Safety of PSMA-Targeted Molecular Radioligand Therapy with ^{177}Lu-PSMA-617: Results from the Prospective Multicenter Phase 2 Trial RESIST-PC (NCT03042312)

Jeremie Calais[1–3], Johannes Czernin[1–3*], Pan Thin[1], Jeannine Gartmann[1], Kathleen Nguyen[1], Wesley R. Armstrong[1], Martin Allen-Auerbach[1–3], Andrew Quon[1–3], Shadfar Bahri[1–3], Pawan Gupta[1], Linda Gardner[1], Magnus Dahlbom[1], Beilei He[4], Rouzbeh Esfandiari[5], David Ranganathan[6], Ken Herrmann[7], Matthias Eiber[8], Wolfgang P. Fendler[7], and Ebrahim Delpassand[5,6*]

[1]Ahmanson Translational Theranostics Division, Department of Molecular & Medical Pharmacology, University of California Los Angeles, Los Angeles, California; [2]Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, California; [3]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, California; [4]Advanced Accelerator Applications, a Novartis Company, Geneva, Switzerland; [5]Excel Diagnostics and Nuclear Oncology Center, Houston, Texas; [6]RadioMedix, Inc., Houston, Texas; [7]Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; and [8]Department of Nuclear Medicine, Technical University Munich, Klinikum rechts der Isar, Munich, Germany

The purpose of this analysis was 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 metastatic castration-resistant prostate cancer after ≥ 1 novel androgen-axis drug, either chemotherapy naïve or postchemotherapy, with sufficient bone marrow reserve, normal kidney function, sufficient PSMA expression by PSMA PET, and no PSMA-negative soft-tissue lesions were eligible. Patients were randomized (1:1) into 2 activity groups (6.0 or 7.4 GBq per cycle) and received up to 4 cycles every 8 wk. The primary safety endpoint was assessed by collecting and grading adverse events using the Common Terminology Criteria for Adverse Events. Patients were followed until disease progression, death, serious or intolerable adverse events, study termination by sponsor, patient withdrawal, lost to follow-up, or 24 mo after the first cycle. **Results**: The study was closed at enrollment of 71 of 200 planned patients because of sponsorship transfer. A total of 64 (90.1%) patients received at least 1 cycle of ^{177}Lu-PSMA-617: 28 (36%) in arm 1 (6.0 GBq) and 41 (64%) in arm 2 (7.4 GBq). 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%, respectively), nausea (52.2%; 43.9%; 46.9%, respectively), and diarrhea (13.0%; 31.7%; 25.0%, respectively). 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): 1 subdural hematoma grade 4, 1 anemia grade 3, 1 thrombocytopenia grade 4, 1 gastrointestinal hemorrhage grade 3, and 1 acute kidney injury grade 3. There were no clinically significant changes in vital signs in electrocardiograms 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-wk intervals with side effects 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.

Key Words: metastatic castration-resistant prostate cancer; radionuclide therapy; molecular radiotherapy; prostate-specific membrane antigen; ^{177}Lu, RESIST-PC; prospective randomized phase 2 trial; theranostics; safety

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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 labeled with lutetium-177 (^{177}Lu) for RLT. β-particles emitted from ^{177}Lu have a short-range of approximately 1 mm, enabling delivery of high doses of radiation to tumors while minimizing damage to surrounding normal tissues.

The RESIST-PC trial was designed in 2017 to assess the efficacy and safety of ^{177}Lu-PSMA-617 using 2 commonly used activity regimen (6.0 and 7.4 GBq per cycle) in patients with progressive metastatic castration-resistant prostate cancer (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

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For correspondence or reprints, contact Jeremie Calais (jcalais@mednet.ucla.edu).
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*Contributed equally to this work.
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cycles) derives mostly from prior empiric 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}Ra, ^{90}Y-ibritumomab-tiuxetan) (*1*,*7*,*8*). The selected 8-wk interval between treatment cycles was based on established hematologic safety considerations (blood count Nadir at 3–6 wk 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*).

RESIST-PC 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 the "Materials and Methods" section) and subsequently closed before reaching the target enrollment in 2018. Because of the early study termination and limited data availability, the efficacy endpoints were not analyzed as initially planned. The efficacy outcome results of the University of California Los Angeles (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.

MATERIALS AND 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) and Excel Diagnostics Nuclear Oncology Center (Houston, TX). The primary objective of the study was to assess the efficacy and safety of 2 ^{177}Lu-PSMA-617 activity regimens (6.0 GBq and 7.4 GBq per cycle) in patients with mCRPC. It was initially an IIT cosponsored by the principal investigators 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 before all 200 planned patients were enrolled in 2018. Here we report the safety evaluation in the patients exposed to the study drug ($n = 64$).

Patients

Patients with progressive mCRPC after abiraterone or enzalutamide, chemotherapy-naive or chemotherapy-treated (regardless the number of prior chemotherapy regimens) were eligible. Patients who had received PSMA-targeted radionuclide therapy were excluded. Pretreatment PSMA PET was required for eligibility (see the "Procedures" section below). Sufficient bone marrow reserve (hemoglobin $\geq$ 9.9 g/dL, platelet count $\geq 100 \times 10^9$/L, white blood cell count [WBC] $\geq 2.5 \times 10^9$/L, and absolute neutrophil count $\geq 1.5 \times 10^9$/L) and Eastern Cooperative Oncology Group Performance Score of 0–2 were required inclusion criteria. Patients with diffuse bone involvement by bone scintigraphy (superscan), impaired kidney function (glomerular filtration rate [GFR] $<$ 40 mL/min, serum creatinine $>$ 1.5$\times$upper limit of normal [ULN], urinary tract obstruction or marked hydronephrosis), or impaired liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $>$5$\times$ULN) 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 traveled to the trial sites per protocol. Patients were prescreened 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 mo 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 lesions visible on anatomic imaging modalities (CT, MRI). No semiquantitative thresholds were applied. OsiriX software (Pixmeo) was used for visual assessment (*12*).

Randomization. Patients were randomized (1:1 ratio) to receive either 6.0 ($\pm$10%, arm 1) or 7.4 GBq ($\pm$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 ^{177}Lu (RadioMedix, Inc.). The labeled product was produced, tested, released, and delivered under good-manufacturing-practice conditions as a sterile, ready-to-use solution for infusion. ^{177}Lu-PSMA-617 was intravenously applied over approximately 15–30 min using an infusion pump at 8 $\pm$ 1 wk intervals up to a maximum of 4 cycles. Salivary glands were cooled using icepacks (started 30 min before injection of ^{177}Lu-PSMA-617 and maintained for 4 h after injection). Treatment cycles continued until disease progression, severe toxicity occurred (see the "Safety Assessments" section below), patient withdrawal, or per investigator decision. Patients were permitted to receive concurrent radiotherapy or other non-chemotherapy treatments.

Safety Assessments. Physical examination, vital signs, and 12-lead electrocardiogram were performed at each site visit. Laboratory tests (comprehensive metabolic panel [CMP], estimated GFR [eGFR], complete blood count [CBC]) were performed at baseline (within 72 h of the first treatment dose) and every 2 wk ($\pm$3 d) after the first dose of study medication, continued until 12 wk after the last dose, and every 3 mo ($\pm$1$\times$wk) thereafter until discontinuation from the study. The CBC, eGFR, and CMP within 2 wk of each subsequent treatment cycle were used to assess the eligibility for the corresponding treatment cycle. Telephone follow-up was performed 7 $\pm$ 3 d after each treatment cycle, and for the follow-up phase in 3 $\pm$ 1 mo intervals until study termination.

Serious AEs (SAEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, whereas 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 on patient/event outcome or action criteria and was used for events that posed a threat to the patient's life or ability to function. Seriousness (not intensity/severity) serves as a guide for defining regulatory reporting obligations.

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

In the case of a patient experiencing the same event more than once, the maximum toxicity grade was presented. Multiple occurrences of the same AEs occurring in 1 individual were counted only once. The local investigators assessed whether 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 before the first dose of ^{177}Lu-PSMA-617 but appeared after 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 d after date of last administration of study treatment or the day before 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 obtained after the first cycle for the first 20 patients (16 from UCLA and 4 from Excel Diagnostics) were analyzed. The estimated cumulated radiation dose after 4 cycles did not exceed the permitted renal dose of 23 Gy in any patient, 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 mo after the first treatment cycle.

Data Management and Quality

Designated investigator staff entered the data into an electronic data/electronic Case Report Form (OpenCLinica eDC). The contract research organization responsible for site monitoring was Pharmtrace. PrimeVigilance was responsible for the pharmacovigilance safety database once Endocyte became the sponsor for this study.

Statistical Analysis

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, version 4.0. Efficacy (assessed by baseline to 12-wk decline in tumor marker level [prostate-specific antigen, PSA $\geq$ 50%] (*14*)) is not reported here due to premature study termination after only 71of 200 patients enrolled. As the power of the predefined test could not be ensured, no formal statistical test for overall response $\geq$ 50% was performed. 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 used descriptive statistics including mean, SD, median and interquartile range (Q1–Q3), and range (minimum–maximum) for continuous variables, and number and percentage for categoric variables. Data were analyzed using SAS, version 9.4 (SAS Institute Inc.).

Role of the Funding Source

RESIST-PC was initially an investigator-sponsored trial. Patients 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 July 5, 2017, and June 22, 2018, a total of 71 patients (51 at UCLA and 20 at Houston) signed informed consent and were randomized (ITT population): 28/71 (39%) in arm 1 (6.0 GBq) and 43/71 (61%) in arm 2 (7.4 GBq). There were 7/71 patients (9.9%) randomized but not treated: 2 with PSMA-negative liver lesions (screen failure), 2 were too weak for treatment, 1 with low platelets (34×10^9/L), 1 withdrew consent, and 1 died. A total of 64/71 (90.1%) patients received at least 1 cycle of ^{177}Lu-PSMA-617 (safety population): 23/64 (36%) in arm 1 (6.0 GBq) and 41/64 (64%) in arm 2 (7.4 GBq). The last visit of the last subject was on January 15, 2020, and the study completion date was January 8, 2021. Seven of 71 (9.9%) deaths were reported during the study from enrollment through the 24-mo follow-up: 4 of 28 (14.3%) and 3 of 43 (7.0%) in the 6.0-GBq and 7.4-GBq treatment arms, respectively (patient disposition [ITT population] in Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Protocol Deviations

Fifty seven/71 subjects (80.3%) experienced protocol deviations (Supplemental Table 2). Most of these included procedures done outside the protocol required timing. In 40 of 71 (56.3%) patients, the pretherapy 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 2 treatment groups and are presented in Table 1. Fifty-four/71 (80.6%) patients had a PSA doubling time $\leq$ 6 mo. Fifty-eight/71 (81.7%) patients underwent at least 1 round of chemotherapy for PCa before study enrollment. Fifty-seven/71 (80.3%) patients underwent at least 1 prior taxane regimen; 54/71 (76.1%) patients had docetaxel and 26/71 (36.6%) had cabazitaxel therapy. Sixty-seven/71 (94.4%) patients were treated with abiraterone and 55/71 (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 of 68 (97%) and ^{18}F-DCFPyL in 2 of 68 (3%) patients. Two patients were excluded from the study because of PSMA-negative liver lesions (screen failure). Overall, 4 of 68 patients (6%) had nodal disease only (N1 or M1a), 62 of 68 (91%) had bone disease (M1b), and 25 of 68 (37%) had visceral metastasis.

Treatment Exposure (Safety Population, *n* = 64)

There were 10/23 (43.5%), 19/41 (46.5%), and 29/64 (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 (Table 2). The mean $\pm$ 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 13/23 (56.5%), 27/41 (65.9%), and 40/64 (62.5%) patients with at least 1 other concurrent systemic therapy for mCRPC during the study (Table 3): hormonal therapy in 12/23 (52.2%), 25/41 (61%), 37/64 (57.8%); abiraterone in 3/23 (13%), 5/41 (12.2%), 8/64 (12.5%); enzalutamide in 2/23 (8.7%), 7/41 (17.7%), 9/64 (14.1%); and other in 10/23 (43.5%), 16/41 (39%), 26/64 (40.6%) in the 6.0-GBq 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).

TABLE 1
Baseline Characteristics (ITT Population)

Characteristic	6.0 GBq arm (n = 28)	7.4 GBq arm (n = 43)	Overall (n = 71)
Age (y)			
Mean (SD)	72.1 (8.39)	69.1 (8.62)	70.3 (8.60)
Minimum; maximum	55; 95	54; 84	54; 95
<65 y (n)	4 (14.3%)	13 (30.2%)	17 (23.9%)
≥65 y (n)	24 (85.7%)	30 (69.8%)	54 (76.1%)
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 (y)			
Mean (SD)	8.06 (7.323)	8.06 (7.152)	8.06 (7.156)
Minimum; maximum	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 (mo)			
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
Minimum; maximum	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
Minimum; maximum	0.6; 1166.0	1.9; 3499.0	0.6; 3499.0
Number of prior chemotherapies per patient			
n	22 (78.6%)	36 (83.7%)	58 (81.7%)
Median	2.0	2.0	2.0
Q1; Q3	1.0; 3.0	1.0; 3.0	1.0; 3.0
Minimum; maximum	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%)
^{223}Ra	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 (mo)			
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
Minimum; maximum	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
Minimum; maximum	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
Minimum; maximum	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
Minimum; maximum	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.

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: 22/23 (95.7%), 39/41 (95.1%), and 61/64 (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: 37/64 (57.8%), 34/64 (53.1%), and 30/64 (46.9%), respectively (Table 4). Notably, none of these events was reported to be severe, except 1 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 than in 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 y (n = 48) and patients aged < 65 y (n = 16).

Anemia, thrombocytopenia, and leukopenia were reported overall in 8/64 (12.5%), 1/64 (1.6%), and 1/64 (1.6%), respectively. Mild decreases in mean white blood cell count, red blood cell count, and platelets (all components) were 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 or ALT levels above the reference 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 [mm Hg], diastolic blood pressure [mm Hg], heart rate [bpm], temperature [°C], and respiratory rate [breaths per min]). There were no clinically significant abnormalities reported of electrocardiogram interpretations.

TEAEs leading to the reduction of ^{177}Lu-PSMA-617 were reported for 2/41 (4.9%) patients in the 7.4-GBq arm; both events

TABLE 3
Concurrent Therapies (Population: Safety Population)

	6.0 GBq (n = 23)	7.4 GBq (n =41)	Overall (n = 64)
Number of patients with at least 1 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
Minimum; maximum	1; 6	1; 6	1; 6

Results given as xx (xx.x) where xx = number of patients, (xx.x) = percentage of patients. Data in parentheses are percentages, unless otherwise indicated.

ADT = Androgen deprivation therapy; RT = radiation therapy.

were anemia. The only TEAE that led to the discontinuation of ^{177}Lu-PSMA-617 was abdominal pain (grade 3 severity) reported in 1 patient in the 7.4-GBq group who had diffuse liver metastases and only received 1 cycle (unlikely related to treatment).

Serious drug-related TEAEs were reported for 5/64 (7.8%) patients overall: 1/23 (4.3%) in the 6.0-GBq group; and 4/41 (9.8%) in the 7.4-GBq group (Table 5). None was considered as *probably* or *definitely* related to treatment by the investigators, and all were reported as *possibly* related to treatment.

There was 1 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 7 deaths reported, there was 1 death in the 7.4-GBq group determined to be possibly related to treatment due to hemotoxicity and gastrointestinal hemorrhage (72 d after last dose, grade 3 severity) and 1 death (94 d 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 d after last dose of ^{177}Lu-PSMA-617, brain metastasis (n = 3), liver metastasis (n = 1)), and 1 death occurred in a patient before he received his first dose of ^{177}Lu-PSMA-617.

No patients developed myelodysplasia during the follow-up period.

DISCUSSION

This randomized phase 2 study compared 2 ^{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 a prior retrospective study 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 nontarget organs.

Because ^{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 of 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 mo of median follow-up, only 5 of 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 of 98 (4%), and 1 (1%) grade 3 acute kidney injury was reported (*18*). In the VISION trial, renal AEs of any grade were observed in 46 of 529 (9%) and of grade 3–5 in 18 of 529 (3.4%) (*19*).

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)		7.4 GBq (n = 41)		Overall (n = 64)	
Adverse event	All severity (n)	Severe (n)	All severity (n)	Severe (n)	All severity (n)	Severe (n)
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. Data in parentheses are percentages, unless otherwise indicated.

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

TABLE 5
Serious Drug-Related TEAEs (Safety Population)

System organ class, preferred term	6.0 GBq (n = 23)	7.4 GBq (n = 41)	Overall (n = 64)
Any Serious Drug Related TEAE	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. 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. Data in parentheses are percentages.

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*). Premedication with antiemetic medication (ondansetron or equivalent) is recommended and side effects usually do not last more than 24–48 h. 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 19.4 and 18.9% and constipation in 38% and 20.2% in the *TheraP and VISION* trials, respectively (*18*,*19*).

Overall, ^{177}Lu-PSMA-617 administered at 6.0 and 7.4 GBq per cycle and 8-wk interval appears to be better tolerated than available chemotherapy options which are associated with potentially life-threatening complications. Grade $\geq$ 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 with 85 patients receiving cabazitaxel for progressing mCRPC, the toxicity profile was more favorable for ^{177}Lu-PSMA-617 than for cabazitaxel, with fewer grade 3–4 AEs (33% vs. 53%), except thrombopenia (11% vs. 0%). Of note, severe neutropenia and diarrhea occurred 3 times less: 4% versus 13% and 19% versus 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 with 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*).

Due to IND sponsorship transfer to Endocyte Inc. and the early study closure before completion of the target enrollment (36%), the study findings are limited by the smaller sample size than the initially planned 200 patients. Thus, efficacy endpoints could not be analyzed as the power of the predefined 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 testing for comparing the 2 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. Because the study was self-funded and patients 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. Thus clinical selection for ^{177}Lu-PSMA-617 may be independent of prior treatments.

In addition, because patients were recruited from all across the United States, 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 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 d 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, 2 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-wk 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.

DISCLOSURE

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KEY POINTS

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

PERTINENT FINDINGS: In this prospective multicenter randomized phase 2 study that included 64 patients with progressive mCRPC, 2 activity regimens of ^{177}Lu-PSMA-617 therapy (6.0 and 7.4 GBq per cycle) 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 patients with mCRPC with a good safety profile.

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