Journal of Nuclear Medicine, published on May 20, 2021 as doi:10.2967/jnumed.121.261982

Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with 177Lu-PSMA-617 for metastatic Castration-reSISTant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort.

Jeremie Calais[1,2,3,4], Andrei Gafita[1], Matthias Eiber[1,5], Wesley R Armstrong[1], Jeannine Gartmann[1], Pan Thin[1], Kathleen Nguyen[1], Vincent Lok[1], Laura Gosa[1], Tristan Grogan[6], Rouzbeh Esfandiari[7], Martin Allen-Auerbach[1,3,4], Andrew Quon[1,3,4], Shadfar Bahri[1,3,4], Pawan Gupta[1], Linda Gardner[1], David Ranganathan[8], Roger Slavik[1], Magnus Dahlbom[1,2], Ken Herrmann[1,9], Ebrahim Delpassand[7,8], Wolfgang P. Fendler[1,9], Johannes Czernin[1,3,4]

[1] Ahmanson Translational Theranostics Division, Department of Molecular & Medical Pharmacology, University of California Los Angeles, CA, USA.

[2] Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, University of California Los Angeles, CA, USA.

[3] Institute of Urologic Oncology, University of California Los Angeles, CA, USA.

[4] Jonsson Comprehensive Cancer Center, University of California Los Angeles, CA, USA

[5] Department of Nuclear Medicine, Technical University Munich, Klinikum rechts der Isar, Munich, Germany

[6] Department of Medicine Statistics Core, David Geffen School of Medicine, University of California Los Angeles, CA, USA.

[7] Excel Diagnostics and Nuclear Oncology Center, Houston, Texas, USA.

[8] RadioMedix, Inc., Houston, Texas, USA.

[9] Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany

Corresponding Author:
Jeremie Calais, MD MSc
Ahmanson Translational Theranostics Division,
Department of Molecular and Medical Pharmacology,
David Geffen School of Medicine,
University of California Los Angeles,
200 Medical Plaza, Suite B114-61,
Los Angeles, CA 90095
E-mail: jcalais@mednet.ucla.edu

Abstract Word count: 335

Body Text Word count: 3069

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

Running Title: LuPSMA Efficacy in the UCLA RESIST trial

ABSTRACT

Objective: To determine prospectively the efficacy profile of 2 activity regimens of Lu-PSMA therapy in patients with progressive metastatic castrate resistant prostate cancer (mCRPC): 6.0 vs 7.4 GBq.

Methods: RESIST-PC (NCT03042312) 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, and sufficient PSMA expression by PSMA PET were eligible. Patients were randomized (1:1) into two activity groups (6.0 or 7.4 GBq) and received up to 4 cycles every 8 weeks. The primary endpoint was the efficacy of Lu-PSMA measured by the PSA response rate (RR) after 2 cycles (≥50% decline from baseline). Secondary endpoints included the PSA-RR (≥50% decline) at any time (best response), and overall survival (OS).

Results: The study was closed at enrollment of 71/200 planned patients because of sponsorship transfer. We report here the efficacy UCLA cohort results only (n=43). The PSARRs after 2 cycles and at any time were 11/40 (28%, 95%CI 15-44), 6/13 (46%, 95%CI 19-75), 5/27 (19%, 95%CI 6-38), and 16/43 (37%, 95%CI 23-53), 7/14 (50%, 95%CI 23-77), 9/29 (31%, 95%CI 15-51) in the whole cohort, the 6.0 GBq and the 7.4 GBq groups, respectively (p=0.12 and p=0.31). The median OS was 14.0 months (95%CI 10.1-17.9), 15.8 (95%CI 11.8-19.4), 13.5 (95%CI 10.0-17.0) in the whole cohort, the 6.0 GBq and the 7.4 GBq groups, respectively (p=0.87). OS was longer in patients who experienced a PSA decline ≥50% at any time than those who did not: median: 20.8 vs. 10.8 months (p=0.005).

Conclusions: In this prospective phase 2 trial of Lu-PSMA for mCRPC the median OS was 14 months. Despite the heterogeneous study population and the premature study termination, the efficacy profile of Lu-PSMA appeared to be favorable and comparable with both activity regimens (6.0 GBq vs. 7.4 GBq). Results justify confirmation with real world data matched pair analysis and further clinical trials to refine and optimize the LuPSMA therapy administration scheme to improve tumor radiation dose delivery and efficacy.

INTRODUCTION

The prostate specific membrane antigen (PSMA) is highly expressed by prostate cancer (PCa) cells and is a relevant target for PCa imaging and therapy. Lutetium-177 PSMA-617 (Lu-PSMA) therapy is an emerging therapeutic option in men with metastatic castrate resistant prostate cancer (mCRPC). Retrospective studies (*1–3*) and recent prospective trials from Australia (single-arm *LuPSMA trial* (*4*,*5*)*,* randomized *TheraP trial* (*6*)*)* reported the efficacy and safety of Lu-PSMA in men with mCRPC.

Here we present the first US prospective results of Lu-PSMA (RESIST-PC, NCT03042312). This multicenter prospective phase 2 study investigated the efficacy and safety of Lu-PSMA in patients who were randomized between two commonly used activity regimens: 6.0 GBq and 7.4 GBq. We hypothesized that the two activities result in comparable antitumor effects and safety profile. This study is the first attempt to compare prospectively 2 activity regimens of Lu-PSMA therapy

The study was investigator-initiated and self-funded but the development rights of PSMA-617 were acquired by Endocyte Inc. during the enrollment phase and the study was closed before reaching the target population (n=71/200). Therefore, data acquisition and analysis as initially planned was not possible. The safety results of both study sites were used for regulatory approval and will be reported separately. We report here the efficacy results of the UCLA single study-site cohort (n=43) with more than 2 years of follow-up after end of therapy.

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). We aimed at assessing the efficacy and safety of two Lu-PSMA activity regimens in patients with mCRPC. The study was investigator-initiated and conducted under a physician-sponsored investigational new drug (IND#133661) application. There was no external funding for this study. Patient were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8. The UCLA institutional review board approved the study protocol (IRB#17-000330) provided in Supplemental Material. The study was registered on ClinicalTrials.gov (NCT03042312). Endocyte Inc. licensed the rights to

the study drug, initiated a prospective international multicenter trial (VISION; NCT03511664) and closed RESIST-PC at a total enrollment of 71 of the 200 planned patients at both sites (see statistics section for rationale of sample size). Here we report the efficacy results of the UCLA cohort only (n=43). The safety results of both study sites were used for regulatory approval and will be reported separately. The corresponding author had complete data access and had final responsibility to submit for publication.

Patients

Patients ≥ 18 years, who had histologically confirmed PCa, castrate levels of serum testosterone (<0.5 ng/ml), progressive disease (biochemical, radiographic, or clinical), who had received abiraterone or enzalutamide, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2, and had the ability to understand and sign the written informed consent form were eligible. We included patients without prior chemotherapy or with any number of prior chemotherapies if at least 6 weeks passed since the last treatment cycle. Patients who had received PSMA-targeted radionuclide therapy were excluded. Pretreatment PSMA PET was required to document sufficient target expression (see Procedures section). Additional inclusion criteria were a 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. 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 . Informed written and verbal consent was obtained from all patients.

Procedures

All patients underwent a screening ^{68}Ga-PSMA-11 PET/CT (≤3 months before enrollment) to confirm PSMA expression assessed visually by the local investigators. Patients with PSMA-negative soft-tissue lesions seen on conventional scans (CT, MRI) were excluded (screening failure). Complete blood counts, kidney and liver function, and serum PSA levels were measured within two weeks of treatment initiation.

Patients were randomized (1:1 ratio) to receive either 6.0 or 7.4 GBq of Lu-PSMA. Randomization (1:1 ratio) was performed in accordance with Vickers et al. (*7*) We concealed allocation by creating a list of random allocations for patients 1 to 200 and stored it 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.

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.

Lu-PSMA was intravenously applied at 8-week intervals (+/- 1 week) up to a maximum of four cycles (cycle #02 at week#08, cycle #03 at week #16, cycle #04 at week #24). Treatment cycles continued until disease progression, severe toxicity occurred, patients withdrew consent, or investigators decided to discontinue treatment.

We performed hematological and serum assessments at baseline and in 2-week intervals up to the 12-week follow-up visit after the last study drug injection. We measured serum PSA levels at baseline and every six weeks. Subsequent assessments continued at three-month intervals until follow-up concluded at 24 months or upon disease progression.

Bone pain intensity was assessed at each cycle applying the pain intensity score (PIS), a component of the Brief Pain Inventory–Short Form (*8*): Scores range from 0 to 10, with lower scores representing lower levels of pain intensity; a change of 2 was required to consider a change relevant (*9*).

Due to cost considerations (no follow-up imaging was built in the study budget), imaging follow-up was performed by patient and referring oncologist preference. Due to the lack of standardization, effective conclusions could not be assured. The imaging follow-up analysis (methods, radiographic progression-free survival (rPFS), disease control rate (DCR) by imaging) is provided in Supplemental Material.

Outcomes

The primary endpoint measure was the PSA response rate (RR) after 2 cycles defined as the proportion of patients with a ≥50% decline in serum PSA levels from baseline.(*10*)

Secondary endpoints included the PSA-RR (≥50% decline) at any time (best response), biochemical progression-free survival (PSA-PFS), pain progression-free survival (pain-PFS) and pain-RR. A post-hoc analysis assessed overall survival (OS). These parameters were defined as the time from first treatment cycle to PSA progression, pain progression, or death from any cause, respectively. We recorded new pain development as a 2-point increase on the PIS without a

decrease in opiate use. Patients were included in the pain analysis if they had available baseline assessments and at least one follow-up data point 4-6 weeks after the last treatment cycle.

All endpoints were analyzed by the local investigators.

Statistical Analyses

Based on prior reports (*1*), we hypothesized that the PSA RR after 2 cycles would range between 38% and 65% for both treatment activities. Based on the design of a single-arm phase 2 study in mCRPC (*11*), we postulated that Lu-PSMA would be considered of value for further study if 50% or more patients met the primary endpoint and not worthy if fewer than 40% achieved it. A sample size of 200 patients was required to distinguish between a 40% and 50% PSA RR with a 78% power (two sided binomial test with alpha 0.05 and beta 0.20).

We employed descriptive statistics including median and interquartile range (IQR) for continuous variables, and number and percentage for categorical variables. We present percentage changes in serum PSA levels as waterfall plot. Kaplan-Meier analysis was used to calculated PSA-PFS, pain-PFS and OS by PSA-RRs. We employed the Log-rank test to evaluate the association between treatment arm and patient outcome. Fisher's exact test determined the association between treatment arm and PSA RRs. We tested each endpoint at a two-sided significance level of 0.05.

In a post-hoc analysis, the effect of treatment activity (6.0 vs 7.4 GBq) on outcome data was adjusted for baseline factors (i.e. ECOG performance score, number of previous chemotherapy lines (0-1 vs. 2), and visceral disease) in multivariate cox / logistic regression models. Hazard ratio (HR) / odds ratio (OR) and their 95% confidence intervals (CIs) were derived.

Because of the early study termination we tested whether the comparison of the 2 activity groups (6.0 GBq vs. 7.4 GBq) would likely have held up in the originally proposed study population of 200 patients with a post-hoc conditional power calculation simulation (*12*). This assumes that the additional patients required completing the originally planned study cohort exhibits similar characteristics as the patients enrolled. The method applies random samples and 1000 iterations to account for sampling variability. If this calculation yields around a conditional power calculation of 80% (i.e. $p<0.05$ in 80% of the 1,000 simulations) then the difference in treatment regimen associated outcomes would be statistically different.

Statistical analyses were performed using SPSS version 22 (IBM, NY, USA) and STATA version 15 (StataCorp LLC, TX, USA).

RESULTS

Enrollment and Baseline Characteristics

We enrolled 51 patients with progressive mCRPC between November 2017 and July 2018 (Flowchart in Supplemental Figure 1). Eight/51 (16%) patients were excluded after enrollment because of disease progression (n=4/8, 50%), negative PSMA PET (n=2/8, 25%), death (n=1/8; 13%) or screen failure (n=1/8; 13%). Forty-three/51 (84%) patients received at least one cycle of Lu-PSMA: 14/43 (33%) and 29/43 (67%) in the 6.0 and 7.4 GBq groups, respectively.

Baseline characteristics are provided in Table 1. In the overall study population, median baseline PSA levels and doubling times were 27.4 ng/ml (IQR 9.5-115.6) and 1.5 months (IQR 1.0-2.3), respectively. Twenty-two/43 patients (51%) had received ≥ two chemotherapy regimens and 35/43 (82%) underwent treatment with both abiraterone and enzalutamide prior to Lu-PSMA. Twenty-nine/43 (67%) patients had > 20 metastasis on PSMA PET.

Cut-off date for follow-up was June 25, 2020. Median follow-up for patients who survived was 24.8 months (IQR 22.9-28.8).

Efficacy Endpoints

PSA response rates: PSA RR after 2 cycles was available in 40/43 patients (93%). Overall PSA RR was 11/40 (28%; $_{95\%}$CI 14.6-43.9) and 16/43 (37%; $_{95\%}$CI 23.0-53.3) after 2 cycles (primary endpoint) and at any time, respectively (Figure 1, Table 2). There was no difference of PSA RRs between the two treatment arms after 2 cycles (p=0.12) or at any time (p=0.31). The median time to best PSA response was 8.9 weeks (IQR, 6.9-25.1) in all 43 patients and 28.8 weeks (IQR, 15.2-36.2) in the 16 PSA responders.

Biochemical Progression Free Survival: At the end of follow-up, 2/43 patients (5%) were alive without PSA progression. The median PSA-PFS was 3.7 months in the overall study population ($_{95\%}$CI 2.0-5.4). It was 2.9 months ($_{95\%}$CI 0.0-9.0) and 3.7 months ($_{95\%}$CI 1.9-5.6) in the 6.0 GBq and the 7.4 GBq groups (p=0.25) respectively (Figure 2, Table 2, Supplemental Figure 2).

Bone pain-Progression Free Survival: The pain RR in evaluable patients was 12/18 (67%), 6/7 (86%), 6/11 (55%) in the overall study population, the 6.0 GBq and the 7.4 GBq group, respectively (p=0.31) (Table 2). Pain-PFS was 8.2 months ($_{95\%}$CI 3.9-12.5), 5.4 months ($_{95\%}$CI not reached),8.2 months ($_{95\%}$CI 2.3-14.1) in the overall study population, the 6.0 GBq and the 7.4 GBq groups, respectively (p=0.94) (Supplemental Figure 3, Table 2).

Overall Survival: At the end of follow-up, 12/14 (86%) and 25/29 (87%) of patients had died in the 6.0 GBq and 7.4 GBq arms, respectively. The median OS of the overall study population was 14.0 months ($_{95\%}$CI 11.8-19.4). The injected activity was not associated with OS: 15.6 ($_{95\%}$CI 11.8-19.4) vs. 13.5 mo ($_{95\%}$CI 10.0-17.0) in the 6.0 GBq and the 7.4 GBq arms (p=0.87), respectively (Figure 2, Table 2, Supplemental Figure 2). Patients who experienced a PSA decline ≥50% at any time (best response; n=16/43, 37%) had a significantly longer OS than those who did not (27/43, 63%): median: 20.8 vs. 10.8 months; *p*=0.005 (Figure 3). However, no significant difference was observed when comparing the OS of patients who had a PSA decline ≥50% after 2 cycles only (n=11/40, 28%) with those who did not (n=29/40, 72%): median: 19.1 vs. 13.7 months; *p*=0.46 (Figure 3).

After adjusting for baseline factors (ECOG, number of previous chemotherapy regimen (0-1 vs. 2), visceral disease), the treatment activity (6.0 vs 7.4 GBq) remained not associated with treatment outcomes (p-values >0.05, multivariate cox / logistic regression models, supplemental Table 1).

The post-hoc conditional power calculation simulation assumed a comparable demographic and disease distribution for 157 simulated patients (to obtain the initially planned population of 200 patients). Randomly sampling (with replacement) 86 patients from the 6.0GBq cohort and 71 patients from 7.4 GBq cohort and repeating this process 1000 times yielded a significant difference (p<0.05) between activity effects on outcome in only 47 of 1000 simulations (4.7%).

DISCUSSION

This prospective randomized phase 2 study compared two Lu-PSMA treatment activity levels in patients with mCRPC who progressed after conventional treatments. PSA RR, PSA-PFS, pain-RR and OS did not differ between the two activity arms (6.0 vs 7.4 GBq). This study is the first attempt to compare prospectively 2 activity regimens of Lu-PSMA therapy. The results are in line with a retrospective study comparing two similar treatment activity levels of Lu-PSMA (6.0 vs 7.5 GBq) (*13*).

The primary efficacy endpoint (i.e. PSA RR after 2 cycles of ≥40% in the whole cohort) was not met possibly due to premature study closure at 36% of the planned enrollment (71/200). This was prompted by the IND sponsorship transfer to Endocyte Inc. and the opening of the phase

3 registration VISION trial (NCT03511664). The current PSA RR is lower than those reported in the australian prospective phase 2 clinical trials, after 2 cycles (28% vs 50% in *LuPSMA trial*), and at any time point (38% vs. 64% in *LuPSMA trial* and 66% in *TheraP Trial*) (*4*,*6*). More rigorous patient selection that included FDG PET to exclude patients with hyperglycolytic but low PSMA expressing lesions resulted in improved PSA RR. Dual-tracer PSMA/FDG PET phenotyping can improve patient selection to LuPSMA therapy and this approach should be further implemented in future prospective trials and clinical practice. However, despite different PSA RRs, OS was similar (median: 14.0 vs. 13.7 months in *LuPSMA trial*)(*5*). Of note, the quality of life improvement previously reported was also observed in our cohort: pain levels improved in 67% of the evaluable patients (*4*–*6*). Further studies on patients reported outcomes are warranted.

A comparative meta-analysis suggested that LuPSMA was less toxic, induced higher PSA RR (mean frequency 44% vs. 22%) and possibly improved OS (median of 14 vs 12 months; p=0.33) compared to other third-line treatments for mCRPC, such as enzalutamide and cabazitaxel (*14*). The multicenter prospective randomized *TheraP trial* comparing LuPSMA to cabazitaxel confirmed these findings with higher PSA RR (66% vs 44%) and less grade 3–4 AEs (33% vs 53%) in the LuPSMA arm.(*6*) Improvement of OS with LuPSMA will be critical for regulatory approval and the results of the VISION trial NCT03511664 (best supportive/standard care versus LuPSMA) are awaited.

A significant association between best PSA RR and OS was observed, in line with prior reports (*3*,*5*). These supports further investigation of PSA RR as an intermediate surrogacy endpoint for OS.

Findings are limited by an early study closure before completing target enrollment (36%). This was beyond the control of the investigators and resulted in a small sample size. Consequently, the distribution between the 2 treatment groups was also altered (14 vs. 29) as 1:1 randomization was performed centrally for both sites. The premature study termination limits the comparison between the 2 treatment activity groups. However, due to the narrow difference in the 2 tested activities (~20%, 6.0 vs 7.4 GBq) even the limited data suggest that there is likely no or only small differences in efficacy between these 2 activities. This is consistent with prior reports that found similar response and toxicity rates to comparable levels of injected activity (6.0 vs 7.5 GBq) (*13*). To further test whether the current results of the comparison of the 2 activity groups (6.0 GBq vs. 7.4 GBq) in this cohort of 43 patients would likely have held up in the originally proposed study population of 200 patients, we conducted a post-hoc conditional power calculation simulation (*12*). After 1000 simulations, only 47 of 1,000 simulations (4.7%) were significant

($p<0.05$). Further calculation revealed that around 3400 patients per group (6800 total) would have been needed to show a significant difference in effectiveness of the 2-activity regimen (conditional power of 80%).

As another limitation, the study population was heterogeneous regarding prior treatment. The study was self-funded and patients were charged for the study drug (cost recovery, Title 21 CFR 312.8). For ethical reasons, the study therefore allowed various prior systemic therapies for inclusion. To correct for heterogeneity in treatment history and baseline characteristics we conducted a standard covariate adjustment analysis (Supplemental Table 1). After adjusting for baseline factors including ECOG, number of previous chemotherapy regimen (0-1 vs. 2), and presence of visceral disease), the treatment activity was still not associated with treatment outcome. Thus, administered activity (6.0 vs 7.4 GBq) did not appear to affect treatment outcome.

To reduce out-of-pocket costs, imaging follow-up modalities were selected by patients and referring oncologists. Thus, a variety of imaging modalities (CT, bone scan, MRI, PSMA, Choline, fluciclovine, FDG) were used to assess radiographic progression which may have increased variance of event data. For instance, PET imaging results in shorter time to progression when compared to conventional anatomic imaging. Due to the lack of standardization, effective conclusions could not be assured. The follow-up imaging analysis is provided in Supplemental Material (Supplemental Tables 2,3 and Supplemental Figure 4).

Finally, there was no central blinded review of the screening PSMA PET and criteria to establish PSMA-target expression were not predefined and left to the discretion of the local investigators. Studies establishing optimal PSMA PET criteria for patient selection and therapy response assessment are warranted.

CONCLUSION:

We report here the UCLA study site efficacy results of the prospective phase 2 study RESIST-PC of Lu-PSMA for mCRPC after more than 2 years of follow-up. The study closed enrollment before reaching the cohort size because of IND sponsorship transfer to Endocyte Inc. The study population was heterogeneous. PSA RR after 2 cycles and at any time were 28 and 38%. Pain RR was 67% and the median OS was 14 months. There was no difference in PSA RR between administration of 6.0 and 7.4 GBq of Lu-PSMA. Results justify confirmation with real

world data analysis and further trials to refine and optimize the LuPSMA therapy administration scheme to improve tumor radiation dose delivery and 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, IBA radiopharma, Janssen, Progenics, POINT biopharma, 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, board member, 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

This was an investigator-initiated and -sponsored trial. There was no external source of funding.

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).

AG was the recipient of the Jonsson Comprehensive Cancer Center Fellowship award and the Dr. Christiaan Schiepers postdoctoral fellowship award.

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, AG, WA, 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, RE, VL, LGo, DR, RS, MD, MAA, AQ, PG, SB, KH, ED, WF, ME, JCa, JCz provided administrative support.

JCa, AG, WA, JG, PT, KN, RE, VL, LGo, LGa, MD, ED, JCz collected and assembled the data.

JCa, AG, WA, TG, JCz 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.

KEY POINTS

QUESTION: What is the efficacy profile of 2 activity regimens of Lutetium-177-PSMA therapy (6.0 GBq vs 7.4 GBq) in patients with metastatic castrate resistant prostate cancer ?

PERTINENT FINDINGS: In this prospective randomized phase 2 study that included 43 patients with progressive mCRPC, Lutetium-177-PSMA therapy resulted in biochemical response in 38% and the median overall survival was 14 months. There was no difference in efficacy between administration of 6.0 and 7.4 GBq of Lutetium-177-PSMA.

IMPLICATIONS FOR PATIENT CARE: Lutetium-177-PSMA therapy using and 6.0 and 7.4 GBq is a therapeutic option for patient with metastatic castrate resistant prostate cancer with a good efficacy.

REFERENCES

1. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med*. 2017;58:85-90.

2. Yadav MP, Ballal S, Sahoo RK, Dwivedi SN, Bal C. Radioligand therapy with ^{177} Lu-PSMA for metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. *AJR Am. J. Roentgenol*. 2019;213:275-285.

3. Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. *Eur. Urol*. 2019;75:920-926.

4. Hofman MS, Violet J, Hicks RJ, et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol*. 2018;19:825-833.

5. Violet J, Sandhu S, Iravani A, et al. Long-Term Follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of 177Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. *J Nucl Med*. 2020;61:857-865.

6. Hofman MS, Emmett L, Sandhu S, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. 2021;397:797-804.

7. Vickers AJ. How to randomize. *J Soc Integr Oncol*. 2006;4:194-198.

8. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. 1994;23:129-138.

9. Mathias SD, Crosby RD, Qian Y, Jiang Q, Dansey R, Chung K. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. *J Support Oncol*. 2011;9:72-78.

10. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34:1402-1418.

11. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol*. 2010;28:1496-1501.

12. Walter SD, Han H, Guyatt GH, et al. A systematic survey of randomised trials that stopped early for reasons of futility. *BMC Med. Res. Methodol.* 2020;20:10.

13. Seifert R, Kessel K, Schlack K, Weckesser M, Bögemann M, Rahbar K. Radioligand therapy using [177Lu]Lu-PSMA-617 in mCRPC: a pre-VISION single-center analysis. *Eur J Nucl Med Mol Imaging*. 2020;47:2106-2112.

14. von Eyben FE, Roviello G, Kiljunen T, et al. Third-line treatment and 177Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. *Eur J Nucl Med Mol Imaging*. 2018;45:496-508.

TABLES

Table 1: Characteristics of the study population at Baseline

Characteristics	Overall (N = 43)	6.0 GBq (N = 14)	7.4 GBq (N = 29)
Age (years)	74 (68-78)	76 (70-79)	72 (65-78)
Time since diagnosis of prostate cancer (years)	7 (4-17)	8 (5-17)	7 (4-15)
Gleason grade group at diagnosis*			
≥4	25 (64%)	9 (69%)	16 (62%)
PSA (ng/ml)	27.4 (9.5-115.6)	31.3 (12.6-160.2)	26.1 (9.5-124.4)
PSA doubling time (month)	1.5 (1.0-2.3)	1.3 (1.0-1.7)	1.8 (1.0-3.2)
Total alkaline phosphatase (U/l)	87 (67-125)	82 (60-175)	94 (69-117)
Hemoglobin (g/dl)	12.0 (10.9-13.2)	12.1 (11.2-12.9)	11.6 (10.8-13.3)
Platelets (´10^3/ml)	208 (160-245)	207 (163-356)	208 (158-238)
ECOG performance status			
0	13 (30%)	8 (57%)	5 (17%)
1	21 (49%)	4 (29%)	17 (59%)
2	9 (21%)	2 (14%)	7 (24%)
Pain at baseline (BPI score)			
No pain	21 (49%)	4 (28%)	17 (58%)
Mild (1-4)	11 (26%)	5 (36%)	6 (21%)
Moderate to severe (5-10)	11 (26%)	5 (36%)	6 (21%)
Previous mCRPC systemic treatments			
Chemotherapy regimen lines			
0	11 (26%)	4 (29%)	7 (24%)
1	10 (23%)	4 (29%)	6 (21%)
2	12 (28%)	3 (21%)	9 (31%)
≥3	10 (23%)	3 (7%)	7 (24%)
Abiraterone	41 (95%)	13 (93%)	28 (97%)
Enzalutamide	37 (86%)	13 (93%)	24 (83%)
Abiraterone + Enzalutamide	35 (82%)	12 (86%)	23 79%)
Radium-223	14 (33%)	4 (29%)	10 (35%)
Prior lines of mCRPC systemic treatment			
1	4 (9%)	1 (7%)	3 (10%)
≥2	39 (91%)	13 (93%)	26 (90%)
≥3	31 (72%)	10 (71%)	21 (72%)
≥4	25 (58%)	8 (57%)	17 (59%)
Extent of disease on PSMA-PET			
≤20 metastases	14 (33%)	4 (29%)	10 (34%)
>20 metastases	29 (67%)	10 (71%)	19 (66%)
Sites of disease on PSMA-PET			
Node only (N1 and/or M1a)	3 (7%)	1 (7%)	2 (7%)
Bone only (M1b)	9 (21%)	3 (21%)	6 (21%)
Node + bone (M1b and (N1 and/or M1a))	15 (35%)	7 (50%)	8 (28%)
Visceral (M1c with/without any other site) **	15 (35%)	3 (21%)	12 (41%)

Data are median (IQR) or n (%). *Data missing for four patients. **Visceral includes lung, liver, rectum, pancreas, peritoneal, brain and adrenal. Abbreviations: PSA, prostate-specific antigen;

ECOG, Eastern Cooperative Oncology Group; BPI, bone pain index; PSMA, prostate-specific membrane antigen.

Table 2. Primary and secondary endpoints results

	Overall (N = 43)	6.0 GBq (N = 14)	7.4 GBq (N = 29)	Hazard Ratio (95%CI)	*P* value
Primary Endpoint					
PSA response after 2 cycles					
No. evaluable patients	40	13	27		
PSA decline ≥50% after 2 cycles	11 (28%, 95%CI 15-44)	6 (46%, 95%CI 19-75)	5 (19%, 95%CI 6-38)	-	.12[a]
Secondary Endpoints					
Best PSA response					
No. evaluable patients	43	14	29		
Best PSA response ≥50%	16 (37%, 95%CI 23-53)	7 (50%, 95%CI 23-77)	9 (31%, 95%CI 15-51)	-	.31[a]
Pain response					
No. of evaluable patients	18	7	11		
Patients with pain improvement, n (%)	12 (67%)	6 (86%)	6 (55%)	-	.31[a]
Pain progression-free survival					
Median, months	8.2 (95%CI 3.9-12.5)	5.4 (not reached)	8.2 (95%CI 2.3-14.1)	0.96 (0.35 to 2.66)	.94
Post-hoc analysis					
Overall survival					
Median, months	14.0 (95%CI 10.1-17.9)	15.8 (95%CI 11.8-19.4)	13.5 (95%CI 10.0-17.0)	0.94 (0.46 to 1.92)	.87

Abbreviations: CI, confidence interval; PSA, prostate specific antigen; [a] *P* values compare the 6.0 and 7.4 GBq treatment arms using exact Fisher

FIGURES

Figure 1

Waterfall plots showing PSA changes relative to baseline after 2 cycles of LuPSMA **(A)** and any time during treatment **(B).**

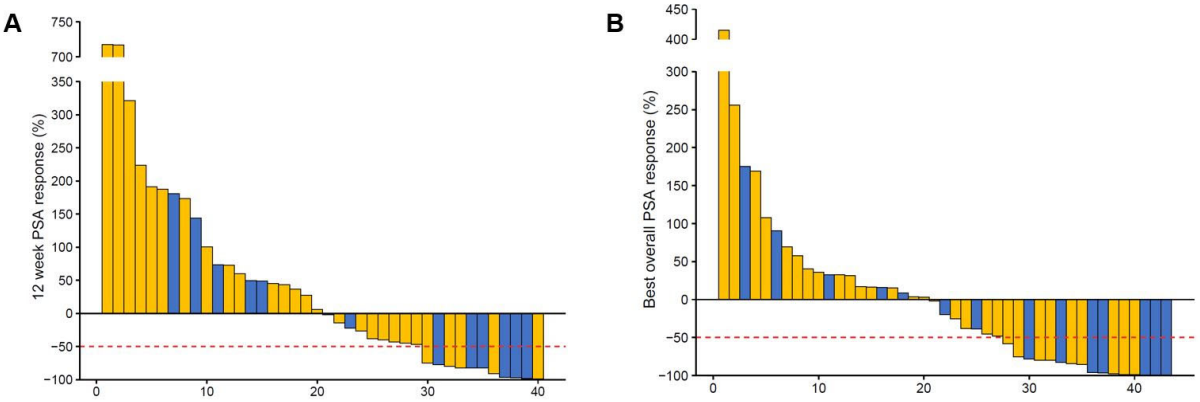


Figure 2: Survival Kaplan-Meier Curves

Kaplan-Meier Curves for PSA progression-free survival (A) and overall survival (B) by treatment arm. Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.

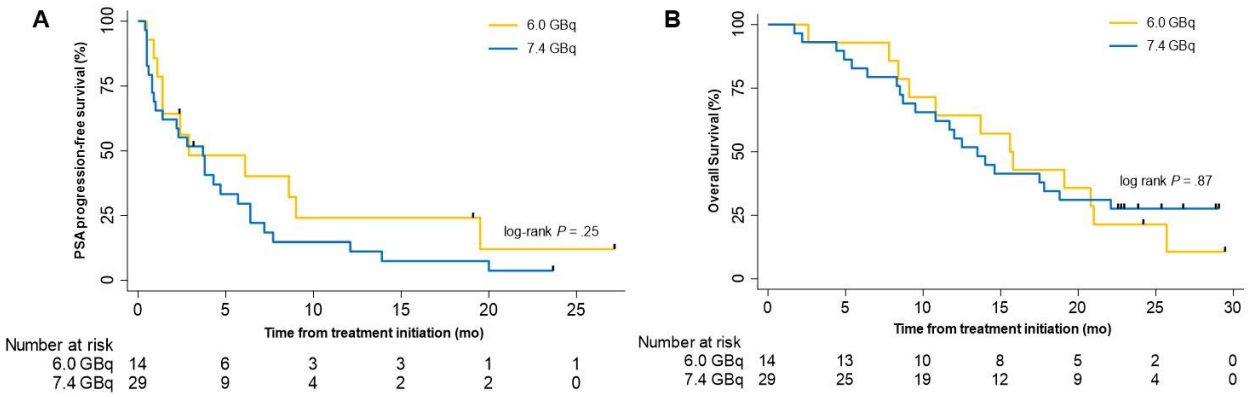
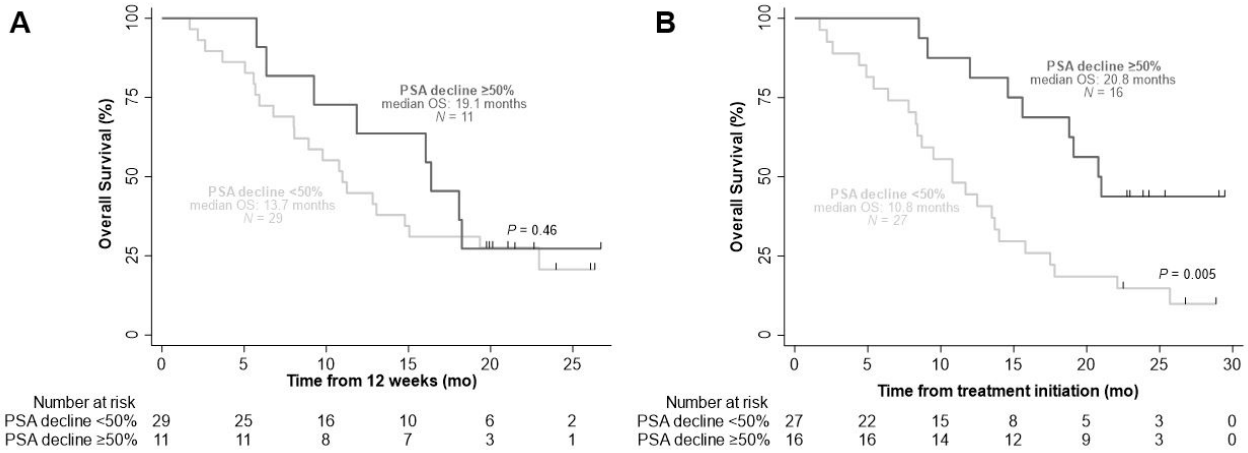
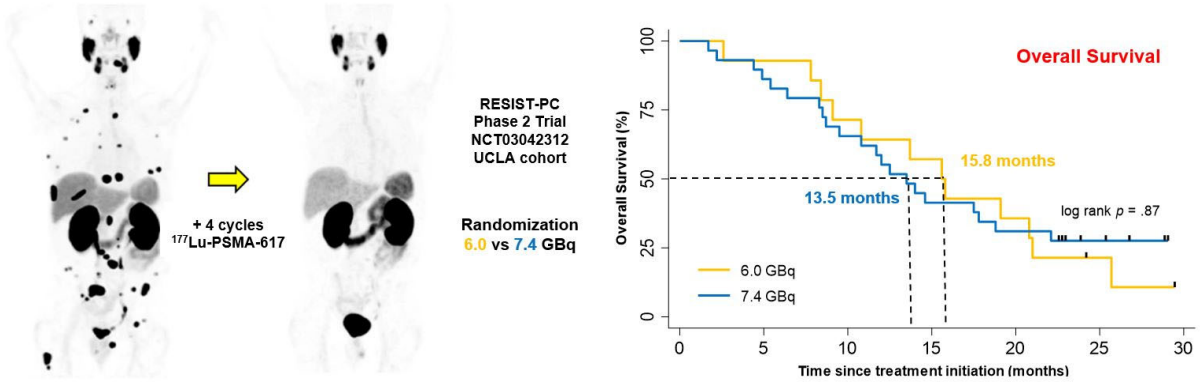


Figure 3

Kaplan-Meier Curves for overall survival by PSA response after 2 cycles (A) and at any time (B), Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.



Graphical Abstract



ONLINE-ONLY SUPPLEMENTAL MATERIAL

Supplemental Section: Follow-up Imaging analysis

Due to cost considerations (no follow-up imaging was built in the study budget), imaging follow-up was performed by patient and referring oncologist preference. We allowed all imaging modalities including CT, bone scan, MRI, FDG PET/CT, choline PET/CT, Fluciclovine PET/CT and PSMA PET/CT. Thus, a variety of imaging modalities were used to assess radiographic progression which may have increased variance of event data. For instance, PET imaging results in shorter time to progression when compared to conventional anatomic imaging.

Local investigator (JCa) assessed radiographic progression using a combination of RECIST 1.1 for CT and MRI, PCWG3 criteria for bone scans, PERCIST for PET imaging and visual overall assessment.

Endpoints based on imaging follow-up included the radiographic progression-free survival (rPFS) and disease control rate (DCR). These parameters were defined as the time from first treatment cycle to radiographic progression or death from any cause, respectively. We defined disease control rates (DCR) at the end of each cycle as the percentage of patients achieving non progressive disease (PD) (i.e stable disease (SD), partial response (PR) or complete response (CR)). PD more than 12 weeks after cycle #04 was not included in the DCR. Kaplan-Meier analysis was used to calculated rPFS. Log-rank test was used to evaluate the association between treatment arm and patient outcome. Each endpoint was tested at a two-sided significance level of 0.05.

Follow-up imaging was available in 42/43 patients (98%), and progression by imaging as determined by the local investigator occurred in 36/43 of patients (84%). At the end of the follow-up 3/43 patients (70%) were still alive without imaging progression. The imaging modality used for assessment of progression was PSMA PET in 15/43 (35%), CT and bone scan in 10/43 (23%), choline PET in 9/43 (21%), fluciclovine PET in 4/43 (9%), FDG PET in 2/43 (5%) and MRI in 2/43 (5%).

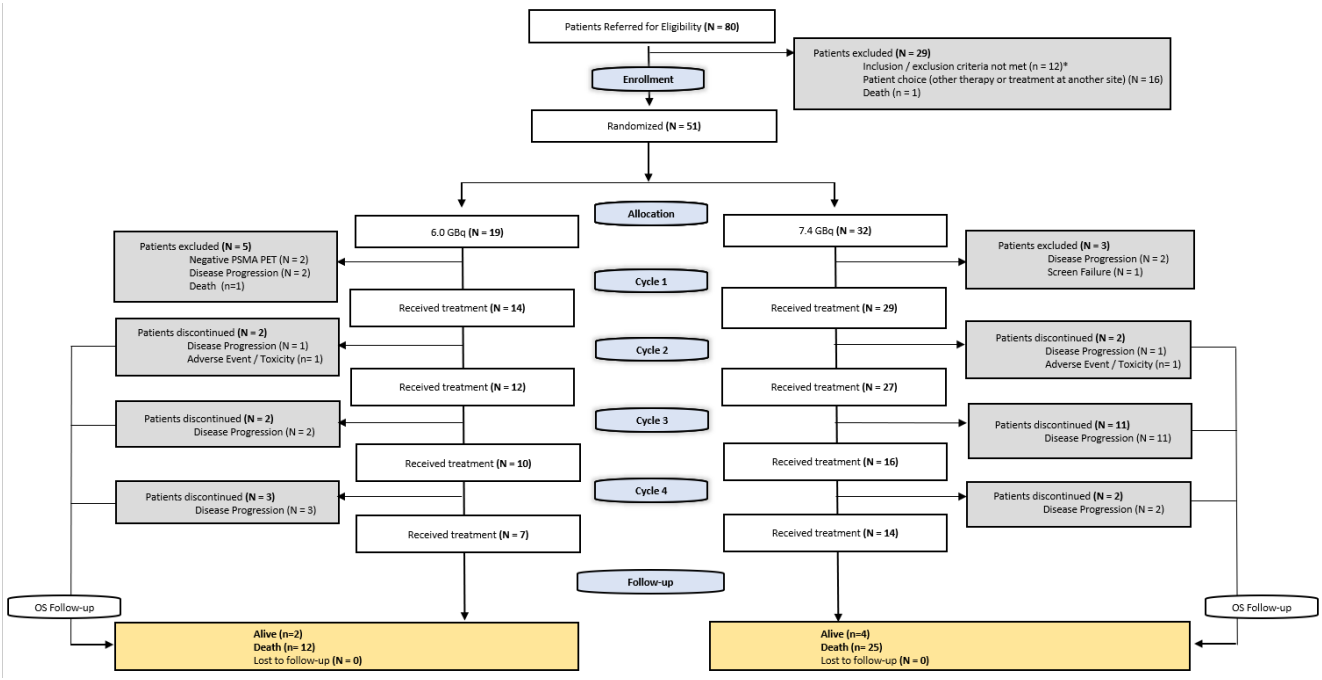
The median rPFS was 4.2 months ($_{95\%}$CI 2.5-5.9), 5.6 months ($_{95\%}$CI 2.6-8.6), 4.2 months ($_{95\%}$CI 2.4-6.0) in the overall study population, the 6.0 GBq and the 7.4 GBq group, respectively (p=0.51) (Supplemental Figure 2, Supplemental Figure 4, Supplemental Table 2). The DCR after cycle #02, #03 and #04 was 44%, 30% and 28%, respectively (Supplemental Table 2, Supplemental Table 3).

Supplemental Figure 1

Study CONSORT flowchart.

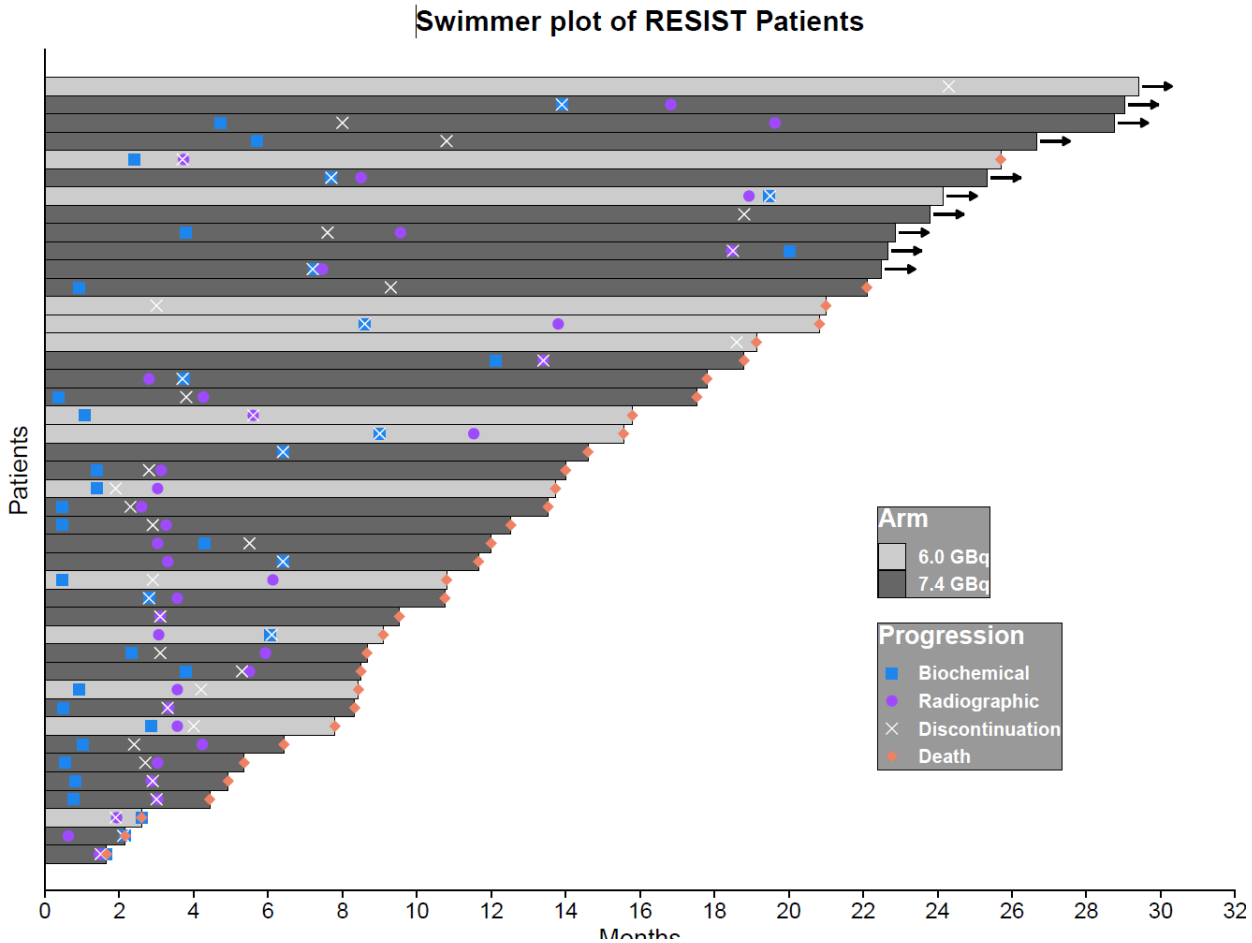
Median follow-up for patients who survived was 24.8 (IQR 22.9-28.8) months.

** details of inc/exc criteria not met: insufficient bone marrow reserve (n=4), no prior abi/enza (n=3), prior Lu-177-PSMA therapy (n=2), ECOG score > 2 (n=1), Kidney obstruction (n=1), Super bone scan (n=1*)



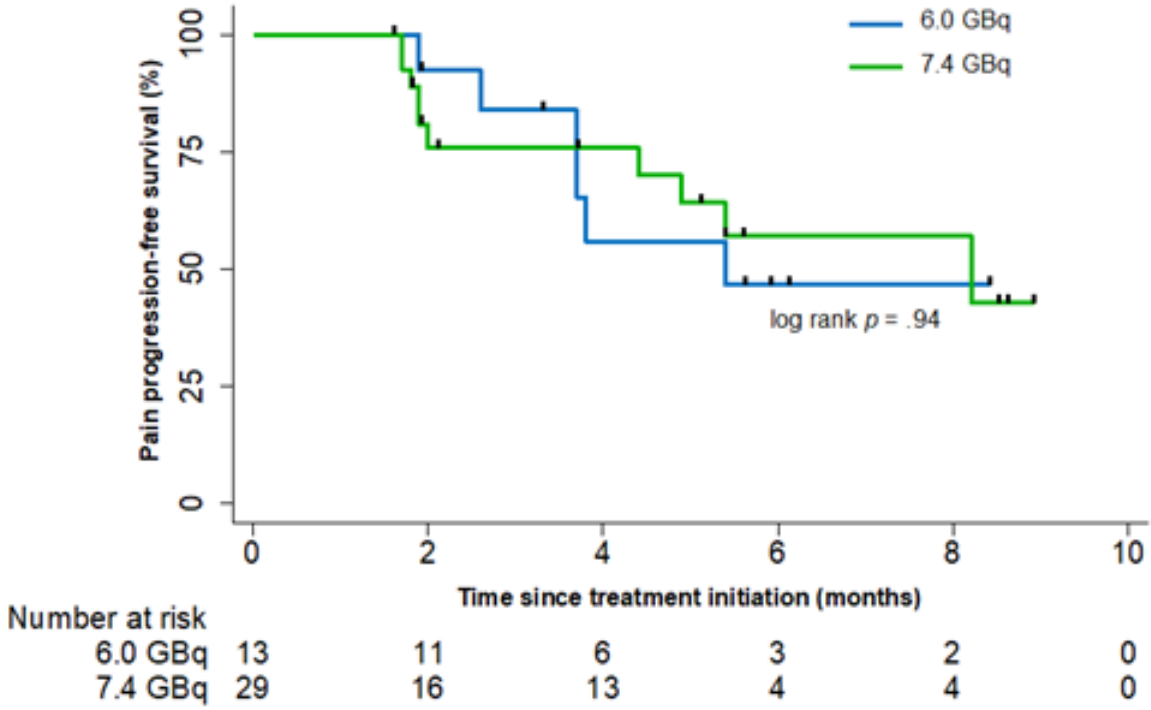
Supplemental Figure 2

Swimmer plot



Supplemental Figure 3

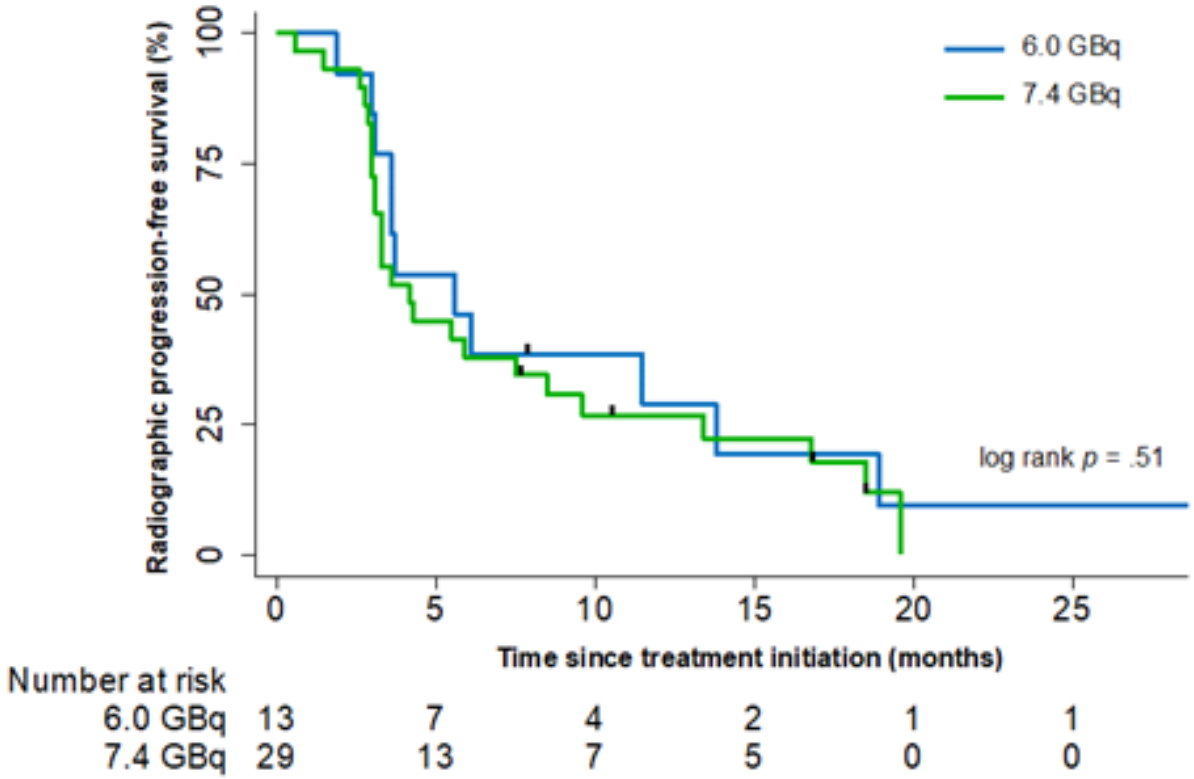
Pain progression-free survival



Kaplan-Meier Curves for radiographic progression-free survival by treatment arm. Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.

Supplemental Figure 4

Radiographic progression free survival



Kaplan-Meier Curves for radiographic progression-free survival by treatment arm. Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.

Supplemental Table 1.

Multivariate cox / logistic regression models

	OS	PSA-PFS	Pain-PFS	rPFS	PSA-RR 12 wk*	Best PSA-RR*
Prior Chemotherapy regimen (0-1 vs ≥2)	1.15 (0.55-2.37) p=0.70	1.52 (0.67-3.43) p=0.30	1.99 (0.63-6.26); p=0.23	1.00 (0.40-2.52); p=0.98	0.41 (0.93-1.87); p=0.25	0.67 (0.18-2.46); p=0.67
ECOG (0-1 vs 2)	1.26 (0.54-2.92); p=0.58	1.31 (0.68-2.53); p=0.41	2.04 (0.69-6.00); p=0.19	1.08 (0.55-2.12); p=0.82	1.06 (0.15-7.20); p=0.94	0.46 (0.08-2.68); p=0.39
Visceral metastasis (no vs yes)	1.94 (0.94-4.0); p=0.70	2.05 (1.00-4.18); p=0.049	2.08 (0.73-5.92); p=0.17	1.79 (0.87-3.69); p=0.11	0.83 (0.16-4.30); p=0.83	0.56 (0.13-2.33); p=0.43
Treatment Activity (6.0 vs 7.4 GBq)	0.83 (0.40-1.75); p=0.64	1.40 (0.68-2.88); p=0.35	0.75 (0.25-2.23); p=0.60	1.20 (0.58-2.49); p=0.61	0.27 (0.06-1.25); p=0.095	0.54 (0.14-2.21); p=0.37

*The effect of treatment dose on outcome data was adjusted for baseline factors in multivariate cox / *logistic regression models. Results are presented in hazard ratio (95%CI) / *odds ratio (95%CI); p value*

Supplemental Table 2:

Imaging Endpoints results

	Overall (N = 43)	**6.0 GBq (N = 14)**	**7.4 GBq (N = 29)**	**Hazard Ratio (95%CI)**	***P* value**
Radiographic progression-free survival					
Median, months	4.2 (95%CI 2.5-5.9)	5.6 (95%CI 2.6-8.6)	4.2 (95%CI 2.4-6.0)	1.26 (0.61 to 2.58)	.51
Disease control rate (DCR) by imaging					
After cycle #02	19 (44%)	6 (43%)	13 (45%)		
After cycle #03	13 (30%)	4 (29%)	9 (31%)		
After cycle #04	12 (28%)	4 (29%)	8 (28%)		

Abbreviations: CI, confidence interval; PSA, prostate specific antigen; P values compare the 6.0 and 7.4 GBq treatment arms using exact Fisher.

Supplemental Table 3:

Disease control rates after each cycle.

		C1	C2	C3	C4
Overall study cohort n=43	SD/PR/CR	19 (44%)	19 (44%)	13 (30%)	12 (28%)
	PD	3 (7%)	18 (42%)	4 (9%)	2 (5%)
	N/A	21 (49%)	6 (14%)	26 (60%)	29 (67%)
Arm 6.0 GBq n=14	SD/PR/CR	6 (43%)	6 (43%)	4 (29%)	4 (29%)
	PD	1 (7%)	5 (36%)	2 (14%)	0 (0%)
	N/A	7 (50%)	3 (21%)	8 (57%)	10 (71%)
Arm 7.4 GBq n=29	SD/PR/CR	13 (45%)	13 (45%)	9 (31%)	8 (28%)
	PD	2 (7%)	13 (45%)	2 (7%)	2 (7%)
	N/A	14 (48%)	3 (10%)	18 (62%)	19 (66%)

The disease control rate (DCR) at the end of each cycle was defined as the number and percentage of patients achieving stable disease (SD), partial response (PR) or complete response (CR). PD: progressive disease.

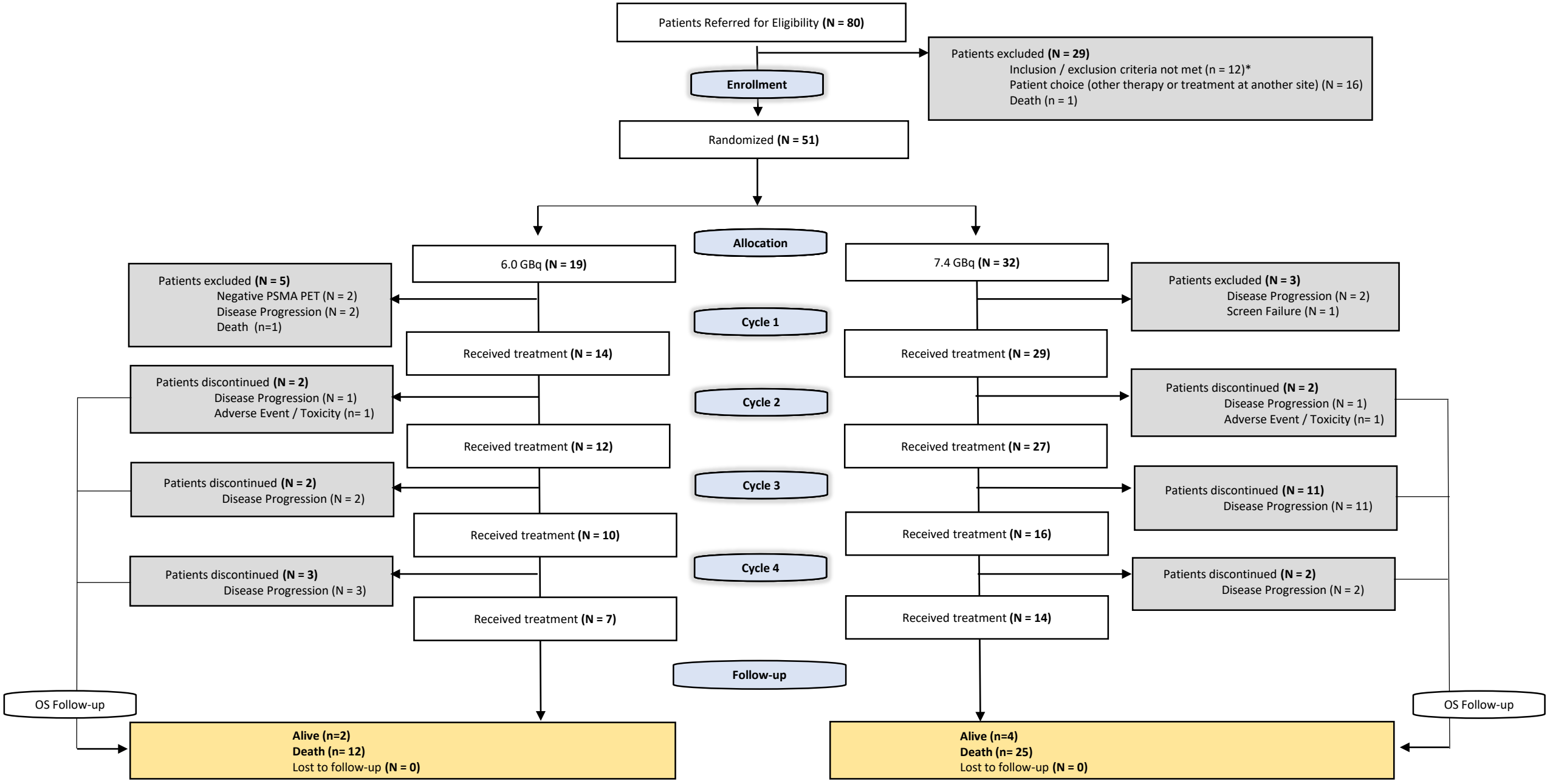


Figure 01. **Study flowchart**. Median follow-up for patients who survived was 24.8 (IQR 22.9-28.8) months.
** details of inc/exc criteria not met: insufficient bone marrow reserve (n=4), no prior abi/enza (n=3), prior Lu-177-PSMA therapy (n=2), ECOG score > 2 (n=1), Kidney obstruction (n=1), Super bone scan (n=1)*