Journal of Nuclear Medicine, published on July 16, 2021 as doi:10.2967/jnumed.121.262543

Safety of PSMA-targeted molecular radioligand therapy with ^{177}Lu-PSMA-617: results from the prospective multicenter phase 2 trial RESIST-PC NCT03042312

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Running Title: LuPSMA safety in the RESIST-PC trial

ABSTRACT

Purpose of the study: To report the safety evaluation of ^{177}Lu-PSMA-617 derived from the cohort of 64 patients exposed to ^{177}Lu-PSMA-617 in the RESIST-PC trial NCT03042312.

Methods: RESIST-PC was a prospective multicenter phase 2 trial. Patients with progressive mCRPC after ≥1 novel androgen-axis drug, either chemotherapy naïve or post-chemotherapy, with sufficient bone marrow reserve, normal kidney function, sufficient PSMA expression by PSMA PET and no visceral PSMA-negative lesions were eligible. Patients were randomized (1:1) into two activity groups (6.0 or 7.4 GBq per cycle) and received up to 4 cycles every 8 weeks. The primary safety endpoint was assessed by collecting and grading Adverse Events (AE) using the CTCAE. Patients were followed until disease progression, death, serious or intolerable AE, study termination by sponsor, patient withdrawal, lost to follow-up or 24 months after the first cycle.

Results: The study was closed at enrollment of 71/200 planned patients because of sponsorship transfer. A total of 64 (90.1%) patients received at least one cycle of ^{177}Lu-PSMA-617: 28 (36%) in Arm 1 (6.0 GBq) and 41 (64%) in Arm 2 (7.4GBq). There were 10 (43.5%), 19 (46.5%) and 29 (45.3%) patients who completed 4 cycles of ^{177}Lu-PSMA-617 in the 6.0 GBq arm, 7.4 GBq arm, and overall, respectively. The most common treatment-emergent adverse events (TEAEs) of any grade in the 6.0 GBq arm, the 7.4 GBq arm and overall, were dry mouth (47.8%; 63.4%; 57.8%, respectively), fatigue (56.5%; 51.2%; 53.1%), nausea (52.2%; 43.9%; 46.9%), and diarrhea (13.0%; 31.7%; 25.0%). Frequencies of all other TEAEs were comparable among the 2 groups (within 10% difference). Serious possibly drug-related TEAEs were reported for 5 (7.8%) patients overall (none were considered as probably or definitely related to treatment): one subdural hematoma Grade 4, one anemia grade 3, one thrombocytopenia grade 4, one gastrointestinal hemorrhage grade 3, and one acute kidney injury grade 3. There were no clinically significant changes in vital signs in ECGs in the 2 treatment groups. No trend to creatinine increase, or increasing frequency of shifts from normal to abnormal over time for any hematologic parameter was noted.

Conclusion: ^{177}Lu-PSMA-617 was safe and well-tolerated at 6.0 and 7.4 GBq per cycle given at 8-week intervals with side effects easily managed with standard medical support. With established safety, further clinical trials applying individualized dosimetry and testing different 177Lu-PSMA-617 administration schemes (activity levels, time intervals) are needed to optimize tumor dose delivery and treatment efficacy.

Keywords: metastatic castration-resistant prostate cancer; radionuclide therapy; molecular radiotherapy; prostate-specific membrane antigen; lutetium-177; RESIST-PC; prospective randomized phase 2 trial; Theranostics; safety

INTRODUCTION

Targeted Molecular Radioligand therapy (RLT) offers the possibility to treat cancer lesions in a specific and tumor-selective manner by targeting cell surface proteins expressed on malignant cells. RLT targeting somatostatin receptor using ^{177}Lu-DOTATATE gained regulatory approval in 2018 in patients with metastatic neuroendocrine tumors based on the results on an industry-sponsored randomized phase 3 trial (*1*) and is now an established therapy. The prostate-specific membrane antigen (PSMA) is a target for prostate cancer (PCa) therapy because it is highly expressed in PCa (*2*). PSMA-617 is a small molecule that clears rapidly from plasma and binds with high affinity to the extracellular domain of PSMA (*3*). It can be labelled with Lutetium-177 (^{177}Lu) for RLT. Beta particles emitted from ^{177}Lu have a short-range of ~1 mm, enabling delivery of high doses of radiation to tumors while minimizing damage to surrounding normal tissues.

The RESIST-PC study was designed in 2017 to assess the efficacy and safety of ^{177}Lu-PSMA-617 using two commonly used activity regimen (6.0 and 7.4 GBq per cycle) in patients with progressive mCRPC. The administration scheme of ^{177}Lu-PSMA-617 (amount of injected peptide or ligand (nmol), amount of injected activity (GBq – mCi), time interval between each cycle or fractionation, number of cycles) derives mostly from prior empirical compassionate use of ^{177}Lu-PSMA-617 in Germany (*4–6*) and prospective trials using other established molecular radionuclide therapy agents (^{177}Lu-DOTATATE, ^{223}Radium, ^{90}Yttrium-ibritumomab-tiuxetan) (*1*,*7*,*8*). The selected 8-week interval between treatment cycles was based on established hematologic safety considerations (blood count Nadir at 3 to 6 weeks after molecular radionuclide therapy administration) reported in the above mentioned randomized prospective phase 3 trials (*1*,*7*,*8*). The 6.0 and 7.4 GBq activity regimens were chosen based on dosimetry data (*9*,*10*) and the NETTER-1 trial experience (*1*).

It was an investigator-initiated trial (IIT) but was switched to a sponsored study after the acquisition of the development rights of PSMA-617 by Endocyte (see Methods section) and subsequently closed before reaching the target enrollment in 2018. Due to the early study termination and limited data availability, the efficacy endpoints were not analyzed as initially planned. The efficacy outcome results of the UCLA study cohort were published separately (*11*). Here we report the safety evaluation of the study drug derived from the multicenter prospective cohort of 64 patients exposed to ^{177}Lu-PSMA-617.

METHODS

Study Design

RESIST-PC was a prospective, randomized, open-label, multicenter phase 2 study conducted at University of California Los Angeles (UCLA; Los Angeles, CA, USA) and Excel Diagnostics Nuclear Oncology Center (Houston, TX, USA). The primary objective of the study was to assess the efficacy and safety of two ^{177}Lu-PSMA-617 activity regimens (6.0 GBq and 7.4 GBq per cycle) in patients with mCRPC. It was an Investigator Initiated Trial (IIT) co-sponsored by the principal investigators (JCz, ED) under a U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) application. The study was approved by the UCLA institutional review board (IRB# 17-000330) and registered on ClinicalTrials.gov (NCT03042312). After the acquisition of the worldwide rights to develop and commercialize PSMA-617 in 2017, the U.S. IND sponsorship was transferred to Endocyte. As the company initiated the prospective international multicenter registration trial (VISION; NCT03511664) the RESIST-PC trial, subsequently identified as PSMA-617-02, was not consistent with the overall company strategy. Thus, the study was closed prior to enrolling all 200 planned patients in 2018. Here we report the safety evaluation in the patients exposed to the study drug (n=64).

Patients

Patients with progressive mCRPC, chemotherapy-naive or chemotherapy-treated following abiraterone and/or enzalutamide, were eligible. Patients who had received PSMA-targeted radionuclide therapy were excluded. Pretreatment PSMA PET was required for eligibility (see procedure section below). Sufficient bone marrow reserve (hemoglobin (Hb) ≥9.9 g/dl, platelet count (PLT) ≥100×10^9/L, white blood cell count (WBC) ≥2.5x10^9/L, and absolute neutrophil count (ANC) ≥1.5×10^9/L and ECOG Performance Score of 0-2 were required inclusion criteria. Patients with diffuse bone involvement by bone scintigraphy (super-scan), impaired kidney function (Glomerular Filtration Rate (GFR) <40 ml/min, Serum creatinine > 1.5xULN, urinary tract obstruction or marked hydronephrosis), or impaired liver function (AST and ALT > 5xULN) were excluded.

Patients were referred specifically to this trial and continued care with their treating medical oncologist or urologist in close coordination with the study site investigators. They visited the trial sites per protocol. Patients were pre-screened based on their prostate cancer history before initial consultation visit. Informed written and oral consent was obtained from all patients during the initial consultation visit.

Procedures

Screening PSMA PET. PSMA PET performed within 3 months before randomization was required for eligibility. Local study-site investigators visually determined sufficient target expression (majority of lesions with uptake equal to or above liver uptake) and absence of PSMA-negative visceral lesions visible on anatomic imaging modalities (CT, MRI). No semi-quantitative thresholds were applied. OsiriX software was used for visual assessment (*12*).

Randomization. Patients were randomized (1:1 ratio) to receive either 6.0 (± 10%, Arm 1) or 7.4 GBq (± 10%, Arm 2) of ^{177}Lu-PSMA-617 per treatment cycle. Randomization (1:1 ratio) was performed in accordance with Vickers et al (*13*). Randomization was not stratified for any variable. A list of random allocations for patients 1 to 200 was created, concealed and stored at the investigator's site without modification. A clinical research coordinator who was not involved in clinical management assigned the randomized allocation. There was no blinding of patients or physicians.

Treatment Intervention. ^{177}Lu-PSMA-617 was radiolabeled with carrier-free Lutetium-177 (RadioMedix, Inc. Houston, TX). The labelled product was produced, tested, released, and delivered under Good Manufacturing Practice (GMP) conditions as a sterile, ready to use solution for infusion. ^{177}Lu-PSMA-617 was intravenously applied over approximately 15-30 minutes using an infusion pump at 8±1 week intervals up to a maximum of four cycles. Cooling of the salivary glands was applied with icepacks (started 30 min prior injection of ^{177}Lu-PSMA-617 and maintained for 4 hours post-injection). Treatment cycles continued until disease progression, severe toxicity occurred (see safety assessments section below), patient withdrawal, or per investigator decision. Patients were permitted to receive concurrent radiotherapy or other non-chemotherapy treatments.

Safety assessments. included laboratory tests, 12-lead electrocardiograms, physical examination, and vital signs. The laboratory tests (CMP, eGFR, CBC) were performed at baseline (within 72 hours of the first treatment dose) and every 2 weeks (± 3 days) after the first dose of study medication, continued until 12 weeks after the last dose, and every 3 months (± 1 week) thereafter until discontinuation from the study. The CBC, eGFR, and CMP within 2 weeks of each subsequent treatment cycle were used to assess the eligibility for the corresponding treatment cycle. Telephone follow-up was performed 7±3 days after each treatment cycles, and for the follow-up phase in 3±1 month intervals until study termination.

Serious AEs (SAEs) were graded according to the CTCAE criteria version 4.0 while AEs were described by severity (i.e., Mild, Moderate, Severe) by the local investigators. Severity was used to describe the intensity of a specific event which can be of relatively minor medical significance (such as a Grade 3 headache). SAE is based is based on patient/event outcome or action criteria and was used for events that pose a threat to patient's life or ability to function. Seriousness (not intensity/severity) serves as a guide for defining regulatory reporting obligations.

In case of occurrence of grade 3-4 SAEs, or severe AEs treatment administration was suspended until resolution (defined as CTCAE grade ≤ 2) up to 12 weeks after the last cycle. Patients were discontinued from the study in case of Grade 4 hematologic SAE during > 3 weeks, Grade 3 renal SAE during > 3 weeks, or any other Grade 3-4 SAEs during > 12 weeks.

In case a patient experienced the same event more than once, the maximum toxicity grade was presented. Multiple occurrences of the same AEs occurring in one individual were counted only once. The local investigators assessed if AEs were study drug-related as follows: not, unlikely, possibly, probably or definitely related. A Treatment Emergent Adverse Event (TEAE) was defined as an AE that was not present prior to the first dose of ^{177}Lu-PSMA-617, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment was a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period was defined as the period from the date of initiation of randomized treatment up to 30 days after date of last administration of study treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurred first.

Kidney dosimetry was required by the FDA to be performed in the initial versions of the study protocol with a discontinuation rule using a maximum threshold dose to the kidneys of 23 Gy. Dosimetry data for the first 20 patients (16 from UCLA and 4 from Excel Diagnostics) were analyzed and the permitted renal dose of 23 Gy was not exceeded in any patient after 4 cycles, demonstrating overall favorable renal dosimetry. Thus dosimetry was no longer required per protocol (protocol PSMA-617-02 amendment 4, June 2018). Final dosimetry analysis will be reported separately.

Study Duration

Patients were followed until disease progression, death, serious or intolerable AE (that in the opinion of the investigator required the patient's discontinuation), study termination by sponsor, patient withdrawal, lost to follow-up or 24 months after the first treatment cycle.

Data Management and Quality

Designated investigator staff entered the data into an electronic data/electronic CRF (eCRF) system (OpenCLinica eDC). The contract research organization (CRO) responsible for site monitoring was Pharmtrace. PrimeVigilance was responsible for the pharmacovigilance safety database once Endocyte became the Sponsor for this study.

Statistical Analyses

The primary endpoints were the efficacy and the safety of ^{177}Lu-PSMA-617. Safety was assessed by collecting and grading AEs using the CTCAE v4.0. Efficacy (assessed by baseline to 12-week decline in tumor marker level (Prostate Specific Antigen (PSA) ≥ 50%(*14*)) is not reported here due to premature study termination after only 71/200 patients enrolled. As the power of the pre-defined test could not be assured, no formal statistical test for overall response ≥50% was carried out. The actual sample size was insufficient to perform the analyses that would allow for appropriate evaluation of effectiveness. Therefore no statistical test for comparing the 2 groups was performed. No interim analysis was planned. Missing data were not replaced. We employed descriptive statistics including mean, standard deviation, median and interquartile range (Q1-Q3), range (min-max) for continuous variables, and number and percentage for categorical variables. Data was analyzed using SAS version 9.4.

Role of The Funding Source

RESIST-PC was initially an investigator sponsored trial. Patient were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8. After the sponsorship transfer, site monitoring, pharmacovigilance and data analysis was supported by Endocyte/Novartis. The corresponding author had complete data access and had final responsibility to submit for publication.

RESULTS

Patient Enrollment

Between 07.05.2017 and 06.22.2018, a total of 71 patients (51 at UCLA and 20 at Houston) signed informed consent and were randomized (ITT population): 28 (39%) in Arm 1 (6.0 GBq) and 43 (61%) in Arm 2 (7.4GBq). There were seven patients (9.9%) randomized but not treated: two with PSMA negative liver lesions (screen failure), two were too weak for treatment,

one with low platelets (34 $\times 10^9$/L), one withdrew consent and one died. A total of 64 (90.1%) patients received at least one cycle of ^{177}Lu-PSMA-617 (Safety population): 28 (36%) in Arm 1 (6.0 GBq) and 41 (64%) in Arm 2 (7.4GBq). The last visit of the last subject was on 01.15.2020 and the study completion date was 01.08.2021. Seven /71 (9.9%) deaths were reported during the study from enrollment through the 24 months follow-up; 4/28 (14.3%) and 3/43 (7.0%) in the 6.0 GBq and 7.4 GBq treatment arms, respectively (Patient Disposition (ITT population) in Supplemental Table 1).

Protocol Deviations

Thirty-one subjects (43.7%) experienced protocol deviations (Supplemental Table 2). The majority of these included procedures done outside of the protocol required timing. In 40/71 (56.3%) patients, the pre-therapy baseline PSA was performed after the randomization and was not included for analysis.

Baseline Characteristics and Prostate Cancer Treatment History (ITT population, n=71)

The demographic and baseline disease characteristics were comparable across the two treatment groups and are presented in Table 1. Fifty-four (81%) patients had a PSA doubling time ≤ 6 months. Fifty-eight (81.7%) patients had at least one chemotherapy for PCa prior to study enrollment. Fifty-seven (80.3%) patients underwent at least one prior taxane regimen; 54 (76.1%) patients had docetaxel and 26 (36.6%) had cabazitaxel therapy. Sixty-seven (94.4%) patients were treated with abiraterone and 55 (77.5%) patients with enzalutamide.

Screening PSMA PET Findings (ITT population, n=71)

A summary of the screening PSMA PET staging of the ITT population is provided in Supplemental Table 3. Three patients did not undergo the screening PSMA PET scan because of poor clinical status/ disease progression (withdrawal). PSMA PET was performed using ^{68}Ga-PSMA-11 in 66/68 (97%) and ^{18}F-DCFPyL in 2/68 (3%) patients. Two patients were excluded from the study because of PSMA-negative liver lesions (screen failure). Overall 4/68 patients (6%) had nodal disease only (N1 or M1a), 62/68 (91%) had bone disease (M1b) and 25/68 (37%) had visceral metastasis.

Treatment Exposure (Safety population, n=64)

There were 10 (43.5%), 19 (46.5%) and 29 (45.3%) patients who completed 4 cycles of Lu177-PSMA-617 in the 6.0 GBq arm, 7.4 GBq arm, and overall, respectively (Table 2). The mean

±SD cumulative activity was 16.9 ±7.6, 21.4 ±8 and 19.8 ±8.1 GBq in the 6.0 GBq arm, 7.4 GBq arm and overall, respectively (Table 2).

There were 13 (56.5%), 27 (65.9%) and 40 (62.5%) patients with at least one other concurrent systemic therapy for mCRPC during the study (Table 3): hormonal therapy in 12 (52.2%), 25 (61%), 37 (57.8%), abiraterone in 3 (13%), 5 (12.2%), 8 (12.5%), enzalutamide in 2 (8.7%), 7 (17.7%), 9 (14.1%) and other in 10 (43.5%), 16 (39%), 26 (40.6%) in the 6.0GBq arm, 7.4 GBq arm, and overall, respectively. Two patients received concurrent radiotherapy: 1 bone lesion (6.0 GBq arm 1) and 1 local recurrence (7.4 GBq arm 2).

Safety Evaluation (Safety population, n=64)

A summary overview of TEAEs that occurred in the study is presented in Supplemental Table 4. Main TEAEs are described in Table 4. In general, incidence of any AE was comparable between the groups: 22 (95.7%), 39 (95.1%) and 61 (95.3%) in the 6.0 GBq group, the 7.4 GBq group, and overall, respectively. The most frequently occurring TEAEs were dry mouth, fatigue, and nausea: 37 (57.8%), 34 (53.1%), and 30 (46.9%), respectively (Table 4). Notably, none of these events was reported to be severe, except one event of nausea in the 7.4 GBq treatment group (but did not require tube feeding, parenteral nutrition, or hospitalization). Dry mouth (47.8% vs 63.4%) and diarrhea (13.0% vs 31.7%) occurred more frequently in the 7.4 GBq group vs. the 6.0 GBq group. Frequencies of all other TEAEs were comparable among the 2 groups (within 10% difference). There were no differences in AEs between patients aged ≥ 65 years (n=48) and patients aged < 65 years (n=16).

Anemia, thrombocytopenia and leukopenia were reported overall in 8 (12.5%), 1 (1.6%) and 1 (1.6%), respectively. Mild decreases in mean WBCs, RBC and platelets (all components) was observed during treatment. However, during follow-up, the mean values tended to increase again. This was observed for the overall patient population, with no relevant differences between the groups. No trend to creatinine increase was observed during the study. There were 4 patients with Grade 3 AST and/or ALT levels above the normal ranges that were primarily explained by liver metastases and were not considered to be related to the study treatment. Alkaline phosphatase (ALP) mean values over time during treatment had no substantial change, but individual patients had variable increase or decrease of ALP that was compatible with the disease. These overall laboratory findings for the patient population showed no relevant differences between the groups. The data must be interpreted with caution due to the small number of patients with available information at some of the time points.

There were no clinically significant changes in vital signs (Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), temperature (°C), and respiratory rate (breaths per min)). There were no clinically significant abnormalities reported of ECG interpretations.

TEAEs leading to the reduction of ^{177}Lu-PSMA-617 were reported for two (4.9%) patients in the 7.4 GBq arm, both events were anemia. The only TEAE that led to the discontinuation of ^{177}Lu-PSMA-617was abdominal pain (Grade 3 severity) reported in 1 (2.4%) patient in the 7.4 GBq group who had diffuse liver metastases and only received one cycle (unlikely related to treatment).

Serious drug-related TEAEs were reported for 5 (7.8%) patients overall: 1 (4.3%) in the 6.0 GBq group; and 4 (9.8%) in the 7.4 GBq group (Table 5). None were considered as *probably* or *definitely* related to treatment by the investigators and all were reported as *possibly* related to treatment.

There was one (1.5%) acute kidney injury reported (Grade 3 severity) in the 7.4 GBq arm. The nephrologist concluded that the creatinine elevation was likely related to concomitant medication with meloxicam. However, it could not be excluded that additional renal toxicity was caused by ^{177}Lu-PSMA-617. The Investigator considered the acute kidney injury as possibly related to the treatment.

Of the seven deaths reported, there was one death in the 7.4 GBq group determined to be possibly related to treatment due to hematoxicity and gastrointestinal hemorrhage (72 days after last dose, Grade 3 severity); and one death (94 days after last dose) in the 6.0 GBq group determined to be possibly related to treatment due to a subdural hematoma. Four deaths were reported as unrelated adverse events (death > 30 days after last dose of Lu177-PSMA-617, brain metastasis (n=3), liver metastasis (n=1)) and 1 death occurred in a patient prior to receiving his first dose of ^{177}Lu-PSMA-617.

No patients developed myelodysplasia during the follow-up period.

DISCUSSION

This randomized phase 2 study compared two ^{177}Lu-PSMA-617 treatment activity levels in 64 patients with mCRPC who progressed after conventional therapies. ^{177}Lu-PSMA-617 was well tolerated irrespective of the activity regimen (6.0 vs 7.4 GBq per cycle, in average 3 cycles per patient), in line with prior studies comparing similar activity levels (*15*). The most frequently

occurring TEAEs were dry mouth, fatigue, and nausea in 57.8%, 53.1%, and 46.9%, of the population; respectively. None of these events was reported to be severe. Serious TEAEs classified as possibly drug-related occurred in only 7.8% patients overall. The safety profile of ^{177}Lu-PSMA-617 in this study was as anticipated based on the mechanism of action and is generally consistent with previous ^{177}Lu-PSMA-617 experiences as documented in literature in similar populations of patients with mCRPC. The low toxicity profile of ^{177}Lu-PSMA-617 is attributed to the high binding affinity to the PSMA target protein and rapid renal excretion, limiting toxicity to non-target organs.

Since ^{177}Lu-PSMA-617 is predominantly excreted by the kidneys, potential nephrotoxicity represents the main safety concern. In our cohort, the renal safety profile was excellent with only 1 /64 (1.5%) acute kidney injury recorded (Grade 3) that was reversible and very likely related to concomitant medication. This is in line with prior reports. In an Australian retrospective cohort study reporting renal outcomes of ^{177}Lu-PSMA-617 therapy (mean cumulative activity 18.86 ±6.7 GBq) after 8 month of median follow-up, only 5/110 (4.5%) patients experienced Grades 1-2 nephrotoxicity with the main risk factor being prior chronic kidney disease (relative risk 4.2) (*16*). In the retrospective German multicenter study, Grade 1-2 renal failure was reported in 12% (*5*). In the phase 2 *LuPSMA trial*, Grade 1-2 renal toxicity was reported in 10% (*17*). In the *TheraP trial,* Grade 1-2 creatinine increase occurred in 4/98 (4%) and one (1%) Grade 3 acute kidney injury was reported (*18*). In the *VISION* trial, renal AEs of any grade were observed in 46/529 (9%) and of Grade 3-5 in 18/529 (3.4%) (*19*).

Bone marrow toxicity was rare, reversible and manageable. Two patients delayed their subsequent cycle because of anemia. Thrombocytopenia and leukopenia were each reported only in 1 patient (1.6%). Hemorrhage/Hematoma and infections were both reported in 4 patients (6.3%). The relationship to study drug in this population of advanced mCRPC patients with multiple bone metastasis at risk of having impaired bone marrow function from the disease, is uncertain. Of note, the incidence of hematologic side effects in our study is slightly lower than that reported in the retrospective German multicenter study (Grade 3-4 anemia 10%, thrombocytopenia 4%, leukopenia 3%)(*5*), the phase 2 *LuPSMA trial* (Grade 3-4 anemia 10%, thrombocytopenia 10%, neutropenia 6%)(*17*) the *TheraP trial* (Grade 3-4 anemia 8%, thrombocytopenia 11%, leukopenia 1%)(*18*) and the *VISION* trial (Grade 3-4 anemia 13%, thrombocytopenia 8%, leukopenia 3%)(*19*). One reason may be that bone marrow may have been involved less frequently or less extensively in our cohort.

Because of the high uptake of PSMA-radioligands in the salivary glands, xerostomia is a known side effect of ^{177}Lu-PSMA-617. Dry mouth occurred in 63.4% in the 7.4 GBq arm and 47.8% in the 6.0 GBq arm (57.8% overall) but was never graded as severe or irreversible, in line with the phase 2 *LuPSMA trial* (Mean injected activity 7.5 GBq, Grade 1-2 xerostomia in 66%, no grade 3-4)(*17*), the *TheraP trial (*injected activity 8.5 GBq Grade 1-2 xerostomia in 60%, no grade 3-4)(*18*) and the VISION *trial (*injected activity 7.4 GBq Grade 1-2 xerostomia in 39%, no grade 3-4)(*19*). Early reports underestimated this side effect (8% in the retrospective German multicenter study, Mean injected activity 5.9 GBq) probably because of the absence of systematic data collection (*5*). Other symptoms such as taste disorder/ dysgeusia (17% in our cohort, 12% in *TheraP*) or decreased appetite (9% in our cohort, 21% in *VISION*) are likely related to the salivary gland toxicity. Of note, we performed cooling of the salivary glands at the time of ^{177}Lu-PSMA-617 administration but without any tangible effect, as previously described (*20*,*21*).

Frequent, non-life threatening but unpleasant side-effects are important to know to adequately inform and, when possible, premedicate patients. Early reports significantly underestimated important side effects: the retrospective German multicenter study reported mild/moderate nausea in 6% and no intestinal transit disorder (*5*). Nausea and vomiting occurred in 46.9% (1.6% severe) and 18.8% (1.6% severe) of our study population, respectively. These numbers are in line with the phase 2 *LuPSMA trial* (nausea 48% and vomiting 22%)(*17*), the *TheraP trial (*nausea 41% and vomiting 13%) (*18*), and the *VISION* trial *(*nausea 35% and vomiting 19%)(*19*). Pre-medication with antiemetic medication (ondansetron or equivalent) is recommended and side-effect usually do not last more than 24-48 hours. Finally, diarrhea was reported in 31.7% of the 7.4 GBq arm and 13.0% of the 6.0 GBq arm (25% overall) and constipation in 23.4% overall. For comparisons, diarrhea was reported in 194% and 18.9%, constipation in 38% and 20.2% in the *TheraP and VISION* trials (*18*,*19*).

Overall, ^{177}Lu-PSMA-617 administered at 6.0 and 7.4 GBq per cycle and 8-week interval, appears to be better tolerated than available chemotherapy options associated with potentially life-threatening complications. Grade≥3 neutropenia occurred in 45% of patients receiving cabazitaxel in the CARD trial and was reported in 32% to 47% of mCRPC patients receiving docetaxel (*22–24*). In the randomized *TheraP* trial that prospectively compared 98 patients receiving ^{177}Lu-PSMA-617 to 85 patients receiving cabazitaxel for progressing mCRPC, the toxicity profile was more favorable for ^{177}Lu-PSMA-617 than fot cabazitaxel with fewer Grade 3-4 AE (33% vs. 53%), except thrombopenia (11% vs 0%). Of note, severe neutropenia and diarrhea occurred 3 times less: 4% vs. 13% and 19% vs. 56%, respectively.

The amount of injected activity (GBq – mCi) has been tailored to meet the dose limits used in external beam radiation therapy (*25*). However, these dose limits are potentially overly conservative due to the low-dose rate exposure from molecular radionuclide therapy compared to high dose rate of external beam radiation. Higher activity regimen were safely administered in the German compassionate use studies (up to 9.7 GBq (range 2-9.7 GBq))(*5*) and the Australian clinical trials (up to 8.7 GBq per (range 4.4-8.7 GBq)) (*18*,*26*,*27*). Of note, in the Phase I dose-escalation study NCT03042468, up to 22.2 GBq per cycle was safely administered with promising early efficacy and tolerability signals (*28*).

Limitations

Findings are limited by early study closure before completing target enrollment (36%). This was due to an IND sponsorship transfer to Endocyte Inc. resulting in a significantly smaller sample size than the initially planned of 200 patients. Thus, efficacy endpoints could not be analyzed as the power of the pre-defined test was insufficient for reliable statistical analysis. Consequently, the distribution between the 2 treatment groups was also altered (i.e. 40% patients assigned to the 6.0 GBq group and 60% assigned to the 7.4 GBq group) and the actual sample size cannot ensure formal statistical test for comparing the two groups. However, due to the small difference in the 2 tested activities (~20%, 6.0 vs 7.4 GBq) even the limited data suggest that there are likely no or only small differences in toxicity between these 2 activities. This is consistent with prior reports that found similar toxicity rates for comparable levels of injected activity (6.0 vs 7.5 GBq) (*15*). The prematurely terminated randomization also makes it impossible to completely exclude differences in baseline characteristics or other possible confounders.

As another limitation, the study population was heterogeneous regarding prior treatments. The study was self-funded and patient were charged for the study drug (cost recovery, Title 21 CFR 312.8). The common denominator for inclusion was mCRPC disease. This reflects the clinical reality of a multitude of treatment options in advanced prostate cancer and clinical selection for ^{177}Lu-PSMA-617 may be independent of prior treatments.

In addition, because patients were recruited from all across the USA strict adherence to protocols was difficult to achieve. Patients were seen at the study site most frequently for treatment only. They were managed by their off-site medical oncologist or urologist who often scheduled study procedures locally when possible. The required protocol procedures were completed locally when possible by treating physicians or alternatively, completed locally at the trial site when patients were seen for treatments. Therefore, rigid adherence to predefined

schedules was frequently not feasible**.** All study procedures falling outside of the predefined protocol time windows (before randomization) were not considered for the analysis. This affected mostly the serum PSA measurements for the efficacy endpoint. It is deemed that protocol deviations did not have an impact on the safety results of this study but the data must be interpreted with caution due to the small number of patients with available data at some of the time points.

Finally, AEs were defined as occurring during the treatment period for only up to 30 days after the last cycle of ^{177}Lu-PSMA-617 which precludes assessments of any potential longer term toxicity.

CONCLUSION:

In the prospective phase 2 multicenter trial RESIST-PC, two activity levels of ^{177}Lu-PSMA-617 were safely administered to 64 patients. There were no efficacy conclusions in this study due to early study termination. Overall, ^{177}Lu-PSMA-617 administered at up to 4 cycles at 8-week intervals was safe and well-tolerated at 6.0 and 7.4 GBq per cycle. Side effects were easily managed with standard medical support.

With established safety, further clinical trials applying individualized dosimetry and testing different ^{177}Lu-PSMA-617 administration schemes (activity levels, time intervals) are needed to optimize tumor dose delivery and treatment efficacy.

DECLARATION OF CONFLICTS OF INTEREST

JCa reports prior consulting activities outside of the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen, IBA radiopharma, POINT biopharma, Progenics, Radiomedix and Telix Pharmaceuticals.

ME was a consultant for ABX, Blue Earth Diagnostics and Progenics and has patent rights on rhPSMA, outside of the submitted work.

KH is a board member and holds equity in Sofie Biosciences. Intellectual property is patented by the University of California and licensed to Sofie Biosciences. KH was a consultant for Advanced Accelerator Applications, Amgen, Bayer, Curium Pharma, GE Healthcare, IPSEN, Janssen Pharmaceuticals, BTG, Sirtex, Novartis, ROTOP, Bain Capital outside of the submitted work.

JCz is a founder and holds equity in Sofie biosciences and Trethera Therapeutics. Intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. JCz was a consultant for Endocyte Inc. (VISION trial steering committee), Actinium Pharmaceuticals and Point Biopharma outside of the submitted work.

WF was a consultant for Endocyte and BTG, and he received fees from RadioMedix, Bayer, and Parexel outside of the submitted work.

DR is an employee and equity holder of RadioMedix.

ED reports equity ownership at Excel Nuclear Oncology Center and RadioMedix.

No other potential conflict of interest relevant to this article was reported.

FUNDING

RESIST-PC was initially an investigator sponsored trial. Patient were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8. After the sponsorship transfer, site monitoring, pharmacovigilance and data analysis was supported by Endocyte. The corresponding author had complete data access and had final responsibility to submit for publication.

Investigators:

JCa is the recipient of grants from the Prostate Cancer Foundation (2020 Young Investigator Award, 20YOUN05), the Society of Nuclear Medicine and Molecular imaging (2019 Molecular

Imaging Research Grant for Junior Academic Faculty), the Philippe Foundation Inc. (NY, USA) and the ARC Foundation (France) (International Mobility Award SAE20160604150).

KH received funding from the German Research Foundation (Deutsche Forschungsgemeinschaft grant HE 5247/4-1).

WF received financial support from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grants FE1573/1-1 / 807122 and FE1573/3-1 / 659216 and DFG Research Training Group 1739).

JCz was supported by the Prostate Cancer Foundation (2019 and 2017 Challenge Award, 19CHAL09, 17CHAL02) and from the Johnson Comprehensive Cancer Center NIH-NCI Cancer Center Support Grant (P30 CA016042).

AUTHORS' CONTRIBUTIONS

JCa, JCz conducted the manuscript writing.

WF, ME, KH, ED, JCa, JCz are the study designers.

JCz and ED served as IND holder and principal investigators.

JG, PT, KN, MAA, RE, DR, KH, ED, WF, ME, JCa, JCz provided administrative support.

JCa, WA, JG, PT, KN, RE, LGa, MD, ED, MA, AQ, SB, PG, JCz collected and assembled the data.

JCa, BH analyzed and interpreted the data.

All Authors read and approved the manuscript.

ACKNOWLEDGEMENTS

We thank all the patients and their referring physicians whose willingness to participate made this study possible. We thank the whole staff team of the UCLA Nuclear Medicine and Theranostics Division whose hard work made this study possible. We thank Dr Lassman (University of Wurzburg, Germany) for his work on the dosimetry analysis.

KEY POINTS

QUESTION: What is the safety profile of 2 activity regimens of ^{177}Lu-PSMA-617 therapy in patients with metastatic castrate resistant prostate cancer ?

PERTINENT FINDINGS: In this prospective multicenter randomized phase 2 study that included 64 patients, two activity regimens of ^{177}Lu-PSMA-617 therapy (6.0 and 7.4 GBq per cycle) for progressive mCRPC were well tolerated. There was no difference in toxicity between administration of 6.0 and 7.4 GBq of ^{177}Lu-PSMA-617 per treatment cycle.

IMPLICATIONS FOR PATIENT CARE: ^{177}Lu-PSMA-617 therapy is a therapeutic option for patient with metastatic castrate resistant prostate cancer with a good safety profile.

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TABLES

Table 1: Baseline Characteristics (ITT Population)

	6.0 GBq Arm N = 28	7.4 GBq Arm N = 43	Overall N = 71
Age (years)			
Mean (SD)	72.1 (8.39)	69.1 (8.62)	70.3 (8.60)
Min; Max	55; 95	54; 84	54; 95
< 65 years, n (%)	4 (17.4)	12 (29.3)	16 (25.0)
≥ 65 years, n (%)	19 (82.6)	29 (70.7)	48 (75.0)
Race / Ethnicity, n (%)			
Asian	1 (3.6)	1 (2.3)	2 (2.8)
Black / African American	0	1 (2.3)	1 (1.4)
Hispanic / Latino	0	1 (2.3)	1 (1.4)
White	26 (92.9)	40 (93.0)	66 (92.9)
Other	1 (3.6)	0	1 (1.4)
Time since initial prostate cancer diagnosis (years)			
Mean (SD)	8.06 (7.323)	8.06 (7.152)	8.06 (7.156)
Min; Max	0.7; 27.2	0.3; 25.9	0.3; 27.2
Initial Gleason Score, categorized n (%)			
4-7	7 (25.0)	13 (30.2)	20 (28.2)
8-10	20 (71.4)	26 (60.5)	46 (64.8)
Unknown	1 (3.6)	4 (9.3)	5 (7.0)
Baseline PSA doubling time (months)			
n	26	41	67
Mean (SD)	4.35 (7.131)	3.89 (3.977)	4.07 (5.376)
Median	1.91	2.46	2.07
Q1; Q3	1.18; 3.38	1.41; 4.90	1.22; 4.90
Min; Max	0.0; 31.4	0.0; 20.7	0.0; 31.4
≤ 6, n (%)	21 (80.8)	33 (80.5)	54 (80.6)
> 6, n (%)	5 (19.2)	8 (19.5)	13 (19.4)
Baseline PSA (ug/L)			
n	12	19	31
Mean (SD)	208.86 (391.804)	287.92 (830.231)	257.32 (686.578)
Median	46.03	19.34	23.66
Q1; Q3	11.28; 99.35	5.34; 68.00	5.59; 93.20
Min; Max	0.6; 1166.0	1.9; 3499.0	0.6; 3499.0
Number of prior chemotherapies per patient			
n	22	36	58
Median	2.0	2.0	2.0
Q1; Q3	1.0; 3.0	1.0; 3.0	1.0; 3.0
Min; Max	1; 7	1; 5	1; 7
Type of prior chemotherapies per patient, n (%)			
Cabazitaxel	9 (32.1)	17 (39.5)	26 (36.6)
Docetaxel	21 (75.0)	33 (76.7)	54 (76.1)
Other	9 (32.1)	18 (41.9)	27 (38.0)
Type of other prior systemic treatment n (%)			
Abiraterone	26 (92.9)	41 (95.3)	67 (94.4)
Enzalutamide	21 (75.0)	34 (79.1)	55 (77.5)
Hormonal therapy	22 (78.6)	39 (90.7)	61 (85.9)
Standard ADT	19 (67.9)	22 (51.2)	41 (57.7)
Radium 223	5 (17.9)	14 (32.6)	19 (26.8)
Other	20 (71.4)	31 (72.1)	51 (71.8)

Table 2: Randomized Treatment Exposure, Summary of Cycles (Safety Population)

	6.0 GBq N = 23	**7.4 GBq N = 41**	**Overall N = 64**
Duration of study treatment (months)			
Mean (SD)	3.49 (2.37)	3.66 (2.01)	3.60 (2.13)
Median	3.71	3.71	3.71
Q1; Q3	1.87; 5.75	1.87; 5.55	1.87; 5.55
Min; Max	0.0; 6.3	0.0; 7.7	0.0; 7.7
Number of cycles started by patient			
Mean (SD)	2.8 (1.23)	3.0 (1.07)	2.9 (1.12)
Median	3.0	3.0	3.0
Q1; Q3	2.0; 4.0	2.0; 4.0	2.0; 4.0
Min; Max	1; 4	1; 4	1; 4
Number of cycles started by patient categories n (%)			
1 cycle	5 (21.7)	3 (7.3)	8 (12.5)
2 cycles	4 (17.4)	15 (36.6)	19 (29.7)
3 cycles	4 (17.4)	4 (9.8)	8 (12.5)
4 cycles	10 (43.5)	19 (46.3)	29 (45.3)
Dose per cycle (GBq/cycle)			
Mean (SD)	5.909 (0.2953)	7.245 (0.5241)	6.765 (0.7891)
Median	6.031	7.363	7.111
Q1 ; Q3	5.696 ; 6.142	7.134 ; 7.486	6.048 ; 7.410
Min ; Max	5.07 ; 6.31	4.91 ; 7.84	4.91 ; 7.84
Cumulative dose (GBq)			
Mean (SD)	16.913 (7.6668)	21.404 (8.0335)	19.790 (8.1376)
Median	18.583	22.287	19.917
Q1; Q3	11.392; 24.169	14.711; 29.454	14.297; 28.394
Min; Max	5.07; 24.91	6.92; 30.59	5.07; 30.59

Results given as xx (xx.x) where xx = number of patients, (xx.x) = percentage of patients.

Duration of study treatment (Months) = (Treatment end date - Treatment start date + 1) / 30.4375

584 **Table 3: Concurrent Therapies (Population: Safety Population)**

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	6.0 GBq N = 23 n (%)	**7.4 GBq N = 41 n (%)**	**Overall N = 64 n (%)**
Number of patients with at least one other treatment	**13 (56.5)**	**27 (65.9)**	**40 (62.5)**
Type of other treatments			
Abiraterone	3 (13.0)	5 (12.2)	8 (12.5)
Enzalutamide	2 (8.7)	7 (17.1)	9 (14.1)
Hormonal therapy	12 (52.2)	25 (61.0)	37 (57.8)
Other	10 (43.5)	16 (39.0)	26 (40.6)
Standard ADT	1 (4.3)	2 (4.9)	3 (4.7)
Bone metastasis RT	1 (4.3)	0	1 (1.6)
Prostate local recurrence RT	0	1 (2.4)	1 (1.6)
Number of other treatments			
n	13	27	40
Mean (SD)	2.8 (1.42)	2.4 (1.39)	2.5 (1.40)
Median	2.0	2.0	2.0
Q1; Q3	2.0; 3.0	1.0; 3.0	1.5; 3.0
Min; Max	1; 6	1; 6	1; 6

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587 Results given as xx (xx.x) where xx = number of patients, (xx.x) = percentage of patients.

588 *ADT = Androgen deprivation therapy; RT = radiation therapy***.**

Table 4: Main treatment-emergent adverse events (more than 5% of patients in either treatment arm, and blood and kidney laboratory tests) (Safety Population)

	6.0 GBq (N=23) n (%)		7.4 GBq (N=41) n (%)		Overall (N=64) n (%)	
	All severity	**Severe**	**All severity**	**Severe**	**All severity**	**Severe**
Patient with Any Event	22 (95.7)	2 (8.7)	39 (95.1)	7 (17.1)	61 (95.3)	9 (14.1)
Dry mouth	11 (47.8)	0	26 (63.4)	0	37 (57.8)	0
Fatigue	13 (56.5)	0	21 (51.2)	0	34 (53.1)	0
Nausea	12 (52.2)	0	18 (43.9)	1 (2.4)	30 (46.9)	1 (1.6)
Diarrhea	3 (13.0)	0	13 (31.7)	0	16 (25.0)	0
Constipation	6 (26.1)	0	9 (22.0)	0	15 (23.4)	0
Vomiting	4 (17.4)	0	8 (19.5)	1 (2.4)	12 (18.8)	1 (1.6)
Taste disorder	4 (17.4)	0	7 (17.1)	0	11 (17.2)	0
Pain	3 (13.0)	0	6 (14.6)	1 (2.4)	9 (14.0)	1 (1.6)
Decreased appetite	1 (4.3)	0	5 (12.2)	0	6 (9.4)	0
Arthralgia	3 (13.0)	0	2 (4.9)	0	5 (7.8)	0
Hemorrhage/Hematoma	1 (4.3)	1 (4.3)	3 (7.3)	1 (2.4)	4 (6.3)	2 (3.1)
Infection	1 (4.3)	0	3 (7.3)	1 (2.4)	4 (6.3)	1 (1.6)
Headache	2 (8.7)	0	2 (4.9)	0	4 (6.3)	0
Dry eye	1 (4.3)	0	3 (7.3)	0	4 (6.3)	0
Back pain	2 (8.7)	0	1 (2.4)	0	3 (4.7)	0
Dyspnea	0	0	3 (7.3)	1 (2.4)	3 (4.7)	1 (1.6)
Key laboratory tests events						
Anemia	4 (17.4)	0	4 (9.8)	1 (2.4)	8 (12.5)	1 (1.6)
Thrombocytopenia	0	0	1 (2.4)	1 (2.4)	1 (1.6)	1 (1.6)
Leukopenia	0	0	1 (2.4)	0	1 (1.6)	0
Lymphopenia	0	0	1 (2.4)	0	1 (1.6)	0
Acute Kidney Injury	0	0	1 (2.4)	1 (2.4)	1 (1.6)	1 (1.6)
GFR decreased	1 (4.3)	0	0	0	1 (1.6)	0

Results given as xx (xx.x) where xx = number of patients with AEs, (xx.x) = percentage of patients. Every patient was counted a single time for each applicable specific AE. All AE tables are coded using MedDRA version 22.1. Preferred terms are sorted in descending frequency of 'All severity' column, as reported in the 'Overall' column.

Table 5: Serious Drug-related TEAEs (Safety Population)

None of the Serious drug-related TEAEs were considered as probably or definitely related to treatment by the investigators and all were reported as possibly related to treatment.

System organ class **Preferred term**	**6.0 GBq** **N = 23** **n (%)**	**7.4 GBq** **N = 41** **n (%)**	**Overall** **N = 64** **n (%)**
Patient with any event	1 (4.3)	4 (9.8)	5 (7.8)
Blood and lymphatic system disorders			
Anemia (*Grade 3*, *possibly related*)	0	1 (2.4)	1 (1.6)
Thrombocytopenia (*Grade 4*, *possibly related*)	0	1 (2.4)	1 (1.6)
Gastrointestinal disorders			
Gastrointestinal hemorrhage (*Grade 3*, *possibly related*)	0	1 (2.4)	1 (1.6)
General disorders			
Death (*Grade 5, possibly related*)	0	1 (2.4)	1 (1.6)
Injury complications			
Subdural hematoma (*Grade 4 possibly related*)	1 (4.3)	0	1 (1.6)
Renal and urinary disorders			
Acute kidney injury (*Grade 3*, *possibly related)*	0	1 (2.4)	1 (1.6)
Respiratory, thoracic and mediastinal disorders			
Pleural effusion (*Grade 3*, *possibly related)*	0	1 (2.4)	1 (1.6)

Results given as xx (xx.x) where xx = number of patients with serious, drug-related TEAEs, (xx.x) = percentage of patients Every patient was counted a single time for each applicable specific serious, drug-related AE with highest severity. A patient with multiple serious, drug-related TEAEs within a system organ class (SOC) was counted a single time for that SOC with the highest severity**.**

SUPPLEMENTAL TABLES:

Supplemental Table 1 Patient Disposition (ITT Population)

	6.0 GBq N = 28 n (%)	**7.4 GBq N = 43 n (%)**	**Overall N = 71 n (%)**
Patients who discontinued from ^{177}Lu-PSMA-617	23 (82.1)	41 (95.3)	64 (90.1)
Reason for discontinuation from ^{177}Lu-PSMA-617			
Completion of 4 RLT cycles	10 (35.7)	19 (44.2)	29 (40.8)
Patient withdrawal	6 (21.4)	6 (14.0)	12 (16.9)
PSA/radiographic progression at ≥ 12 weeks	7 (25.0)	16 (37.2)	23 (32.4)
Patients who completed the study	18 (64.3)	31 (72.1)	49 (69.0)
Reason for study completion			
Completed	1 (3.6)	0	1 (1.4)
Death	3 (10.7)	2 (4.7)	5 (7.0)
Progressive disease	14 (50.0)	29 (67.4)	43 (60.6)
Patients who early discontinued from the study	10 (35.7)	12 (27.9)	22 (31.0)
Reason for early discontinuation from the study			
Administrative reason	1 (3.6)	1 (2.3)	2 (2.8)
Adverse event	0	1 (2.3)	1 (1.4)
Lost to follow-up	1 (3.6)	3 (7.0)	4 (5.6)
Occurrence of condition*	4 (14.3)	2 (4.7)	6 (8.5)
Patient withdrawal	4 (14.3)	5 (11.6)	9 (12.7)
Total number of deaths	4 (14.3)	3 (7.0)	7 (9.9)

*Any occurrence of conditions that prevented the patient's participation in the study.
AE = Adverse event; RLT = Radioligand therapy.

Supplemental Table 2 : Summary of Protocol Deviations (ITT Population)

Protocol Deviation Category	6.0 GBq (N=28)		7.4 GBq (N=43)		Overall (N=71)	
	n (%) [m]		n (%) [m]		n (%) [m]	
	Any	Important	Any	Important	Any	Important
Patient with at least one protocol deviation	19 (67.9) [95]	9 (32.1) [13]	38 (88.4) [249]	22 (51.2) [32]	57 (80.3) [344]	31 (43.7) [45]
Procedure Violation	17 (60.7) [93]	8 (28.6) [12]	38 (88.4) [239]	20 (46.5) [29]	55 (77.5) [332]	28 (39.4) [41]
Drug Dosing	1 (3.6) [1]	0	5 (11.6) [7]	0	6 (8.5) [8]	0
Informed Consent Procedure	1 (3.6) [1]	1 (3.6) [1]	2 (4.7) [2]	2 (4.7) [2]	3 (4.2) [3]	3 (4.2) [3]
Inc-/Exclusion Criteria	0	0	1 (2.3) [1]	1 (2.3) [1]	1 (1.4) [1]	1 (1.4) [1]

n is the number of subjects, [m] is the number of protocol deviations

Supplemental Table 3: Screening PSMA PET/CT findings

T+= Prostate fossa lesion(s) ; N1 = pelvic LN lesion(s); M1a = extra-pelvic LN lesions(s); M1b = bone lesion(s); M1c (visceral lesion(s).

	6.0 GBq Arm		7.4 GBq Arm		Overall	
	n=26	%	n=42	%	n=68	%
T+	7	26.92%	9	21.43%	16	23.53%
N1	9	34.62%	17	40.48%	26	38.24%
M1a	16	61.54%	23	54.76%	39	57.35%
Abdominal	9	56.25%	17	73.91%	26	66.67%
Upper-Diaphragm	14	87.50%	23	100.00%	37	94.87%
Inguinal	3	18.75%	2	8.70%	5	12.82%
M1b	25	96.15%	37	88.10%	62	91.18%
< 5	3	12.00%	5	13.51%	8	12.90%
> 5	16	64.00%	22	59.46%	38	61.29%
Diffuse	6	24.00%	10	27.03%	16	25.81%
M1c	9	34.62%	16	38.10%	25	36.76%
Liver	2	22.22%	11	68.75%	13	52.00%
Lung	3	33.33%	5	31.25%	8	32.00%
Adrenal	2	22.22%	2	12.50%	4	16.00%
Brain	1	11.11%	1	6.25%	2	8.00%
Colon	1	11.11%	1	6.25%	2	8.00%
Muscle	0	0.00%	2	12.50%	2	8.00%
Penis	0	0.00%	1	6.25%	1	4.00%
Pancreas	0	0.00%	1	6.25%	1	4.00%
Bladder	1	11.11%	0	0.00%	1	4.00%
Peritoneum	1	11.11%	0	0.00%	1	4.00%
N1/M1a (LN only)	1	3.85%	3	7.14%	*4*	5.88%
M1b (bone only)	7	26.92%	12	28.57%	*19*	27.94%
M1c (visceral only)	0	0.00%	0	0.00%	*0*	0.00%
N1/M1a M1b (LN + bone)	9	34.62%	11	26.19%	*20*	29.41%
N1/M1a M1c (LN + visceral)	0	0.00%	2	4.76%	*2*	2.94%
M1b M1c (bone + visceral)	1	3.85%	3	7.14%	*4*	5.88%
N1/M1a M1b M1c (LN + bone + visceral)	8	30.77%	11	26.19%	*19*	27.94%

Supplemental Table 4: Summary Table of Treatment Emergent Adverse Events – Safety Population

	6.0 GBq N = 23 n (%)	**7.4 GBq N = 41 n (%)**	**Overall N = 64 n (%)**
Patients with at least one TEAE	22 (95.7)	39 (95.1)	61 (95.3)
Patients with at least one serious TEAE	4 (17.4)	8 (19.5)	12 (18.8)
Patients with at least one drug-related TEAE	20 (87.0)	37 (90.2)	57 (89.1)
Patients with at least one serious drug-related TEAE	1 (4.3)	4 (9.8)	5 (7.8)
Patients having a TEAE leading to reduction of ^{177}Lu-PSMA-617	0	2 (4.9)	2 (3.1)
Patients having a TEAE leading to discontinuation of ^{177}Lu-PSMA-617	0	1 (2.4)	1 (1.6)
TEAE leading to death	2 (8.7)	1 (2.4)	3 (4.7)

Results given as xx (xx.x) where xx = number of patients with adverse events, (xx.x) = percentage of patients. TEAE = is considered study drug-related if relatedness is recorded as possible, probably, definite, or when the value is missing.