SP 17-000330-AM-S

ENDOCYTE

PROTOCOL NO. PSMA-617-02:

PSMA-DIRECTED ENDORADIOTHERAPY OF CASTRATION-RESISTANT PROSTATE CANCER (RESIST-PC). A PHASE II CLINICAL TRIAL

Clinical Protocol No.:	PSMA-617-02
CT.gov Study Number	NCT03042312
IND No.:	133661
Phase of Study:	Phase II
Investigational Products:	^{177}Lu- PSMA-617
Sponsor:	Endocyte, Inc. 3000 Kent Avenue - Suite A1-100 West Lafayette, Indiana 47906-1075 (765) 463-7175
Medical Monitor:	[redacted], M.D., M.H.S., M.Sc. Endocyte, Inc. 8910 Purdue Road, Suite 250 Indianapolis, Indiana 46268 [redacted]
Version 1.0	28 December 2016
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Version 3.0	29 June 2017
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Version 5.0	01 June 2018

Approval:

[signed electronically in MasterControl]

Medical Monitor Signature *Date*

SYNOPSIS

Sponsor:

Endocyte, Inc.

3000 Kent Avenue – Suite A1-100

West Lafayette, Indiana 47906-10758

(765) 463-7175

Name of Finished Product:

^{177}Lu-PSMA-617

Name of Active Ingredient:

2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid

Study Title:

PSMA-directed endoRadiothErapy of castration-reSISTant Prostate Cancer (RESIST-PC). A phase II clinical trial.

Study Number:

NCT03042312

Study Phase:

Phase II

Primary Objective:

To assess safety and efficacy defined as >50% decline in PSA after ^{177}Lu-PSMA-617 in patients with metastatic castration resistant prostate cancer

Secondary Objectives for each Treatment Dose:

1. To determine maximum PSA decline.
2. To determine PSA progression-free survival (PFS), measured from start of therapy until death or PSA progression.
3. To determine radiographic PFS, measured from start of therapy until death or radiographic progression using RECIST 1.1/PCWG criteria.
4. To determine disease control rate (DCR) defined as the proportion of patients achieving RECIST stable disease (SD), partial response (PR) or complete response (CR).
5. To determine impact on bone pain level
6. To determine impact on quality of life
7. To determine impact on performance status (ECOG)

Study Design:

Open-label, prospective, multicenter clinical trial.

Study Population:

Patients with metastatic castration resistant prostate cancer

Inclusion Criteria:

1. Prostate cancer proven by histopathology
2. Unresectable metastases
3. Progressive disease, both docetaxel naive and docetaxel treated.
4. Castration resistant disease with confirmed testosterone level ≤50 ng/ml under prior androgen deprivation therapy (ADT)
5. Positive ^{68}Ga-PSMA-11 PET/CT or diagnostic ^{177}Lu-PSMA-617 scintigraphy or any equivalent PSMA-directed imaging
6. ECOG 0-2
7. Sufficient bone marrow capacity as defined by WBC ≥2500/µl, PLT count ≥100.000/µl, Hb≥9.9 g/dl and ANC≥1500 mm3 for the first cycle and WBC ≥2.000/µl, PLT count ≥75.000/µl, Hb≥8.9 g/dl and ANC≥1000 mm^3 for the subsequent cycles
8. Signing of the Informed Consent Form
9. Patients enrolling in this trial should have received either Enzalutamide or Abiraterone

Exclusion Criteria:

1. Less than 6 weeks since last myelosuppressive therapy (including

Docetaxel, Cabazitaxel, ^{223}Ra, ^{153}Sm) or other radionuclide therapy.
2. Glomerular Filtration Rate (GFR) <40 ml/min
3. Serum creatinine > 1.5xULN
4. AST and ALT > 5xULN
5. Urinary tract obstruction or marked hydronephrosis
6. Diffuse bone marrow involvement confirmed by super-scans

*super-scan is defined by kidney uptake equal or below background due to diffuse bone involvement on staging PET/CT or scintigraphy

Test Product; Dose; and Mode of Administration:

Randomization into two treatment doses; radioligand therapy (RLT) by repeated i.v. application of 6.0 GBq (±10%, **arm 1**) or 7.4 GBq (±10%, **arm 2**) ^{177}Lu-PSMA-617 every 8±1 weeks; RLT until reaching four cycles.

Study Duration:

Patients will be followed until either of the following conditions occur:

1. 24 month after the first treatment.
2. Progression by RECIST 1.1/PCWG criteria.
3. Death.

Safety Assessments:

AE and safety assessments will be performed through the following mechanisms, also listed in Appendix II:

a. Following laboratory tests will be performed at baseline (within 72 hours of first treatment dose) and then every 2 weeks (+/- 3 days) after first dose, continued until 12 weeks after the last dose and then every 3 months (+/- 1 week) thereafter until the end of follow-up visits (24 months from 1st therapy date) or upon disease progression. The CBC and CMP within 2 weeks of each subsequent treatment cycle will be used to assess eligibility of the corresponding treatment cycle.

1. Complete metabolic panel and eGFR
2. CBC

b. Telephone Follow-up: 7(±3) days after each treatment cycle and for follow-up phase every 3 (±1 month) until the end of follow-up visits (24 months).

Following conditions if in view point of investigators deemed study related, will result in permanent discontinuation:

i. Grade 3-4 non-hematologic toxicities with select exceptions for:

1. Grade 3 fatigue < 10 days

2. Grade 3 nausea, vomiting, and diarrhea and grade 4 vomiting and diarrhea that persist for < 72 hours in the absence of maximum medical therapy.

3. Asymptomatic grade 3 non-hematological laboratory abnormalities that resolve in 72 hours.

4. Grade 3 infections that resolve under medical treatment within 10 days

ii. AST/ALT > 3x ULN and bilirubin > 2x ULN

iii. Grade 4 Hematological toxicities persisting >3 weeks.

iv. Grade 3 Hematological abnormalities that do not return to baseline for > 12 weeks.

Data Safety Monitoring Board (DSMB) and Data Safety Monitoring Plan (DSMP):

A Data Safety Monitoring Board (DSMB) has established and will evaluate safety throughout the study. The DSMB will advise the Sponsor, Investigators and investigational sites regarding the continuing safety of study patients and the patients yet to be recruited to the study as well as maintaining validity and scientific merit of the study. The DSMB will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study.

The Excel Diagnostics DSMB will serve as the lead site DSMB. At UCLA, DSMB oversight will be provided by JCCC Data Safety Monitoring Board (DSMB). The monitoring board will meet quarterly to review safety records including compliance with follow up visits.

Interim safety analyses: 4 interim safety analyses will be conducted by DSMB that will be initiated at the time when 25%, 50%, 75% and 100% of the total ^{177}Lu-PSMA-617 treatments in the trial have been completed. The DSMB will meet and assess up-to-date safety information within two weeks of a treatment exposure rate being achieved (i.e., the point when 25%, 50%, 75% and100% of treatments have occurred). Further patients may only be randomized two weeks after the treatment exposure rate has been reached and after a positive opinion from the DSMB.

Efficacy Assessment for each treatment arm:

Primary objective:

12 week PSA response: Proportion of patients with PSA-decline of ≥50% at 12 (±1) week after the first RLT [1].

Secondary objectives:

1. Maximum PSA response: Maximal baseline to follow-up PSA decline at any time during or after therapy [1]

2. Time to PSA progression, for each treatment arm. [1]
   a. for patients with PSA decline: Time from baseline to time the PSA increases to 25% and 2 ng/ml above nadir which is confirmed by a second value ≥3 weeks later
   b. for patients without PSA decline: Time from baseline to time the PSA increases to 25% and 2 ng/ml above baseline which is confirmed by a second value ≥3 weeks later
3. Radiographic progression free survival (rPFS), for each treatment arm.
4. Change in Pain, Quality of Life and ECOG performance score: Questionnaires will be completed at baseline and at 3, 6, 9, 12, 18 and 24 month, for each treatment arm

Number of patients enrolled:

As per statistical evaluation, total of 200 patients will be required to have statistical power to achieve the primary endpoints of the study.

Date of Original Protocol: December 28th, 2016

Date of Most Recent Protocol Amendment (if applicable): 09/18/2017

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LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
DCR	Disease Control Rate
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GH	Growth hormone

Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactic dehydrogenase
MBq	MegaBequerel
mCi	milliCurie
mo	months
GBq	gigabecquerel
MR	Magnetic resonance
MRI	Magnetic resonance imaging
N/A	Not applicable
NDA	New Drug Application
PCa	Prostate cancer
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-free survival
PSA	Prostate-specific antigen
PR	Partial response
RBC	Red blood cell

RECIST	Response Evaluation Criteria In Solid Tumors
RLT	Radioligand therapy
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical analysis plan
SD	Stable disease
SE	Standard error
SPECT	Single-photon emission computerized tomography
PSMA	Prostate-specific membrane antigen
US	United States
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

1.1 Background

According to the American Cancer Society more than 1 million people in the United States are diagnosed with cancer each year. For American *males,* prostate cancer is the second most common cause of cancer related death [2]. A recent publication [3] estimated the prevalence of prostate cancer as 2,219,280 in the US in 2009 and 3,072,480 in 2020, and incidence of metastatic Castration Resistant Prostate Cancer (mCRPC) as 36,100 and 42,970, respectively. Various therapies have been developed to improve survival of patients with advanced prostate cancer. However, despite such efforts currently all-cause mortality in prostate cancer has been estimated at 168,290 in 2009 and 219,360 in 2020, with 20.5% and 19.5% of these deaths, respectively, occurring in men with mCRPC.

Patients with metastatic castration-resistant prostate cancer (mCRPC) have a poor prognosis, and those patients with metastases are expected to survive ≤19 mo [3] . As patient disease progresses, quality of life deteriorates, and until recently, few treatment options were available. Several new therapies have shown an improvement in overall survival for patients with mCRPC who have already received chemotherapy with docetaxel (Fig. 1) [4] [5] [6, 7] [8]. The impact of these new data on clinical practice, treatment sequencing, and best care for individual patients is not yet fully established.

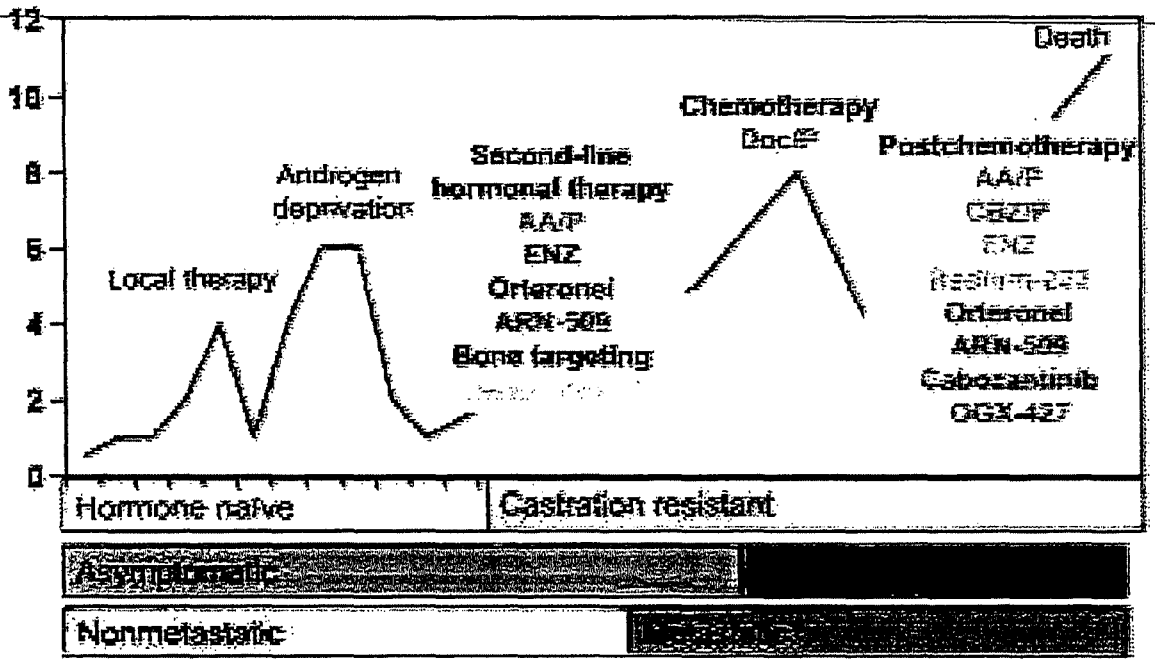


Figure 1: Current, ongoing, and future landscape in the management of castration-resistant prostate cancer.

Color key: green = US Food and Drug Administration/European Medicines Agency (FDA/EMA) approved; light green = trial results in high-risk patients positive, but not approved; orange = prospective, randomized, phase 3 clinical trial completed, results positive, FDA/EMA approval awaited; blue = prospective, randomized, phase 3 clinical trial completed, results awaited; purple = promising agent, phase 3 clinical trials ongoing. * Trial results for denusomab in high risk patients positive, but not approved. AA/P = abiraterone acetate with prednisone; ENZ = enzalutamide; Doc/P = docetaxel plus prednisone; CBZ/P = cabazitaxel plus prednisone.

1.1.1. Current treatment options for metastatic castration-resistant prostate cancer: before docetaxel

Sipuleucel-T

Sipuleucel-T is an autologous vaccine consisting of individually collected antigen-presenting cells that are exposed to the fusion protein prostatic acid phosphatase and granulocyte colony-stimulating factor (GCSF), and then reinfused in the patient at weeks 0, 2, and 4. In the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study, median survival with sipuleucel-T was 25.8 mo compared with 21.7 mo with placebo [9]. It has to be considered, however, that only patients with a good Eastern Cooperative Oncology Group performance status of 0–1, asymptomatic or mildly symptomatic osseous metastases, and

absence of visceral metastases were included in the trial.

Abiraterone acetate

The COU-AA-302 (Cougar 302) trial randomized 1088 men with mCRPC to receive abiraterone acetate with prednisone (AA/P) or placebo [4] with the primary end points of overall and radiographic progression-free survival (rPFS) by central review. Median overall survival was 35.3 mo and 27.2 mo in the AA/P group and in the placebo group, respectively ($p = 0.01$) [10]. Also, the co-primary end point of rPFS was significantly improved in the AA/P group, at 16.5 mo, as compared to 8.3 mo in the placebo arm ($p < 0.001$). On all secondary end points, AA/P treatment resulted in significantly improved effects.

Docetaxel/prednisone

In 2004, cytotoxic treatment with docetaxel plus prednisone (Doc/P) was the main option for treatment of mCRPC based on the TAX 327 trial [11]. The median survival was 18.9 mo versus 16.4 mo in the group of patients who received mitoxantrone/prednisone ($p = 0.009$), the 3-yr overall survival rate was 18.6% versus 13.5%, and pain response was 35% versus 22%. It has been shown recently that Doc/P is active in men with symptomatic mCRPC and especially in patients with poorly differentiated prostate cancer (PCa) (Gleason score: 8–10) [12]. Subsequent studies using combinations with docetaxel have not further improved the oncologic outcome [3]. The results of the Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer (READY) and the Aflibercept in Combination with Docetaxel in Metastatic Androgen-Independent Prostate Cancer (VENICE) trial were disappointing [13] [11]. The median survival after docetaxel and docetaxel/dasantinib was 21.2 mo versus 21.5 mo, respectively, and the median survival after docetaxel versus docetaxel plus afilbercept was 21.1 mo versus 22.1 mo, respectively. The differences in the patient cohorts of the Cougar 302, IMPACT, and TAX 327 trials make

it evident that AA/P will be used for asymptomatic or mildly symptomatic mCRPC with a low metastatic burden, whereas Doc/P might be the treatment of choice in men with symptomatic mCRPC and/or a high metastatic burden as well as an undifferentiated PCa.

1.1.2. After docetaxel treatment

Docetaxel rechallenge

The scientific evidence of this approach results from large, retrospective series that identified patients who might be good candidates for re-exposure [14] [15] [16]. Patients who responded with a ≥30% decrease in prostate-specific antigen (PSA) level, maintained for at least 8 wk after first exposure to docetaxel, demonstrated a positive PSA response in about 55% to 60% of the cases during re-exposure without increasing treatment related toxicity.

Abiraterone acetate plus prednisone

AA/P versus placebo was evaluated in the Cougar 301 trial, which randomized 1195 patients with progressive mCRPC who failed docetaxel-based chemotherapy [5]. The median follow-up in the overall study population was 12.8 mo. Overall survival was significantly improved from 10.9 mo in the placebo arm to 14.8 mo in the AA/P arm ($p < 0.001$). All secondary end points were met and all end points demonstrated a significantly improved benefit for the AA/P group. Adverse events with regard to the CYP 17 blockade were observed significantly more often in the AA/P arm (55% vs 43%; $p < 0.001$).

Recently, Goodman et al. [17] demonstrated that AA/P is effective even in patients with liver or lung metastases, although to a lesser degree. The overall survival times were 12.9 mo versus 8.3 mo in the placebo group (p = 0.022). Albiges et al. [18] described an AA withdrawal syndrome that developed in 32% of 66 patients who had been treated for a mean period of 5.7 mo. Clayton et al. [19] presented data from a population-based study that included 187 mCRPC patients with a mean PSA serum concentration of 138 ng/ml who were treated with AA/P. The

median overall survival was only 9.3 mo and might reflect the oncologic efficacy of AA/P in a real-world patient population with high metastatic burden.

Enzalutamide (formerly MDV3100)

Enzalutamide (ENZ) acts as an androgen receptor (AR)-signaling inhibitor, and it was evaluated in the Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy (AFFIRM) trial, which randomized 1199 mCRPC patients to receive ENZ or placebo [8]. The median follow-up was 14.4 mo and the median overall survival was 18.4 mo and 13.6 mo ($p < 0.0001$) in the ENZ group and in the placebo group, respectively, with a 37% reduction in relative risk for death. All secondary end points were met with a statistically significant benefit in the ENZ arm. With regard to safety, the ENZ group experienced fewer grade 3/4 toxicities than the placebo group (53% vs 45%). The risk of seizures was slightly elevated in the ENZ group, with a frequency of 0.6% versus 0% in the placebo group.

Recently, Scher et al. [20] demonstrated that the use of corticosteroids in parallel to ENZ not only increased grade 3/4 side effects from 34.4% to 63.3%, but it also decreased overall survival to a median 11.5 mo. These data suggest that one of the other second-line therapies, such as AA/P or cabazitaxel plus prednisone (CBZ/P), might be the drug of choice, rather than ENZ, in patients who need corticosteroids for the management of associated comorbidities.

Sternberg et al. [21] reported that ENZ is equally effective in patients aged >75 yr, with a median survival time of 18.2 mo as compared to the placebo group with 13.3 mo ($p = 0.0044$).

Fleming et al. [22] identified a longer disease history (7.9 yr vs 5.9 yr), a better PSA response (87% vs 52%), and a lower metastatic burden associated with long-term response of 35% and 22% after 12 mo and >18 mo, respectively. These data seem to be important for the decision-making process about the most appropriate therapy for mCRPC patients following docetaxel chemotherapy.

Cabazitaxel plus prednisone

In the XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone-Refractory Metastatic Prostate Cancer (TROPIC) trial, 755 patients with mCRPC who progressed during or after docetaxel-based chemotherapy were prospectively randomized to receive CBZ/P or mitoxantrone/prednisone (MP) at 21-d intervals for 10 cycles [5]. The primary end point was achieved and CBZ/P treatment resulted in a median overall survival of 15.1 mo in the CBZ/P compared to 12.7 mo in the mitoxantrone/prednisone group (hazard ratio [HR]: 0.70; 95% confidence interval [CI], 0.59–0.83; $p < 0.0001$). All secondary end points of the trials were reached and they were in favor of CBZ. The most common side effects were neutropenia (CBZ/P group: 82% vs MP group: 58%), leukopenia (CBZ/P group: 68% vs MP group: 42%), and anemia (CBZ/P group: 11% vs MP group: 5%). Diarrhea was the most common non-hematologic side effect and occurred in 6% of the CBZ/P group and <1% of the MP group.

On the other hand, the German compassionate use program (CUP) included 111 patients with mCRPC who met the inclusion criteria of the TROPIC trial; the frequency of neutropenia, leukopenia, and anemia decreased to 7.2%, 9.0%, and 4.5%, respectively [23]. Grade 3/4 gastrointestinal toxicity was observed in only 0.9% of the patients. The most likely reason for the improved toxicity profile is the experience of the investigators, guideline-compliant application of GCSF even at cycle 1, and preventive measures with regard to the treatment of diarrhea.

Recently, Heidenreich et al. [24] analyzed the European CUP, including 746 mCRPC patients, with regard to the frequency and management of adverse events in senior adults. In that study, 325 (43.5%) patients were aged ≥70 yr and 145 (19.4%) men were ≥75 yr. The type and the frequency of grade 3/4 side effects did not differ significantly between the younger and the older patients except that the frequency of grade 3/4 neutropenia was slightly higher in the group of men aged ≥75 yr (19.7% vs 15%). Furthermore, GCSF was used more often at cycle 1 (58.5% vs 47%) and throughout CBZ/P treatment (66.8% vs 58%) in the ≥75 age group

versus the <70 age group. In their analysis, Heidenreich et al. [24] developed a risk model to predict grade ≥3 neutropenia and/or neutropenic complications based on a multivariate analysis. Age ≥75 yr, cycle 1, and neutrophil count <4000/mm3 before CBZ injection were associated with neutropenic complications. It has to be mentioned that even in the presence of these risk factors, prophylactic application of GCSF significantly reduced neutropenic complications by 30% (odds ratio: 0.70; 95% CI, 0.50–0.99; p = 0.04).

Bone-targeting agents

More than 90% of patients with CRPC have bone metastases, which are a major cause of death, disability, and decreased quality of life, as well as increased cost of treatment [25]. Zoledronic acid and the receptor activator of nuclear factor κB (RANK) ligand inhibitor denosumab are the two US Food and Drug Administration–approved bone-targeting agents in the management of CRPC [3].

In a phase 3 study, the median time to first on-study, skeletal-related event was 20.7 mo with denosumab compared with 17.1 mo with zoledronic acid (HR: 0.82; 95% CI, 0.71–0.95; p = 0.0002 for noninferiority; p = 0.008 for superiority) [26]. In a recent, prospective, randomized, double-blind, placebo-controlled trial, Smith et al. [27] evaluated the therapeutic efficacy of denosumab 120mg every week versus placebo in 1423 men with nonmetastatic CRPC and aggressive PSA kinetics (PSA level >8.0 ng/ml and/or PSA doubling time <10 mo). The median time to first bone metastases was significantly prolonged by 4.3 mo (29.5 mo vs 25.2 mo; p = 0.028). Bone metastases-free survival was significantly improved by 16%, 23%, and 29% in patients with a PSA doubling time of <10 mo, <6 mo, and <4 mo, respectively.

Radium-223

Radium-223 is a radiopharmaceutical that acts as a calcium mimic and targets new bone growth in and around bone metastases via heavy alpha particles that have an ultrashort range of <100µm. A Phase 3 Study of Radium-223 Dichloride in Patients with Symptomatic

Hormone Refractory Prostate Cancer with Skeletal Metastases (ALSYMPCA), which included 921 CRPC patients, the median overall survival was 14.9 mo in patients treated with radium-223 compared with 11.3 mo in the placebo group (HR: 0.695; 95% CI, 0.581–0.8732; $p <$ 0.0001) [7].

1.1.3. New and emerging developments

Agents targeting steroidogenesis

Orteronel (TAK-700) selectively blocks 17,20-lyase, resulting in fewer mineralocorticoid effects than AA [28]. In the phase 2 portion of a dose-finding study, Orteronel (TAK-700) 400mg twice daily with prednisone 5mg twice daily resulted in a reduction in PSA level ≥50% in 52% of the 96 chemotherapy-naïve mCRPC patients at 12 wk. There are two ongoing phase 3 clinical trials in the prechemotherapy (n = 1454) and postchemotherapy (n = 1083) landscape of mCRPC that are evaluating the oncologic activity of orteronel. Both trials have completed recruitment.

Galeterone (TOK-001) has combined activity: It inhibits the human CYP17 enzyme, it has pure antagonistic activity toward the AR, and it inhibits the binding of androgens to both mutant and wild-type AR [29]. In the Androgen Receptor Modulation Optimized for Response (AMORI) trial, 49% of chemotherapy-naïve mCRPC patients experienced a PSA-level reduction of ≥30%, and a ≥50% reduction was achieved by 22% [30]. Despite the absence of steroid co-treatment, no adrenal mineralocorticoid excess was observed and a phase 2 trial is underway.

Androgen-receptor blocking agents

ARN-509 is a full antagonist to AR overexpression: It inhibits androgen-dependent gene description, and it impairs nuclear translocalization and DNA binding of AR [31]. Currently, three prospective randomized phase 3 clinical trials are underway including (1) patients with

high-risk and nonmetastatic CRPC, (2) treatment-naïve patients with mCRPC, and (3) patients with progression following AA/P treatment. Preliminary results have been presented for the first two groups and a ≥50% decline in PSA level was achieved in 91% of patients with high-risk and nonmetastatic CRPC and in 88% of treatment-naïve patients with mCRPC. The most common side effects were tolerable fatigue and gastrointestinal events.

ODM-201 is another antiandrogen with similar mechanisms of actions as described for ENZ and ARN-509 [31]. The potential advantage of ODM-201 is that it does not cross the blood– brain barrier and so might prevent the development of seizures. ENZ-4176 is a novel, nucleic acid–based antisense oligonucleotide against AR, which results in selective and specific downregulation of AR mRNA and protein.

Heat shock proteins

Heat shock proteins (HSPs) have been identified as AR coactivators and chaperone proteins that are increased in PCa cell lines after castration [32]. Quite recently, antisense oligonucleotides targeting HSP27 were evaluated in a phase 2 clinical trial including 72 patients chemotherapy-naïve mCRPC patients who received OGX-427 plus prednisone versus prednisone alone. At 12 wk, 71% and 40% of the patients were progression-free after OGX-427 or prednisone, respectively. A decline of ≥50% in PSA level was observed in 50% and 20% in the OGX-427 group and in the prednisone group, respectively. Furthermore, measurable disease response occurred in 44% and 0% of the OGX-427 group and the prednisone group, respectively.

1.1.4 Targeted therapies

Cabozantinib

Cabozantinib is another promising bone-targeting agent that inhibits both vascular endothelial growth factor and met proto-oncogene (hepatocyte growth factor receptor; MET). In a

prospective, randomized, placebo-controlled, phase 2 clinical trial, 171 mCRPC patients were enrolled to receive cabozantinib (100mg daily) or placebo [33]. Random assignment was halted early based on the observed activity of cabozantinib. Respectively 5% and 75% of patients treated with cabozantinib had a confirmed partial response and stable disease. The median progression-free survival was 29.7 wk, 23.9 wk, and 5.9 wk for patients who were docetaxel naïve, docetaxel pretreated, and on placebo treatment ($p < 0.001$), respectively. Interestingly, PSA changes did not correlate with the antitumor effects in bone metastases and soft-tissue lesions. However, patients with complete resolution (n = 14; 12%) or partial resolution (n =65; 56%) of bone scans experienced significantly better response rates to soft-tissue metastases as compared to men with stable or progressing bone scans (81% vs 61%), and they also experienced longer progression-free survival rates at 6 mo (56% vs 48%, respectively). Cabozantinib has significant antitumor activity and a well-tolerated toxicity profile, so it might be well integrated into the therapeutic armamentarium to treat mCRPC.

Targeted radionuclide Therapy

Over the past several decades, numerous combined diagnostic and therapeutic radioligands (Theranostics) were designed to target receptors on the cancer cell surface. Antibodies (whole or small fragments), small molecules, peptides with affinities to receptors (agonist or antagonist) have demonstrated in vivo efficacy for targeting cancers based on up-regulated antigens or receptor populations. This approach, also called radioligand therapy (RLT), presents several advantages over conventional chemotherapy. The expression of the antigens or special receptors can be identified by a diagnostic probe before exposing patients to therapeutic doses of these agents allowing identification of suitable subjects for therapeutic procedures and preventing unnecessary exposure of the patients to radiation without significant benefit. This approach allows the physician to select only those patients with high expression of the target prior to treatment. Since the unused radioactive materials are excreted from the body, RLTs are generally well tolerated with no significant or generally reversible or

manageable side effects as has been demonstrated for ^{177}Lu-DOTATATE treatment in patients with neuroendocrine tumor [34].

Prostate cancer demonstrates high expression levels of prostate-specific membrane antigen (PSMA) on its cell surface. Thus PSMA has become a biomarker for prostate cancer [35] [36] and has attracted significant interest as a target for the imaging [37] [38] and therapy [39, 40]. In particular, development of small urea-based PSMA ligands have received significant interest due to their high affinity for PSMA [41] [42]. The urea-based PSMA ligands were modified to deliver a variety of radio-imaging nuclides for both PET and SPECT. Gallium (^{68}Ga) labeled urea-based PSMA ligands have been developed as diagnostic agents and studied by several groups [43] [44]. More recently a Lutetium (^{177}Lu) labeled urea based PSMA ligand (DOTA PSMA or PSMA 617) were evaluated in preclinical and clinical phase. Characteristics of ^{177}Lu labeled PSMA are described below.

1.2 Characteristics of 177 Lu-DOTA-PSMA (177Lu-PSMA-617)

Lutetium (^{177}Lu) –DOTA PSMA has three components: PSMA is the targeting vector , DOTA (1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid) is a radiometal chelator and a linking group, and ^{177}Lu is the beta emitter that upon internalization delivers radiation to the nucleus of tumor cells to cause DNA damage [43] [44, 45]. The targeting vector utilizes glu–urea–lys sequence which is an inhibitor capable of binding to the domain of PSMA. These components have been previously used in human subjects and in medical research.

1.3 Background of Drug Development

There is substantial previous pre-clinical and clinical experience with ^{177}Lu-PSMA-617 published in peer reviewed medical literature from multiple medical centers throughout the world. Sponsors are relying on studies published in the peer viewed medical journals for

preclinical and preliminary clinical information. Summary of such reports is given below.

1.3.1 Preclinical Studies.

Martina Benesova et al. [46] performed a preclinical evaluation of radiolabeled PSMA-617. PSMA-617 was synthesized by solid phase peptide synthesis. PSMA-617 can be labeled with ^{177}Lu and Ga-68. Both in vivo and vitro studies were performed using LNCaP cell lines expressing PSMA. PSMA-617 showed highest inhibition potency Ki = 6.91±1.32 for Lu complex; 6.40 ± 1.02nM for Ga complex. PSMA-617 showed higher specific internalization in LNCaP cells.

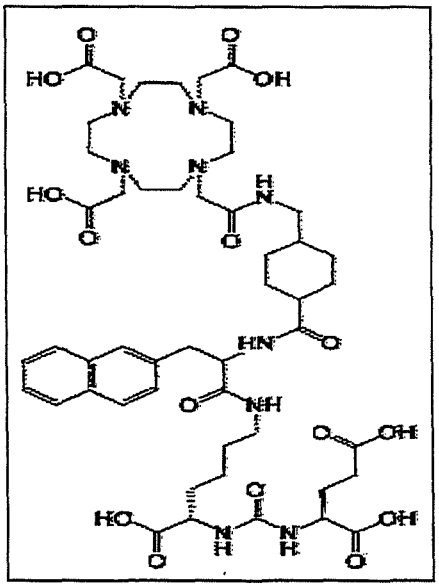


Figure 2: Structure of PSMA 617. Chemical Name 2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid.

The i.v. administered Lu-PSMA-617 effectively cleared the blood by 1 hr. Clearance of radioactivity occurred largely through the renal system. As a result of this, the kidneys exhibited significant uptake 137. 2 ± 77.8% ID/g; this could be effectively blocked (0.85 ± 0.22 %ID/g)

by co-injection of PMPA [2 mg/kg], a high affinity inhibitor of PSMA. At 24 hr ^{177}Lu-PSMA-617 shows rapid clearance from the kidney 2.13 ± 1.36 %ID/g highlighting its potential use as theranostic agent. At 1 hr time point ^{177}Lu-PSMA-617 displayed good in vivo tumor targeting with 11.20 ± 4.17 %ID/g. Accumulation in tumor was PSMA specific with reduction to 0.64 ±0.07 %ID/g by coinjection of 2-PMPA. At 24 h post injection 10.58 ± 4.50 %ID/ uptake was retained in the tumor tissue. For all other non-target tissues, ^{177}Lu- PSMA-617 demonstrated rapid clearance. The ratio of tumor to blood was 1058; tumor to muscle was 529 at 24 hr post injection. These favorable pharmacokinetics are crucial for imaging and therapy. The detailed biodistribution results are summarized in Figure 3. ^{68}Ga-PSMA 617 showed similar uptake in the LnCaP tumors (11.20± 4.17 %ID/g). It also shows similar pharmacokinetic clearance profile compared with ^{177}Lu- PSMA-617.

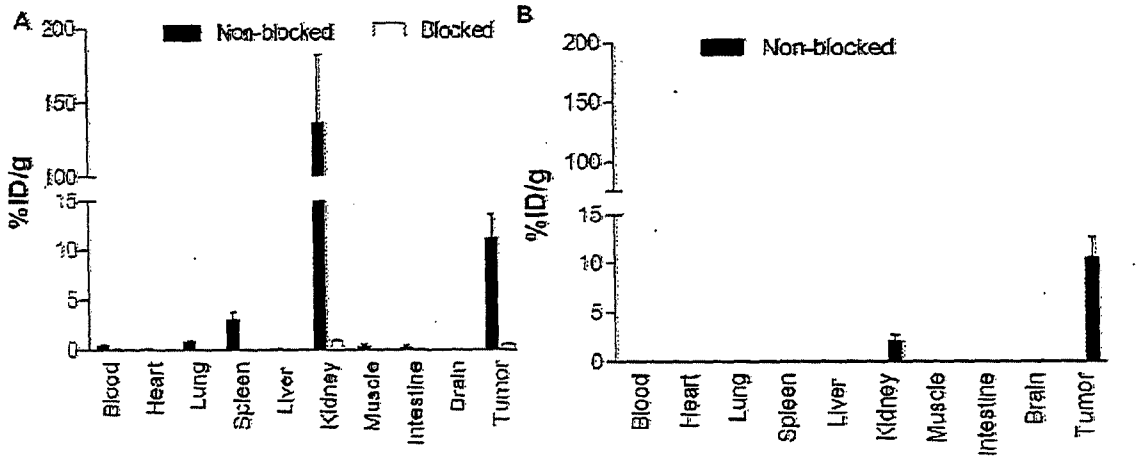


Figure 3: Distribution assay of ^{177}Lu-PSMA-617 in BALB/c mice with LNCap xenografts at 1 h (a) and 24 h (B) post injection.

In summary authors concluded the present radiotracer is suitable for theranostic application in human prostate cancer.

1.3.2 Clinical Studies

Current literature is available to evaluate management of patients with prostate cancers. The studies presented in this section were chosen based on novelty of the approach (initial report of application, variables for analyses) and/or the number of patients included.

Clemens Kratochwil et al. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2015; 42:6 ;987-988. [47]

Study Design: First reported application of ^{177}Lu-PSMA-617 for treatment of a patient with mCRPC. Patient had proven PSMA expression and PSA of 38.0 ng/ml prior to treatment and has received 7.4 GBq of ^{177}Lu-DKFZ-617 in 2 cycles 3 months apart.

Toxicity: No potential side effects were reported in this study.

Results: After the radiotherapy ^{177}Lu-PSMA-617, PSA level of patient decreased to 4.6 ng /ml. PET/CT images showed no signs of metastases lesions either shrunk or were undetectable.

Conclusion: Authors are planning to conduct multicenter a clinical trial as soon as possible to examine clinical potential of ^{177}Lu-PSMA-617.

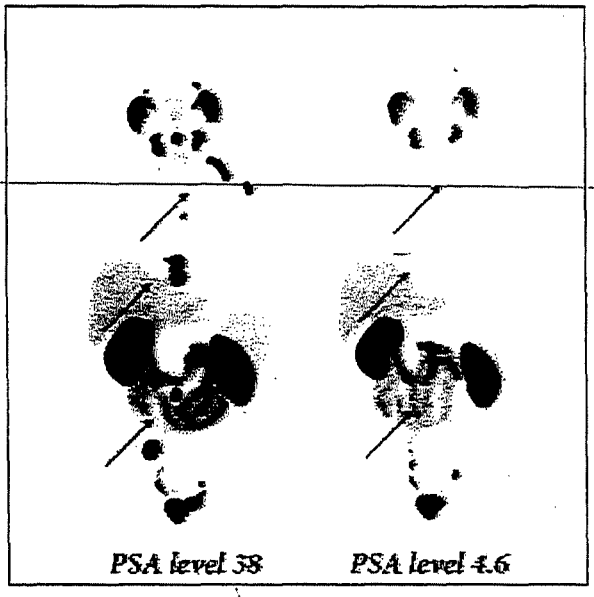


Figure 4: Above Image has recently awarded as image of Year Award and the Berson-YalowAward at the 2015 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) in Baltimore, USA.

Hojjat Ahmadzadehfar et al. Early side effects and first results of radioligand therapy with ^{177}Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-center study. *EJNMMI Research* 2015; 5:36. [48]

Study Design: A total of 10 consecutive hormone and /or chemo refractory PCa patients with distant metastases and progressive disease with rising PSA levels were recruited in this study. All patients had prior history or were under therapy with enzalutamide and/or abiraterone. Four patients had received ^{223}Ra-dichtochloride (1-4 cycles). All 10 patients underwent with ^{68}Ga-PSMA HBED-CC (^{68}Ga-PSMA) PET /CT prior to therapy to evaluate PSMA expression. Ten patients were treated with range of 4.1-6.1 GBq dose of ^{177}Lu-DKFZ-617 PSMA. All patients were treated with single dose of ^{177}Lu-PSMA-617. The mean and median PSA levels prior to therapy were 339.4 and 298.5 ng/ml. Complete blood chemistry, renal and liver function tests were performed a day before and 2 after the radiotherapy. Patients were followed via telephone every week for safety assessment.

Toxicity: No patient experienced any side effects immediately after injection of ^{177}Lu-DKFZ-617 PSMA. Relevant hematotoxicity (grade 3 or 4) occurred 7 weeks after the administration in just one patient. The same patient showed a leucopenia grade 2. Two patients showed a disturbance of only 1 hematologic cell line, whereas one patient showed a reduction of grades 1 and 2 in leucocytes and thrombocytes, respectively. Six patients did not show any hematotoxicity during the 8 weeks after therapy. There was no relevant nephrotoxicity (grade 3 or 4).

Results: Eight weeks after the therapy, seven patients (70 %) experienced a PSA decline, of which six experienced more than 30 % and five more than 50 %. Three patients showed a progressive disease according to the PSA increase.

Conclusions: ^{177}Lu-DKFZ-617 PSMA radiotherapy with single dose for the treatment of metastatic prostate cancer patients without any other therapy option is safe and seems to have a low early side-effect profile with evidence of positive response to the therapy according to PSA decline in 70 % of patients. The authors also stated ^{177}Lu-DKFZ-617 PSMA has potential to exhibit suitable agent for radionuclide radiotherapy.

Clemens Kratochwil, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with Lu-177 labeled PSMA-617 J Nucl Med March 16, 2016 [49]

Study Design: Radionuclide therapy with ^{177}Lu-PSMA-617 was performed on 30 patients with PSMA positive tumors were enrolled in this study. 30 patients were treated with 1-3 cycles of 177Lu-PSMA-617. Pharmacokinetic and radiation dosimetry was also evaluated during course of the study.
Results: 21 of 30 patients showed response to therapy; for 13/30 the PSA decreased >50%. After 3 cycles 8/11 patients achieved a sustained PSA response (>50%) for over 24 weeks. ^{177}Lu-PSMA-617 showed fast renal wash out within 48 hours of injection. Patients showed mild nausea, fatigue and Xerostomia (<10%) over a period of time. No acute hematotoxicity was observed during the study. Dosimetry results revealed that ^{177}Lu-PSMA-617 has an exposure of 0.75 Gy/GBq for kidney 0.03 Gy/GBq red-marrow, 1.4 Gy/GBq salivary glands and 6-22 Gy/GBq for tumour lesions.

Conclusion: Based on the results authors concluded that targeted radioligand therapy with 177Lu- PSMA-617 is safe and promising therapy option for metastasized castrate resistant prostate cancer.

Ahmadzadehfar H, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-SMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016 Feb 8. doi: 10.18632/oncotarget.7245. [50]

Study Design: Radionuclide therapy with ^{177}Lu-PSMA-617 was performed in 24 hormone and/or chemo-refractory PC patients. Forty-six cycles of ^{177}Lu-PSMA-617 were performed. Side effects and response rate was assessed.
Results: Eight weeks after the first cycle of ^{177}Lu-PSMA-617 therapy 79.1% experienced A decline in PSA-level. Eight weeks after the second cycle of Lu-PSMA therapy 68.2% experienced a decline in PSA relative to the baseline value. Apart from two cases of grade 3 anemia, there was no relevant hemato- or nephrotoxicity (grade 3 or 4).
Conclusion: ^{177}Lu-PSMA-617 is a safe treatment option for metastatic PC patients and has a low toxicity profile. A positive response to therapy in terms of decline in PSA occurs in about 70% of patients.

Madhav Prasad Yadav, et al. ^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2016 Aug 10. [51]

Study Design: Radionuclide therapy with ^{177}Lu-PSMA-617 was performed in 31 patients with progressive disease despite second-line hormonal therapy and/or docetaxel chemotherapy. Patients underwent 1 to 4 cycles after a ^{68}Ga-PSMA-HBED-CCP ET/CT for inclusion (mean activity 5069 ± 1845 MBq). Hematological, kidney function, liver function tests, and serum PSA levels were recorded before and after therapy at 2 weeks, 4 weeks, and 3 month intervals. Biochemical response was assessed with trend in serum PSA levels. Metabolic response was assessed by PERCIST 1 criteria. Clinical response was assessed by visual analogue score (VASmax) analgesic score (AS), Karanofsky performance status (KPS), and toxicity and response criteria of the Eastern Cooperative Oncology Group (ECOG) criteria.

Results: Biochemical response in terms of complete response (CR), partial response(PR), stable disease (SD), and progressive disease (PD) was observed in 2/31, 20/31, 3/31, and 6/31 had, respectively. Mean VASmax and mean analgesic scores decreased from 7.5 to 3 and 2.5 to 1.8 after therapy, respectively Mean KPS and mean ECOG performance status score improved from 50.32 to 65.42 after therapies, respectively. Two patients experienced grade I and grade II hemoglobin toxicity each. None of the patients experienced nephrotoxicity or hepatotoxicity.

Conclusion: ^{177}Lu-DKFZ-PSMA-617 radionuclide therapy is a safe and effective approach in the treatment of mCRPC patients.

1.3.3 Sponsors Experiences

1.3.3.1 Preclinical Toxicity Studies

The aim of study was to evaluate toxicity of PSMA-617. PSMA-617 applied once weekly by intravenous administration to male rats over 22 days. The animals were treated with 40, 160 or 400 µg of PSMA-617/kg b.w. by tail vein intravenous bolus injection on test days 1, 8, 15 and 22. The control group was treated with physiological saline. No deaths were noted. No signs of local or systemic intolerance reactions were observed. Body weight and body weight gain, food intake, and drinking water consumption were not influenced. No test item-related changes were noted for the hematological and biochemical parameters, the urinary status, the eyes and optic region, the auditory acuity, the relative and absolute organ weights, and the myeloid: erythroid ratio. No test item-related abnormalities were noted during macroscopic inspection at necropsy and at histopathological examination.

Under the test conditions of this study, the no-observed-adverse-effect-level (NOAEL) was 400 µg PSMA-617 / kg b.w. administered once weekly by intravenous bolus injection. This dose was the highest dose tested. Detailed description of this study is attached in appendix I.

1.3.3.2 Summary of Human Studies - German Multicenter Experience

Rahbar K, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med. 2016 [52]

Study design: Retrospective acquisition and pooling of data for toxicity and PSA response in patients after ^{177}Lu-PSMA-617 RLT performed in Germany until July 2015 was initiated by the German Society of Nuclear Medicine for research purpose. The following contains a summary of the collected data.145 patients with metastatic castration-resistant prostate cancer received a median of two cycles (range 1 to 4) of ^{177}Lu-PSMA RLT at twelve German Nuclear Medicine Clinics. Data on safety and efficacy were reported. Table 1 lists the **administered ^{177}Lu-PSMA-617 activity** for this study cohort.

Table 1. Administered ^{177}Lu-PSMA-617 activity (n = 248 RLT cycles)

Administered activity (GBq)	Cycle 1	Cycle 2	Cycle 3	Cycle 4
<3.5	9	3	0	1
> 3.5 – 4.5	32	14	2	0
> 4.5 – 5.5	16	12	9	0
> 5.5 – 6.5	71	37	14	2
> 6.5	17	8	1	0

Results:

A. Toxicity: Nuclear medicine physicians responsible for ^{177}Lu-PSMA RLT and subsequent follow-up reported potentially related or unrelated adverse events based on a standard template. In addition toxicity was determined by baseline and follow-up findings for serum creatinine, AST, ALT, white blood cell count, hemoglobin and platelet count for 121 of 145 (83%) patients. The follow-up period for adverse events was 2 to 30 weeks. Reported toxicity sorted by organ system is given in Table 1. Grade 3-4 anemia occurred in 15 (10%) patients and grade 3-4 thrombocytopenia occurred in 5 (4%) patients. The rate of grade 3-4 events was low for all other categories (0 to 3 patients; 0 to 2%).

There were fewer hematologic adverse events when compared to patients with metastatic castration resistant prostate cancer treated with placebo or ^{223}Ra within the ALSYMPCA trial [7] (grade ≥3 anemia: 14% in the placebo and 13% in the 223Ra group; grade ≥ thrombocytopenia: 3% in the placebo and 7% in the ^{223}Ra group). Toxicity data thus indicate a favorable safety profile for RLT using 2-7 GBq ^{177}Lu-PSMA-617 per cycle in patients with metastatic castration resistant prostate cancer.

Majority of patients received 5.5 – 6.5 GBq (median 6.0 GBq) or >6.5 GBq (median 7.4 GBq) per cycle. Toxicity rates were comparably low: 9 of 71 (13%) patients with 5.5 – 6.5 GBq and 3 of 17 (18%) patients with >6.5 GBq during the first RLT developed grade 3-4 toxicity.

Table 2. Adverse events after ^{177}Lu-PSMA-617 as determined by blood tests (n=121) or physician reports (n=145)

Organ system	Category	Evaluated for N	All grades	Grade 3-4
Blood and Lymphatic disorders				
	Leukopenia	121	48 (40%)	4 (3%)
	Anemia	145	50 (34%)	15 (10%)
	Thrombocytopenia	121	38 (31%)	5 (4%)
Gastrointestinal disorders				
	AST elevation	121	27 (19%)	0 (0%)
	ALT elevation	121	11 (8%)	0 (0%)
	Xerostomia	145	11 (8%)	0 (0%)
	Nausea	145	9 (6%)	0 (0%)
	Dysgeusia	145	6 (4%)	0 (0%)
	Ascites	145	2 (1%)	0 (0%)
	Biliary obstruction	145	0 (0%)	1 (1%)
General disorders				
	Fatigue	145	19 (13%)	1 (1%)
	Pain	145	5 (3%)	0 (0%)
	Ileus	145	1 (1%)	0 (0%)
Urinary disorders				
	Renal failure	121	14 (12%)	0 (0%)
	Urinary tract inf.	145	1 (1%)	0 (0%)
Cardiovascular disorders				
	Edema	145	2 (1%)	0 (0%)
	Lung embolism	145	0 (0%)	3 (2%)
Respiratory, thoracic and mediastinal disorders				
	Pleural effusion	145	1 (1%)	0 (0%)
	Dyspnea	145	1 (1%)	0 (0%)
Neurologic disorders				
	Vertigo	145	1 (1%)	0 (0%)
	Stroke	145	0 (0%)	2 (1%)
Musculoskeletal disorders				
	Bone fracture	145	0 (0%)	3 (2%)

Efficacy

Serial PSA levels at baseline and follow-up were recorded for 99 of 145 patients (68%). Response was expressed as percent change in serum PSA from baseline to the lowest PSA level measured at follow-up (best PSA response).

Over the entire follow-up period 45 of 99 (45%) patients demonstrated a PSA decline ≥ 50% and were considered biochemical responders. Any PSA decline occurred in 59 of 99 (60%) patients (Figure 7). After the first cycle a PSA decline ≥ 50% occurred in 40 of 99 (40%), any PSA decline in 65 of 99 (66%) patients (Figure 8A). After the second therapy cycle of ^{177}Lu-PSMA-617 RLT a PSA decline ≥ 50% occurred in 35 of 61 (57%) and any PSA decline in 44 of 61 (72%) patients (Figure 8B). Patients receiving a third or fourth cycle of therapy showed a PSA decline ≥ 50% in 13 of 20 (65%) and 3 of 3 (100%) patients, respectively.

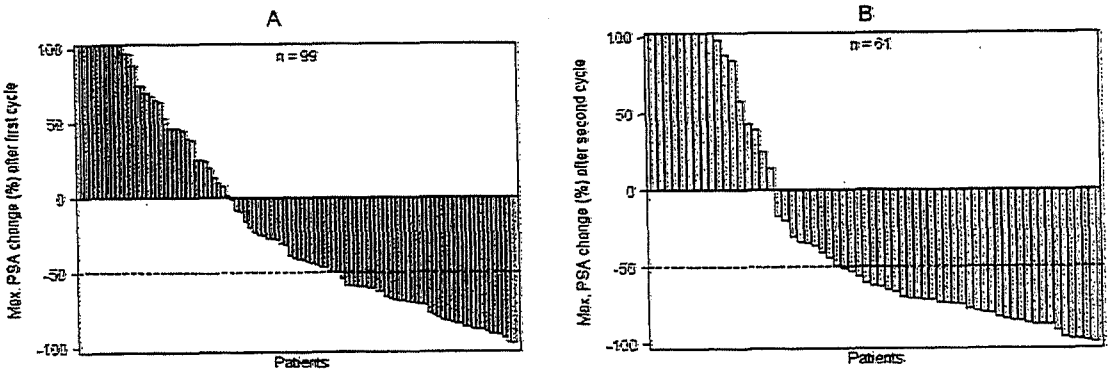


Figure 7. Waterfall plot of maximum PSA change (%) from baseline over total follow-up period. PSA increase of more than 100% was cropped due to simplification.

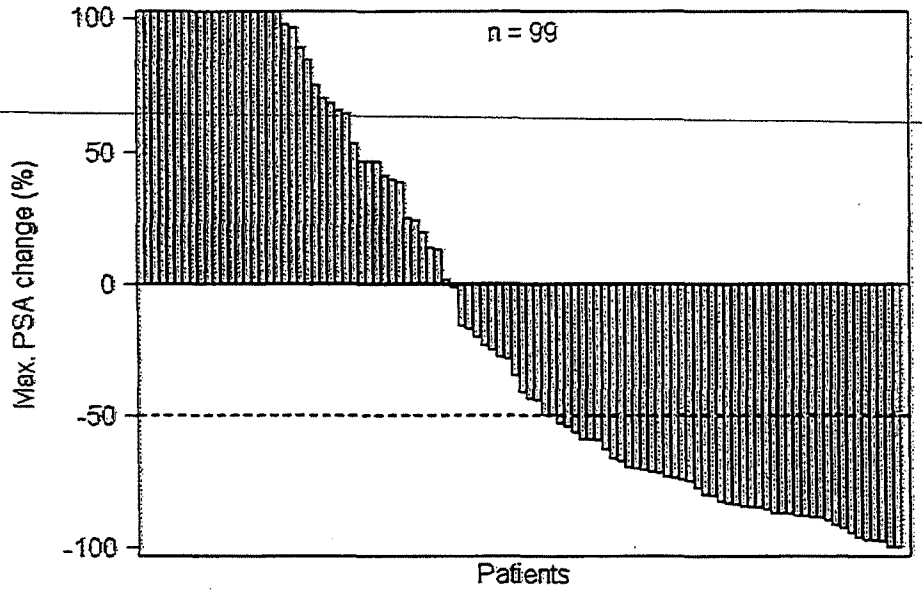


Figure 8. Waterfall plots of maximum PSA change (%) after the first cycle (A) and after the second cycle (B). PSA increase of more than 100% was cropped due to simplification.

Response rate was higher than the rate in patients with metastatic castration resistant prostate cancer treated with abiraterone (best PSA response >50% after abiraterone plus prednisone: 43% (25 of 58) patients) [53]. Data thus indicate good efficacy for ^{177}Lu-PSMA RLT in patients with metastatic castration resistant prostate cancer. Response rates were not significantly associated with mean activity per cycle (p=0.46) or cumulative activity after two cycles (p=0.22).

2. Study Objectives

Primary Objectives:

1. To assess the clinical safety of ^{177}Lu-PSMA-617 by evaluation of adverse events (AE) using the Common Terminology Criteria for Adverse Events (CTCAE)

2. To assess the efficacy as defined by proportion of patients with PSA-response of ≥50% decline at 12-weeks from baseline

Secondary Objectives:

1. Maximum PSA response: Maximal baseline to follow-up PSA decline at any time during or after therapy [1]

2. To determine the time to PSA progression, separate for treatment doses: time from inclusion to date until PSA progression or death (whichever occurs first) [1]

   a. for patients with PSA decline: Time from baseline to time the PSA increase to 25% and 2 ng/ml above nadir which is confirmed by a second value ≥3 weeks later

   b. for patients without PSA decline: Time from baseline to time the PSA increase to 25% and 2 ng/ml above baseline

3. To determine radiographic Progression-free Survival (rPFS), for each treatment dose: time from inclusion to date when first site of disease is found to progress or death (whichever occurs first)

   a. Nodal and visceral disease is evaluated on cross-sectional imaging using RECIST 1.1/PCWG criteria

   b. Bone metastases are evaluated using bone scintigraphy and new lesions have to be confirmed on a second scan (2+2 rule) using PCWG criteria

4. To determine disease control rate (DCR) defined as the proportion of patients achieving RECIST 1.1/PCWG criteria stable disease (SD), partial response (PR) or complete response (CR).

5. Change in Pain and Quality of Life: Pain and "Epic-26" Questionnaires will be completed at baseline and at 3, 6, 9, 12, 18 and 24 mo. Pain response will be determined in accordance with PCWG [1].

6. Change in ECOG Performance Score.

3. Investigational Plan

3.1 Overall Study Design and Dosing of Targeted PSMA Radioligand Therapy (RLT)

This is a open-label, multicenter, prospective trial. Upon inclusion patients will be randomized into two treatment doses. RLT will be performed by repeated i.v. application of 6.0 GBq (±10%) or 7.4 GBq (±10%) ^{177}Lu-PSMA-617 every 8±1 weeks until reaching four cycles or threshold maximum dose to the kidneys of 23 Gy. All doses after labeling will be presented in

buffered solution for intravenous injection.

In total, 200 subjects with histologically proven prostate cancer and mCRPC will be enrolled. Salivary protection will be accomplished by applying ice pack starting 30 minutes prior to infusion of radiopharmaceutical and will continue for 4 hours. Subjects will be recruited at up to 3 Nuclear Medicine sites selected for this project. Each subject will undergo a screening visit within 14 days prior to receiving study drug.

Dosimetry was required to be performed in the initial versions of the study according to dosimetry protocol (Appendix V) provided by Prof.r. [redacted] to determine dose to the kidneys. Treatment was continued until either of the following conditions applied:

- PSA/radiographic progression at ≥12 weeks as defined above
- Completion of four RLT cycles
- 23 Gy kidney dose would be exceeded by the next cycle as estimated by dosimetry
- Patient withdrawal (e.g. appearance of intolerable adverse events)

Dosimetry data for 20 patients on study (16 from UCLA and 4 from Excel Diagnostics) was analyzed and it was found that the permitted renal dose of 23 Gy was not exceeded in any patient after 4 cycles demonstrating overall favorable renal dosimetry and dosimetry is no longer required per protocol. (see Section 8.4.3 for additional details)

Primary objectives of the study is efficacy and safety.

Efficacy is determined by PSA response rate: Patients with baseline to follow-up decline in tumor marker level (PSA) ≥50% at 12 (±1) week will be considered responders.

For safety assessment, vital signs will be measured within 20 minutes before and for up to an hour after administration of ^{177}Lu-PSMA-617. Blood samples will be collected for CBC and CMP with eGFR at baseline (within 72 hours of first treatment dose) and then every 2 weeks (+/- 3 days) after first dose continued until 12 weeks after the last dose and then every 3 months (+/- 1 week) thereafter until the end of follow-up visits (24 months from 1st therapy date). The CBC and CMP within 2 weeks of each subsequent treatment cycle will be used to assess

eligibility of the corresponding treatment cycle. CBC will be performed every 7 days for patients who experienced toxicity more than grade II due to this study (based on NCI CTCAE Ver.4) until recovery which is defined as grade 2 toxicity or lower. CTCAE v 4.0 will be used to evaluate renal toxicity. For more information, please refer to the Schedule of Events (Appendix II).

3.2 Rationale for Study Design

3.2.1 Rationale for a regimen with multiple therapy cycles

Activity given during targeted radionuclide therapy is limited by radiation dose to healthy organs. Based on dosimetry radiation dose to healthy organs and subsequent maximal cumulative activity can be calculated. To obtain optimal safety margin maximal cumulative activity is not given in one treatment session but approached by application of a defined fraction of this activity in several cycles. The administration of a standard activity over several treatment cycles allows for early and individual estimation of radiation dose and tolerability. The efficacy and safety of a sequential approach was proven in patients with ^{223}Ra therapy for metastatic castration-resistant prostate cancer (mCRPC) [7] and in patients with ^{177}Lu-DOTATATE therapy for midgut neuroendocrine tumor (NET) [54] each in prospective, double-blind, randomized, international, and multicenter phase III trials. Based on this evidence targeted PSMA Radioligand Therapy (RLT) will be performed by sequential applications of ^{177}Lu-PSMA-617 with treatment-free intervals.

3.2.2 Rationale for eight weeks interval

Highest level of evidence for subacute adverse events after radionuclide therapy was published for patients with non-Hodgkin's lymphoma. Witzig et al analyzed safety and efficacy of ^{90}Y-Ibritumomab Tiuxetan in 73 patients in a prospective Phase III randomized trial. This study reports neutrophil, platelet and hemoglobin nadir approximately six weeks after application of the beta emitter [55]. Based on this study ^{177}Lu-PSMA-617 RLT will be performed by

sequential applications with a treatment-free interval of eight weeks to minimize risk of repeated ^{177}Lu-PSMA-617 therapy before reaching blood level nadir. This scheme is also supported by safety data from the phase III NETTER-1 trial on safety and efficacy of ^{177}Lu-DOTATATE in patients with midgut NET. Here ^{177}Lu-DOTATATE was administered at seven to nine week intervals and rate of severe adverse events was below 10% for 115 patients in the treatment arm [54].

3.2.3 Rationale for dose regimen

Ahmadzadehfar et al reports safety and efficacy after application of a mean activity of 6.0 GBq ^{177}Lu-PSMA-617 in 24 patients with mCRPC [50]. Patients were treated with up to two cycles of ^{177}Lu-PSMA-617 RLT at eight week intervals. Grade 3 hematotoxicity occurred in two patients. No nephrotoxicity or hepatotoxicity grade ≥3 was documented. Kratochwil et al reports safety and efficacy after repeated application of ^{177}Lu-PSMA-617 in 30 mCRPC patients [49]. 19 of 30 patients (63%) received 6.0 GBq ^{177}Lu-PSMA-617 every two mo. One patient developed grade 3 anemia, one patient grade 3 thrombocytopenia. Both patients had diffuse pattern of bone marrow infiltration at baseline. The German Society of Nuclear Medicine (DGN) performed a questionnaire based survey on the use of ^{177}Lu-PSMA-617 RLT in December 2015. Nuclear Medicine Clinics in Germany reported compassionate use of ^{177}Lu-PSMA-617 RLT in 145 mCRPC patients until June 30th 2015 [52]. Majority of patients received 5.5 – 6.5 GBq (median 6.0 GBq) or >6.5 GBq (median 7.4 GBq) per cycle (Table 1) and rate of serious adverse events was below 20% for both subgroups. Phase III data for ^{177}Lu-DOTATATE, a similar RLT for midgut NET patients, demonstrates a rate of severe adverse events below 10% after application of four cycles of 7.4 GBq in 115 patients [54]. Thus, present evidence indicates that repeated applications of 6.0 or 7.4 GBq ^{177}Lu-PSMA-617 RLT are well tolerated with low to very low rates of serious adverse events.

Standard activities of 6.0 and 7.4 GBq are also supported by dosimetry data available in more

than ten patients [56] [57]. Maximal cumulative activity is limited by the absorbed dose in critical organs. Dosimetry identifies kidney and salivary glands as organs with highest absorbed dose [56] [57]. Thus maximum cumulative activity is determined by absorbed kidney dose. Based on earlier evidence obtained from external beam radiotherapy the maximum tolerable per kidney dose is generally accepted 23 Gy [58]. Dosimetry after ^{177}Lu-PSMA-617 application revealed absorbed doses of 0.6 Gy/GBq per kidney [56] [57]. Therefore maximum cumulative activity for ^{177}Lu-PSMA-617 RLT is considered 38.3 GBq (38.3 GBq x 0.6 Gy/GBq = 23.0 Gy radiation dose per kidney). Both the application of four cycles of 6.0 GBq (total 24.0 GBq) or 7.4 GBq (total 29.6 GBq) ^{177}Lu-PSMA-617 results in lower cumulative activities with acceptable safety margin. Whether either activity regimen is associated with longer rPFS is unknown and will be evaluated as secondary endpoint of this trial.

Salivary glands receive highest off-target radiation dose according to dosimetry [56] [57]. Absorbed dose after four cycles of 6.0 or 7.4 GBq ^{177}Lu-PSMA-617 (34.0 Gy or 41.6 Gy respectively) falls within the range of maximum tolerable dose reported for salivary glands in the literature [58] [59] [60]. Maximum tolerable dose to the bone marrow is generally accepted 2 Gy [61]. Bone marrow dose will not exceed this limit after four cycles of 6.0 or 7.4 GBq ^{177}Lu-PSMA-617 [57]

3.2.4 Determination of Sample Size

Sample size calculation was based on the primary endpoint of this protocol, i.e. baseline to 12-week decline in tumor marker level (PSA) ≥50% [53]. Based on a recent publication [52], we estimate that the proportion of patients who meet the primary end point will range between 38% and 65% for both treatment doses. We thus define the following null hypothesis: Less than 40% of patients will reach the endpoint after ^{177}Lu-PSMA RLT. ^{177}Lu-PSMA RLT would therefore be considered worthy of further study if 50% or more patients met the end point and not worthy of further study if 40% and less achieved the end point. This rationale was adapted

from a single-arm study on mCRPC patients with same end point definition, published 2010 in the Journal of Clinical Oncology [53]. We have performed power analysis for the two-sided binomial test (beta 0.2, alpha 0.05) to measure the efficacy of ^{177}Lu-PSMA RLT. A sample size of 200 achieves 78% power (beta 0.2) at a given alpha of 0.05 to distinguish between 40% versus 50% response rates. The power analysis was performed by a trained Biostatistician from the Department of Biostatistics, University of California at Los Angeles using Power Analysis and Sample Size (PASS) 14 software (NCSS LLC).

3.3 Study Duration and Dates

The duration of subject participation will be from the time of signing informed consent through the 24 months post-injection visit or progression. Subjects will be deemed enrolled in the study once the subject signs informed consent.

3.4 Randomization protocol

Randomization will be performed in accordance with Vickers et al. [62]. In order to obtain adequate "allocation concealment" a list of random allocations was created for patients 1 through 200. This list will be stored at investigator's sites and will not be modified. The list will only be accessible for researchers or study personnel not actively involved in the recruitment process.

3.5 Dose modification

In some circumstances, it might be necessary to suspend treatment with ^{177}Lu-PSMA-617, adapt the posology (i.e. administer a half activity), or even definitively stop administration, as described in the following tables. Table 3 lists conditions, if deemed study related by the DSMB, will result in permanent discontinuation.

Table 3: Criteria for permanent discontinuation of treatment with ^{177}Lu-PSMA-617

Definitively stop further administrations in patients who have experienced or are at risk of any of the following conditions during treatment:
a) Severe heart failure (defined as grade III or IV of the NYHA classification)
b) Hypersensitivity to the active substance or to any of the components of this radiopharmaceutical
c) Grade 3 hematologic toxicities that persist > 12 weeks and Grade 4 that persist > 3 weeks.
d) Grade 3 renal toxicity as determined by serum creatinine measurements
e) AST/ALT > 3x ULN and bilirubin > 2x ULN
f) Grade 3-4 non-hematologic toxicities with **select exceptions** for - Grade 3 fatigue < 10 days - Grade 3 nausea, vomiting, and diarrhea and grade 4 vomiting and diarrhoea that persist for < 72 hours in the absence of maximum medical therapy - Asymptomatic grade 3 non-hematological laboratory abnormalities that resolve in 72 hours - Grade 3 infections which do not improve under i.v. medication within 10 days
In case some specific adverse reactions to ^{177}Lu-PSMA-617 persist or reoccur, see Table 5

Table 4: When to suspend treatment with ^{177}Lu-PSMA-617?

Suspend treatment with ^{177}Lu-PSMA-617 in patients who have experienced or are at risk of any of the following conditions during treatment:	
Criterion	**Action**
Occurrence of an intercurrent disease (e.g. urinary tract obstruction, ...) which according to the physician opinion could increase the risks linked to ^{177}Lu-PSMA-617 administration.	Suspend administration until resolution or stabilization. Treatment can be resumed after resolution or stabilization. Resolution is defined as grade II toxicity or lower. (by CTCAE) at the time of the next treatment. Treatment can be suspended up to 12 weeks after the last infusion. After that treatment with ^{177}Lu-PSMA-617 must be definitively stopped.
In case of some specific adverse reactions to ^{177}Lu-PSMA-617, see Table 5	See Table 5

Table 5: When to adapt ^{177}Lu-PSMA-617 posology?

Adapt ^{177}Lu-PSMA-617 posology according to the following actions in patients who have presented any of the following severe adverse reactions:	
Severe adverse reactions / Dose-modifying toxicity (DMT) criteria	**Action**
Anemia, thrombocytopenia or neutropenia of grade 3 or superior (CTCAE 4.0)	1. Suspend treatment with ^{177}Lu-PSMA-617 2. Monitor biological parameters every 2 weeks, and eventually treat appropriately if needed; in case of renal function impairment, good hydration is recommended if not otherwise contraindicated. a. If the observed toxicity continues beyond 12weeks after the last infusion, treatment with ^{177}Lu-PSMA-617 must be definitively stopped. definitively stopped. b. If the observed toxicity resolves within 12weeks after the last infusion, it is possible to continue treatment with ^{177}Lu-PSMA-617 by infusing a half activity. 3. Even if the half activity is well tolerated (i.e. no DMT re-occurrence), the next remaining treatment administration should be continued with the reduced (half) activity but, if DMT recurs after treatment with a half dose, treatment with ^{177}Lu-PSMA-617 must be permanently stopped.
Renal toxicity as defined by grade 3 toxicity by serum creatinine (CTCAE 4.0)	
Liver toxicity as defined as AST and ALT >3xULN	
Any serious or intolerable adverse event not listed in Table 2 that in the opinion of the investigator, requires the subject's discontinuation	

4. Study Population Selection

4.1 Study Population

It is anticipated that a total of 200 subjects will be recruited. Such a number is considered appropriate to achieve statistical power for the endpoints of this clinical trial. The patients will be recruited at up to 3 clinical sites. The dose being administered will be prepared at [redacted]. [redacted] and shipped to the trial sites.

4.2 Inclusion Criteria

1. Prostate cancer proven by histopathology
2. Unresectable metastases
3. Progressive disease, both docetaxel/cabazitaxel naive and docetaxel/cabazitaxel treated.
4. Castration resistant disease with confirmed testosterone level ≤50 ng/ml under prior androgen deprivation therapy (ADT)
5. Positive ^{68}Ga-PSMA-11 PET/CT or diagnostic ^{177}Lu-PSMA-617 scintigraphy or any equivalent PSMA-directed imaging
6. ECOG 0-2
7. Sufficient bone marrow capacity as defined by WBC ≥2500/µl, PLT count ≥100.000/µl, Hb≥9.9 g/dl and ANC≥1500 mm3 for the first cycle and WBC ≥2.000/µl, PLT count ≥75.000/µl, Hb≥8.9 g/dl and ANC≥1000 mm3 for the subsequent cycles
8. Signing of the Informed Consent Form
9. Patients enrolling in this trial should have received either enzalutamide or abiraterone.

4.3 Exclusion Criteria

1. Less than 6 weeks since last myelosuppressive therapy (including Docetaxel, Cabazitaxel, ^{223}Ra, ^{153}Sm)
2. Glomerular Filtration Rate (GFR) <40 ml/min
3. Serum creatinine >1.5xULN; AST and ALT >5xULN
4. Urinary tract obstruction or marked hydronephrosis
5. Diffuse bone marrow involvement confirmed by super-scans

5. Study Treatment(s)

5.1 Description of Treatments(s)

5.1.1 Study drug

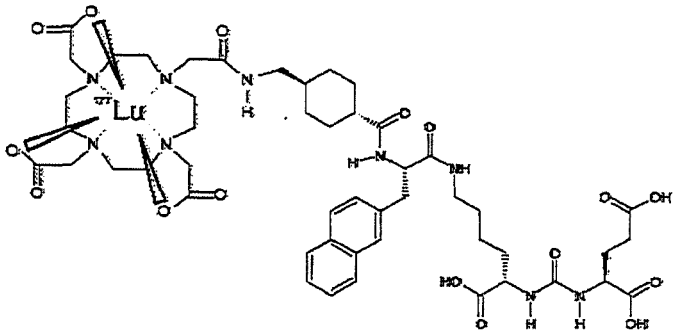
The agent to be evaluated in the present study is ^{177}Lu-PSMA-617. Its chemical name is lutetium-177-Nα-2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-

1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid.

^{177}Lu-PSMA-617 is radiolabelled with carrier-free lutetium-177 (^{177}Lu), a synthetic, low-energy beta and gamma emitting isotope of lutetium, the last element in the lanthanide series of metallic elements. Carrier-free 177Lu is generated by neutron irradiation of the isotope ytterbium-176 (176Yb) and subsequent fractionation of 177Lu and 176Yb with caution chromatography. Key physical characteristics of 177Lu are summarised below:

Physical Half-life T½	**Decay Product**	**Main Emission (β^-)**	**Maximum Range (β^-)**	**Main Emission (γ)**
6.6 d	^{177}Hf	498 keV	1.7mm	208 keV 113 keV

The structural formula of ^{177}Lu-PSMA-617 is shown below:



The chemical formula of ^{177}Lu-PSMA-617 is $Lu_1C_{49}H_{68}N_9O_{16}$. The molar weight is 1214.1 g/mol.

5.1.2 Pharmaceutical Properties of ^{177}Lu-PSMA-617

^{177}Lu-PSMA-617 is administered intravenously.

A description of ^{177}Lu-PSMA-617 solution for infusion is shown in below table:

Composition of ^{177}Lu-PSMA-617 solution

Pharmaceutically active component	^{177}Lu-PSMA-617
Physical dose	≤ 7.4 GBq / cycle
Substance dose	[redacted] µg PSMA-617
Primary unit dose container	20 mL glass vial containing 5 - 15 mL of stabilised aqueous solution
Appearance	Clear, colourless or slightly yellowish solution, without visible particles
pH	4.0 - 7.5
Bacterial endotoxin	≤ 100 EU/Dose
Radionuclidic purity	≥ 99.99%
Sterility	Sterile

The components include ^{177}Lu-PSMA-617, [redacted], and water for injection. The labelled drug product is produced, tested and released under GMP conditions by [redacted]. as a sterile solution for injection infusion, ready for use. The labelled drug product will be manufactured upon individual order and delivered directly to the study sites.

Patients will be randomized into two treatment doses; radioligand therapy (RLT) by repeated i.v. application of 6.0 GBq (±10%, arm 1) or 7.4 GBq (±10%, arm 2) ^{177}Lu-PSMA-617 every 8±1 weeks; RLT will be performed until reaching four cycles or threshold maximum dose to the kidneys of 23 Gy as determined by dosimetry, after the first treatment.

5.2. Treatment(s) administered

Cold ice pack in the region of salivary glands will start 30 minutes prior to administration of the investigational drug and will continue for 4 hours. Intravenous access will be inserted in either arm. Assurance will be made to have reliable IV line with no evidence of extravasation or infiltration. Investigational drug will be infused over approximately 15-30 minutes using infusion pump. Patients will be monitored for any evidence of pain, or burning sensation during the infusion.

5.3 Restrictions

5.3.1 Fluid and Food Intake

Subjects should follow their normal diet before and after the administration of the study drug. Subjects should be encouraged to increase fluid intake at baseline and after each image acquisition to maintain proper hydration throughout the study period and decrease radiation exposure to the urinary bladder. There are no dietary or food restrictions for this study.

5.3.2 Subject Activity Restriction

There are no activity restrictions.

5.4 Dosing Compliance

All study drug administration will be administered under the supervision of the investigator. Details of study drug injection will be captured in each subject's source documents.

5.5 Packaging and Labeling

^{177}Lu-PSMA-617 will be supplied in vials for injection in appropriate packaging.

The outer packaging of ^{177}Lu-PSMA-617 will contain label(s) which will include the following minimum information:

- Name and address of Manufacturer Study number
- Investigator identification
- Name of study drug and formulation
- Dosage strength

- Batch number
- Patient number
- Expiry date (or retest date)
- Storage instructions
- "For Clinical Trial Use only"

A system of medication numbering in accordance with all requirements of Good Manufacturing Practice (GMP) and any other applicable regulatory requirement will be used for all study drugs. This will ensure that for each patient, any dose of study drug can be identified and traced back to the original bulk ware of the active ingredients. Lists linking all numbering levels will be maintained by the institutions in charge of study drug packaging.

5.6 Storage and Accountability

5.6.1 Storage

The drug product contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use is limited to a facility licensed by applicable government regulations and/or local/state laws. Unused or residual waste should be disposed of as radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidance.

5.6.2 Accountability

In accordance with International Conference on Harmonization (ICH) and US Food and Drug Administration (FDA) requirements, the investigator and/or drug dispenser must at all times be able to account for all study drugs furnished to the institution. The appropriate site personnel must sign, date and immediately forward to the sponsor or sponsor's designee the packing slip for clinical shipment included with each shipment.

No study drug is to be used outside of this study. The investigator or designee will record the use of the study drug on the appropriate Drug Accountability record. All study radiopharmaceuticals must be accounted for, whether used or unused, during the course of and at the conclusion of the study. The shipment of drugs from the sponsor or designee to the investigator or other designated persons cooperating with the investigator will be accompanied by a receipt form that indicates the lot number(s) and the amount of drug provided for the study. This form will be signed, dated and returned to the sponsor or designee.

The investigator is responsible for ensuring that study drug is recorded, handled and stored safely and properly in accordance with ICH and applicable government regulations, local/state laws, and used in accordance with this protocol.

5.7 Investigational Product Retention at Study Site

Unused product will be disposed of according to institutional regulations. Record the use and/or disposal of the study drug on the Drug Accountability record. This Drug Accountability record should account for the receipt and disposition of all clinical supplies shipped to the investigator and must be available for review by the study monitor.

6. Study Procedures

6.1 Informed Consent

All subjects must sign and personally date an IRB/IEC approved informed consent form after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the study drug prior to the initiation of any study-related procedures. This must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP) and government regulations, including (as applicable) the US Code of Federal Regulations Title 21 CFR 50.20 through 50.27.

The subject must be made aware and agree that personal information may be reviewed during an audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available. A copy of the Informed Consent Form is attached as Exhibit.

6.2 Medical History

A relevant medical history and subject demographics will be obtained at the screening visit. Cancer medical history includes review of disease history, cancer staging, biopsy results, any past/present cancer therapies (e.g., hormone, drug, biologic, radiologic, or surgical treatment). Demographic information to be collected includes date of birth, race, ethnicity, height, and weight.

6.3 Vital Signs

Vital signs will include measurement of blood pressure, temperature, respiratory rate, pulse Oximetry (only at baseline) and heart rate.

6.4 Dispensing Study Drug

The estimated radioactive dose will be determined by measuring the amount of radioactivity in the syringe pre- and post-injection, using an appropriately calibrated radioisotope dose calibrator in accordance with the nuclear medicine department's SOPs.

Any complication related to administration of the drug (e.g., overdose, observable extravasation, medication error) is a protocol-related event and will be reported to the pharmacovigilance designee. Refer to Section 7 for contact information.

6.5 Clinical Laboratory Tests

Clinical laboratory tests will include hematology and clinical chemistry. Clinical laboratory analytes to be assessed in the study are shown in Table 6. Timing of collection of clinical

laboratory tests are presented in Section 8.

Table 6: Laboratory Analytes Assessed

Hematology	Clinical Chemistry
Hematocrit	eGFR
Hemoglobin	Bilirubin
RBC count	Creatinine
WBC count	Glucose
WBC differential	Urea nitrogen
Platelets	BUN/creatinine
ANC	AST/SGOT
MCV/MCH/MCHC	ALT/SGPT
Eosinophils	Alkaline phosphatase
Basophils	PSA*
Lymphocytes	
RDW	

*PSA will be done only at the time intervals called by the protocol.

6.6 Sample Collection, Storage and Shipping

Blood samples will be collected using accepted phlebotomy techniques by trained site personnel.

All samples for clinical laboratory testing will be processed and analyzed at an accredited laboratory

6.7 Electrocardiogram

Continuous ECG monitoring at least 15 minutes prior to administration of the study drug and up to at least 1 hour after administration will be performed during treatment cycle 1 and 2. Also a 12 lead ECG will be performed at two time points: before injection of Lu-177 PSMA-617 for all treatment cycles and after the salivary protection is completed.

6.8 Adverse Events

Immediate adverse drug reactions will be collected from the time of ^{177}Lu-PSMA-617 injection

until 24 hours post-injection visit. Data will be collected for any adverse events (AEs) as defined in Section 7.

All study monitoring will be performed at the primary clinical study sites in accordance with Good Clinical Practice (GCP). All records related to this study will be retained at each clinical site. Serious adverse reactions will be collected and reported to FDA and IRB according to 21 CFR 312.32. Annual reports on the progress of the investigation and any adverse events related to the investigational drug will be prepared and reported to FDA according to 21 CFR 312.33.

6.9 Removal of Subjects from the Trial or Study Drug

The investigator may withdraw a subject from the trial for any of the following reasons:

1. Protocol violation
2. Serious or intolerable adverse event (that in the opinion of the investigator, requires the subject's discontinuation),
3. Investigator withdraws the subject (at the investigator's discretion for reasons other than an adverse event),
4. Sponsor terminates the study,
5. Subject requests to be discontinued from the study, or
6. Subject is lost to follow-up

During course of the study patients have the right to withdraw their consents any time without need for explaining the reason of consent withdrawal to the investigator or sponsor. Principal investigator will closely monitor patients during the course of the study and will consider terminating investigational product administration or any other trial related procedures in order to maintain the safety of subjects. In cases of withdrawal either in patient's favor or principal investigator decision due to the safety issues or technical issues, withdrawn subjects will be replaced in order to maintain data integrity but follow up visits will be continued to maintain safety of patients based on the visits predicted in the protocol.

7. Reporting Safety Information

Any untoward medical event that occurs from the time that the subject is administered ^{177}Lu-PSMA-617 until the subject completes the study will be reported. Serious adverse events and non-serious adverse events will be collected and reported as required under 21 CFR 312.32 until the final study visit. Toxicity will be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

7.1 Adverse Events

7.1.1 Definitions

An **adverse event (AE)** is any untoward medical occurrence in a study subject that is administered a pharmaceutical product, at any dose, which does not necessarily have a causal relationship with the treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

A **serious adverse event (SAE)** is any untoward medical occurrence that falls into one or more of the following categories:

1. Results in death
2. Is life-threatening: An event which, in the view of the investigator, places the subject at immediate risk of death from the event as it occurred and does not include an event which hypothetically might have caused death if it were more severe.
3. Requires subject hospitalization or prolongation of existing hospitalization: For the seriousness criterion of subject hospitalization to apply, an overnight stay in the hospital is required. Admission to an emergency room and release without an overnight stay would not satisfy the subject hospitalization seriousness criterion.
4. Results in persistent or significant disability/incapacity: Persistent or significant

disability/incapacity is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.

5. A congenital anomaly/birth defect: A congenital anomaly/birth defect is defined as a condition believed to have been the result of exposure to study drug just before conception or during pregnancy.
6. Any other important medical event: An important medical event may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment, the event may significantly jeopardize the subject's health or may require medical or surgical intervention to prevent one of the outcomes listed in the serious definitions above. An important medical event may include development of drug dependency or drug abuse.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.2 Reporting Serious Adverse Events

Seriousness is based on subject, event outcome, or action criteria that are usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining the sponsor's regulatory reporting obligations to the applicable regulatory authorities. Adverse event severity and seriousness should be assessed independently by investigators. If the investigator is unsure if the event is serious it should be classified as serious.

Sponsors of the study, and the investigators are responsible for reporting relevant SAEs as safety reports to the FDA and other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, the US Code of Federal Regulations Title 21 CFR 312.32 for Good Clinical Practice, and/or local regulatory requirements. The investigators must report all SAEs to project pharmacovigilance designee within 24 hours, by telephone,

email or fax, and confirm that the information was received.

A Serious Adverse Event Report (SAER) must be completed by the investigator or designee and faxed or emailed to project pharmacovigilance designee within 24 hours after the investigator first becomes aware of the serious event. A separate SAER will be needed for each reported SAE so that the onset, resolution date, causality and outcome can be assessed for each event. A copy of the source documents relevant to the event should be forwarded to sponsor's pharmacovigilance designee with the SAER form. The SAER form must be signed and dated by the investigator. If paper SAE forms are used, the original copy of the SAER form should remain at the investigational site. All SAEs are also to be entered into the CRF.

In case of death, a comprehensive narrative report of the case should be prepared by the investigator and sent to project pharmacovigilance designee with the SAER. If an autopsy is performed, a copy of the autopsy report should be actively sought by the investigator and sent to the sponsor or designee as soon as available. A copy of the autopsy report should remain at the investigational site with the subject's source documents.

A new follow-up SAER form will be completed by the investigator if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow-up SAER must be signed and dated by the investigator. The follow-up form and any additional source documentation regarding the event will be sent to project pharmacovigilance designee.

If a serious medical occurrence or death is reported to the investigator outside the follow up window which is believed to be related to the administration of the study drug, it is the investigator's responsibility to report this occurrence to project pharmacovigilance designee. Such occurrences will be reported using a SAER form or other form of communication deemed appropriate by the investigator and pharmacovigilance designee.

Sites must contact project pharmacovigilance designee to report all SAEs within 24 hours, by telephone, e-mail, or fax. Contact information for SAE reporting is presented in Table 7.

Table 7: Pharmacovigilance Designee
[redacted]
[redacted]
[redacted]
[redacted]
PHONE: [redacted]
FAX: [redacted]
Email: [redacted]

Sites must also report all overdoses, extravasations and medication errors to the project pharmacovigilance designee.

7.2 Adverse Event Data Collection

The investigator will elicit information through non-leading questioning and examination of the subject about the occurrence of adverse events from the time that the subject is administered ^{177}Lu-PSMA-617 until study completion.

AE monitoring will be performed through following mechanisms, also listed in Appendix II:

a. Safety lab tests: CBC and CMP with eGFR will be performed at baseline (within 72 hours of first treatment dose) and then every 2 weeks (+/- 3 days) after first dose, continued until 12 weeks after the last dose and then every 3 months (+/- 1 week) thereafter until the end of follow-up visits (24 months from 1st therapy date) or upon disease progression. The CBC and CMP within 2 weeks of each subsequent treatment cycle will be used to assess eligibility of the corresponding treatment cycle.

b. Telephone follow up: 7 (±3) days after each treatment cycle and for follow-up phase, every 3 (±1) month until the end of follow up visits (24 months).

AEs can be reported any time after study enrollment until the end of the subject's study participation. For each event, the following information will be recorded in the subject's source documents and entered into the Adverse Event CRF according to the instructions below:

Classification of the Event as serious or non-serious: Classify the event as serious or non-serious (see definitions in Section 7).

Description of Signs or Symptoms: Whenever possible, record a specific diagnosis for the event. If a diagnosis cannot be made, then record each sign or symptom representing a distinct medical concept separately, (e.g. nausea and vomiting should be recorded as separate events).

Onset Date and Time: Record the date and time the event starts. If a laboratory result is reported as an AE, record the start date as the date of collection of the first lab sample that shows the change.

Stop Date and Time: Record the date and time the event resolves, returns to baseline, or resolves with sequelae.

Grade: Refer to the common terminology criteria for adverse events (CTCAE) Version 4.

Relationship to the Study Drug:

We make every effort to evaluate the relationship between the study drug and the AE as determined by the investigator per the definitions below:

1. Related: The event is reasonably suspected of a causal relationship to the study drug. Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to

suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

ASSESSING RELATIONSHIP TO STUDY TREATMENT

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment;
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable;
- Whether the event is known to be associated with the study treatment or with other similar treatments;
- The presence of risk factors in the study subject known to increase the occurrence of the event;
- The presence of non-study treatment-related factors which are known to be associated with the occurrence of the event.

2. Not Related: The event is definitely due to causes separate from study drug administration such as:

- documented pre-existing condition
- technical and manual procedural problem
- concomitant medication
- subject's clinical state

3. Adverse Event Outcome:

- Recovered/Resolved without sequelae
- Recovered/Resolved with sequelae
- Not Recovered/Not Resolved: event is ongoing at the end of the AE collection period.
- Death (Fatal): the event description must be the primary cause of death.

7.3 Clinical Significance

7.3.1 Reporting and Evaluation of Clinical Laboratory Test Results

The investigator should assess all clinical laboratory results for clinical significance and record the assessment in source documents.

The investigator should evaluate any laboratory result change from pre- and post-study drug administration to determine if the change meets the definition of an AE or SAE. **Record any clinically significant lab results determined to meet the definition of an AE and SAE on the AE CRF and SAER form, respectively.**

7.3.2 Repeat Testing

Additional laboratory testing may be performed at the discretion of the investigator.

7.3.3 Vital Signs

The investigator should evaluate any vital sign changes pre- and post-study drug administration to determine if the change meets the definition of AE or SAE. Vital sign measurements may be repeated at the discretion of the investigator. **Record any clinically significant vital sign measurement that meets the definition of an AE and SAE on the AE CRF and SAER form, respectively.**

8. Study Activities

Visit-specific schedule for efficacy and safety variables is presented in Appendix II.

8.1 Screening Visit

- Written informed consent
- Demographic information
- Relevant medical history
- Prior therapy for Prostate cancer
- Medication assessment
- Histology
- Vital signs
- Questionnaires
- Morphological and PSMA-ligand imaging studies if no comparable available within 12 weeks of treatment.

8.2 Within 2 Weeks of Screening

- Clinical laboratory testing (see Section 6)

8.3.1 Pre-dose and Dosing Procedures

- Pre-dose vital signs – within 20 minutes before dose
- Blood tests (CBC, CMP and PSA) within 72 hours of first treatment cycle
- Apply Ice pack to the salivary glands approximately 30 minutes prior to investigational drug injection and continue for 4 hours.
- Adequate hydration of the patient (IV or oral).
- Inject study drug ^{177}Lu-PSMA-617
- Post-dose vital signs
- Adverse events

8.3.2 Post-Dose Procedures

Adverse events during the entire stay.

One post-therapy whole body scintigraphy will be performed (optional).

8.3.3 ECG Procedures

Continuous ECG monitoring at least 15 minutes prior to administration of the study drug and up to at least 1 hour after administration will be performed during treatment cycle 1 and 2. Also a 12 lead ECG will be performed at two time points: before injection of Lu-177 PSMA-617 for all treatment cycles and after the salivary protection is completed.

8.4 Follow-up

8.4.1 PSA Measurements

At baseline, then every 6 weeks during the treatment period and every 3 (±1) months after the last treatment until reaching endpoint or 24 month after the first treatment.

8.4.2 Imaging Studies

Baseline imaging within 12 weeks of start of therapy including (a) CT of the chest Preferably with contrast and CT or MRI of the Abdomen and pelvis preferably with contrast and (b) bone scintigraphy or (c) equivalent to above [1].

Relevant imaging studies will be performed before third RLT cycle, 3 (±1) months after the last RLT, then every 3 (±1) months in follow-up period until reaching the endpoint or 24 month after the first treatment.

At each subsequent RLT cycle visit and with every long term follow-up visit, any concomitant cancer-related therapy since last visit will be documented.

8.4.3 Dosimetry

Prior versions of the protocol mandated dosimetry studies aimed at assessing kidney dosimetry associated with the intravenous application of ^{177}Lu-PSMA-617.

Dosimetry data of 20 patients (16 from UCLA and 4 from Excel Houston) was analyzed and it was found that the renal dose limit of 23 Gy was not exceeded in any patient after 4 cycles and no additional on study dosimetry is required.

Below are the individual dosimetry measurements for each patient performed during cycle #1.

Table 8: Individual Dosimetry Measurements for Patients Performed During Cycle 1.

Pt. #	Activity (GBq)	Dosimetry Right Kidney (Gy/GBq)	Dosimetry Right Kidney (Gy)	Dosimetry Left Kidney (Gy/GBq)	Dosimetry Left Kidney (Gy)
[redacted]					

[redacted]

After an average injected activity of 6.75 ±0.81 GBq (range 5.1-8.1) the mean absorbed kidney dose was 0.42 ±0.17 Gy/GBq (range 0.21-0.9) corresponding to a cumulated absorbed dose of 2.79 ± 1.12 Gy (range 1.37-5.61).

These results are consistent with prior studies as shown in the following table.

Table 9: Prior Completed Study Dosimetry Measurements

Author	Journal	year	n=	Activity GBq	Activity range	mean kidney dose Gy/GBq
Scarpa et al.	*Eur J Nucl Med Mol Imaging*	2017	10	6.1	5.4–6.5	0.60 ± 0.36
Yadav et al.	*Nucl Med Com*	2017	26	2.52	1.1-5.5	0.99 ± 0.31
Kabasakal et al.	*Mol Imaging Radionucl Ther*	2017	7	5.2	3.6-7.4	0.82 ± 0.25
Fendler et al.	*Oncotarget*	2017	15	5.23	3.7-6.0	0.6 ± 0.3
Baum et al.	*J Nucl Med*	2016	30	5.76	3.6–8.7	0.8 ± 0.4
Delker et al.	*Eur J Nucl Med Mol Imaging*	2016	5	3.6	3.4-3.9	0.6 ± 0.2

Furthermore the absorbed kidney dose limit of 23 Gy is an assumption derived from external beam radiation therapy (63) which probably does not predict renal toxicity from radionuclides. Correction of these data for radionuclide therapy suggested a renal absorbed biologic effective dose (BED) limit of 37 Gy (64).

8.4.4 Follow-up Labs for Hematological and Kidney Toxicities

All enrolled patients will follow the scheduled follow up visits.

Hematologic laboratory testing (CBC and CMP with eGFR) will be performed every 2 weeks (+/- 3 days) after first dose, continued until 12 weeks after the last dose and then every 3 months (+/- 1 month) thereafter until the end of follow-up visits (24 months from 1st therapy date) or upon disease progression. The CBC and CMP within 2 weeks of each subsequent treatment cycle will be used to assess eligibility of the corresponding treatment cycle. CBC will be performed every 7

days for patients who experienced toxicity more than grade II due to this study (based on NCI CTCAE Ver.4) until recovery which is defined as grade 2 toxicity or lower.

In order to detect myelodysplasia, patients who withdrawn by the investigator for safety reasons will only perform CBC test until the end of their follow up visits as long as they do not start other cytotoxic therapies.

Patients on protocol should also have a physical exam and in-person physician evaluation periodically while on study and until recovery from last dose. During dosing period and longterm follow up period local physical exam will be done as per clinical routine.

8.4.5 Telephone Follow ups

7 (± 3) days after each treatment cycles until completion of 4 cycles and for follow up phase , every 3 months (+/- 1 month) until the end of follow up visits (24 months).

8.4.6 Longterm Follow ups

At each follow-up visit (every 3 (±1) months) following tasks will be performed:

1. Physical exam, vital signs
2. Documentation of concomitant cancer related therapies since last visit
3. Laboratory tests (CBC, CMP with eGFR and PSA)
4. Relevant imaging studies
5. Quality of life questionnaire and ECOG performance score (baseline, 3, 6, 9, 12, 18, 24 months from first RLT cycle)

9. Quality Control and Assurance

The study sites are chosen with regard to the capability and expertise of the principal investigators and the site staff. Prior to initiation of the study, the investigator and the sponsor's representative will meet to discuss the study design and conduct of the study. The investigator will sign the protocol acknowledging that he understands the design and all procedures and intends to conduct the study and all procedures according to protocol.

During the study, a representative of the sponsors will make periodic visits to the investigational site while the study is in progress to check the accuracy and completeness of the data being entered. Site visits will be conducted to inspect study data, subjects' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines. The investigator will permit authorized representatives and the respective local and national health authorities to inspect facilities and records relevant to this study, if needed.

Subject data will be collected on source documents and entered in the CRF. Data will be reviewed and validated. The investigator will sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject in the study.

Records of subjects, source documents, monitoring visit logs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, and distribution and return records), and other sponsor correspondence pertaining to the study will be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. At the end of the study, CRF data will be provided to the sponsor.

10. Planned statistical methods

10.1 Primary endpoints

1. **Safety** of ^{177}Lu-PSMA-617 RLT will be assessed by analysis of toxicity. Descriptive statistics (number and percentage) will be reported separately for AE in total and SAE based on CTC. These descriptive statistics will be presented for the whole treatment as well as separate for each cycle. In addition, the relationship of AE to the study drug (related, not related) will be reported. Both results from laboratory test, physical examinations and patients surveys will be included.
2. **Efficacy** of ^{177}Lu-PSMA-617 will be reported using descriptive statistics by means of number and percentage of patients with ≥50% decline at 12-weeks from baseline.

10.2. Secondary endpoints

1. Descriptive analyses (median, standard deviation) will be used to determine the **progression-free survival (PFS)**, measured from start of therapy until death or PSA progression. PSA progression is defined a) for patients with PSA decline after start of treatment as time from baseline to time the PSA increases to 25% and 2 ng/ml above nadir which is confirmed by a second value ≥3 weeks later or b) for patients without PSA decline as time from baseline to time the PSA increases to 25% and 2 ng/ml above baseline which is confirmed by a second value ≥3 weeks later [1]. Data will be given separately for the both treatment groups (6.0 vs. 7.4 GBq ^{177}Lu-PSMA-617) and a statistical significant difference will be tested.
2. Each clinical site will perform image analysis on their own patients. Descriptive analyses (median, standard deviation) will be used to determine the **radiographic**

progression-free survival (rPFS), measured from start of therapy until death or radiographic progression. Radiographic progression is defined as a) for extraskeletal disease progressive disease (PD) following Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [65] and/or b) skeletal disease the development of ≥2 new lesions on first post-treatment bone scan, with at least two additional lesions on the next scan (2+2 rule). The date of progression is the date of the first post-treatment scan, when the first two new lesions were documented. This approach is applied in accordance to PCWG criteria to exclude pseudoprogression in the absence of symptoms or other signs of progression [1]. Data will be given separately for the both treatment groups (6.0 vs. 7.4 GBq ^{177}Lu-PSMA-617) and a statistical significant difference will be tested.

3. Descriptive analysis will be used to determine the **disease control rate (DCR)** at the end of each cycle defined as the number and percentage of patients achieving a) RECIST stable disease (SD), partial response (PR) or complete response (CR) for extraskeletal tumor manifestation and b) PCWG non-progressive disease for skeletal manifestations.
4. Descriptive analysis will be used to evaluate the impact on **bone pain level** by determining the proportion of patients with pain response defined by improvement from baseline (all patients with ≥4/10) of at least 2-point absolute improvement without an overall increase in opiate use.
5. Change in **Quality of Life** over time will be documented by comparing the summary scores investigated by the Quality of life questionnaire "EPIC-26" at baseline and at 3, 6, 9, 12, 18 and 24 months after start of ^{177}Lu-PSMA-617 RLT [66].
6. Changes in **performance status (ECOG)** from baseline will be evaluated over time at 3, 6, 9, 12, 18 and 24 months after start of ^{177}Lu-PSMA-617 RLT.

11. Administrative Considerations

11.1 Investigators and Study Administrative Structure

This study will be conducted in accordance with the Declaration of Helsinki, ICH E6 Guideline and government regulations, including (as applicable) the US Code of Federal Regulations Title 21 CFR 312.50 through 312.70, directive 2001/20/EC of 4 April 2001 and implementing directives and regulations. To ensure compliance the investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals. The investigator must conduct the trial as outlined in the protocol and in accordance with the Declaration of Helsinki and government regulations, including (as applicable) the US Code of Federal Regulations Title 21 CFR 56 – Institutional Review Boards. The administrative structure of the study (e.g., monitoring and vendor personnel, statistician, and laboratory facilities) and a complete and controlled list of the investigators participating in this study can be found in the study file maintained by the sponsor or its agent.

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The protocol, informed consent form, and any advertisement for the recruitment of subjects must be reviewed and approved by an appropriately constituted IRB or IEC, as required in Chapter 3 of the ICH E6 Guideline and government regulations, including (as applicable in the region) the US Code of Federal Regulations Title 21 CFR 56.107 through 56.115 of Good Clinical Practice. Written IRB approval must be provided to sponsor or designee prior to shipment of study drug or subject enrollment. The investigator is committed in accordance with local requirements to provide the IRB with updates, and to inform the IRB of any emergent problem, SAEs, and/or protocol amendments.

11.3 Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the Declaration of Helsinki.

11.4 Subject Information and Consent

It is the responsibility of the investigator to obtain written informed consent from subjects. All subjects must sign and personally date an approved informed consent form after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the study drug. This must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for GCP, and the requirements of (as applicable in the region) the US Code of Federal Regulations Title 21 CFR 50.20 through 50.27 of Good Clinical Practice.

The subject must be made aware and agree that personal information may be scrutinized during audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available. Prior to IRB/IEC submission, the investigator must send a copy of the informed consent form to be used at their institution to sponsor or designee for review to assure compliance with the ICH E6 and government regulations of the region.

11.5 Subject Confidentiality

Data collected during this study may be used to support the development, registration or marketing of ^{177}Lu-PSMA-617. All data collected during the study will be controlled by sponsor or designee and sponsor will abide by all relevant data protection laws. In order to maintain subject privacy, all CRFs, study drug accountability records, study reports and communications will identify the subject by initials and the assigned subject number. The investigator will grant monitor(s) and auditor(s) from sponsor or its designee and regulatory

authority (ies) access to the subject's original medical records for verification of data entered into the CRF and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Written authorization is to be obtained from each subject prior to enrollment into the study in accordance with the applicable privacy requirements [e.g., the Health Insurance Portability and Accountability Act (HIPAA) of 1996 Standards for Privacy of Individually Identifiable Health Information.

11.6 Study Monitoring

11.6.1 Data and Safety Monitoring Plan (DSMP)

Excel Diagnostics is the lead site; the Excel Diagnostics Data Safety Monitoring Board (DSMB) will serve as overall DSMB for both sites. At UCLA, DSMB oversight will be provided by JCCC Data Safety Monitoring Board (DSMB). The monitoring board will meet quarterly to review safety records including compliance with follow up visits.

The Excel Diagnostics DSMB consists of:

- [redacted], MD Radiologist, [redacted]
- [redacted], MD Radiologist, [redacted]
- [redacted], MD Oncologist, [redacted]
- [redacted], MD Family Practitioner, [redacted]

The Data Safety Monitoring Boards will evaluate safety throughout the study. The DSMB will advise the Sponsor, Investigators and investigational sites regarding the continuing safety of study patients and the patients yet to be recruited to the study as well as maintaining validity and scientific merit of the study. The DSMB will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study. Each DSMB will evaluate and advise locally throughout the trial at the pre-specified milestones

of 25%, 50%, 75% and 100% completion. UCLA JCCC DSMB will send their reports to the lead site DSMB for overall analysis.

Copies of all monitoring and audit reports must be submitted by Endocyte to the lead site DSMB within 10 working days of receipt by Endocyte.
Endocyte will be responsible for ensuring that all reportable adverse events are submitted to the appropriate regulatory body.(FDA, NIH, etc.).Adverse events will be recorded and reported to the FDA as well as applicable IRBs and the JCCC DSMB per the regulatory body and institutional committee requirements (refer to JCCC DSMB) website.

Specific interim safety analyses will be done as follows:
Interim safety analyses: 4 interim safety analyses will be conducted by both DSMBs Analyses will be initiated at the time when 25%, 50%, 75% and 100% of the total ^{177}Lu-PSMA-617 treatments in the trial have been completed. The DSMBs will meet and assess up-to-date safety information within two weeks of a treatment exposure rate being achieved (i.e., the point when 25%, 50%, 75% and 100% of subjects have completed their treatments). Further patients may only be randomized two weeks after the treatment exposure rate has been reached and after a positive opinion from the DSMBs. An interim analysis for overall survival will be performed at the time of the final PFS analysis. UCLA JCCC DSMB will send its summary reports based on a predetermined frequency to the lead site DSMB for overall safety analysis as the Excel Diagnostics DSMB will be serving as the overall DSMB for both sites.

11.6.2 Monitoring Procedures

An appropriate representative of the sponsors (Study Monitor) will oversee the progress of the study, and ensuring it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable regulatory requirements.

An initiation visit will be made by the study monitor at each site to discuss the protocol and the obligations of both the Sponsor and the investigator. The investigator must allow the study monitor to perform periodic, interim monitoring visits. The actual frequency of monitoring visits will be dependent on the enrollment rate and performance at each site. The purposes of these visits are to verify that written informed consent was obtained prior to each subject's participation in the trial, and to:

- assess the progress of the study
- review the compliance with the study protocol
- determine whether all AEs and SAEs were appropriately reported
- determine whether the investigator is maintaining the essential documents
- discuss any emergent problem
- check the CRF for accuracy and completeness
- validate the contents of the CRF against source
- assess the status of drug storage, dispensing and retrieval
- retrieve study data

All data required by the protocol must be reported accurately on the CRF and must be consistent with the source documents. Source documents are original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays or other diagnostic images, subject files, pharmacy records and laboratory records). The investigator will make available the source documents for inspection. This information will be considered as confidential.

During scheduled monitoring visits, the investigator and the investigational site staff should be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to CRF entries, respond to data clarification requests and respond to any

other study-related inquiries of the monitor. The investigational site staff in addition to the study coordinator should also include nuclear medicine staff, radiopharmacist, and radiology staff.

The study monitor will perform a closeout visit at the conclusion of the investigator's involvement in the study.

11.6.3 Auditing

The investigator will make all pertinent records available including source documentation for inspection by regulatory authorities and for auditing by the sponsor. This information will be considered as confidential. Clinical Research Compliance Officers from the UCLA JCCC Office of Regulatory Compliance will be conducting the auditing for the UCLA site.

Representatives of local or foreign health authorities may review the conduct or results of the study at the investigational site. The investigator must promptly inform the sponsor of any audit requests by health authorities, and will provide sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

11.7 Case Report Forms and Study Records

Sponsor will provide a CRF and CRF instructions for the entry of study data. CRFs must be completed for each subject. All study data will be entered on CRFs from original source data. Entries should be made on the case report forms directly and promptly onscreen.

The CRF will be reviewed, signed and dated by the investigator.

11.8 Protocol Violations/Deviations

Protocol violations/deviations will be documented by investigator and submitted to the IRB/IEC, as required by IRB/IEC requirements.

11.9 Access to Source Documentation

During the study, a representative of the sponsor will make periodic visits to the investigational sites while the study is in progress to check the accuracy and completeness of the data being entered. Site visits will be conducted to inspect study data, subjects' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines.

The investigator will permit authorized representatives of the sponsor and the respective local And national health authorities to inspect facilities and records relevant to this study, if needed.

11.10 Data Generation and Analysis

Sponsor(s) or its designee will be responsible for data collection, data management, generation of data outputs and statistical analysis of all data.

11.11 Retention of Data

As described in the ICH GCP Guidelines, 'essential documents', including copies of the protocol, subject identification codes, CRF, source data, informed consent form(s) and other documents pertaining to the study conduction must be kept for the maximum period of time as required by the study site. This time period must be at least two years after the last follow up of the patients enrolled.

No study document should be destroyed without prior written agreement between sponsors and the investigators. Originals of all documentation generated by sponsor and copies of

outgoing sponsor correspondence concerning the study will be stored and retained in a safe area under the control of sponsor for the lifetime of the product. In particular, the final report must be retained by sponsor, or the subsequent owner, for 5 years beyond the lifetime of the study drug.

11.12 Financial Disclosure

All investigators must provide financial disclosure information in accordance with the US Code of Federal Regulations Title 21 CFR 54.2 through 54.6.

11.13 Publication and Disclosure Policy

All unpublished documentation (including the protocol, CRF and Investigator Brochure (IB) given to the investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of sponsor. The submission of these documents to the IRB is expressly permitted. The investigator agrees that sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country. The results of the study may be presented during scientific symposia or published in a scientific journal only after review by sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

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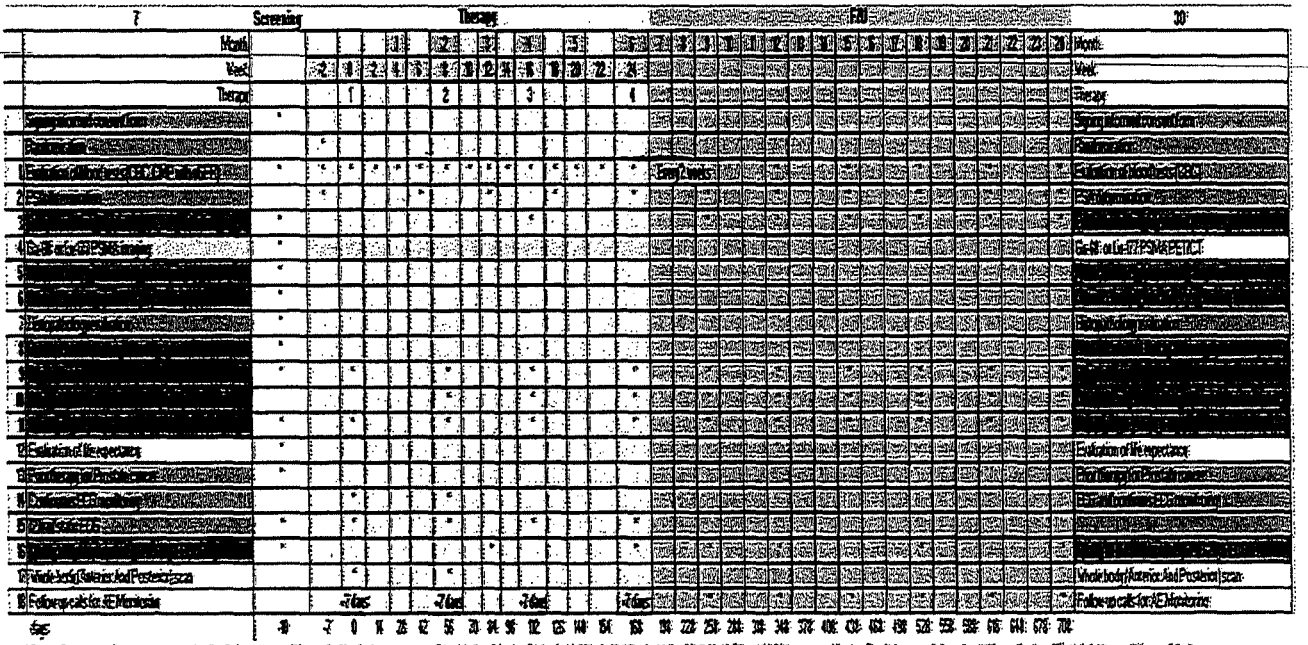
Appendices

Appendix 1- Preclinical Toxicity studies

This exhibit is 303 pages. Therefore we are providing it in the attached CD.

Appendix II: Visit Specific Schedule



Appendix III: Principal Investigator Signature

I have read this clinical protocol, no. ^{177}Lu-PSMA-617-02, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

_____ _____

Principal Investigator Signature Date

_____

Name (Printed)

_____

Title (Printed)

Baseline and follow-Up Questionnaire for Pain and Adverse Events

PATIENT INFORMATION

Last name: _____ First Name: _____

Date of Birth: _____ Medical Record Number: _____

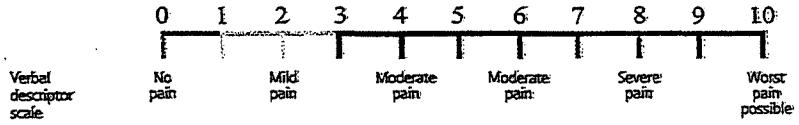
Change of pain medication since last ^{177}Lu-PSMA-617 cycle

□ No change
□ Change in dosage/administration: medication _____ □ increase or □ decrease
□ Addition/removal of medication: medication _____ □ addition or □ removal

Pain □ No or □ Yes:

Locations: _____

Overall level:



Change since last cycle: □ increase, □ no change, □ decrease

Nausea
□ No nausea
□ Nausea with loss of appetite only
□ Nausea with eating/drinking less than usual
□ Had to go to hospital for nausea

Vomiting
□ No vomiting
□ 1 - 2 episodes per day
□ 3 - 5 episodes per day
□ more than 5 episodes per day

Dry mouth
□ No dry mouth
□ Dry or thick saliva
□ Normal eating only with water/lubricants possible
□ Tube feeding or total i.v. nutrition

Taste
□ Normal taste
□ Altered taste but no change in diet
□ Altered taste with change in diet

Fatigue
□ No fatigue
□ Fatigue relieved by rest
□ Fatigue not relieved by rest, limiting work
□ Fatigue not relieved by rest, limiting self-care

Hematoma
□ No Hematoma
□ Occurrence of hematoma without known event

Fever
□ No fever
□ 38.0 - 39.0 °C (100.4 - 101.2 °F)
□ >39.0 - 40.0 degrees °C (101.3 - 104.0 °F)
□ >40.0 °C (>104.0 °F)

Urinary retention
□ Able to void normally
□ Able to void with some pressure
□ Unable to void or voiding only after catheter/intervention/treatment

Diarrhea
□ Normal bowel movements
□ Increase by <4 stools per day

Other (symptom, grade: mild/moderate/severe):
_____
_____

□ Increase by 4-6 stools per day _____

□ Increase by more than 6 stools per day _____

□ Had to go to hospital for diarrhea _____

Date: _____ Name: _____ Signature: _____

EPIC-26

The Expanded Prostate Cancer Index Composite

Short Form

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month _____ Day _____Year_____

Name (optional): _____

Date of Birth (optional): Month _____ Day _____ Year _____

Do Not Mark in This Space

1. Over the **past 4 weeks**, how often have you leaked urine?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 23/
About once a week..... 4
Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

No urinary control whatsoever..... 1
Frequent dribbling..... 2 (Circle one number) 26/
Occasional dribbling..... 3
Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None 0
1 pad per day..... 1
2 pads per day..... 2 (Circle one number) 27/
3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Dripping or leaking urine	0	1	2	3	4	28/
b. Pain or burning on urination.....	0	1	2	3	4	29/
c. Bleeding with urination.....	0	1	2	3	4	30/
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4	31/
e. Need to urinate frequently during the day.....	0	1	2	3	4	33/

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 34/
Moderate problem..... 4
Big problem..... 5

Do Not Mark in This Space

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Losing control of your stools.....	0	1	2	3	4	52/
d. Bloody stools	0	1	2	3	4	53/
e. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your ability to have an erection?.....	1	2	3	4	5	57/
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5	58/

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all	1		
Not firm enough for any sexual activity	2		
Firm enough for masturbation and foreplay only	3	(Circle one number)	59/
Firm enough for intercourse	4		

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one	1		
I had an erection LESS THAN HALF the time I wanted one	2		
I had an erection ABOUT HALF the time I wanted one	3	(Circle one number)	60/
I had an erection MORE THAN HALF the time I wanted one	4		
I had an erection WHENEVER I wanted one	5		

Do Not Mark in This Space

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes.....	0	1	2	3	4
b. Breast tenderness/enlargement..	0	1	2	3	4
c. Feeling depressed.....	0	1	2	3	4
d. Lack of energy.....	0	1	2	3	4
e. Change in body weight.....	0	1	2	3	4

THANK YOU VERY MUCH!!

EPIC-SF 6.2002

Appendix VI: Dosimetry protocol attached as pdf copy
***Not applicable to previous versions of protocol**