TITLE: Phase I/II dose-escalation study of fractionated dose ^{177}Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

All abbreviations used throughout the protocol must be defined.

ADT	Androgen Deprivation Therapy
AE	Adverse Event
CRF	Case Report Form
CTC	Circulating Tumor Cells
CTSC	Clinical Translational Science Center
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IND	Investigational New Drug
IRB	Institutional Review Board
mAb	Monoclonal Antibody
mCRPC	Metastatic Castration Resistant Prostate Cancer
MTD	Maximum Tolerated Dose
PCa	Prostate Cancer
PSMA	Prostate Specific Membrane Antigen
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
WCM	Weill Cornell Medicine

Protocol Summary

Full Title:	Phase I/II dose-escalation study of fractionated dose ^{177}Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer
Short Title:	Fractionated ^{177}Lu-PSMA-617 for mCRPC
Clinical Phase:	Phase I
Principal Investigator:	Scott T. Tagawa, MD, MS
Sample Size:	*N*= 4 - 63 (3+3 study design up to 6 dose-escalation cohorts in phase I (up to 36), additional 10-21 in phase II (up to 27 including phase I cohort)
Accrual Ceiling:	This study will enroll up to 63 subjects who receive treatment
Study Population:	Adult male patients of >18 years age with patients with documented progressive metastatic CRPC
Accrual Period:	3 years
Study Design:	Phase I dose escalation study with ^{177}Lu-PSMA-617 using dose fractionation regimen will be performed in patients with documented progressive metastatic CRPC. The cumulative ^{177}Lu dose **[100 mCi (3.7 GBq) – 600 mCi (22.2 GBq)]** will be escalated in up to 6 different dose levels (3 + 3 study design). Additional 10-21 subjects will be enrolled at the MTD/RP2D level in 2-stage design to further assess safety and tolerability and to obtain a preliminary assessment of efficacy.
Study Duration:	Primary treatment phase is approximately 3 months after screening
Study Agent/ Intervention Description:	1) **^{177}Lu-PSMA-617** [50mCi (1.85GBq) - 300mCi (11.1GBq)] intravenous X2 doses, 2 weeks apart (Visit 1 and 3) 2) **^{68}Ga-PSMA-HBED-CC** [5 ±2mCi or 185 ±74MBq] intravenous during screening and at 12 weeks (±1 week) with standard imaging
Primary Objective:	• Determine the dose limiting toxicity (DLT) of fractionated dose of ^{177}Lu-PSMA-617 (phase I) • Determine the maximal tolerated and recommended phase II dose of ^{177}Lu-PSMA-617 in a 2-week dose-fractionation regimen (phase I) • To assess the proportion with PSA decline following treatment with the RP2D of fractionated dose ^{177}Lu-PSMA-617 (Phase II)

Secondary Objectives:

- To assess the rate of PSA decline following fractionated ^{177}Lu-PSMA-617
- To assess radiographic response rate by RECIST 1.1 with PCWG3 modifications
- To assess biochemical and radiographic progression-free survival by PCWG3 criteria
- To assess overall survival following fractionated ^{177}Lu-PSMA-617
- To assess safety of fractionated ^{177}Lu-PSMA-617 as assessed by CTCAE 4.0
- To assess changes in CTC count as measured by CellSearch and the rate of favorable CTC count and LDH at 12 weeks following fractionated ^{177}Lu-PSMA-617
- To examine whole body distribution of ^{177}Lu-PSMA-617
- Estimate radiation dosimetry of ^{177}Lu-PSMA-617 and correlate toxicity with radiation dosimetry

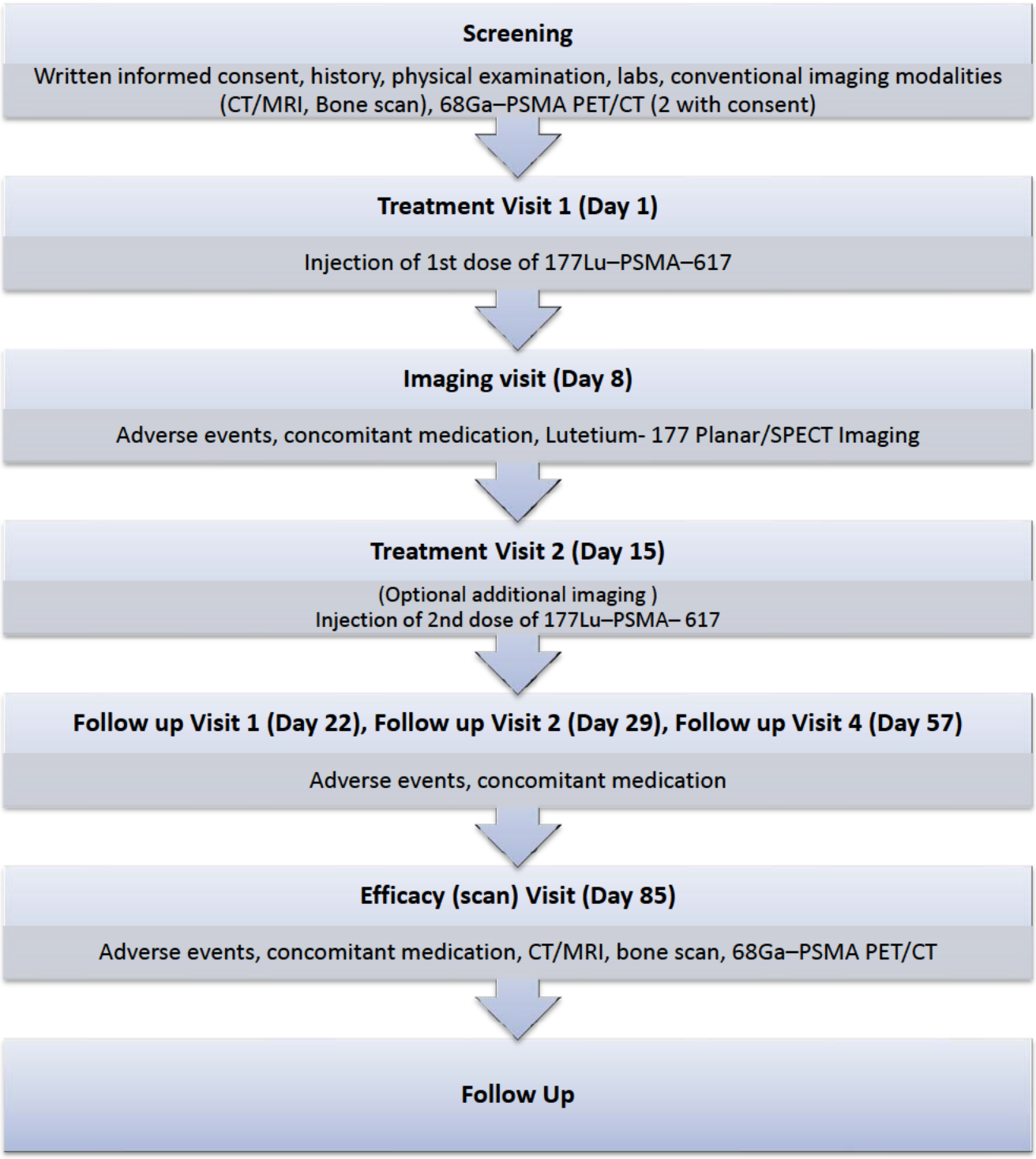
Exploratory Objectives:

- Disease assessment with ^{68}Ga-PSMA-HBED-CC PET/CT prior to and following investigational treatment
- To assess genomic DNA repair pathways in relationship to outcome following fractionated dose 177Lu-PSMA-617
- To assess patient reported outcomes using FACT-P and the Brief Pain Inventory short form
- To assess the immune effect of ^{177}Lu-PSMA-617
- To assess reproducibility of ^{68}Ga-PSMA-HBED-CC PET/CT

Endpoints:

Dose limiting toxicity (DLT), Adverse event rate, Maximum tolerated dose (MTD), Recommended phase II dose, response rate, progression free survival.

Schema


Screening
Written informed consent, history, physical examination, labs, conventional imaging modalities (CT/MRI, Bone scan), 68Ga–PSMA PET/CT (2 with consent)
Treatment Visit 1 (Day 1)
Injection of 1st dose of 177Lu–PSMA–617
Imaging visit (Day 8)
Adverse events, concomitant medication, Lutetium- 177 Planar/SPECT Imaging
Treatment Visit 2 (Day 15)
(Optional additional imaging)
Injection of 2nd dose of 177Lu–PSMA– 617
Follow up Visit 1 (Day 22), Follow up Visit 2 (Day 29), Follow up Visit 4 (Day 57)
Adverse events, concomitant medication
Efficacy (scan) Visit (Day 85)
Adverse events, concomitant medication, CT/MRI, bone scan, 68Ga–PSMA PET/CT
Follow Up

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1. STUDY OBJECTIVES:

The objectives of this clinical trial are as follows:

1.1 Primary Objectives

- Determine the Dose limiting toxicity (DLT) of fractionated dose of ^{177}Lu-PSMA-617
- Determine the cumulative maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of ^{177}Lu-PSMA-617 in a 2-week dose-fractionation regimen

1.2 Secondary Objectives

- To assess the rate of PSA decline following fractionated ^{177}Lu-PSMA-617
- To assess radiographic response rate by RECIST 1.1 with PCWG3 modifications
- To assess biochemical and radiographic progression-free survival by PCWG3 criteria
- To assess overall survival following fractionated ^{177}Lu-PSMA-617
- To assess safety of fractionated 177Lu-PSMA-617 as assessed by CTCAE 4.0
- To assess radiographic progression-free survival by PCWG3 criteria
- To assess changes in CTC count as measured by CellSearch and the rate of favorable CTC count and LDH at 12 weeks following fractionated 177Lu-PSMA-617
- To examine whole body distribution of 177Lu-PSMA-617
- Estimate radiation dosimetry of 177Lu-PSMA-617 and correlate toxicity with radiation dosimetry

1.3 Exploratory Objectives

- Disease assessment with ^{68}Ga-PSMA-HBED-CC PET/CT prior to and following investigational treatment
- To assess genomic DNA repair pathways in relationship to outcome following fractionated dose 177Lu-PSMA-617
- To assess patient reported outcomes using FACT-P and the Brief Pain Inventory short form
- To assess the immune effect of ^{177}Lu-PSMA-617
- To assess the reproducibility of ^{68}Ga-PSMA-HBED-CC PET/CT

2. BACKGROUND:

2.1. Disease

Prostate cancer (PC) is a significant health burden, with 220,800 new diagnoses and 27,540 deaths in the United States in 2015(Siegel, Miller et al. 2015). Despite advances in diagnostic technology and treatment strategies, up to 40% of patients treated with

primary therapy with curative intent will experience disease progression. Additionally, prostate cancer treatment can have a major detrimental impact on patients' quality of life, with incontinence and sexual dysfunction rates up to 18% and 90%, respectively, 15 years after therapy (Resnick, Koyama et al. 2013). The poor quality of life and prognosis of these patients has invigorated research with the goals of understanding the biological mechanisms behind PC progression and identifying novel therapeutic targets.

Localized PC is treated primarily with surgery or radiation therapy, with or without hormonal therapy, although another option for some men is active surveillance or observation, since some men will continue to be asymptomatic until death from another cause (Albertsen, Hanley et al. 1998, Albertsen, Hanley et al. 2005). Although therapy for localized disease may be successful at eradicating the disease, some patients suffer recurrence or present with advanced disease.

First line therapy for advanced PC is androgen deprivation with a mean duration of efficacy of 12-18 months, although there is a wide variation in response in this heterogeneous disease. Upon progression, the disease becomes castration-resistant and subsequently many such patients develop frank metastasis. Metastatic castration-resistant prostate cancer (mCRPC) poses a particular clinical challenge in need of additional therapeutic approaches beyond classic androgen deprivation therapies. Currently, the chemotherapy compounds docetaxel and cabazitaxel, the androgen receptor signaling inhibitor enzalutamide, CYP-17-inhibitor abiraterone, autologous cellular immuno therapy with sipuleucel-T, and the bone-seeking α-emitter ^{223}Ra have shown improved overall survival (OS) and most have demostrated quality of life advantages as well (Petrylak, Tangen et al. 2004, Tannock, de Wit et al. 2004, de Bono, Oudard et al. 2010, Kantoff, Higano et al. 2010, Fizazi, Scher et al. 2012, Scher, Fizazi et al. 2012, Parker, Nilsson et al. 2013, Beer, Armstrong et al. 2014, Ryan, Smith et al. 2015). In all cases, however, these now established therapies become ineffective in controlling tumor progression over time(Antonarakis, Lu et al. 2014). Novel therapies are urgently needed in order to further ameliorate the course of the disease.

2.2. PSMA

In PC, the most well established, prostate-restricted, cell surface antigen yet identified is prostate specific membrane antigen (PSMA)(Horoszewicz, Kawinski et al. 1987, Israeli, Powell et al. 1993, Israeli, Powell et al. 1994, Troyer, Beckett et al. 1995, Wright, Haley et al. 1995). PSMA is a trans- membrane protein with a 707-amino-acid extracellular portion. The PSMA gene (FOLH1) is located on the short arm of

chromosome 11.

Although first thought to be entirely prostate-specific, subsequent studies have demonstrated that PSMA is also expressed by cells of the small intestine, proximal renal tubules and salivary glands(Troyer, Beckett et al. 1995). PSMA is expressed in the apical region of normal prostatic cells, the epithelium surrounding prostatic ducts(DeMarzo, Nelson et al. 2003). Dysplastic changes in the prostate result in the expression of PSMA on the luminal surface of prostatic ducts (Huang, Teh et al. 2003, Wu, Xu et al. 2012). Increasing prostate cancer stage and grade result in higher cell membrane PSMA expression (Silver, Pellicer et al. 1997, Bostwick, Pacelli et al. 1998). The eventual progression to advanced prostate cancer and castrate resistance corresponds to further increases in PSMA expression (Evans, Smith-Jones et al. 2011). PSMA expression in prostate cancer cell membranes is 100- to 1000-fold that in normal cells (Silver, Pellicer et al. 1997, Bostwick, Pacelli et al. 1998). Thus, PSMA represents a promising target for imaging and therapy of prostate cancer.

2.3. Radionuclide-chelating PSMA ligands

Targeted radionuclide therapy (both monoclonal antibody and/or urea based peptides) is a state of the art and rapidly developing therapy option for different cancer types. The potential advantage of targeted radionuclide therapy is saving the normal tissue while giving a high radiation dose to the tumor.

After rather unsuccessful therapy with ^{90}Y-CYT-356 monoclonal antibody (mAb) that binds to the intracellular domain of PSMA(Deb, Goris et al. 1996), phases 1 and 2 clinical trials utilizing the PSMA mAb J591, radiolabelled with ^{90}Y (Yetrium-90) or ^{177}Lu (Lutetium-177), have shown promising results(Bander, Milowsky et al. 2005, Vallabhajosula, Goldsmith et al. 2005, Vallabhajosula, Goldsmith et al. 2005, Tagawa, Milowsky et al. 2013).

Also, PSMA has recently been discovered as a promising target for radioisotope based approaches, both for PET imaging, for example, using 68Ga-labeled PSMA ligands(Afshar-Oromieh, Haberkorn et al. 2012, Afshar-Oromieh, Haberkorn et al. 2013, Afshar-Oromieh, Zechmann et al. 2014, Chakraborty, Tripathi et al. 2015, Eiber, Nekolla et al. 2015, Uprimny, Kroiss et al. 2015), and for therapy, for example, using ligands labeled with either β- or α-emitting nuclides such as ^{131}I (Iodine-131), ^{177}Lu (Lutetium-177), and ^{225}Ac (Actinium-225)(Zechmann, Afshar-Oromieh et al. 2014, Ahmadzadehfar, Rahbar et al. 2015, Kratochwil, Giesel et al. 2015). Despite encouraging early results, data about intended and unintended effects of PSMA- based radioligand therapies (RLTs) are still scarce.

2.3.1. Prior clinical experience with PSMA small molecule(s) in men with prostate cancer:

Results from selective clinical trials using radiolabeled PSMA ligand for diagnosis and treatment of prostate cancer are reported here under:

I. ^{68}Ga-PSMA:

a) Diagnostic value of ^{68}Ga-PSMA-HBED-CC PET/CT imaging in the diagnosis of recurrent prostate cancer(Afshar-Oromieh, Avtzi et al. 2015):

The study reports data from a retrospective analysis of 319 patients who underwent ^{68}Ga-PSMA-ligand PET/CT from 2011 to 2014. The ^{68}Ga-PSMA-HBED-CC solution was applied to the respective patient via an intravenous bolus injection (mean of 172.4 MBq ±70.9, range 40 – 400 MBq, median 161 MBq). A non-contrast-enhanced CT scan was performed 1-hour post tracer injection. Histological verification was performed in 42 patients after the ^{68}Ga-PSMA-ligand PET/CT. Tracer uptake was measured in 901 representative tumor lesions. 82.8% of the patients had at least one lesion indicative of PC was detected. Tumor-detection was positively associated with PSA level and Androgen deprivation therapy (ADT). Gleason Score and PSA doubling time (PSA-DT) were not associated with tumor-detection. The average maximum standardized uptake value (SUVmax) of tumor lesions was 13.3 ± 14.6 (0.7-122.5). Amongst lesions investigated by histology, 30 were false-negative in 4 different patients, and all other lesions (n = 416) were true-positive or true-negative. A lesion-based analysis of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) revealed values of 76.6%, 100%, 91.4% and 100%. A patient-based analysis revealed a sensitivity of 88.1%.

b) PET imaging with a ^{68}Ga-PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumor lesions (Afshar-Oromieh, Malcher et al. 2013):

Initial clinical studies with the ^{68}Ga-labeled *PSMA-HBED-CC* were conducted at Heidelberg University Hospital and the German Cancer Research Center to assess

the biodistribution of ^{68}Ga-PSMA-HBED-CC in normal tissues and tumor lesions. A total of 37 patients with prostate cancer and rising PSA levels were subjected to ^{68}Ga-PSMA-HBED-CC PET/CT imaging. Quantitative assessment of tracer uptake was performed 1 and 3 h post-injection by analysis of mean and maximum standardized uptake values (SUVmean/max) of several organs and 65 tumor lesions. Subsequently, tumor to background ratios were calculated.

The ^{68}Ga-PSMA-HBED-CC PET/CT images showed intense tracer uptake in both kidneys and salivary glands. Moderate uptake was seen in lacrimal glands, liver, spleen and in small and large bowel. Quantitative assessment revealed excellent contrast between tumor lesions and most normal tissues. Of 37 patients, 31 (83.8 %) showed at least one lesion suspicious for cancer at a detection rate of 60 % at PSA <2.2 ng/ml and 100 % at PSA >2.2 ng/ml. Median tumor to background ratios were 18.8 (2.4-158.3) in early images and 28.3 (2.9-224.0) in late images. Within healthy organs, kidneys and salivary glands demonstrated the highest radiotracer uptake. Lesions suspicious for prostate cancer presented with excellent contrast as early as 1-hour after injection with high detection rates even at low PSA levels.

c) ^{68}Ga-labeled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: Comparison with ^{18}F-FECH (Afshar-Oromieh, Haberkorn et al. 2012):

This study was also published by the Heidelberg group, compared ^{68}Ga-PSMA-HBED-CC PET/CT imaging to standard choline-based PET/CT. Thirty-seven patients with biochemical relapse of prostate cancer [mean prostate-specific antigen (PSA) 11.1 ± 24.1 ng/ml, range 0.01-116] were retrospectively analyzed after ^{18}F-fluoromethylcholine and ^{68}Ga-PSMA PET/CT within a time window of 30 days. Radiotracer uptake that was visually considered as prostate cancer was semi-quantitatively analyzed by measuring the maximum standardized uptake values (SUVmax) of the scans acquired 1-hour after injection of ^{68}Ga-PSMA complex solution (median 132 MBq, range 59-263 MBq) and ^{18}F-fluoromethylcholine (median 237 MBq, range 114-374 MBq), respectively. In addition, tumor to background ratios were calculated.

The results showed a total of 78 lesions characteristic for prostate cancer that were detected in 32 patients using ^{68}Ga-PSMA-HBED-CC PET/CT imaging and 56 lesions were detected in 26 patients using choline PET/CT. The higher detection rate in ^{68}Ga-PSMA-HBED-CC PET/CT imaging was statistically significant (p=0.04). In five patients no lesion was found with both methods. All lesions detected by ^{18}F-fluoromethylcholine PET/CT were also seen by ^{68}Ga-PSMA-HBED-CC PET/CT imaging. In ^{68}Ga-PSMA-HBED-CC PET/CT imaging SUVmax was clearly (>10 %) higher in 62 of 78 lesions (79.1 %) and the tumor to background ratio was clearly (>10 %)

higher in 74 of 78 lesions (94.9 %) when compared to ^{18}F-fluoromethylcholine PET/CT.

The authors concluded that ^{68}Ga-PSMA-HBED-CC PET/CT can detect lesions characteristic for prostate cancer with improved contrast when compared to standard ^{18}F-fluoromethylcholine PET/CT, especially at low PSA levels.

d) Comparison of PET/CT and PET/MRI hybrid systems using a ^{68}Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience (Afshar-Oromieh, Haberkorn et al. 2014):

Subsequently, the Heidelberg group evaluated the feasibility of PET/MRI imaging with ^{68}Ga-PSMA-HBED-CC. Twenty patients underwent PET/CT 1-hour after injection of the ^{68}Ga-PSMA-HBED-CC followed by PET/MRI 3-hours after injection. Data from the two investigations were first analyzed separately and then compared with respect to tumor detection rate and radiotracer uptake in various tissues. To evaluate the quantification accuracy of the PET/MRI system, differences in SUVs between PET/CT and corresponding PET/MRI were compared with differences in SUVs between PET/CT 1-hour and 3-hours after injection in another patient cohort. This cohort was investigated using the same PET/CT system. With PET/MRI, different diagnostic sequences, higher contrast of lesions and higher resolution of MRI enabled a subjectively easier evaluation of the images. In addition, four unclear findings on PET/CT could be clarified as characteristic of prostate cancer metastases by PET/MRI. However, in PET images of the PET/MRI, a reduced signal was observed at the level of the kidneys (in 11 patients) and around the urinary bladder (in 15 patients). This led to reduced SUVs in six lesions. SUVmean values provided by the PET/MRI system were different in muscles, blood pool, liver and spleen.

The authors concluded that prostate cancer was detected more easily and more accurately with Ga-PSMA PET/MRI than with PET/CT and with lower radiation exposure. Consequently, this new technique could clarify unclear findings on PET/CT. However, scatter correction was challenging when the specific ^{68}Ga-PSMA- HBED-CC was used. Moreover, direct comparison of SUVs from PET/CT and PET/MR needs to be conducted carefully.

II. ^{177}Lu-PSMA-617:

a) ^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer (Yadav, Ballal et al. 2016):

Thirty-one mCRPC patients with progressive disease despite second-line hormonal therapy and/or docetaxel chemotherapy were recruited for the study. All underwent ^{68}Ga-PSMA-HBED-CC PET/CT, prior to therapy with ^{177}Lu-DKFZ-PSMA-617. The mean activity administered was 5.07 ± 1.85 GBq ranging over one to four cycles. Study reported decline in PSA from baseline. Based on biochemical response criteria, 25/31 had either complete response, partial response or stable disease while 6 continued to have disease progression. The mean ECOG performance status improved from 2.54 to 1.78 after therapy. Two patients experienced grade I and grade II hemoglobin toxicity each, while none experienced nephrotoxicity or hepatotoxicity.

b) ^{177}Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer (Rahbar, Bode et al. 2016):

28 consecutive patients with mCRPC who have exhausted conventional therapeutic options were treated with 1 or 2 cycles of ^{177}Lu-PSMA-617. Mean administered activity at first therapy was 5.92 ± 0.44 GBq of ^{177}Lu-PSMA-617 and 5.86 ± 0.73 GBq at the second therapy. All patients underwent ^{68}Ga-PSMA-PET/CT prior to therapy. Any PSA decline occurred in 59% and 75% of patients after 1 and 2 Cycles. Similarly, a PSA decline of 50% or greater occurred in 32% and 50%. Hematologic and renal parameters changed insignificantly; permanent xerostomia or other safety-related toxicity did not occur. The estimated median survival was 29.4 weeks, which was significantly longer than survival in the historical best supportive care group.

c) PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{177}Lu-Labeled PSMA-617 (Kratochwil, Giesel et al. 2016):

The authors reported their experience with ^{177}Lu-PSMA-617-targeted radionuclide therapy in a case series of mCRPC patients resistant to other treatments. Patients were screened with either ^{99m}Tc-MIP1427 SPECT/CT (500-700 MBq) or ^{68}Ga-PSMA- 11 PET/CT (150 MBq ± 20%). 30 patients received 1 to 3 cycles of ^{177}Lu-PSMA-617 (3.7 to 6 GBq per cycle) at 2 months interval. While 21 had a PSA response, 13 had a >50% PSA decrease. After 3 cycles, 8 of the 11 patients achieved a sustained PSA response (>50%) for over 24 weeks, which also correlated with radiologic response (decreased lesion number and size). Acute hematological toxicity was mild. Diffuse bone marrow involvement was a risk factor for higher grade myelosuppression but could be identified by PSMA imaging in advance. Xerostomia, nausea, and fatigue occurred sporadically (<10%). Clearance of non-tumor-bound tracer was predominantly renal and widely completed by 48 hours. Safety dosimetry revealed kidney doses of approximately 0.75 Gy/GBq, red marrow doses of 0.03 Gy/GBq, and salivary gland doses of 1.4 Gy/GBq, irrespective of tumor burden and consistent on subsequent cycles. Mean tumor-absorbed dose ranged from 6 to 22 Gy/GBq during cycle 1.

Pre-therapeutic dosimetry of normal organs and tissues of 177Lu-PSMA-617 in CRPC (Kabasakal, AbuQbeitah et al. 2015):

Seven patients were screened after receiving 75–150 MBq of 68Ga-PSMA-11 intravenously. PET/CT images were acquired 45–60 min post-injection. All had intense tracer uptake at the lesions. They then received 177Lu-PSMA-617 activity ranged from 185 to 210 MBq with a mean of 192.6 ± 11.0 MBq. The highest radiation estimated doses were calculated for parotid glands and kidneys. Calculated radiation-absorbed doses per megabecquerel were 1.17 ± 0.31 mGy for parotid glands and 0.88 ± 0.40 mGy for kidneys. The radiation dose given to the bone marrow was significantly lower than those of kidney and parotid glands ($p < 0.05$). The calculated radiation dose to bone marrow was 0.03 ± 0.01 mGy/MBq.

Table 1: Calculated radiation-absorbed doses (mGy/MBq 177Lu-PSMA-617) of organs of each patient

Patient	Age	GS	PSA (ng/ml)	Parotid gland	Kidney	Bone marrow	Liver	Total body	Residence time (h)
1	65	8	48	1.66	0.76	0.025	0.27	0.049	24.6
2	62	9	110	0.96	1.66	0.048	0.46	0.094	46.3
3	57	8	19	0.94	0.98	0.037	0.23	0.058	49.4
4	65	7	89	1.48	0.52	0.021	0.25	0.035	27.6
5	63	9	235	1.07	0.69	0.058	0.34	0.098	62.0
6	65	9	78	1.25	1.03	0.030	0.22	0.057	26.5
7	70	8	19	0.80	0.51	0.022	0.18	0.036	28.7
Mean	63.9	8.3	85.4	1.17	0.88	0.034	0.28	0.061	37.9
SD	3.9	0.8	74.5	0.31	0.40	0.014	0.09	0.026	14.6

*GS Gleason score, PSA prostate-specific antigen

Table 2: Maximum amount of radioactivity (GBq) to reach radiation-absorbed dose limits

Patient	Parotid gland (30 Gy)	Kidney (23 Gy)	Bone marrow (2 Gy)	Liver (32 Gy)	Total Body (2 Gy)
1	18.1	30.4	79.6	116.4	41.2
2	31.1	13.8	41.9	69.7	21.4
3	31.8	23.5	54.2	137.6	34.6

4	20.3	44.0	95.7	126.3	57.0
5	28.0	33.2	34.3	95.0	20.3
6	24.0	22.4	66.0	142.4	34.9
7	37.5	44.9	89.7	181.3	56.2
Mean	27.2	30.3	65.9	124.1	37.9
SD	6.9	11.5	23.7	35.7	14.8

*Organ radiation-absorbed dose constraints in parentheses

d) ^{177}Lu-PSMA Radioligand Therapy of mCRPC: Safety and Efficacy (Baum, Kulkarni et al. 2016):

This study analyzed the safety and efficacy of the ^{177}Lu-labeled DOTAGA-based PSMA ligand ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) (^{177}Lu-PSMA) in patients with mCRPC. 56 patients were enrolled and treated with ^{177}Lu-PSMA. ^{68}Ga-PSMA-(N,N'-bis-[2- hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid) (^{68}Ga-PSMA) PET/CT was used for patient selection and follow-up after therapy. ^{177}Lu-PSMA demonstrated high absorbed tumor doses (median 3.3 mGy/MBq) compared with the levels in normal organs. Parotid glands received higher doses (1.3 mGy/MBq) than kidneys (0.8 mGy/MBq). All patients tolerated the therapy without any acute adverse effects. Except for mild reversible xerostomia in 2 patients, no long-term side effects were observed. A decrease in PSA levels was noted in 45 patients (80.4%). Of the 25 patients monitored for at least 6 months after 2 or more therapy cycles, ^{68}Ga-PSMA PET/CT revealed partial remission in 14, stable disease in 2, and progressive disease in 9 patients. Contrast-enhanced CT revealed partial remission in 5, stable disease in 13, and progressive disease in 7 patients. The median progression-free survival was 13.7 months, and the median overall survival was not reached during follow-up for 28 months.

Additional therapeutic studies using different radiolabled PSMA ligands are summarized in the table below:

Table 3: ^{117}Lu-PSMA-617: Pilot studies of targeted radionuclide therapy

Radioligand Therapy	N	Dose (GBq), Range	Total doses*	Reference
^{131}I-MIP-1095	28	2 – 7.2	1	Zechmann
^{177}Lu-DKFZ-PSMA-617	1	7.4	1	Kratochwil
^{177}Lu-PSMA-617	30	3.7 – 6	1-3	Kratochwil
^{177}Lu-PSMA I&T	56	3.6 – 8.7	1-5	Baum
^{177}Lu-PSMA-617	9	5.28 – 5.77	1	Hohberg
^{177}Lu-DKFZ-PSMA-617	5	3.4 – 3.9	2	Delker
^{177}Lu-DKFZ-PSMA-617	10	4.1- 6.1	1	Ahmadzedehfar
^{177}Lu-PSMA-617	7	5.5 - 7.4	1	Das
^{177}Lu-PSMA-617	23	7.4	1	Demir
^{177}Lu-PSMA-617	28	6	1-2	Rahbar
^{177}Lu-PSMA-617	31	1.1- 5.5	1-4	Yadav
^{177}Lu-PSMA I&T	1	8	1	Weineisen
^{177}Lu-PSMA I&T	22	3.4 – 7.4	1-4	Heck
^{177}Lu-PSMA-617	1	?	3	Schlenkhoff
^{177}Lu-PSMA-617	43	6	1-4	Zimbelmann
^{177}Lu-PSMA-617	5	5.8 – 7.4	1	Chakraborty

e) German collaborative publication

The largest published experience is a retrospective case series of 145 patients with mCRPC treated at 12 centers in Germany between February, 2014 and July, 2015.(Rahbar et al, J Nuc Med 2017) While not a prospective research study, in general the patients included men who had tumor progression despite abiraterone (64%) and/or enzalutamide (52%) and had either received chemotherapy (54%) or were unfit/refused chemotherapy. Patients also received radium-223 if able/eligible (17%). Treatment was administered only if PSMA uptake was demonstrated on PSMA imaging. On average, 5.9 GBq was administered per dose (range 2-8 GBq). Retreatment was allowed at physician discretion. Of assessable patients (n=99), 60% had PSA decline after initial treatment, with at least 50% PSA decline occurring in 40%. Safety was assess by retrospective chart review with charts available in all 145 and labs available in 121 (83.4%). Grade >2 hematologic AEs occurred in 12% (grade 3/4 anemia in 10%, grade 3/4 leukopenia in 3%, and grade 3/4 thrombocytopenia in 4%). Other AEs of any grade that occurred $\geq$4% include AST elevation 19%, fatigue 13%, renal failure 12%, ALT elevation 8%, xerostomia 8%, nausea 6%, dysgeusia 4%. While retrospective in nature, this represents the largest published series and demonstrates some biochemical anti-tumor activity without a high occurrence of high-grade adverse events.

2.4. Investigational Agent

During the last two decades, many efforts have been undertaken to develop PSMA-ligands(Hillier, Maresca et al. 2009, Barrett, Coleman et al. 2013). One of these ligands, the small molecule Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)], also known as PSMA-11®, PSMAHBED, Glu-CO-Lys(Ahx)-HBED-CC, DKFZ-PSMA-11, PSMA-HBED-CC,
PSMA-HBED, PSMA or Prostamedix™, developed at the German Cancer Research

Center Heidelberg (DKFZ), has become the most clinically used radiotracer. This compound shows a strong binding affinity to PSMA as well as a highly efficient internalization into PCa cells(Eder, Schafer et al. 2012, Eder, Neels et al. 2014). PET/CT-imaging with ^{68}Ga-PSMA-11 has demonstrated this novel method as an important imaging modality for diagnosing recurrent PCa(Afshar-Oromieh, Haberkorn et al. 2014, Afshar-Oromieh, Zechmann et al. 2014, Afshar-Oromieh, Avtzi et al. 2015, Eiber, Maurer et al. 2015). Perera et al., did systematic review of ^{68}Ga-PET articles and Sixteen articles involving 1309 patients were analyzed. On per-patient analysis, the summary sensitivity and specificity were both 86%. On per lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively(Perera, Papa et al. 2016).

Meanwhile modifications of PSMA-11 have resulted in the development of another novel small molecule PSMA-ligand, PSMA-617. In preclinical studies, this ligand showed a significantly improved binding affinity to PSMA as well as a highly efficient internalization into PCa cells(Benesova, Schafer et al. 2015). PSMA-617 can be labeled with radionuclides like ^{68}Ga(Gallium-68), ^{177}Lu(Lutetium-177), ^{111}In(Indium-111), and ^{90}Y(Yetrium-90) and, therefore, be used for PET-imaging as well as for radioligand-based therapy. Preclinical assays of PSMA-617 showed Ki values of 2.3 ± 2.9 nM, demonstrating a significant improvement compared to PSMA-11 (12.0 ± 2.8 nM). Based on these results, PSMA-617 has one of the highest binding affinities to the PSMA receptor, which have been published, so far. In preclinical studies, tumor-to-background ratios of up to 1,058 were observed at 24h post infusion. In addition, the internalization of the PSMA-617 into the PCa cells is highly effective: Internalized fraction: 17.67 ± 4.34 % IA/106 LNCaP cells (PSMA-11: 9.47 ± 2.56 % IA/106 LNCaP cells)(Eder, Schafer et al. 2012, Benesova, Schafer et al. 2015). Since 2013, ^{177}Lu-PSMA-617 has been increasingly used for radioligand therapy of metastatic PCa patients in several centers (Bad Homburg, Bonn, Cologne, Freiburg, Heidelberg, Istanbul, Melbourne, LMU Munich, Münster)(Kratochwil, Giesel et al. 2015).

Diagnostic evaluation with ^{68}Ga-PSMA-HBED-CC followed by therapy with ^{177}Lu-PSMA-617 is thus opening a new theranostic potential of nuclear medicine. Initial studies in patients have demonstrated the utility of ^{177}Lu-PSMA-617 for the treatment of disseminated prostate cancer(Ahmadzadehfar, Rahbar et al. 2015, Kratochwil, Giesel et al. 2015). Dosimetric evaluation has shown that the critical organs are the parotid glands, and that up to 27 GBq (~700 mCi) of ^{177}Lu-PSMA-617 can be administered without crossing the 30 Gy critical dose threshold to the parotid glands(Kabasakal, AbuQbeitah et al. 2015).

2.5. Rationale

A. Rationale for the appropriate radioisotope:

As described earlier, targeted radionuclide therapy as a treatment choice for mCRPC patients is being actively studied at various centers in the world (especially Europe and Australia). When compared to monoclonal antibodies, the low molecular weight compounds have a higher permeability into solid tumors, offer a significant advantage in achieving higher tumor uptake as well as a high percentage of specific binding. Additionally, small molecules display more rapid tissue distribution and faster blood clearance compared with intact immunoglobulins. These properties often lead to an enhanced target to non-target tissue ratio, which is important not just for imaging but also for successful application of therapeutic absorbed doses.

Following tumor localization, the radiometal is trapped within the cell, leading to higher accretion of radionuclide by the tumor. ^{131}I has lower energy β□particles and longer physical half-life (max β^- 0.61 MeV; $T_{½}$ = 8.04 d) compared to that with ^{90}Y(max β^- 2.28 MeV; $T_{½}$ = 2.67 d). Because of its higher energy, ^{90}Y may be appropriate for larger tumors while ^{131}I may be more cytotoxic for smaller, micro-metastatic lesions. Since ^{90}Y does not emit any γ photons, the corresponding ^{111}In labeled antibodies are generally used as chemical and biological surrogates to study biodistribution and estimate radiation dosimetry of ^{90}Y labeled antibodies. In addition to ^{90}Y, the lanthanide radiometal, ^{177}Lu (max β^- 0.497 MeV; $T_{½}$ = 6.74 d) is potentially useful for RIT. Also ^{177}Lu has useful gamma photons (γ = 0.21 MeV) for biodistribution and dosimetry studies. Therefore, ^{177}Lu may have the advantages of both ^{131}I and ^{90}Y and may be the most appropriate radionuclide for therapy. Type of radiation and energy associated with some of the prevalent radioisotopes is summarized in the table hereunder:

Table 4: Radionuclides for Therapy

Radioisotope	$T_{½}$		E. Max	Range Max
	Hours	Emission	KeV	mm
I-131	193	β^-	610	2.9
		γ	364	
Lu-177	162	β^-	498	2.0
		γ	208	
Y-90	64	β^-	2250	11.0
Bi-213	0.76	α	8400	0.1
		γ	440	
At-211	7.2	α	5870 & 7450	0.055-0.08
		X-	77-92	
Ac-225	240	α		
		γ		
Ra-223	273.6	α	5871	
Th-227	449	α		
		γ		

B. Rationale for Dose-Fractionated regimen:

Pre-clinical models do not always predict toxicity in humans, but based upon the available data, the pre-clinical models combined with animal and human dosimetry data have predicted the toxicity seen with anti-PSMA radioimmunotherapy (i.e. radiolabeled monoclonal antibody) and anti-PSMA radioligand therapy (i.e. radiolabeled peptides).
With radioimmunotherapy, one would predict that the dose-limiting organ is bone marrow, based upon the kinetics / circulation time and exposure of the bone marrow to circulating radiolabeled antibody before it gets into tumors days later. With radioligand therapy, one would predict that there is comparatively very little bone marrow exposure, but there would be more exposure to sites of PSMA expression that are not exposed to (bulky) full-length antibodies. Based upon the available data, this has been born out in human subjects (for radioimmunotherapy) and human patients (for radioligand therapy).

We have conducted a series of overlapping, but sequential phase I and II clinical trials evaluating radiolabeled anti-PSMA monoclonal antibody J591. These studies are summarized immediately below with additional details about dose-fractionation (as requested) following the summary.

- Initial (1st in human) studies of trace-labeled ^{111}In-DOTA-J591: demonstrated safety and targeting of J591 in men with mCRPC (Bander 2003, Nanus 2003, Morris 2005)
- Phase I (single-dose) ^{90}Y-J591: demonstrated safety, targeting, and preliminary
- Phase I (single-dose) ^{177}Lu-J591: demonstrated safety, targeting, and preliminary efficacy in mCRPC (Bander 2005)
- Phase II (single dose) ^{177}Lu-J591: demonstrated efficacy in initial 32 subjects, subsequent analysis with significant dose-response and preliminary biomarkers (Tagawa 2008)
- Phase I fractionated-dose ^{177}Lu-J591 dose-escalation study: demonstrated safety, confirming hypothesis that higher cumulative doses could be administered as a split dose (Tagawa 2010)
- Phase II (single dose) ^{177}Lu-J591 expansion phase: confirmed efficacy and dose-response with exploratory biomarkers (Tagawa 2013)
- Phase I fractionated-dose ^{177}Lu-J591 plus docetaxel: demonstrated the ability to safely combine fractionated ^{177}Lu-J591 with docetaxel 75 mg/m^2 in men with mCRPC (Tagawa 2014)
- Phase I fractionated-dose ^{177}Lu-J591 expansion phase: provided efficacy data, confirmed dose-response, continued analysis of exploratory biomarkers (Tagawa 2016)

Taken together, with >250 patients treated on these sequential clinical trials, we have

drawn the following conclusions: (i) there is a clear dose-response with more responses and longer survival at higher doses; (ii) there is clear dose-toxicity response in terms of myelosuppression (which is both predictable and reversible); (iii) dose-fractionation allows higher cumulative dose with comparatively less toxicity (including allowing concurrent chemotherapy); and (iv) without pre-selection for PSMA expression, approximately 90% have accurate tumor targeting, though the small minority with low/no PSMA expression by imaging have a lower likelihood of response. While ^{177}Lu-J591 mAb demonstrated significant efficacy, the major limitation in the optimization of therapeutic dose is the hematological toxicity (described in greater detail below).

With a single-dose, 70 mCi/m^2 of ^{177}Lu-J591 was the MTD, with dose-limiting myelosuppression in those receiving 75 mCi/m^2 (with 2 of 3 with dose-limiting hematologic toxicity).[Bander 2005] In the phase II study, this was confirmed with 70 mCi/m^2 of ^{177}Lu-J591 being tolerable with reversible myelosuppression, but with a significant amount of manageable grade 4 myelosuppression (including approximately 40% platelet transfusion).[Tagawa 2013]

In radiotherapy, the anti-tumor response has been thought to be primarily due to induction of apoptosis by radiation (Meyn 1997, Mirzaie-Joniani 2002, Kroger 2001, DeNardo 2002). However, the degree of anti-tumor response following the administration of targeted radionuclides depends on several variables, especially total (cumulative) radiation dose to the tumor, dose-rate and tumor radiosensitivity. Single-agent RIT, although potentially useful for slowing solid tumor growth, has not been effective in controlling aggressive tumors, which often have p53 and other mutations and are less susceptible to apoptosis, the apparent mechanism of cell death from low dose-rate radiation.(Burke 2002) Bone marrow is the dose-limiting organ in RIT in the absence of marrow reconstitution.(Larson 2015, Ali 2016) Dose-fractionation is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose-rate.(DeNardo 2002, Shen 2002, O'Donoghue 2000) The main reason for using dose fractionation is to take advantage of the difference between early-responding and late-responding tissues. The radiation effect on early-responding tissue can be reduced by prolonging the treatment time and dose fractionation. The radiation effect on late-responding tissues will not be changed significantly if the total dose is not changed.(DeNardo 2002, O'Donoghue 2000) Preclinical data have shown that dose fractionation or multiple low dose treatments can decrease toxicity while increasing the efficacy.(Kroger 2001, Vriesendorp 1993, Buchsbaum 1995) Similarly, there is some clinical evidence that bone marrow toxicity can be reduced with some modest increase in the cumulative maximum tolerated dose.(DeNardo 1998, Steffens 1999, Hindorf 2003) Based upon these data, we performed two sequential studies of fractionated dose ^{177}Lu- J591.

As described in in the paragraph above, dose-fractionation of external-beam radiation as well as radioimmunotherapy has been demonstrated to have less toxicity and might be more efficacious by delivering active radiation over a more prolonged period of time to

tumor cells. Based upon the half-life of ^{177}Lu-J591 combined with the kinetics of radiolabeled intact monoclonal antibody, we chose a 2-week interval between ^{177}Lu-J591 doses:

i) Phase I trial of fractionated dose ^{177}Lu–J591 in men with metastatic castration–resistant prostate cancer (Tagawa et al 2010, Tagawa et al 2016)

Men with progressive metastatic CRPC received 2 fractionated doses two weeks apart. Initially, 6 cohorts of 3-6 pts got 2 doses of 177Lu-J591 2 weeks apart (20 mCi/m2, escalating to 45 mCi/m2 x2). Subsequently, pts enrolled in 2 expansion cohorts at the recommended phase 2 doses (RP2D). Planar 177Lu-J591 imaging was semi- quantitatively scored. The endpoints were PSA changes and survival (OS); as well as CTC count (CellSearch) changes in the expansion cohorts. 49 patients, with median age 74.1 years (range 55-95), median PSA of 44.9 ng/mL (1.9-766.5); 83.7% with bone, 61.2% with lymph node, 40.8% with visceral metastasis. 8.2% were CALGB (Halabi) low, 34.7% were intermediate, 57.1% were in high-risk group. RP2D's of fractionated 177Lu-J591 were 40 mCi/m2 x2 or 45 mCi/m2 x2 with option for GCSF. PSA changes for the low dose group were reported as 6.3% showing >50% PSA decline, 12.5% reporting >30% PSA decline, and 37.5% with any PSA decline. within RP2D group 21.2% showing >50% PSA decline, 42.4% reporting >30% PSA decline, and 66.7% with any PSA decline. The median overall survival for low dose group was 14.6 months and for RP2D group was 27.7 months. Accurate targeting of 177Lu-J591 was seen in 79.6%. Patients with lower PSMA expression by imaging were less likely to respond (p=0.07). Of 25 with CTC counts, 14 declined, 8 stably favorable, and 3 increased. RP2D was associated with more PSA declines (p=0.036) and longer OS (p=0.004), even after controlling for CALGB prognostic grouping (adjusted HR 0.42 [95% CI 0.21, 0.84] p=0.01). Predictable, reversible myelosuppression was seen. 36 (73.5%) patients had grade 3/4 heme toxicities; 19 (57.6%) had Grade 4 heme toxicities in RP2D cohorts with 45.4% receiving prophylactic platelet transfusions (median 1, range 1-4) and 6 GCSF. 14 (28.6%) had infusion reactions (without pre-meds), with 1 patient having Grade 2 infusion reaction leading to withdrawing from the study prior to his 2nd dose. 5 (10.2%) had transient Gr 1/2 AST/ALT. This study concluded that fractionated 177Lu–J591 is well tolerated with predictable, reversible myelosuppression and PSA and CTC declines. Additionally, with dose-fractionation, the cumulative dose MTD is 14–28% higher than single dose MTD with similar toxicity.

Table 5: Toxicities data from Phase 2 single dose 177Lu-J591 Study and Phase 1 fractionated 177Lu-J591 study:

	Single Dose		Fractionated Dose		
Cumulative Dose (mCi/m^2)	65	**70**	**70** (35 + 35)	80 (40 + 40)	90 (45 + 45)

Platelets Grade 4	27%	56.3%	40%	50%	58.8%
Platelet Transfusion	7%	41%	0%	31.3%	52.9%
Neutropenia Grade 4	0%	37.5%	0%	31.3%	29.4%
Febrile Neutropenia	0%	2.1%	0%	0%	5.8%

In addition, fractionated dosing allowed concurrent dosing with myelosuppressive chemotherapy:

ii) Phase I trial of fractionated dose ^{177}Lu–J591 plus docetaxel/prednisone in men with metastatic castration–resistant prostate cancer (Tagawa et al 2014, Batra et al 2015):

Following progression on primary hormonal therapy, chemotherapy can offer symptomatic improvement as well as incremental survival benefit. However, responses are transient and all men eventually suffer from progression of disease as described above with single–agent anti–PSMA based radioimmunotherapy. The combination of taxane chemotherapy with radiotherapy has been used in several diseases because of the radiosensitizing effects of taxane–based chemotherapy. In addition to favorable results from fractionated RIT and the radiosensitizing effects of taxane–based chemotherapy, it is hypothesized that the additional debulking by chemotherapy will overcome some of the limits imposed by the physical characteristics of ^{177}Lu. Based upon this theory, a phase I trial of docetaxel and prednisone with escalating doses of fractionated ^{177}Lu–J591 was initiated. 15 men with median age 69.1 (49.3-80.8) were enrolled. The MTD/RP2D of ^{177}Lu-J591 was 40 mCi/m^{2}x2 doses (delivered with cycle 3 of docetaxel), with 73.3% showing >50% PSA decline, 80.0% reporting >30% PSA decline, and 86.7% with any PSA decline. Predictable, reversible myelosuppression was seen. Even at the highest dose level, no dose limiting toxicity was observed, with short-term / reversible grade 4 neutropenia in 33% and grade 4 thrombocytopenia in 13%.

Aside from the overall rates of dose limiting toxicity, the combined studies have also consistently demonstrated the kinetics of myelosuppression, with nadir neutrophil and platelet counts 28-32 days following the last administered dose of ^{177}Lu-J591.

With small-molecule radioligand therapy, both the predicted and reported toxicities are much different. One would predict very little myelosuppression, but if it were to occur, it would be expected to have kinetics similar to (or more quickly than) typical cytotoxic chemotherapy, as the clearance of the myelotoxic drug is quick (minutes to hours rather than days to weeks for antibodies). In fact (with the known caveats of retrospective studies), this is the reported human experience. Essentially no grade 4 neutropenia or

thrombocytopenia has been reported within months of exposure to ^{177}Lu-PSMA radioligands (see details below).

While we have published on the long-term follow up with ^{177}Lu-J591 with no cases of attributable permanent myelosuppression and/or myelodysplasia/leukemia, results are unknown with ^{177}Lu-PSMA RLT. The available data with up to 6 months of reported post-treatment follow up are:

1. No attributable grade 4 hematologic (or other) toxicity has been reported at any time (the one case of grade 4 thrombocytopenia is reported with a patient with grade 4 platelet count at pre-treatment baseline)
2. Repeat dosing has been performed in many patients at 8-12 weeks after initial dosing and in all cases, white blood cell count and platelet counts were acceptable prior to subsequent doses (up to 5 doses, with dose #5 approximately 40 weeks after dose #1)

The Table below is a summary of the prior summary anti-PSMA RLT Table which includes the severe leukocyte/neutrophil and platelet count rates following 177Lu-radiolabeled anti-PSMA peptides. In addition to the Table, a multicenter review of 177Lu-PSMA-617 data of 82 patients receiving at single dose (mean 5.9 GBq) revealed no grade 4 hematologic or non-hematologic toxicity.[Rahbar et al, J Nucl Med 2016]

Table 6: Toxicities data following anti-PSMA radioligand therapy

Radioligand Therapy	N	Dose (GBq), Range	Total doses	Grade 4 neutropenia	Grade 4 platelets	Reference
^{177}Lu-PSMA-617	30	3.7 – 6	1-3	0	0*	Kratochwil et al 2015
^{177}Lu-PSMA I&T	56	3.6 – 8.7	1-5	0	0	Baum et al 2016
^{177}Lu-PSMA-617	9	5.28 – 5.77	1	NR	NR	Hohberg et al 2016
^{177}Lu-DKFZ-PSMA-617	5	3.4 – 3.9	2	NR	NR	Delker et al 2015
^{177}Lu-DKFZ-PSMA-617	10	4.1- 6.1	1	0	0	Ahmadzedehfar et al 2016
^{177}Lu-PSMA-617	7	5.5 - 7.4	1	NR	NR	Das et al 2016
^{177}Lu-PSMA-617	23	7.4	1	NR	NR	Demir et al 2016
^{177}Lu-PSMA-617	28	6	1-2	0	0	Rahbar et al 2016
^{177}Lu-PSMA-617	31	1.1- 5.5	1-4	0	0	Yadav et al 2016
^{177}Lu-PSMA I&T	2	5.7 - 8	1	0	0	Weineisen et al 2015

^{177}Lu-PSMA I&T	22	3.4 – 7.4	1-4	0	0	Heck et al 2016
^{177}Lu-PSMA-617	43	6	1-4	0	0	Zimbelmann et al 2016
^{177}Lu-PSMA-617	5	5.8 – 7.4	1	0	0	Chakraborty et al 2016

*One patient had pre-treatment baseline platelet count of grade 4
NR = not reported

A dose fractionated regimen provides the theoretic benefit of higher cumulative radiation dose to the target tissue/organ while limiting toxicities secondary to non- specific binding of the radiolabeled ligand. In addition to the toxicity data provide above, our group has consistently seen evidence of dose-response (see Table below), justifying a dose-escalation study.

Group	N	Any PSA decline	≥30% PSA decline	> 50% PSA decline	Median OS mo [95% CI]*
Total	49	55.1%	32.7%	16.3%	22.9 [16.2, 29.7]
Low doses	16	37.5%	12.5%	6.3%	14.6 [9.9, 19.4]
RP2D	33	66.7%	42.4%	21.2%	27.7 [15.8, 39.6]
40 x2 cohort	16	50.0%	25.0%	12.5%	19.6 [9.1, 30.2]
45 x2 cohort	17	87.5%	58.8%	29.4%	48.3 [16.0, 80.6]

2.6. Risk/Benefit Assessment

Based on findings by groups based in Europe, the most common toxicities reported are leukopenia, anemia, thrombocytopenia, transaminitis, fatigue, renal failure, and xerostomia. All of these toxicities are reportedly mild and transient. mCRPC patients treated with RIT using ^{177}Lu-PSMA-617 have shown improved survival.

2.7. Correlative Studies Background

2.7.1. Archival tissue and Cell-Free plasma DNA to assess genomic alterations:

PC is a clinically heterogeneous disease, with marked variability in patient outcomes. Defining the genomic alterations in PC has improved classification of tumors: 50% harbor TMPRSS2-ERG gene fusion, and ERG+ and ERG- classes of prostate cancer are recognized as distinct biological entities. Recently described were mutations in SPOP in up to 15% of PC, and SPOP mutations define a novel, ERG- molecular subclass of PC. The ERG+ and SPOP mutant subclasses of PC remain relevant, at roughly similar frequencies, in advanced disease. These findings raise the possibility that PC could transition from a poorly understood, clinically heterogeneous disease to a collection of homogenous subtypes, identifiable by molecular criteria, associated with distinct risk profiles, and potentially amenable to specific therapeutic strategies. In PC models, ERG expression results in relative resistance to ionizing radiation.

Conversely, preliminary data from our collaborators has shown that SPOP mutant prostate cancers show increased genomic instability, that SPOP plays a role in double strand DNA break repair, and SPOP mutations result in increased sensitivity to DNA damage. Finally, PC with other specific defects in DNA repair genes (such as BRCA2) have also been shown to be preferentially sensitive to DNA damaging therapy. Therefore, distinct molecular phenotypes of prostate cancer may have predictable and exploitable differences in sensitivity to DNA damaging agents such as Lutetium-177. We will collect archival tumor tissue (preferentially from metastatic biopsies) plus a single-sample of blood for germline control with the plan for utilization of our CLIA- approved whole exome platform.(Beltran 2012, Beltran 2015, Beltran 2016) In addition, we will collect samples for cfDNA analysis prior to treatment, at 1 month, and at 3- months, using the platform developed in collaboration with others as part of a PCF Challenge Award and other studies.(Beltran 2016, Romanel 2015, Carreira 2014) As discussed below, we will describe findings from this exploratory endpoint in this study with the plan to analyze these findings with relationship to efficacy and toxicity across current and prior studies, in particular at doses found to have efficacy.

2.7.2. CTC Count:

Circulating tumor cell (CTC) counts via the CellSearch platform were demonstrated to be prognostic in men with advanced prostate cancer prior to systemic therapy and a "conversion" from an unfavorable count ($\geq$5 CTCs/7.5 mL) was associated with a median similar to those starting with favorable counts, leading to clearance of this particular test by the FDA (de Bono, Scher et al. 2008). More recently, the combination of CellSearch CTC enumeration and serum LDH have been demonstrated to have prognostic value, meeting Prentice criteria for survival surrogacy in the setting of abiraterone/prednisone treatment in men with mCRPC previously treated with docetaxel (Scher, Heller et al. 2015)

2.7.4 Immune assays

While there are only a selected number of prospectively performed studies of PSMA-targeted radionuclide therapy, it is clear that there are a subset that respond well for a durable period of time (i.e. "the tail of the curve") and those that do not respond or have PSA declines for a short period of time. It has been proposed that radiation may generate immune responses with an abscopal response documented. As in most cases, PSMA-targeted radionuclide therapy successfully targets (by imaging) all known sites of disease, an abscopal response is difficult to document. However, sublethal doses of radiation may still well generate an immune response. We plan to study this effect with assays of immunogenic cell death and antigen spread. We will assess immunogenic cell death by assessing high mobility group box 1 (HMGB1) in serum and

calreticulin on CTCs. We will also collect serum and assay antigen spread by comparing pre-treatment to post-treatment with cancer-associated protein microarrays.

2.7.5 Molecular imaging:

While there is an increasingly large body of clinical data for PSMA PET imaging (above), reproducibility of imaging has not been well studied in a test—retest format.

3. SUBJECT SELECTION

3.1. Study Population

Subjects who have documented progressive metastatic CRPC disease, who meet the inclusion and exclusion criteria will be eligible for participation in this study.

3.2. Inclusion Criteria

1. Histologically or cytologically confirmed adenocarcinoma of prostate

2. Documented progressive metastatic CRPC based on Prostate Cancer Working Group 3 (PCWG3) criteria, which includes at least one of the following criteria:
   - PSA progression
   - Objective radiographic progression in soft tissue
   - New bone lesions

3. ECOG performance status of 0-2

4. Have serum testosterone ≤ 50 ng/dL. Subjects must continue primary androgen deprivation with an LHRH/GnRH analogue (agonist/antagonist) if they have not undergone orchiectomy.

5. Have previously been treated with at least one of the following in any disease state:
   - Androgen receptor signaling inhibitor (such as enzalutamide)
   - CYP 17 inhibitor (such as abiraterone acetate)

6. Have previously received taxane chemotherapy (in any disease state), been determined to be ineligible for taxane chemotherapy by their physician, or refused taxane chemotherapy.

7. Age ≥ 18 years

8. Patients must have normal organ and marrow function as defined below:

○ Absolute neutrophil count	≥2,000 cells/mm^3
○ Hemoglobin	≥9 g/dL
○ Platelet count	≥150,000 x $10^9/\mu L$
○ Serum creatinine	≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min/1.73 m^2 by Cockcroft-Gault
○ Serum total bilirubin	≤1.5 x ULN (unless due to Gilbert's syndrome in which case direct bilirubin must be normal
○ Serum AST and ALT	≤3 x ULN in absence of liver metastases; < 5x ULN if due to liver metastases (in both circumstances bilirubin must meet entry criteria)

9. Ability to understand and the willingness to sign a written informed consent document.

3.3. Exclusion Criteria

1. Implantation of investigational medical device ≤4 weeks of Treatment Visit 1 (Day 1) or current enrollment in oncologic investigational drug or device study
2. Use of investigational drugs ≤4 weeks or <5 half-lives of Cycle 1, Day 1 or current enrollment in investigational oncology drug or device study
3. Prior systemic beta-emitting bone-seeking radioisotopes
4. Known active brain metastases or leptomeningeal disease
5. History of deep vein thrombosis and/or pulmonary embolus within 1 month of C1D1
6. Other serious illness(es) involving the cardiac, respiratory, CNS, renal, hepatic or hematological organ systems which might preclude completion of this study or interfere with determination of causality of any adverse effects experienced in this study
7. Radiation therapy for treatment of PC ≤4 weeks of Day 1 Cycle 1

8. Patients on stable dose of bisphosphonates or denosumab, which have been started no less than 4 weeks prior to treatment start, may continue on this medication, however patients are not allowed to initiate bisphosphonate/Denosumab therapy during the DLT-assessment period of the study.

9. Having partners of childbearing potential and not willing to use a method of birth control deemed acceptable by the principle investigator and chairperson during the study and for 1 month after last study drug administration

10. Currently active other malignancy other than non-melanoma skin cancer. Patients are considered not to have "currently active" malignancy if they have completed any necessary therapy and are considered by their physician to be at less than 30% risk of relapse.

11. Known history of known myelodysplastic syndrome

4. OVERVIEW OF STUDY DESIGN AND METHODOLOGY

4.1. Study Design

This is an open−label, single−center Phase I dose escalation trial designed to determine the cumulative MTD in a dose fractionation regimen in which ^{177}Lu-PSMA-617 will be given in 2 doses, 2 weeks apart. The dose escalation will start at 100 mCi (3.7 GBq) x 2 doses and escalate in increments of 50 mCi (1.85 GBq) for each dose to a maximum of 300 mCi (11.1 GBq) x 2 doses.

Patients must have documented progressive metastatic CRPC disease based on Prostate Cancer Working Group 3 (PCWG3) criteria in order to be eligible for enrollment. Upon meeting the inclusion and exclusion criteria and signing the informed consent and HIPPA form, subjects will undergo the screening. As part of the screening, subjects will get a single dose of ^{68}Ga-PSMA-HBED-CC and will have a PET/CT. Nuclear Medicine physician(s) will review the PET/CT scans to document PSMA expression at tumor site(s).

^{177}Lu-PSMA-617 dose fractionation regimen will be performed in patients with documented progressive metastatic CRPC. The ^{177}Lu dose **(50 mCi – 300 mCi or 1.85 – 11.1 GBq)** will be escalated in up to 6 different dose levels (3+3 at each dose level). Initially 3 subjects will be enrolled in Cohort 1 (100 mCi or 3.7 GBq x2 doses 2 weeks apart) and if any grade ≥3 toxicity is reported, then the next 3 subjects will be enrolled

in Cohort -1 (50 mCi or 1.85 GBq x2 doses 2 weeks apart) before proceeding to higher dose cohorts. Subjects will have Lutetium-177 Planar/SPECT Imaging on Day 8 (±1day) after the first dose of ^{177}Lu-PSMA-617. Optimal images will be performed on selected consenting subjects between initial treatment on D1 and D4 and prior to treatment #2 on D15. The enrollment ceiling of the dose escalation portion of the study is up to 46 study participants (six groups, with 3+3 subjects in each group). Each patient would receive 2 doses of the investigational agent, 2 weeks apart. The total dose received in 2 treatments will be **100 – 600 mCi (3.7 – 22.2 GBq)**.

Upon completion of investigational treatment with 2 doses of ^{177}Lu-PSMA-617, subjects will undergo ^{68}Ga-PSMA-HBED-CC injection and same day PET/CT at the end of study visit to document treatment response. Subsequently survival data and additional treatment(s) information will be captured from their routine Standard of care (SOC) visits.

Table 7: Treatment Plan with ^{177}Lu-PSMA-617

Cohort	Treatment Dose mCi (GBq)		Total	Dose	Subjects
	Day 1	Day 15	mCi (	GBq)	(n)
-1	50 (1.85)	50 (1.85)	100 (	3.7)	1-6
1	100 (3.7)	100 (3.7)	200 (	7.4)	1-6
2	150 (5.55)	150 (5.55)	300 (	11.1)	1-6
3	200 (7.4)	200 (7.4)	400 (	14.8)	3-6
4	250 (9.25)	250 (9.25)	500 (	18.5)	3-6
5	300 (11.1)	300 (11.1)	600 (	22.2)	3-6

4.2 Rationale for Dose-Escalation Strategy:

This study will use a modified phase I 3+3 dose-escalation study design, with the planned initial and subsequent cohorts described in Table 7. This study design is well-described and accepted by the clinical and scientific community, so we will not provide complete details here. Briefly, this design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. Given the fact that some pre-existing clinical efficacy and toxicity data exists with the study drug, we will allow up to 6 subjects to be treated at a given dose-level even in the absence of DLT. The MTD is defined as the highest dose level with an observed incidence of DLT in no more than one out of six patients treated at a particular dose level. The dose escalation scheme provides the following probabilities of escalation based on the true chances of DLT at a specific dose level. One can see that the probability of escalation is high if the toxicity risks are low:

True Probability of Toxicity:	.05	.10	.20	.30	.40	.50	.60
Probability of Escalation:	.97	.91	.71	.49	.31	.17	.08

As there is a reasonably large pool of short- and long-term experience with PSMA-directed 177Lu, we will transition to a phase II cohort will be enrolled at the MTD/RP2D to gain additional safety data as well as preliminary efficacy data. We will enroll up to 27 subjects in the Phase II trial utilizing a Simon two-stage design (including the 3-6 patients used for establishing the MTD). For the phase II portion, we will define evaluable patients as those who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or withdrawal. Sample size recommendations for the two-stage design are determined according to Simons two-stage minimax design. The first stage will accrue a total of 16 patients (including those who were treated at the MTD in the phase I portion), if 6 or fewer of the first 16 evaluable patients do not experience a 30% decline in PSA, the study will be terminated and declared to have a negative result. If 7 or more patients out of the first 16 evaluable patients experience a 30% decline in PSA, 9 more patients will be accrued in Stage 2 (total sample size of 27). The new regimen will be declared to have activity and be worthy of further testing if 13 or more patients experience a 30% PSA decline among the 27 patients who are part of the phase II trial.

5. REGISTRATION PROCEDURES

5.1. Identification of subjects:

Patients diagnosed with documented progressive metastatic CRPC disease who

are visiting Oncology Clinic at NYPH-Cornell Campus for their standard of care visit, will be approached for recruitment for this study. Investigators or delegates under their direct supervision may perform pre–screening of these potential subjects.

5.2. Consent process

Potential subjects will have a discussion with the investigator/delegate including the rationale for the study, investigational nature of the protocol and study drug and the voluntary nature of participation, potential risks and benefits, alternatives to participation, and study procedures. Individuals will have the opportunity to read the written informed consent document at their leisure (preferably outside of the clinical area for > 1 day) and the opportunity to have questions answered in a private location with the understanding that should they decide not to participate, they will still be able to receive any available standard of care therapy. Potential subjects will also have the opportunity to obtain the advice of their treating physician. Investigators or delegates under their direct supervision will verify the subject's understanding of the investigational and voluntary nature of the study, the potential risks and benefits, study procedures, and alternatives prior to signing of the written informed consent.

5.3. Central Patient Registration

Subjects will be assigned a sequence number for the protocol and will be centrally registered with the Weill Cornell Medicine (WCM), Division of Hematology and Medical Oncology Clinical Research Office with the following documents:

- WCM Patient registration form
- First and last page of the fully executed informed consent form (including HIPPA), plus additional pages if checkboxes for correlative studies are required.
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Entry of screening information into WCM web–based system

Central registration information is reviewed and entered into the HemOnc centralized research database. Documentation of patient registration will be confirmed prior to release of study agent by nuclear medicine.

6. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section can only be performed after obtaining informed consent.

All on–study visits and dosing should be scheduled from Day 1 (date of the first infusion) on the study. It is very important that protocol procedures are performed at the time–points stipulated below. When it is not possible to perform the study visit at the exact time–point, the visit maybe performed within the acceptable visit window as defined in the visit–specific section below.

After obtaining informed consent from the enrolled subject(s), screening and study related treatment procedures will be performed as outlined in Table 8 and described in detail in Section 6.1.

7. Schedule of Evaluations Table 8: Schedule of trial events:

	Screening	Treatment Visit 1 (Day 1)	Imaging visit (Day 8±1)	Treatment Visit 2 (Day 15 ±1)	F/U Visit 1 (Day 22±3)	F/U Visit 2 (Day 29 ±3	F/U Visit 3 (Day 43 ±3)	F/U Visit 4 (Day 57 ±3)	F/U Visit 5 (Day 71 ±3)	Scan Visit (Day 85±7)	Short-Term F/U[k]	Progression	Long-Term F/U
Informed Consent	x												
Demographics	x												
Medical History	x	x	x	x	x	x		x		x	x	x	
Physical Exam	x	x	x	x	x	x		x		x	x	x	
Performance Status	x	x	x	x	x	x		x		x	x	x	
Vital Signs[a]	x	x	x	x	x	x		x		x	x	x	
PRO[l]	x	x	x	x	x	x		x		x	x[l]	x	
CBC with diff, plts[b]	x	x	x	x[c]	x	x	x	x	x	x	x	x	
Serum Chemistry[d]	x	x	x	x	x	x	x	x	x	x	x	x	
PSA	x	x		x		x		x		x	x	x	
LDH		x		x		x		x		x	x	x	
Testosterone	x									x		x	
CTC Count[e]	x	x[e]								x			
CTC for Research[f]	x	x[f]								x			
Cell-Free DNA Research sample[g]	x	x[g]								x		x	

Immune research sample[m]	x	x[m]								x			
^{68}Ga-PSMA infusion & PET CT[n]	x									x			
Radiographic evaluation[h]	x									x	x[h]		x[h]
^{177}Lu-PSMA-617 infusion		x		x									
^{177}Lu-PSMA-617 Planar/SPECT imaging[i]			x[i]	x[i]									
Archival Tissue	x												
Adverse Event Monitoring		x	x	x	x	x		x		x	x	x	
Concurrent Medications	x	x	x	x	x	x		x		x	x	x	
Survival Assessment[j]												x	x

a: Vital signs will include height and weight during screening and at least weight thereafter

b: Any subject with grade >2 neutropenia or thrombocytopenia at any time point will be followed at least weekly until resolution to grade 1

c: Any subject with grade ≥2 neutropenia or thrombocytopenia at Treatment Visit 2 will initially not be eligible to receive the second ^{177}Lu-PSMA-617 injection. The dose will be held until the toxicity has resolved to grade 1 for a maximum of 2 weeks. If the toxicity has not resolved after 2 weeks, the dose will be discontinued.

d: CMP (with direct bilirubin in subjects with known Gilbert's syndrome)

e: CTC enumeration via CellSearch methodology may be obtained during screening or prior to Treatment Visit 1

f: CTC collection for research purposes may be performed during screening or prior to Treatment Visit 1: two 2.3% sodium citrate "light blue top" tubes (5.4 mL whole blood)

g: Cell-Free DNA BCT® may be obtained during screening or prior to Treatment Visit 1 and will be whole blood collection in a tube intended for collection, stabilization and transportation of cell-free plasma DNA. 10 mL tube will be used for collecting whole blood for research purposes

h: Radiographic evaluation will include bone scan, CT/MRI of abdomen/pelvis, and Chest x-ray (CXR waived if CT/MRI includes chest). Following mandatory repeat imaging with Scan/Efficacy visit, continued repeat imaging is recommended approximately 12 weeks until radiographic progression as part of standard care.

i: Planar/SPECT imaging one week after the ^{177}Lu-PSMA-617 1st dose infusion in all subjects. Optional imaging will be performed on consenting subjects betweenTreatment Visit 1 (Between D2-D4) or prior to Treatment Visit 2 (D15 ±1).

j: Survival assessment and relevant medical history to be collected until death

k: Short-term follow up to be completed q4 weeks following the scan visit until 6 months from the 1st treatment visit. Subjects who are progression-free at 6 months will continue with q4-week labs and q12-week standard imaging per guidelines (as in h above).

l: PRO = patient reported outcomes = BPI-SF and FACT-P; to be performed at time points specified during treatment phase, then q12 weeks (at imaging time points) during short-term follow up until radiographic progression

m: serum for immune assays; 1 sample to be collected at any time during screening prior to Treatment Visit 1, then again during Scan/Efficacy visit

n: PSMA imaging is planned for all subjects. However, in the event of unavailability of radiotracers, subjects will be allowed to enroll and receive treatment without PSMA imaging. Optional repeat ^{68}Ga-PSMA PET/CT will be repeated prior to treatment or 6-48 hours after treatment in consenting subjects.

6.1.1. Screening Visit

The following procedures must be completed no more than 1 month prior to enrollment and no more than 4 weeks following enrollment.

- Informed Consent
- Demographics
- Medical History
- Previous therapy
- Surgical report will include date and type of surgery +/- lymphadenectomy
- Radiotherapy report will include modality of therapy with prescribed dose and field and dates of therapy
- Previous systemic (hormonal, chemo, other) therapy – drugs, doses, dates of therapy
- Complete Physical Exam including height and weight
- Brief Pain Inventory
- Vital Signs
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- Testosterone
- CTC count via CellSearch methodology (may be collected prior to treatment C1D1, do not need to repeat if has known result within 1 month of C1D1)
- CTC for Research (may be collected prior to treatment C1D1)
- Cell-Free DNA BCT® Research blood sample (may be collected prior to treatment C1D1)
- Immune research blood sample (may be collected prior to treatment C1D1)
- CT or MRI (abdomen-pelvis), up to 1 month prior to enrollment
- Bone scan, up to 1 month prior to enrollment
- Any confirmatory tests to assess equivocal results of bone scan should also be completed within a month of enrollment
- CXR, up to 1 month prior to enrollment (CXR waived if CT chest performed)
- Single intravenous dose of ^{68}Ga-PSMA-HBED-CC (5±2mCi or 185±74MBq) at least 1 week prior to ^{177}Lu-PSMA-617 infusion
- ^{68}Ga-PSMA-HBED-CC PET/CT scan to confirm the PSMA expression at the tumor site(s). PET/CT scans will be obtained 1 to 3 hours after the infusion of ^{68}Ga-PSMA-HBED-CC. Optional repeat ^{68}Ga-PSMA-HBED-CC injection and PET/CT prior to treatment in consenting subjects for research purposes.
- Archival tissue for PSMA expression and genomic studies to identify DNA

damage

Screening (except required ^{68}Ga-PSMA-HBED-CC PET/CT scan) and visit #1 may occur on the same day provided results are available, all entry criteria are met, and the subject is registered on the study prior to dosing. In this instance, duplicate procedures do not need to be performed. ^{68}Ga-PSMA-HBED-CC should occur at least 2 days prior to Treatment Visit #1.

6.1.1.1. R e –screening

Subjects who are unable to complete the initial screening or are not initially eligible will be permitted undergo repeat screening (with repeat written informed consent).

6.1.2. Treatment Phase

The treatment and early monitoring phase comprises of 8 visits spanning over approximately 12 weeks.
Platelets, absolute neutrophil count,, bilirubin, transaminases, and serum creatinine must be performed with results available and within range of eligibility criteria within 1 week prior to treatment initiation on C1D1.
Details for each visit are listed below:

6.1.2.1 ^{177}Lu-PSMA-617 infusion (Treatment Visit 1 Day 1)

The following procedures must be completed on the day of treatment with ^{177}Lu-PSMA-617:

- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- LDH
- Single intravenous dose of ^{177}Lu-PSMA-617 (Dose based on the Cohort in which the subject is enrolled)
- Adverse event evaluation
- Concomitant medications
- Concomitant procedures

As stated above, platelets, absolute neutrophil count,, bilirubin, transaminases, and

renal function assessment must be available within 1 week prior to treatment on D1 and meet eligibility criteria.

For Treatment Visit 2 (**Day 15 ±1 day**), grade ≥ 2 thrombocytopenia or neutropenia within 24 hours of the second dose of ^{177}Lu-PSMA-617 requires a subject's treatment to be held until the toxicity has resolved to least grade 1. If the toxicity has not resolved after 2 weeks of monitoring, the subject's ^{177}Lu-PSMA-617 treatment will be permanently discontinued and will be termed dose-limiting toxicity

6.1.2.2 Imaging visit (Day 8 ±1)

- Planar/SPECT imaging
- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- Adverse event evaluation
- Concomitant medications

^{177}Lu-PSMA-617 infusion (Treatment Visit 2 Day 15 ±1 day)

The following procedures must be completed on the day of treatment with ^{177}Lu-PSMA-617:

- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- LDH
- Single intravenous dose of ^{177}Lu-PSMA-617 (Dose based on the Cohort in which the subject is enrolled)
- Adverse event evaluation
- Concomitant medications
- Concomitant procedures
- Optional imaging will be performed on consenting subjects between Treatment Visit 1 (Between D1-D4) and/or prior to Treatment Visit #2 on (D15 ± 1)

6.1.2.2 Follow-up visits: Follow up Visit 1 (Day 22 ±3), Follow up Visit 2 (Day 29 ±3), Follow up Visit 4 (Day 57 ±3)

- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA (Follow up Visits 2 & 4)
- LDH (Follow up Visits 2 & 4)
- Adverse event evaluation
- Concomitant medications

6.1.2.3 Follow-up lab visits: Follow up Visit 3 (Day 43 ±3); Follow up Visit 5 (Day 71 ±3)

- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)

These visits may be performed with any licensed provider at any CLIA certified lab, provided that the results are available/provided to the Investigator within allowable windows.

6.1.3. Scan (initial efficacy) Evaluation Visit (Day 85 ± 7); note that these study procedures are not expected to occur on a single day**)**

The following procedures must be completed during the initial scan visit(s):

- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- LDH
- Testosterone
- CTC count via CellSearch methodology
- CTC for research
- Cell-Free DNA BCT® Research blood sample
- Immune research blood sample
- Same standard radiographic imaging modality as baseline (CT/MRI and bone scan +/- CXR)
- Single intravenous dose of ^{68}Ga-PSMA-HBED-CC (5±2mCi or 185±74MBq)
- PET/CT scan will be obtained between 1 and 3 hours post-injection of ^{68}Ga- PSMA-HBED-CC
- Adverse event evaluation
- Concomitant medications
- Concomitant procedures

6.1.4 Short term follow up (q4 week visits x3 following Efficacy/Scan visit)

Unless subjects withdraw or initiate new treatment, the following procedures must be completed every 4 weeks (+/- 7 days) after the scan visit:

- Targeted Physical Examination with vital signs and weight
- Interim Medical History
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)

- PSA
- LDH

These visits may be performed with any licensed provider at any CLIA certified lab, provided that the results are available/provided to the Investigator within allowable windows. Repeat CT and bone scan are recommended with the final short-term follow up visit (approx. 6 months after enrollment).

6.1.5 Progression

If a subject will not initiate a new treatment, then progression is considered to be by PCWG3 radiographic progression or clinical progression. However, if a subject has PSA progression and will initiate a new systemic therapy, then progression procedures should be performed prior to starting new therapy. Any procedure already performed for another visit within 2 weeks of the progression visit does not need to be repeated.

The following procedures must be completed during the progression visit:

- Targeted Physical Examination with vital signs and weight
- Medical History
- Brief Pain Inventory, FACT-P
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- LDH
- Testosterone
- Cell-Free DNA BCT® Research blood sample
- Immune research blood sample
- Adverse event evaluation
- Concomitant medications
- Concomitant procedures

6.1.6 Long Term Follow Up

Survival assessment and relevant medical history to be collected until death.
Information may be collected from external providers.
Per PCWG3, we recommend follow up CT and bone scans q12 weeks until radiographic progression

6.2. Treatment Administration

6.2.1. Agent Administration

Treatment will be administered only to eligible subjects under the supervision of the investigator or identified co-investigator(s). Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 13. Appropriate dose modifications/delays of the study drug are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

6.2.2. Study drug preparation

[redacted] produces both peptides/ligands, PSMA-HBED-CC and PSMA-617. Upon purchase and shipment to Weill Cornell Medicine, they will be labeled with either ^{68}Ga or ^{177}Lu with final products being ^{68}Ga-PSMA-HBED-CC and ^{177}Lu-PSMA-617, respectively. Radionuclide conjugation will be done at the Division of Nuclear Medicine, Department of Radiology, Weill Cornell Medicine.

The material produced are subjected to quality assurance testing as outlined in the Food and Drug Administration "Points to Consider". All production data and supporting documents, together with the results of all quality assurance testing, have been provided to and reviewed by the Food and Drug Administration (^{68}Ga-PSMA-HBED-CC, IND# 124495 and ^{177}Lu-PSMA-617, IND # 131966).

6.2.3. Route of Administration

^{68}Ga-PSMA-HBED-CC and ^{177}Lu-PSMA-617 will be administered as an intravenous infusion.

6.2.4. Dose levels for ^{177}Lu-PSMA-617

Subject(s) enrollment will be done as 3+3 study design at each dose level. Initially at least 3 subject(s) will be enrolled in Cohort 1 (100 mCi or 3.7 GBq x2 doses 2 weeks apart) with dose escalation (or de-escalation as described above in Section 4 / Table 7).. The enrollment ceiling of the dose escalation portion of the study is up to 46 study participants (six groups, with 3+3 at each dose level). Additional 10 subjects will be enrolled at the MTD dose level to further assess safety and tolerability and to obtain a preliminary assessment of efficacy. Each patient would receive 2 doses of the investigational agent, 2 weeks apart. The total dose received in 2 treatments in phase 1 will be **100 – 600 mCi or 3.7 – 22.2 GBq**. The total dose for phase 2 is 600 mCi (22.2 GBq).

6.2.5. Dose levels for ^{68}Ga-PSMA-HBED-CC

All subjected enrolled will receive **5 ±2mCi or 185 ±74MBq** of ^{68}Ga-PSMA-HBED-CC during the screening visit and EOS visit.

6.2.6. Study drug premedication

No pre-medication is required. Individual subjects may receive pre-medication at the discretion of their treating physician provided that they are not prohibited medications per study.

6.2.7. Study drug administration

Intravenous access must be well established prior to initiating infusion. At the time of dosing, the IV line will be connected to an infusion container containing the prepared volume of ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617.

6.2.8. Monitoring Vital signs pre/post ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617 infusion

The infusion of ^{177}Lu-PSMA-617 and subsequent monitoring will occur in a facility that is equipped for cardio–pulmonary resuscitation. The dispensed dose will be infused under the supervision of nuclear medicine physician or designee under the supervision of a nuclear medicine physician. Infusion–related

reactions (fever, rigors) will be treated with acetaminophen, meperidine and diphenhydramine hydrochloride as clinically appropriate. Other allergic events will be managed as follows: rash, pruritus, urticaria and wheezing will be treated with diphenhydramine hydrochloride, meperidine and/or steroids as clinically appropriate. Anaphylaxis or anaphylactoid signs or symptoms will be treated with steroids and/or epinephrine as clinically indicated. Vital signs will be monitored during the infusion. Systolic and diastolic blood pressure (mm Hg), temperature, pulse rate (beats/minute), and respiratory rate (breaths/minute), will be recorded with the patient in sitting position. Any clinically significant change in the vital signs will be recorded as AEs. Serial vital signs including temperature, BP, and heart rate will be monitored within 30 minutes before the infusion, within 30 minutes and at 60 minutes (+/-10) after the infusion. If any subject has any adverse reaction at 60 minutes, they will stay longer until it is resolved.

6.2.9. Imaging Plan

A. ^{68}Ga-PSMA-HBED-CC PET/CT Scan

Patient preparation should be according to the policies and procedures of the local imaging site (CIBC). The patient does not need to be fasting for either the infusion or

the scans. The use of intravenous or oral contrast will not be permitted. Specifications for acquiring the ^{68}Ga-PSMA-HBED-CC PET/CT scans will be provided in study specific documentation by the study chair or the co-investigators from the Division of Nuclear Medicine. PET/CT should be obtained during the Screening Visit as well as at the end of study visit. The images are acquired between 1 and 3 hours after the ^{68}Ga-PSMA-HBED-CC infusion. Image acquisition will be from vertex of skull to mid thighs.

B. ^{177}Lu-PSMA-617 Planar/SPECT imaging

Patient preparation should be according to the policies and procedures of the local imaging site (CIBC). The patient does not need to be fasting for either the infusion or the scans. The use of intravenous or oral contrast will not be permitted. Specifications for acquiring the ^{177}Lu-PSMA-617 planar/SPECT images will be provided in study specific documentation by the study chair or the co-investigators from the Division of Nuclear Medicine. Planar/SPECT images should be obtained during the Imaging Visit (Day 8 ±1) on all subjects after the ^{177}Lu-PSMA-617 infusion. Image acquisition will be from vertex of skull to mid thighs. Optional images will be performed on selected consenting subjects between initial Treatment Visit (between D1 - D4) and prior to Treatment Visit 2 (Day 15 ±1).

Managing toxicity

NCI CTCAE version 4.0 is used to grade all adverse events.

- Grade ≥ 2 thrombocytopenia or neutropenia within 24 hours of the second dose of ^{177}Lu-PSMA-617 (Treatment Visit 2) requires a subject's treatment to be held until the toxicity has resolved to least grade 1. If the toxicity has not resolved after 2 weeks of monitoring, the subject's ^{177}Lu-PSMA-617 treatment will be permanently discontinued and will be termed dose-limiting toxicity.

Dose-limiting toxicity (DLT) is defined as:

- Grade 4 hematologic toxicity that is deemed at least possibly related to ^{177}Lu-PSMA-617 will be termed dose-limiting toxicity.

- Any grade > 2 non-hematologic toxicity deemed to be at least possibly related to ^{177}Lu-PSMA-617 will require a subject's ^{177}Lu-PSMA-617 treatment to be permanently discontinued and will be termed dose-limiting toxicity.

Maximum Tolerated Dose (MTD) is defined as:

- The dose that produces an "acceptable" level of toxicity or that, if exceeded, would put subjects at "unacceptable" risk for toxicity. Definition of the MTD

usually relies on the sample, as MTD is defined as the dose level at which more than two patients over six experienced dose-limiting toxicity (DLT).

Note: toxicities as described above will be considered DLT if they are at least possibly related to ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617 as judged by the investigator. Attribution will be reviewed by the study chair and discussed with the medical monitor if there are questions about severity or attribution.

6.3. General Concomitant Medication and Supportive Care Guidelines

All medications that are administered during the study must be recorded in the patient's CRF and in the source documents. Concomitant medications for other medical conditions are permitted as clinically indicated subject to approval by the study chair.

Subjects will be advised to use contraceptive precautions to avoid pregnancy during the treatment phase since the effects of investigational agents on sperms and embryos are unknown.

6.4. Duration of Therapy and Criteria for Removal from Study

Duration of treatment portion of the study (excluding screening time) will be approximately 85 Days (±7 days). By signing the informed consent form and agreeing to participate in this study, the subjects are required to participate in entirety up to the completion of all scheduled visits and study procedures, or until one of the following criteria applies:

- A protocol violation occurs
- Disease progression occurs
- A serious or intolerable adverse event occurs (that in the opinion of the Investigator, requires the subject's discontinuation)
- The Investigator withdraws the subject (at the Investigator's discretion for reasons other than the adverse event)
- The Principle Investigator terminates the protocol
- The subject requests to be discontinued from the protocol
- The subject is lost to follow–up
- Intercurrent illness that prevents administration of ^{68}Ga-PSMA-HBED-CC or ^{177}Lu- PSMA-617
- Previous anaphylactic reaction to PSMA peptides/ligands

The investigators or physicians may stop the protocol or terminate a subject's participation in the protocol at any time should they judge:

- That it is not in the subject's best interest to continue
- If the subject experiences a protocol–related injury
- If the subject needs life–saving medications/procedures/treatment
- If the subject does not comply with the study plan
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

They may also remove the subject from the study for various other administrative and medical reasons. They can do this without the patient's consent.

6.5. Duration of Follow Up

Patients will be followed until death for survival assessment. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

8. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dosing modifications. Unless there are specific reasons not to do so, all patients who are eligible for the trial will receive 5 ±2 mCi (185 ±74 MBq) of ^{68}Ga- PSMA-HBED-CC during the Screening Visit and the Efficacy/Scan visit. During the treatment phase, the subject will receive ^{177}Lu-PSMA-617 x 2 doses based on the dose-level/Cohort to which he is assigned. The study chair must clear any dosing delays due to logistical issues (e.g. subject scheduling and/or radionuclide shipping that fall outside of a 2–day window).

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with *Investigational Agent* can be found in Section 13.

9.1. Investigational Agent

PSMA-617 and PSMA-HBED-CC were initially purchased from [redacted] and in the later part of the study PSMA-617 will be provided by [redacted] Lignads will be shipped to and stored at WCM as per manufacturer's guidelines. Upon subject's enrollment and confirmation of date of infusions, these peptides will be labeled with Lutetium-177 or Gallium-68 respectively.

The material produced are subjected to quality assurance testing as outlined in the Food and Drug Administration "Points to Consider". All production data and

supporting documents, together with the results of all quality assurance testing, have been provided to and reviewed by the Food and Drug Administration.

9.2. Availability

^{177}Lu-PSMA-617 (IND# 131966) and ^{68}Ga-PSMA-HBED-CC (IND# 124495) are investigational agents supplied to investigators by Weill Cornell Medicine.

9.3. Agent Ordering

Upon enrollment of the subject, the WCM Study Coordinator will be notified about the ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-HBED-CC infusion dates. The WCM Study Coordinator will arrange with the staff of Nuclear Medicine Division at WCM for the timely labeling and delivery of the radiolabeled PSMA peptides to the site of infusion.

The dates for study visits will be confirmed with the subject, site of infusion, and site of imaging.

9.4. Agent Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from Sponsor on a Drug Accountability Record Form (DARF).

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1. Cell-Free Plasma DNA:

Peripheral blood will be collected in two 10 mL Cell-Free DNA BCT® tubes (Streck) at the specified time points (Screening and EOS visit) and processed per the lab manual. These samples are collected for research purposes only and will not be billed to the subject. The cell-free plasma DNA will be analyzed for genomic studies and to identify DNA repair alterations.

9.1.2. Archival tissue:

Archival tissue will be requested during the screening visit. Unstained slides containing tumor material from archival paraffin-embedded tissue should be obtained per the lab manual. If available, metastatic tissue is preferred to prostate biopsy/prostatectomy specimens. The tissue will be analyzed for PSMA expression, DNA repair pathways, and other genomic analyses for research purposes only.

9.1.4 Immune assays

Serum samples will be obtained during screening prior to treatment and at the main efficacy visit for immune biomarkers and processed as per the lab manual. CTC collection for calreticulin expression analysis will be collected during screening or on D1 prior to treatment and at the D85 scan visit and processed as per the lab manual. CTCs for immune analysis will be collected at the WCM site only. Results of these assays will not be billed to the patient and are for research purposes only.

9.2. Imaging Studies

Imaging studies (including ^{68}Ga-PSMA-HBED-CC PET/CT and ^{177}Lu-PSMA-617 Planar/SPECT Imaging) will be performed as described in schedule as well as clinically indicated to assess disease response. In subjects enrolled in this study, the measurable disease response will be calculated using Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) with PCWG3 modifications.

Consenting subjects will undergo an optional study involving two scans with ^{68}Ga-PSMA-HBED-CC (with a minimum of 6 h and maximum of 2 days between the two injections). This cohort of patients will be analyzed to ensure that the peak standardized uptake values (including SUV_{mean}, SUV_{max}, SUV_{peak} (SUV_{peak} not applicable to brain) of the lesions in the same patient/lesion is within an acceptable range of repeatability (+/- 30%) as demonstrated by prior radionuclide repeatability studies such as FDG and FLT.

10. MEASUREMENT OF EFFECT:

10.1 CTC count response

All subjects in this study will get blood samples drawn (at screening and EOS visit) for CTC enumeration by CellSearch methodology. Our primary analysis will assess those whose CTC counts drop to less than 5 or stay below 5 (responders) vs. those who remain at least 5 or above (non-responders) at EOS visit.

In addition, it appears that decreases in CTC counts with therapy are a favorable marker even if the count remains at least 5. We will also analyze % changes in CTC counts with at least 50% decline in CTC count from baseline considered a response at 12 weeks. Best response will also analyzed (% increase or best % decrease at any point will also be reported in a waterfall plot).

As reported in phase III studies of men with mCRPC, a favorable CTC count and LDH level at 12 weeks has been associated with overall survival. We will report the

proportion of subjects who have CTC count <5 and normal LDH at the initial scan (efficacy) visit time point.

Additional reports associate an undetectable CTC count at 12 weeks as prognostic. We will report the proportion of subjects who have an undetectable CTC count at the initial scan (efficacy) visit time point.

10.2 Biochemical (PSA) response

PSA response will be determined by comparing the PSA levels after therapy to the baseline, pre-treatment PSA. Declines of $\geq$ 30% confirmed by a second PSA value $\geq$ 2 weeks later, will be reported. Subjects must not demonstrate clinical or radiographic (CT and/or MR) evidence of disease progression during this time period.

10.3 Duration of PSA response

Duration of PSA response is defined as the time from the first 25% PSA decline until the PSA value is confirmed to increase by 25% above the nadir, provided that the increase is at least 2 ng/mL above the nadir.

10.4 Duration of CTC response

Duration of CTC response is defined from the first CTC count drop to <5 (or $\leq$50% of baseline) to the time CTC count increases to $\geq$5 (or $\geq$25% increase from nadir).

10.5 PSA Progression

PSA progression will be defined as a rise of > 25% above either the pretreatment level or the nadir PSA level (whichever is lowest). PSA must increase by > 2 ng/ml to be considered progression. Confirmation requires a second consecutive rising PSA at least 2 weeks apart.

10.6 PSA Stabilization

PSA stabilization is referred to as any set of PSA values that do not meet the criteria for PSA response or PSA progression.

10.7 Time to PSA Progression

Time to PSA progression is defined as the interval between initiating treatment until the PSA rises 25% above nadir provided that the increase is at least 2 ng/mL.

10.8 Change in lesion size

In subjects with measurable disease, complete response (CR) is defined as complete disappearance of all measurable and evaluable lesions by physical examination or imaging studies and normalization of PSA with no appearance of new lesions for > 1 month. Partial response (PR) is defined as a 30% or greater reduction in the sum longest uni-dimensional diameter of all measurable lesions. There may be no new lesions. Stable Disease (SD) is characterized by subjects who do not meet the criteria of PR and who are without signs of progressive disease for at least 1 month. Disease Progression (DP) is defined as a greater than 20% increase in the sum longest uni- dimensional diameters of the indicator lesions or the appearance of new lesions. Bone scan progression (evaluable disease only) is requires at least 2 new lesions seen

on a scan subsequent to baseline followed by a repeat scan at least 6 weeks later with at least one new additional lesion.

Conventional Imaging studies (MRI, CT, Bone Scan) along with investigational images (^{68}Ga-PSMA-HBED-CCPET/CT imaging and ^{177}Lu-PSMA-617) will be performed during the study visits or as clinically indicated to assess disease response. In subjects enrolled in this study, the measurable disease response will be calculated using Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) with PCWG3 modifications.

Radiographic scans will be used to assess best overall response and radiographic progression based on modified RECIST criteria for soft-tissue lesions and protocol-specific criteria for bone lesions Baseline images should be taken during Screening as close as possible to, and never more than 28 days before study visit 1. Every effort must be made to ensure the same radiographic method is used before and after treatment at scheduled visits. Radiographic progression free survival will be evaluated based on these results.

Analysis of Efficacy:
Median bPFS, rPFS, and OS, including survival curves, will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier estimates. Percent change in PSA from baseline will be described by mean/median and standard deviation/inter-quartile range, as appropriate, depending on the distribution of percent change from baseline. Modified RECIST response (i.e., CR, PR, and CR/PR proportions), CTC count response proportion, defined favorable LDH/CTC proportion, and associated 95% confidence intervals, will be estimated via binomial proportions.

All subjects will undergo baseline and subsequent ^{68}Ga-PSMA-HBED-CC PET/CT, and

those treated with ^{177}Lu-labeled products will undergo planar +/- SPECT imaging. We will analyze the data for associations with response to treatment as well as survival by chi-square tests/Fisher's exact tests and log-rank tests, respectively. For pre/post imaging comparisons, McNemar's chi-square test and paired t-tests/Wilcoxon signed- rank tests will be used, as appropriate. We plan to report data for each individual study as well as across the studies.

10.9 Patient reported outcomes

Initial bone-targeted β-emitters were approved for the control of painful bone metastases. Radium-223 dichloride appears to be associated with improved/preserved patient reported outcomes as well. We will assess pain prior to and following treatment with the brief pain inventory (and will also collect pain medication data). We will assess global and prostate cancer specific patient reported outcomes with the FACT-P questionnaire. As with the other correlative studies, we will plan to report results for this individual study as well as across current and prior studies, particularly examining subjects that receive what we believe are efficacious doses.

11. Data Reporting / Regulatory Considerations

11.1. Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

11.1.1. REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2. Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Should an external sponsor be identified, they will have the opportunity to review and approve the changes prior to submission of these changes

to the local IRB and distribution to participating sites.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

This is a phase 1 study of subjects with documented progressive metastatic CRPC with the primary endpoint of determination of MTD (or recommended phase II dose). In general, if there are sufficient numbers of subjects, descriptive statistics (e.g., number of observations, means, standard deviations, medians, and ranges) will be used to summarize data and selected endpoints may be summarized by dosing regimen. Otherwise, subject listings will be provided. No formal hypothesis testing is planned.

The dose-escalation schedule (using 3+3 modified Fibonacci escalation), definitions of DLT, and determination of MTD are defined above (Section 6.2.10). The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. The maximum tolerated dose is defined as the highest dose level with an observed incidence of DLT in no more than one out of six patients treated at a particular dose level. The dose escalation scheme provides the following probabilities of escalation based on the true chances of DLT at a specific dose level. One can see that the probability of escalation is high if the toxicity risks are low.

True Probability of Toxicity	0.05	0.10	0.20	0.30	0.40	0.50	0.60
Probability of Escalation	0.97	0.91	0.71	0.49	0.31	0.17	0.08

12.2. Phase II

We will enroll up to 27 subjects into the Phase II portion (including the 3-6 used for establishing the MTD). We will define evaluable patients as patients who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal.

Sample size recommendations for the two-stage design are determined according to Simon's two-stage minimax design. We project a 30% PSA decline proportion of 35%, below which the regimen will be unacceptable and a 30% PSA decline proportion of 60%, above which the regimen will be considered worthy of further exploration. The null hypothesis that the 30% PSA decline proportion is less than or equal to 35% will be tested against the alternative hypothesis that the 30% PSA decline proportion is greater than or equal to 60%.

The sample size computations were performed assuming a 0.10 one-sided level of significance and 90% power assuming a historical control value for PSA decline of 35% and the alternative hypothesis of 60%. If 6 or fewer of the first 16 evaluable patients do not experience a 30% decline in PSA (stage 1), the study will be terminated and declared to have a negative result. If 7 or more patients out of the first 16 evaluable patients experience a 30% decline in PSA, ongoing accrual will proceed to the target sample size of 27 patients (stage 2). The new regimen will be declared active in this patient population and worthy of further testing if 13 or more patients experience a 30% PSA decline among the 27 patients entered. This two-stage design yields a 0.90 probability of a positive result if the true 30% PSA decline proportion is 60%. It yields a 0.90 probability of a negative result if the true 30% PSA decline proportion is 35%. An exact 95% binomial confidence interval will be constructed for the proportion of patients with PSA decline.

12.3. Sample Size/Accrual Rate

The planned sample size for this dose escalation Phase I study is between 6-36 and between 16-27 for phase II. The accrual rate is anticipated to be 1-2 patients/month on average (with expected pauses between dose-escalation cohorts and between stage 1 and stage 2 of the phase II trial).

12.4. Stratification Factors

This is not a randomized trial and there are no planned stratification factors. Descriptive statistics will be utilized. Stopping rules for futility are in place as per Section 4.2.

12.5. Analysis of Endpoints

12.5.1. Analysis of Primary Endpoints

The primary endpoint will be the proportion of subjects with DLT from Treatment Visit 1 through **Efficacy/Scan Visit.**. The MTD is the highest dose amongst the different dose-level cohorts in this study at which no more than 2 (33%) of the subjects in a cohort experience DLT.

12.5.2. Analysis of Secondary Endpoints

For PSA response, CTC response and Imaging response, descriptive analysis will be performed. For imaging response RECIST criteria with PCWG3 modifications will be applied. Biomarker and patient reported outcome data will be analyzed within this

study as well as across additional radiolabeled-PSMA studies.

12.6. Interim Analysis

No interim analysis is planned (though safety analyses will occur in real-time and prior to each dose-escalation). During phase II, ongoing analysis during Step 1 will determine whether or not to proceed to step 2.

12.7. Reporting and Exclusions

12.7.1. Evaluation of toxicity

All subjects will be evaluable for toxicity from the time of their first infusion with ^{68}Ga-PSMA-HBED-CC as well as when they receive their first treatment with ^{177}Lu-PSMA-617. The distributions of the maximum observed grade toxicity will be tabulated for each type of toxicity and presented by dose level and overall. Results will be summarized with descriptive statistics.

12.7.2. Evaluation of response

Subjects who complete ^{177}Lu-PSMA-617 treatment and at least 12 weeks of subsequent follow-up evaluations (as described in the schedule calendar-section 6.1.) will be considered evaluable (consistent with PCWG3 guidelines). As the timing of response is not known, should the anticipated time to response be determined to be earlier than with other therapies using alternative markers of response, we may not replace subjects who are not evaluable through week 12 on study.

13. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about

causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1. Investigational Agent Risks

There are no known contraindications for ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617. Because of the potential for infusion or allergic reaction, the subject should be monitored for safety for one hour following the infusion.

Based on prior studies, the known side effects, risks, and hazards associated with the administration of ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617 include: infusion reaction (fever, chills, rash, hypotension, and/or hypertension after injection), xerostomia, renal insufficiency, hematological/bone marrow toxicity (thrombocytopenia, neutropenia) and transient hepatic enzyme elevations. In addition, allergic reactions including anaphylaxis are a possibility.

Precautions/monitoring:

The infusion of ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617 and subsequent monitoring will occur in a facility that is equipped for cardio–pulmonary resuscitation. The dispensed dose will be infused under the supervision of nuclear medicine physician or designee under the supervision of a nuclear medicine physician. Infusion–related reactions (fever, rigors) will be treated with acetaminophen, meperidine and diphenhydramine hydrochloride as clinically appropriate. Vital signs will be monitored before/after the ^{68}Ga-PSMA-HBED-CC or ^{177}Lu-PSMA-617 infusion. Systolic and diastolic blood pressure (mm Hg), temperature, pulse rate (beats/minute), and respiratory rate (breaths/minute), will be recorded with the patient in sitting position. Any clinically significant change in the vital signs will be recorded as AEs. Serial vital signs including temperature, BP, and heart rate will be monitored within 30 minutes of the infusion, and within 30 minutes and 60 minutes (+/- 10) after the infusion. If any subject has any adverse reaction at 60 minutes, they will stay longer until it is resolved.

13.1.2. Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - **Definite** – The AE *is clearly related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The

reaction can be confirmed with a positive re–challenge test or supporting laboratory data.

- **Probable** – The AE *is likely related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- **Possible** – The AE *may be related* to the study treatment. A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Unlikely** – The AE *is doubtfully related* to the study treatment. The current state of knowledge indicates that a relationship is unlikely.
- **Unrelated** – The AE *is clearly NOT related* to the study treatment. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.

13.1.3. Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart.

13.1.4. Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

[redacted]

13.2. Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1. Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy,

which can be accessed via the following link:

[redacted]

13.2.2. Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

[redacted]

13.3. AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

14. Data and Safety Monitoring Plan (DSMP)

This study will utilize the Weill Cornell Medicine (WCM) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring this study for safety concerns, with ongoing updates from the Study Chair on a continuous basis.

The Weill Cornell's DSMB is comprised of medical specialists and advisors on human rights issues in human subjects research. The DSMB currently has 9 members, meets at quarterly intervals during the year, and carries out ongoing review of protocols submitted throughout the year. Once a protocol has been submitted and approved by the Institutional Review Board (IRB) and is recommended for oversight by the DSMB, the Board determines if the protocol will be reviewed quarterly, semi–annually, or annually.

The DSMB evaluates the accumulated data from the study in order to monitor the

safety of subjects throughout the trial and reviews the risks and benefits, as well as the efficacy, of the study. The DSMB will also evaluate the overall trial conduct and progress. Ultimately, the DSMB validates the continuation of the trial or determines if a study needs modification or termination.

Reports to the DSMB will include the following items for review:

1. Completed DSMB Periodic Review Form.
2. Synopsis of the study to date.
3. IRB approved consent form.
4. IRB current protocol.
5. Summary table of study results.
6. Adverse event table.
7. Data safety monitoring plan.

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subject research projects and to protect the safety of human subjects. Safety monitoring can be viewed as any process during a clinical trial that involves the review of accumulated outcome data for groups of patient−subjects to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998, 2000) specify that all clinical trials should have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities will be commensurate with the nature, size, and complexity of the trial in accordance with institutional policies and will be determined after IRB and DSMB review of the protocol immediately prior to study activation. For a small, single−center study, usually a statistician in conjunction with a Safety Officer performs the monitoring. For that single−site, high−risk trials, a DSMB may be appropriate. For larger, single or multi−site studies, a committee, often called a Data Safety Monitoring Board (DSMB), usually performs the monitoring. Ongoing review of the data by an independent individual or committee assures the investigators, the IRB, the study's sponsor, and the funding agency that the trial can continue without jeopardizing subjects' safety.

Weill Cornell Medicine requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

For this study, the DSMB will be notified after each cohort has been completed prior to dose escalation to the next cohort. In addition, a report will be made to the DSMB every 6 months.

14.1 *Medical Monitor*

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the appropriate committees/agencies. This individual will be a qualified physician, other than the principal Investigator, not associated with this particular study, able to provide medical care to research subjects for conditions that may arise during the conduct of this study, and will monitor the subjects during the conduct of the study.

[redacted], MD will serve as the Medical Monitor for this study.

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Appendix A

Performance Status Criteria:

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	**Normal activity. Fully active, able to carry on all pre-disease performance without restriction.**	**100**	**Normal, no complaints, no evidence of disease.**
		90	**Able to carry on normal activity; minor signs or symptoms of disease.**
1	**Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).**	**80**	**Normal activity with effort; some signs or symptoms of disease.**
		70	**Cares for self, unable to carry on normal activity or to do active work.**
2	**In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.**	**60**	**Requires occasional assistance, but is able to care for most of his/her needs.**
		50	**Requires considerable assistance and frequent medical care.**
3	**In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.**	**40**	**Disabled, requires special care and assistance.**
		30	**Severely disabled, hospitalization indicated. Death not imminent.**
4	**100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.**	**20**	**Very sick, hospitalization indicated. Death not imminent.**
		10	**Moribund, fatal processes progressing rapidly.**
5	**Dead.**	**0**	**Dead.**

Appendix B

WCMC IRB SAE Reporting Forms

http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html