeks by ^{68}Ga-NeoBOMB1 PET/MRI

b: Subjects will be followed by chart review for 12 months from initial scan date. If a subject transfers clinical care from Stanford Healthcare, investigators may request records from the treating physician.

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick when given by IV injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. Because the radioactivity is very short-lived, the expected radiation exposure of the whole body and critical organs is low. The substance amount (PSMA R2 and NeoBOMB1) is so small that it does not affect the physiological processes of the body.

This research study involves exposure to radiation from one ^{68}Ga-NeoBOMB1 PET/MRI. There is no radiation exposure from MRI. The estimated effective dose for total human body, for an injected dose of 150 to 250 MBq is between 5.85 to 9.75 mSv, approximately equal to 11.7 to 19.5% of the limit that radiation workers (for example, a hospital X-ray technician) can receive in one year.

This research study also involves exposure to radiation from one ^{68}Ga-PSMA-R2 PET/MRI. There is no radiation exposure from MRI. The effective dose from ^{68}Ga-PSMA-R2 PET is similar to ^{68}Ga-PSMA-11 or ^{68}Ga-PSMA-617. The estimated effective dose for total human body, for an injected dose of 150 to 250 MBq, is between 3.15 to 5.25 mSv, approximately equal to 6.3-10.5% of the limit that radiation workers (for example, a hospital X-ray technician) can receive in one year.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects because of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (ie, each dose will be double checked for dosimetry and quality by a researcher and technologist). The study Principal Investigator (PI) or his designee will report unexpected 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 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. MEASUREMENTS

10.1 Primary outcome measure

The principal goal of this study is to compare the diagnostic performance of ^{68}Ga-NeoBOMB1 PET/MRI and ^{68}Ga-PSMA R2 PET/MRI to that of MR alone in clinically (PSA) recurrent but CT-negative prostate cancer patients. The gold standard will be based on either biopsy or one-year follow-up with imaging.

Specifically, it is expected that:

1. At least 30% of these patients will have one or more lesions detected on ^{68}Ga-NeoBOMB1 PET/MRI or ^{68}Ga-PSMA R2 PET/MRI.

2. The proportion of patients with detected lesions will be higher for ^{68}Ga-NeoBOMB1 PET/MRI or ^{68}Ga-PSMA R2 PET/MRI than for MR alone.

- Primary Outcome measure: Number of lesions detected by investigational imaging agent
- Timeframe: Within 30 days
- Description: The number of lesions detected on ^{68}Ga- NeoBOMB1 PET/MRI, ^{68}Ga-PSMA R2 PET/MRI, and conventional MR will be compared. Outcome will be reported as number of lesions detected per patient for each imaging method.

10.2 Measurement Methods

PET images will be interpreted using the AW software (GE Healthcare) 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.

10.4 Secondary Outcome Measure

- Secondary Outcome measure: Predictive value of malignancy
- Timeframe: After 1 year clinical follow-up
- Description: The predictive value of ^{68}Ga- NeoBOMB1 PET/MRI and ^{68}Ga-PSMA R2 PET/MRI imaging will be evaluated based on biopsy and/or imaging results during 12 month standard clinical follow-up. Outcome will be reported as- percentage of detected lesions that were confirmed to be malignant for each imaging method.

11. STATISTICAL CONSIDERATIONS

11.1 Statistical Design

Prospective single center, single-arm study. Patients will be scanned with ^{68}Ga-NeoBOMB1 PET/MRI and ^{68}Ga-PSMA R2 PET/MRI. MRI and PET/MRI scans will each be evaluated separately by two readers.

11.2 Randomization

Patients will be randomized equally between having the ^{68}Ga-NeoBOMB1 PET/MRI scan done first or the ^{68}Ga-PSMA R2 PET/MRI.

11.3 Interim analyses

We will evaluate if ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 will have the same findings as what was noted with Ga68 PSMA-11 and Ga68 RM2 (bombesin), ie, about 2/3 same findings, while 1/3 will show different findings. We will do the interim analysis after enrollment of 20 participants. If all participants will have the same findings or if one

radiopharmaceutical will outperform the other (no additional lesions found by one vs another), the study will be discontinued.

11.4 Key variables

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

Test to be evaluated: ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 positivity will be determined by the operator as uptake more than the adjacent background (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-NeoBOMB1 PET/MRI and ^{68}Ga-PSMA R2 PET/MRI.

11.4.2 Analysis Plan

- Sensitivity, specificity, and positive and negative predictive value of imaging modalities will be estimated.
- Sensitivity and specificity of PET/MRI and MR alone will be compared by McNemar tests of paired proportions.
- The number and type of discrepancies between ^{68}Ga-NeoBOMB1 and ^{68}Ga-PSMA R2 will be tabulated.
- We will explore hypotheses about the reasons for such discrepancies, such as PSA level/velocity, Gleason score, and location.

11.5 Sample size justification

The following estimate is for a per-lesion analysis. We expect approximately 70% of patients (~35) to have one or more PET-positive findings and approximately 1/3 to be biopsied. Our existing data for ^{68}Ga PSMA-11 and ^{68}Ga-RM2 (please see attached publications) indicate no false positive findings based on biopsy. We cannot predict an average number of lesions per patient given small data available to date, but if only half of the positive patients have more than one lesion, this will easily yield 50 lesions. We also expect the sensitivity of MR alone to be roughly 40%, while that of PET to be roughly 60% or more. A sample size of 50 patients will provide 90% power at one-sided 5% error to detect such a difference. Participants who complete only one PET/MRI scan (either due to withdrawal of consent or loss to follow-up) will not be replaced with additional subjects.

11.6 Accrual estimates

We expect the accrual of 50 patients over 24 months. There are approximately 10 prostate cancer patients scanned each week in Nuclear Medicine to evaluate for metastatic disease. We plan to enroll 50 participants over 24 months and this is achievable given our experience with other protocols and the expected support from the referring physicians, Drs Hancock, Sonn, and Srinivas.

Inclusion/Exclusion Criteria Checklist

Protocol Title:	^{68}Ga NeoBOMB1 and ^{68}Ga-PSMA R2 PET/MRI PET/MRI in Patients with Biochemically Recurrent Prostate Cancer
Protocol Number:	46258
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) 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 i. A rise of PSA measurement of 2 or more ng/mL over the nadir	☐	☐	☐
3. Able to provide written consent	☐	☐	☐
4. 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. Inability to lie still for the entire imaging time	☐	☐	☐
3. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia radiation phobia, etc.)	☐	☐	☐
4. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance.	☐	☐	☐
5. Metallic implants (contraindicated for MRI)	☐	☐	☐
6. Known allergy, hypersensitivity, or intolerance to the investigational product or its excipients.	☐	☐	☐

*****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:	

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