Journal of Nuclear Medicine, published on November 15, 2019 as doi:10.2967/jnumed.119.236414

Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 (^{177}Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer

Short running title: Lu-177 PSMA-617 in prostate cancer

John Violet[1], Shahneen Sandhu[2,3], Amir Iravani[3,4],Justin Ferdinandus[4], Sue-Ping Thang[4], Grace Kong[3,4], Aravind Ravi Kumar[3,4], Tim Akhurst[3,4], David Pattison[4], Alexis Beaulieu[3], Jennifer Mooi[2], Ben Tran[2,3], Christina Guo[2,3], Victor Kalff[4], Declan G Murphy[3,5], Price Jackson[6], Peter Eu[4], Mark Scalzo[4], Scott Williams[1,3], Rodney J. Hicks[3,4] and Michael S. Hofman[3,4]

1 Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne VIC, Australia,
2 Medical Oncology, Peter MacCallum Cancer Centre, Melbourne VIC, Australia,
3 Sir Peter MacCallum Department of Oncology, Peter MacCallum Cancer Centre, Melbourne VIC, Australia,
4 Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne VIC, Australia,
5 Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne VIC, Australia,
6 Medical Physics, Peter MacCallum Cancer Centre, Melbourne VIC, Australia

Key Words: prostate specific membrane antigen, PSMA, theranostics, prostate cancer, Lutetium-177

Corresponding authors:
Professor Michael Hofman, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne 3000, Australia. michael.hofman@petermac.org . Tel: +61 3 8559 5000

Dr John Violet, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne 3000, Australia. john.violet@petermac.org . Tel: +61 3 8559 5000

Word count: 3394

Financial support: Supply of Lutetium-177 from Australian Nuclear Science and Technology Organisation (ANSTO, Sydney, Australia) and PSMA-617 from Advanced Biochemical Compounds (ABX, Radeberg, Germany) and Endocyte (a Novartis company).

Interim results of this study were presented at 2019 ASCO Genitourinary Symposium (San Diego) and the 2018 Society of Nuclear Medicine and Molecular Imaging Scientific Meeting (Philadelphia).

Disclaimer: see end of manuscript for author disclosures

Objectives: Lutetium-177 (^{177}Lu)-PSMA-617 (LuPSMA) is a radioligand with high affinity for prostate specific membrane antigen (PSMA) enabling targeted beta-irradiation of prostate cancer. We have previously reported favorable activity with low toxicity in a prospective phase II trial involving 30 men with metastatic castrate-resistant prostate cancer (mCRPC). We now report their longer-term outcomes including a 20 patient extension cohort and outcomes of subsequent systemic treatments following completion of trial therapy.

Methods: 50 patients with PSMA-avid mCRPC who had progressed after standard therapies received up to 4 cycles of LuPSMA every 6 weeks. Endpoints included PSA response (PCWG2), toxicity (CTCAE v4.03), imaging response, patient-reported health-related quality of life (QoL), progression-free and overall survival. We also describe, as a novel finding, outcomes of men who subsequently progressed and had further systemic therapies, including LuPSMA.

Results: 75 men were screened to identify 50 patients eligible for treatment. Adverse prognostic features of the cohort included short median PSA doubling time (2.3 months) and extensive prior treatment including prior docetaxel (84%), cabazitaxel (48%), and abiraterone and/or enzalutamide (92%). The mean administered radioactivity was 7.5 GBq/cycle. PSA decline ≥ 50% was achieved in 32 of 50 patients (64%, 95% CI 50-77%), including 22 patients (44%, 95% CI 30-59%) with ≥ 80% decrease. Of 27 patients with measurable soft tissue disease, 15 (56%) achieved an objective response by RECIST 1.1. The most common toxicities attributed to LuPSMA were self-limiting G1-2 dry mouth (66%), transient G1-2 nausea (48%), G3-4 thrombocytopenia (10%) and G3 anemia (10%). Brief pain inventory severity and interference scores decreased at all time points including at the 3 month follow-up with a decrease of -1.2 (95% CI -0.5 to -1.9, p=0.001) and 1.0 (95% CI -0.2 to -0.18, p=0.013), respectively. At a median follow-up of 31.4 months, median OS was 13.3 months (95% CI 10.5-18.7) with a significantly longer survival of 18.4 months (95% CI 13.8-23.8) in patients achieving a PSA decline ≥ 50%. At progression following prior response, further LuPSMA was administered to 15 (30%) patients (median 2 cycles commencing 359 days from enrolment) with PSA decline ≥ 50% in 11 patients (73%). 4 of 21 patients (19%) receiving other systemic therapies upon progression experienced PSA decline ≥ 50%. There were no unexpected adverse events with LuPSMA re-treatment.

Conclusions: This expanded 50 patient cohort of men with extensive prior therapy confirms our earlier report of high response rates, low toxicity and improved QoL with LuPSMA radioligand

therapy. Upon progression, re-challenge LuPSMA demonstrated higher response rates than other systemic therapies.

Keywords: LuPSMA, theranostics, prostate cancer, radioligand therapy, prostate specific membrane antigen, theranostics

INTRODUCTION

Most prostate cancers express prostate specific membrane antigen (PSMA) on their surface with increased expression in higher-grade and castration resistant cancers (*1-3*). PSMA represents an excellent target for both the imaging and therapy of prostate cancer and is the focus of extensive research (*4-6*). Lutetium-177 (^{177}Lu) PSMA-617 (LuPSMA) is a radiolabeled small molecule that binds with high affinity to the enzymatic site of PSMA enabling highly targeted delivery of beta radiation to prostate cancer cells. Multiple mainly retrospective series of beta radiolabeled small molecules targeting PSMA have demonstrated that treatment is effective in patients with advanced and heavily pre-treated prostate cancers (*7-13*).

In a prospective phase II clinical trial we demonstrated single-agent activity of LuPSMA in thirty men with mCRPC who had progressed on most systemic therapies (*14*). Encouraging clinical, biochemical and imaging responses were observed with limited acute normal tissue toxicity in this heavily-treated cohort of men. Furthermore we also observed improvement in quality of life measures. Radiation dosimetry in these men demonstrated high tumor absorbed doses yet low exposure of critical normal tissues (*15*). These dosimetric findings have also been observed by other groups in retrospective analyses (*16-21*) and suggest that multiple cycles of therapy can be safely administered without a significant risk of either acute or delayed radiation toxicity.

We now present longer-term follow-up in an expanded 50 patient cohort to validate our earlier clinical findings and assess overall survival and any late toxicity. Additionally, we report outcomes of patients treated within the original trial protocol who subsequently received additional cycles of LuPSMA therapy or other systemic therapies at relapse, documenting their response to treatment and patterns of failure.

MATERIALS AND METHODS

This was an investigator-initiated, single-institution phase II trial that initially recruited thirty patients. Given the high clinical activity observed, the study was expanded to a total of fifty patients. Patients were treated and monitored as previously described(*14*). All patients signed written informed consent and the protocol was approved by the institutional ethics board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was sponsored by the Peter MacCallum Cancer Centre. Study data were collected and

managed using REDCap electronic data capture tools (*22*). The trial was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12615000912583.

Inclusion criteria mandated patients had pathologically confirmed mCRPC with progressive disease after standard therapies, including taxane-based chemotherapy and second-generation anti-androgen therapy (abiraterone, enzalutamide or both) unless deemed medically unsuitable or refused by the patient. Patients must have had progressive disease within the prior 12 months as defined by radiographic progression or new pain in an area of radiographically evident disease and Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2. Patients were excluded if they had an estimated glomerular filtration rate (eGFR) < 40 mL/min, platelet count <75,000 x 10^9/L, neutrophil count < 1.5 x 10^9/L, Hb < 9.0g/dL, albumin ≤ 25g/L, prior radiotherapy (within 6 weeks) to sole sites of assessable disease or uncontrolled intercurrent illness.

All patients underwent imaging with both ^{68}Ga-PSMA-11 (PSMA PET) and ^{18}F-FDG PET/CT (FDG PET). Inclusion mandated PSMA intensity at sites of disease to be significantly greater than normal liver, defined by SUVmax of tumor involvement of at least 1.5 times SUVmean of liver. Patients were excluded if FDG PET demonstrated major discordant disease, i.e. sites of FDG-positive and PSMA-negative disease, which we anticipated would be less likely to respond to therapy.

Procedures

Assessments. At baseline, all patients underwent ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT, radionuclide bone scan, contrast-enhanced CT of the chest, abdomen and pelvis, ^{51}Cr-EDTA eGFR, full blood count, urea and electrolytes, liver function tests, lactate dehydrogenase, testosterone and PSA. Safety reviews and blood tests (full blood count, urea and electrolytes, liver function tests and PSA) were performed at 2 and 4 weeks after each 6-weekly treatment cycle. Additionally, all patients were reviewed 24 hours after LuPSMA administration. In the event of significant toxicities (Grade > 1 hematological toxicity), full blood counts were repeated weekly until resolution. Patient-reported health-related quality of life (HRQoL) outcomes were assessed using the EORTC Quality of Life Questionnaire for cancer patients (EORTC-QLQ-C30) (*23*) and Brief Pain Index (BPI) (*24*) questionnaires prior to each cycle of therapy and at 12-week follow-up. Adverse events were graded and causality assigned according to Common

Terminology Criteria for Adverse Events (CTCAE) v4.03 at each clinical review up to the 12-week follow-up visit after the last administration of LuPSMA. Beyond the 12-week follow-up visit, only adverse events deemed to be related to treatment were reported. At the 12-week follow-up visit, ^{51}Cr-EDTA eGFR, ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT, bone-scan and CT chest-abdomen-pelvis were repeated. Low dose CT of post-treatment SPECT/CT were also utilized to assess soft tissue RECIST response. Thereafter, patients were managed at the discretion of the treating physician and followed for biochemical progression, further anti-cancer treatments and overall survival. The study protocol mandated formal assessment 3 monthly to 12 month follow-up. PSA re-assessment, however, was performed more frequently in most patients.

Administration of therapy. LuPSMA was administered intravenously over a period of 2-10 minutes. Patients were encouraged to be well hydrated by consuming 1.5 L of oral fluids on the day of LuPSMA administration. No specific measures to minimize xerostomia were used. The administered radioactivity was adjusted according to tumor burden, patient weight and renal function starting from a dose of 6 GBq. This was adapted from our ^{177}Lu-DOTATATE experience (*25*); activity was increased by 1 GBq if there were >20 sites of disease, or decreased by 1 GBq if <10 sites. Activity was increased by 0.5 GBq per factor if weight >90 kg or eGFR >90 mL/min, and decreased by 0.5 GBq if weight <70 kg or eGFR <60 mL/min. Patients could receive up to 4 cycles of LuPSMA, every 6 weeks.

Radiation emission was measured with a hand-held gamma counter and patients were discharged when below 9 μSv/hour at 2 meters as per local regulations; this generally occurred within 2-4 hours and following first bladder voiding. Planar and quantitative single photon emission computed tomography/computed tomography (qSPECT/CT) scans were acquired at 4, 24 and 96-hours following LuPSMA therapy in the first 30 patient cohort for dosimetry studies. As a result of their findings(*15*) only 24-hour imaging was performed in the expanded cohort to confirm tumor localization.

Cycle delays and early treatment cessation in exceptional responders. In patients with cytopenias (Hb <9.0 g/dL, platelet count <75,000 x 10^9/L, neutrophil count <1.5 x 10^9/L), bloods were repeated weekly and therapy delayed until recovery to acceptable levels. If post-therapy imaging demonstrated no or minimal uptake of radionuclide at sites of tumor, indicative of an ‘exceptional’ response to prior cycles, no further cycles were administered. Treatment was also

ceased in patients who were deemed to be no longer clinically benefiting from treatment after multidisciplinary discussion.

Re-treatment. Patients who initially responded to therapy defined by PSA decline ≥ 50% with imaging response and subsequently progressed were considered for further LuPSMA as part of a compassionate access program using the Australian Therapeutic Goods Administration Special Access Scheme. The selection criteria and procedures as per the study protocol. Patients underwent repeat ^{68}Ga-PSMA-11 and ^{18}F-FDG imaging to confirm they had sufficiently PSMA-avid disease and no sites of discordant disease.

Outcomes and Statistical analysis

The initial sample size of 30 was pragmatic and this was later expanded to 50 based on department resources and supply agreement for ^{177}Lu. Primary endpoints included PSA response defined as a ≥50% PSA decline from baseline, toxicity according to CTCAE v4.03, imaging responses and patient-reported quality of life (QoL). Secondary endpoints were overall survival (OS) and PSA progression-free survival (PFS) defined by time to PSA progression as per PCWG2; both endpoints measured from the date of patient enrolment/consent. A further secondary endpoint was determination of the radiation dosimetry of therapy and has been reported separately(*15*).

For PSA response, the best percentage change in PSA levels was recorded with a two-sided exact binomial 95% confidence interval. Time to event outcomes including PSA PFS and overall survival were analyzed using Kaplan-Meier statistics; to compare groups logrank test was applied. Linear mixed models (LMM) were used to assess the EORTC-QLQ-C30 and BPI endpoints; no imputation for missing values was used. Mean differences from baseline and 95% confidence intervals were estimated from the LMM contrasts. Statistical analyses were conducted using R-Statistics 3.4.0 with ggplot2 package.

RESULTS

The initial 30 patient cohort was recruited between August 2015 and December 2016 and the 20 patient expanded cohort enrolled from March 2017 to June 2017. Results are reported following a median follow-up of 31.4 months (interquartile range 25.1 – 36.3 months; cut-off date 29 May 2019). 75 patients were screened in order to identify 50 evaluable patients as outlined in Figure 1. 16 patients were excluded owing to either low PSMA-expression (n=8) or discordant sites of

FDG-positive PSMA-negative disease (n=8); the outcomes of these patients have been reported previously (*26*).

Patient characteristics are outlined in Table 1. Patients were heavily pre-treated with 84% receiving prior docetaxel and 92% receiving prior therapy with a second-generation anti-androgen (Abiraterone or Enzalutamide). Median PSA doubling time prior to first administration of LuPSMA was 2.3 months.

The median number of cycles received on protocol was 4 (range: 1-4). 21 patients received fewer than 4 cycles due to progressive disease during therapy (n=10), an exceptional response to therapy (n=8), prolonged cytopenias (n=2) and non-cancer related death (n=1). The mean injected activity delivered per cycle was 7.5 GBq (range 4-8.9 GBq) with a mean cumulative activity of 24.7 GBq. Median time to first treatment after enrolment was 5.0 weeks and time between cycles was 6.0 weeks. Whole body planar imaging at 24 hours post treatment demonstrated an average retention of 22.6% (range 4.6-45.5%).

Biochemical and imaging response

The primary endpoint of PSA decline greater than or equal to 50% from baseline was seen in 64% of patients (95% CI 50-77%) with a ≥80% decline seen in 44% of patients (95% CI 30-59%) (Figure 2). Eight patients (16%) achieved a ≥98% PSA decline (see Figure 3).

Imaging response was assessed at 3 months following the last cycle of therapy and is shown in Table 2. In 27 patients with measurable soft tissue disease on CT at baseline, 56% had an objective response (complete or partial response) by RECIST 1.1. Complete or partial molecular imaging responses on ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT were seen in 42% and 30%, respectively. The most common pattern of progression was in marrow (56%), typically at new sites compared to baseline evaluation, or in the liver (19%).

Treatment related toxicity

Therapy was well tolerated with no infusion related complications or treatment related deaths. Treatment related toxicities causally related to therapy are outlined in Table 3. The most common acute toxicity was xerostomia reported in 66% of patients and was grade 2 or less in severity and transient. Grade 1-2 nausea and vomiting were seen in 48% and 26% respectively; this generally occurred within the first 24 hours of therapy, was transient and manageable with

anti-emetics. Grade 3-4 toxicity was primarily hematological including lymphopenia (32%), thrombocytopenia (10%), anemia (10%) and neutropenia (6%). No episodes of neutropenic sepsis were observed. Grade 4 toxicity was limited to a single case of thrombocytopenia. Grade 1-2 renal injury occurred in 10% of patients; in 28 patients who had ^{51}Cr-EDTA measured before and 3 months after completion of LuPSMA, there was a mean decline of 11.7 mL/min (95% CI -19 to -4 mL/min).

No patients developed myelodysplasia during the extended follow-up period. Of note, one patient with lymph node-only disease had pancytopenia (grade 2 thrombocytopenia, grade 2 neutropenia and grade 3 anemia) commencing following cycle 3. Platelet nadir occurred at 28 days with full recovery. Bone marrow biopsy demonstrated no specific cause. Restaging ^{68}Ga-PSMA-11 PET/CT upon progression again demonstrated only nodal disease.

Quality of life

HRQoL assessments were available for 79% of time-points with missing data attributable to death (9%), illness (7%) or not recorded (4%). Overall, global health status improved significantly on the EORTC QLQ-C30 by cycles 2 and 3, with an increase of 6 and 7, respectively (95% CI 0-11 and 1-13, p=0.04 and 0.03, respectively); at 3-month follow-up this was stable compared to baseline. Changes in specific functional scales or symptom items are shown in Supplementary Figure 1-2, Supplementary Table 1.

Overall, BPI pain severity and interference scores decreased at all time points including at the 3 month follow-up with a decrease of -1.2 (95% CI -0.5 to -1.9, p=0.001) and 1.0 (95% CI -0.2 to -0.18, p=0.013), respectively (see Figure 4, Table 4). The pain scale on the EORTC QLQ-C30 was also improved (supplementary Table 1), concordant with the BPI findings.

PSA progression-free and overall survival

At time of analysis, 43 of 50 patients were deceased. Median OS was 13.3 months (95% CI 10.5-18.7) (Figure 5). Survival was significantly longer in patients who achieved PSA decline ≥ 50%, with a median of 18.4 months (95% CI 13.8-23.8) compared to 8.7 months if PSA decline < 50% (95% CI 6.5-13.4). PSA response at 12 weeks was predictive of survival with an optimal cut-off defined at 34% (supplementary Figure 3).

All patients eventually had PSA progression with the longest duration of response being 31 months in a patient with lymph node only disease. Median PSA PFS was 6.9 months (95% CI 6.0-8.7). PSA PFS was also significantly longer in patients with PSA decline ≥ 50% of 8.2 months (95% CI 6.9 – 10.3) compared to 4.2 months for those with a decline of <50% (95% CI 3.9-7.1). In 37 patients with ≥3 PSA values at baseline and time of progression, the mean PSA doubling time was 1.4 months at time of progression compared to 3.3 months at baseline (p=0.002).

Re-treatment cohort

On progression, 30 patients went on to receive further systemic therapy. At first relapse, these included LuPSMA (n=14), Cabazitaxel (n=7), Docetaxel (n=6), Mitoxantrone (n=1), and Olaparib (n=1). At subsequent progression, additional lines of therapy included Cabazitaxel (n=7), Pembrolizumab (n=4), Docetaxel (n=2), LuPSMA (1 n=) (following Olaparib), Enzalutamide (n=1) and Carboplatin (n=1). In total, 15 patients received further LuPSMA and 21 patients had at least one line of other systemic therapy.

Of 15 patients receiving further LuPSMA at first or second relapse after initial response to LuPSMA, 11 (73%) had a PSA decline ≥ 50% (see Figure 6). Re-treatment commenced a median of 359 days after study enrolment (median 2 cycles, range 1-5). The mean best percentage fall in PSA in LuPSMA responders was 76.7% (range 60-98). However, responses following further LuPSMA were less durable (see Table 5). The median overall survival from time of study enrolment in the 15 patients who received re-treatment was 26.6 months.

Treatment emergent adverse events were similar to initial therapy. One patient, already described above with node only disease, experienced pancytopenia with G4 thrombocytopenia, G4 neutropenia and platelet nadir at 42 days, G3 lymphopenia and G2 anemia. This patient went on to receive Cabazitaxel chemotherapy without significant cytopenias. One patient experienced grade 3 chronic kidney disease with eGFR declining progressive from 91 mL/min at baseline to 38 mL/min over the course of 30 months after receiving 9 LuPSMA treatments. Two patients died within 30 days of LuPSMA administration from subdural hematomas unrelated to treatment, 7 and 24 days post LuPSMA administration.

Of 21 patients receiving other systemic therapies at first or second relapse, 4 (19%) had a PSA decline ≥ 50%. Twelve of these had undergone ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT imaging

prior and in 6 patients disease was PSMA-positive without FDG-discordance indicating potential suitability for further LuPSMA therapy. Two patients had PSMA 'superscans' with pancytopenia and 4 patients had PSMA-positive disease with FDG discordance and were thus deemed unsuitable for further LuPSMA therapy.

DISCUSSION

In a prospective phase II clinical trial we have previously reported high single-agent activity of LuPSMA in thirty patients with mCRPC (*14*), confirming findings observed from numerous retrospective series (*7,8,10,11,27,28*). In this expanded cohort of patients, we report a PSA ≥50% response rate in 64% compared to 57% in the original cohort. Importantly, no new or delayed treatment related toxicity was reported except for G1-2 renal injury. We also report for the first time patterns of disease progression following treatment with this novel therapeutic agent and the outcome of patients who were re-treated with additional systemic agents, including further doses of LuPSMA, at disease progression.

Approximately one third of screened patients in this cohort were declined LuPSMA therapy, largely due to either low PSMA expression or the presence of PSMA-negative, FDG-positive disease ("FDG discordant disease") on pre-treatment screening (see Supplementary Figure 4). These stringent selection criteria have likely enriched our cohort with patients most likely to benefit from LuPSMA therapy and explains our relatively high PSA response rates compared to other series who did not perform screening FDG PET studies. Radiation dosimetry from the original cohort (*15*) and others (*29*) shows that SUVmean of screening PSMA PET correlates with absorbed dose in tumor. We have also reported that "whole body" tumor dose correlates with therapeutic response (*15*) justifying our approach to limiting treatment with single agent LuPSMA to patients with relatively high uptake on diagnostic PSMA scanning. Nevertheless, we acknowledge that patients with more heterogeneous PSMA expression may have still derived clinical benefit from LuPSMA treatment, particularly if this were combined with other effective systemic therapies.

The optimal dose and administration schedule for LuPSMA is not clearly defined and the choice of treatment cycles in the design of this study was pragmatic. Therefore, in some patients who relapsed following completion of study therapy, and who continued to fulfill study eligibility criteria, namely maintained expression of PSMA, we administered further cycles of therapy via a compassionate access program. Administration of further therapy in this group of patients was

effective, achieving a PSA response rate of ≥50% in 73% of patients. These findings suggest that progression after therapy in responding patients should not be a barrier to further treatment, as long as patients are carefully selected. The findings also provide safety data to support administering more than 4 cycles of therapy. One of our patients has had 9 cycles of therapy between 2017-19 and continued to benefit from LuPSMA treatment but had declining renal function. Loss of renal cortical mass due to the age of the population and prior obstructive uropathy may render men with advanced prostate cancer at an increased risk of progressive renal impairment due to a greater percentage of the residual nephron mass being within the 1-3 mm range of beta radiation emitted by LuPSMA as it is excreted by the kidneys.

It is of interest that patients who went on to receive further other systemic therapies, primarily salvage systemic chemotherapy, had much worse biochemical responses. In a single patient treated with a PARP inhibitor without any response, subsequent biochemical response was achieved following further LuPSMA therapy. Nevertheless, the duration of response in patients given additional LuPSMA was significantly shorter than following de-novo treatment. The high rate of eventual treatment failure supports efforts to increase the depth and durability of response, which may require combination therapies to enhance control of micrometastatic disease, increase radiosensitivity of disease sites or activate an adaptive immune response. Trials are currently underway to test combination therapies with LuPSMA to assess the safety and efficacy of such approaches (NCT03874884, NCT03658447). First, however, we await the results of two key randomised controlled trials currently underway; the ANZUP TheraP trial comparing ^{177}Lu-PSMA-617 to cabazitaxel (NCT03392428) and the Endocyte VISION trial comparing ^{177}Lu-PSMA-617 in combination with best supportive care/standard of care (BSC/BSoC) to BSC/BSoC alone (NCT03511664).

Following initial response, patients predominantly progressed with new focal or diffuse areas of involvment in the bone or new hepatic metastases. Diffuse marrow infiltration was the most common pattern of eventual demise manifesting as leucoerythroblastic pancytopenia and sufficient to cause cessation of LuPSMA treatment. Liver metastases were the second most common pattern of progression; these generally had low PSMA expression and high metabolic activity in line with recent data (*30*).

The high response rates and limited toxicity of LuPSMA has stimulated interest in the wider application of this therapy earlier in the course of the disease(*31,32*). Radiation dosimetry suggests that earlier introduction of therapy should be safe but data on long-term toxicity to

verify this is sparse given the current application of therapy in end-stage patients who, even with excellent responses to treatment, have a relatively limited prognosis. Renal function requires ongoing monitoring in patients receiving serial treatment.

CONCLUSIONS

This study confirms the findings of our earlier report, demonstrating high therapeutic efficacy and low toxicity of ^{177}Lu-PSMA-617 (LuPSMA) in men with mCRPC who have progressed after standard therapies. The study also provides evidence of improvement in quality of life in multiple domains. Finally, we demonstrated high response rates but less durable responses in patients re-challenged with LuPSMA upon progression.

DISCLOSURES

MH is the chair of the ANZUP TheraP Study which receives research support from Prostate Cancer Foundation of Australia (PCFA), Endocyte (a Novartis company) and Australian Nuclear Science and Technology Organisation (ANSTO, Sydney, Australia). MH additionally receives research support from the Movember Australia, Prostate Cancer Foundation (PCF), Prostate Cancer Foundation of Australia (PCFA) and the Victoria Cancer Agency (VCA). Unrelated to this work, he has received honorarium and travel support for educational lectures from Janssen, Ipsen and Sanofi Genzyme. RJH holds shares in Telix on behalf of the Peter MacCallum Cancer Centre and has received travel support from GE Medical Systems and Siemens Healthineers. BT receives consulting and honoraria from Amgen, Astellas, Bayer, Bristol-Myers Squibb, IQVIA, Janssen-Cilag, Sanofi, Novartis, Ipsen, and research funding from Amgen, Astellas. Other authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

We thank the Australian Nuclear Science and Technology Organisation (ANSTO, Sydney, Australia) for supplying ^{177}Lu (no carrier added). PSMA-617 was supplied by Advanced Biochemical Compounds (ABX, Radeberg, Germany) and subsequently Endocyte (a Novartis company).

We thank the nuclear medicine and nursing staff at the Peter MacCallum Cancer Centre and all the patients who participated in the study. MH and SS thanks the Peter MacCallum Foundation

for providing a Clinical Fellowship directly supporting this research. We also thank Dr Mathias Bressel (Biostatistician) for analysis of the quality of life data.

KEY POINTS

Question: What is the role of Lutetium-177-PSMA-617 (LuPSMA) in men with metastatic castration-resistant prostate cancer who have progressed after standard therapies?

Pertinent findings: In this 50 patient phase II single center clinical trial, we observed high response rates (PSA decline ≥ 50% in 64%) with low toxicity and improved health-related quality of life. Furthermore, in patients re-challenged with LuPSMA upon progression, the response rate was high, whilst responses to other forms of systemic therapies were lower.

Implications for patient care: In men with limited therapeutic options and PSMA-avid prostate cancer at, LuPSMA is an effective therapy with low toxicity.

REFERENCES

1. Smith-Jones PM, Vallabahajosula S, Goldsmith SJ, et al. In vitro characterization of radiolabeled monoclonal antibodies specific for the extracellular domain of prostate-specific membrane antigen. *Cancer Res.* 2000;60:5237-5243.

2. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem.* 2004;91:528-539.

3. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. *Urology.* 1998;52:637-640.

4. Hofman MS, Murphy DG, Williams SG, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. *BJU Int.* 2018;122:783-793.

5. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol.* 2019.

6. Farolfi A, Fendler W, Iravani A, et al. Theranostics for Advanced Prostate Cancer: Current Indications and Future Developments. *Eur Urol Oncol.* 2019;2:152-162.

7. Ahmadzadehfar H, Rahbar K, Kurpig S, et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res.* 2015;5:114.

8. 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.

9. Yadav MP, Ballal S, Tripathi M, et al. 177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2017;44:81-91.

10. Heck MM, Retz M, D'Alessandria C, et al. Systemic Radioligand Therapy with (177)Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer. *J Urol.* 2016;196:382-391.

11. Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. *J Nucl Med.* 2016;57:1006-1013.

12. Kulkarni HR, Singh A, Schuchardt C, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016;57:97S-104S.

13. Emmett L, Crumbaker M, Ho B, et al. Results of a Prospective Phase 2 Pilot Trial of (177)Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. *Clin Genitourin Cancer.* 2019;17:15-22.

14. Hofman MS, Violet J, Hicks RJ, et al. [(177)Lu]-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.

15. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of (177)Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. *J Nucl Med.* 2019;60:517-523.

16. Hohberg M, Eschner W, Schmidt M, et al. Lacrimal Glands May Represent Organs at Risk for Radionuclide Therapy of Prostate Cancer with [Lu]DKFZ-PSMA-617. *Mol Imaging Biol.* 2016.

17. Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:42-51.

18. Kabasakal L, AbuQbeitah M, Aygun A, et al. Pre-therapeutic dosimetry of normal organs and tissues of (177)Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:1976-1983.

19. Okamoto S, Thieme A, Allmann J, et al. Radiation dosimetry for 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer: Absorbed dose in normal organs and tumor lesions. *J Nucl Med.* 2016.

20. Yadav MP, Ballal S, Tripathi M, et al. Post-therapeutic dosimetry of 177Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer. *Nucl Med Commun.* 2017;38:91-98.

21. Fendler WP, Kratochwil C, Ahmadzadehfar H, et al. [177Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer]. *Nuklearmedizin.* 2016;55:123-128.

22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42:377-381.

23. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365-376.

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

25. Hofman MS, Hicks RJ. Peptide receptor radionuclide therapy for neuroendocrine tumours: standardized and randomized, or personalized? *Eur J Nucl Med Mol Imaging.* 2014;41:211-213.

26. Thang SP, Violet J, Sandhu S, et al. Poor Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer with Low Prostate-specific Membrane Antigen (PSMA) Expression Deemed Ineligible for (177)Lu-labelled PSMA Radioligand Therapy. *Eur Urol Oncol.* 2018.

27. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with 177Lu-Labeled PSMA-617. *J Nucl Med.* 2016;57:1170-1176.

28. Yadav MP, Ballal S, Tripathi M, et al. 177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2016.

29. Wang J, Zang J, Wang H, et al. Pretherapeutic 68Ga-PSMA-617 PET May Indicate the Dosimetry of 177Lu-PSMA-617 and 177Lu-EB-PSMA-617 in Main Organs and Tumor Lesions. *Clin Nucl Med.* 2019;44:431-438.

30. Paschalis A, Sheehan B, Riisnaes R, et al. Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer. *Eur Urol.* 2019.

31. Murphy DG, Sathianathen N, Hofman MS, Azad A, Lawrentschuk N. Where to Next for Theranostics in Prostate Cancer? *Eur Urol Oncol.* 2019;2:163-165.

32. Murphy DG, Hofman MS, Azad A, Violet J, Hicks RJ, Lawrentschuk N. Going nuclear: it is time to embed the nuclear medicine physician in the prostate cancer multidisciplinary team. *BJU Int.* 2019.

33. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50 Suppl 1:122S-150S.

Table 1: Patient characteristics

Characteristic	Median / number (%)	Range
Age (years)	71	50 - 87
Time since diagnosis of prostate cancer (years)	8	2 - 17
Gleason score	8	6 - 10
Alkaline phosphatase (U/L)	131	49 -1896
Haemoglobin (g/L)	117	88 - 151
Lactate dehydrogenase (U/L)	268	148 - 1331
PSA (ng/mL)	189.8	7 – 4022
PSA doubling time (months)	2.3	-5.8 to 22.9
ECOG performance status		
0	20 (40%)	
1	22 (44%)	
2	8 (16%)	
Prior therapies		
Abiraterone or Enzalutamide or both	46 (92%)	
Docetaxel	42 (84%)	
Cabazitaxel	24 (48%)	
Docetaxel + Enzalutamide/ Abiraterone +/- Cabazitaxel	39 (78%)	
Stage of disease (PSMA PET)		
Node only (M1a)	2 (4%)	
Bone (M1b)	38 (76%)	
Visceral (M1c)	10 (20%)	
Pain at baseline (BPI pain severity score)		
No pain (<1)	8 (16%)	
Mild (1-4)	29 (58%)	
Moderate to severe (5-10)	13 (26%)	

Table 2: Imaging response at 3 months after the last cycle of induction LuPSMA

	Bone scintigraphy	Soft-tissue lesions on CT (nodal and &/or visceral)[1] (n=27)	PSMA PET	FDG PET
CR	16 (32%)	5 (19%)	6 (12%)	7 (14%)
PR		10 (37%)	15 (30%)	8 (16%)
SD		0	0	3 (6%)
PD	12 (24%)	9 (33%)	14 (28%)	15 (30%)
Not performed	22 (44%)	3 (11%)	15 (30%)	17 (34%)

CR: complete response. PR: partial response. SD: stable disease. PD: progressive disease. PET responses were assessed visually using Hicks criteria(*33*). RECIST 1.1 with PCWG2 caveats; CT component of post-therapy SPECT/CT was also utilized for soft tissue measurements. Not performed: due to clinical progression or death.

Table 3: Treatment related toxicity occurring up to 12 weeks after treatment cessation

	Grade 1	Grade 2	Grade 3	Grade 4
Dry mouth	29 (58%)	4 (8%)	0 (0%)	0 (0%)
Lymphocytopenia	7 (14%)	13 (26%)	16 (32%)	0 (0%)
Thrombocytopenia	11 (22%)	3 (6%)	4 (8%)	1 (2%)
Fatigue	15 (30%)	3 (6%)	1 (2%)	0 (0%)
Nausea	20 (40%)	4 (8%)	0 (0%)	0 (0%)
Anaemia	3 (6%)	6 (12%)	5 (10%)	0 (0%)
Neutropenia	6 (12%)	6 (12%)	3 (6%)	0 (0%)
Bone Pain	5 (10%)	4 (8%)	0 (0%)	0 (0%)
Vomiting	11 (22%)	2 (4%)	0 (0%)	0 (0%)
Anorexia	8 (16%)	0 (0%)	0 (0%)	0 (0%)
Dry eyes	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Renal injury	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Weight loss	3 (6%)	1 (2%)	0 (0%)	0 (0%)

Data are n (%). Possibly, probably or definitely related treatment-emergent adverse events graded with CTCAE v4.03.

Table 4: BPI mean difference in scores from baseline (95% confidence intervals)

	Cycle 2 – Baseline		Cycle 3 – Baseline		Cycle 4 – Baseline		3 month FU – Baseline	
Number evaluable	46		36		29		26	
Dimension	Mean (95% CI)	p-value	Mean (95% CI)	p-value	Mean (95% CI)	p-value	Mean (95% CI)	p-value
Pain severity	**-0.9 (-1.5 to -0.3)**	**0.004**	**-0.9 (-1.5 to -0.2)**	**0.011**	-0.6 (-1.3 to 0.1)	0.096	**-1.2 (-1.9 to -0.5)**	**0.001**
Pain interference	**-0.7 (-1.4 to -0.1)**	**0.023**	**-1 (-1.7 to -0.3)**	**0.007**	**-0.9 (-1.6 to -0.1)**	**0.021**	**-1 (-1.8 to -0.2)**	**0.013**

Table 5: Summary of patients who received further LuPSMA upon progression

	No. of LuPSMA cycles		Best % PSA decline		PSA PFS* (days)	
Pt no	Initial	Re-treatment	Initial	Re-treatment	Initial	Re-treatment
2	4	2	39	60	485	106
3	4	2	94	64	249	75
5	2	3	99	80	248	259
7	4	3	92	54	538	132
18	3	3	100	98	566	432
22	4	2	89	70	314	90
23	4	5	97	63	469	291
24	4	1	15	NR	266	NR
29	4	1	100	85	929	In follow-up
32	4	1	50	NR	245	NR
34	4	2	100	NR	273	NR
35	4	4	99	98	296	237
38	2	3	100	98	293	179
44	4	1	91	73	302	123
45	4	1	69	NR	484	NR

*Measured from date of first treatment for on study LuPSMA, and from date re-treatment to PSA nadir. NR: no response

FIGURES

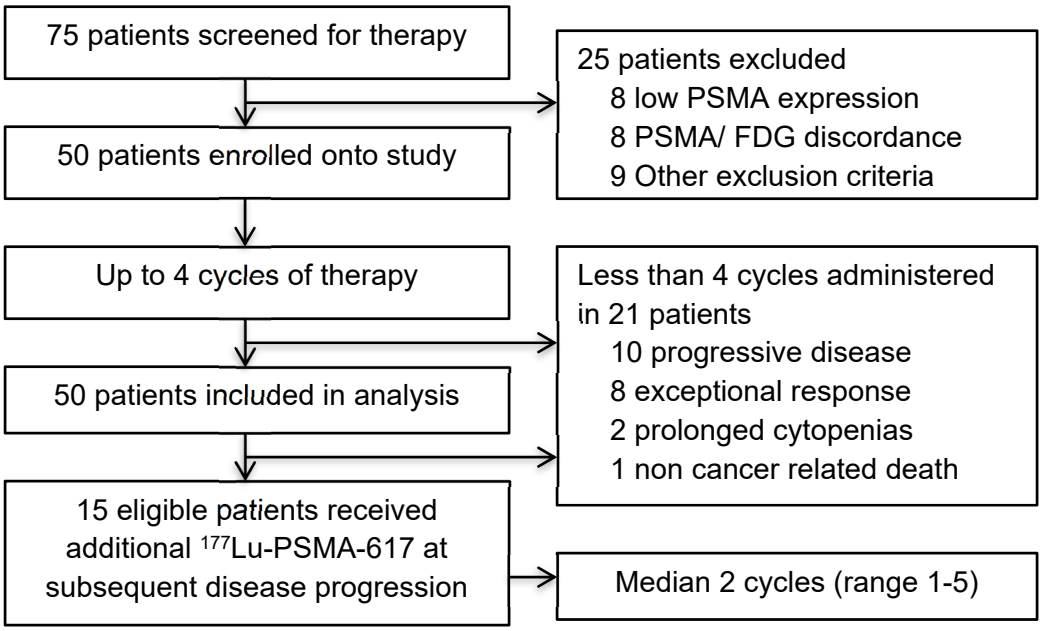


Figure 1: Study schema

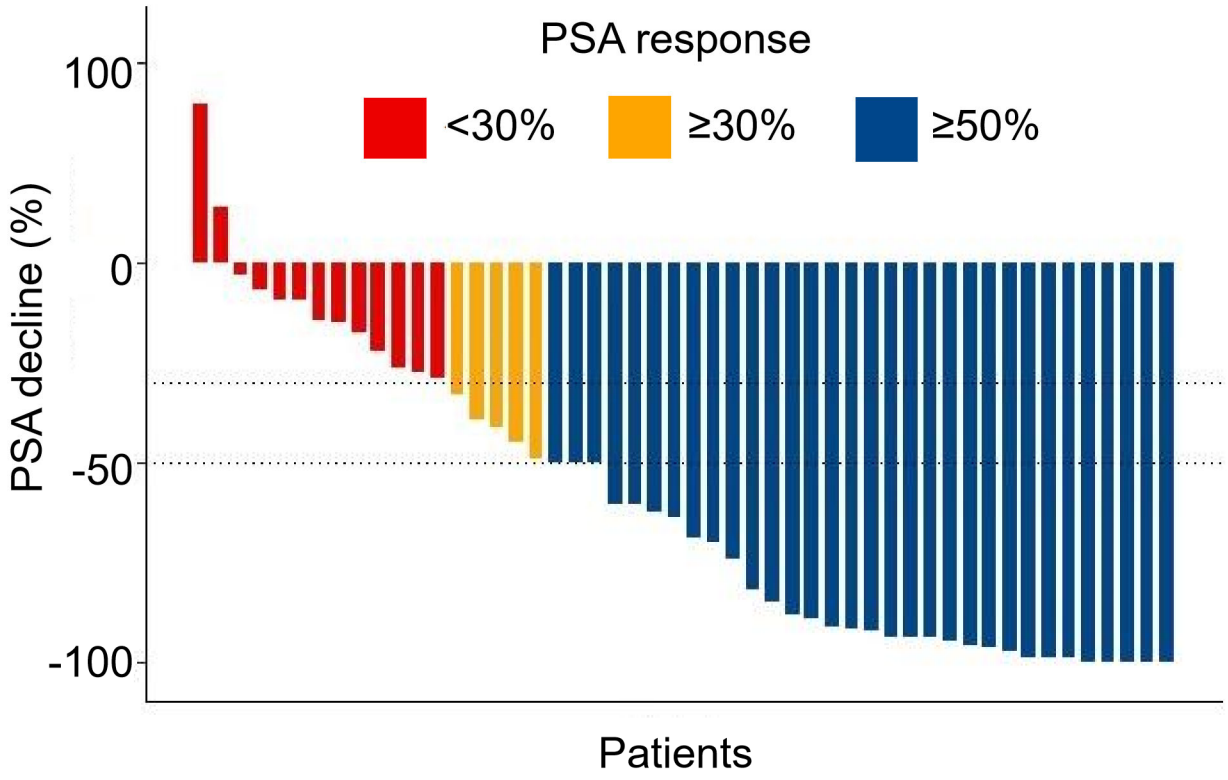


Figure 2: Waterfall Plot of best PSA decline compared to baseline

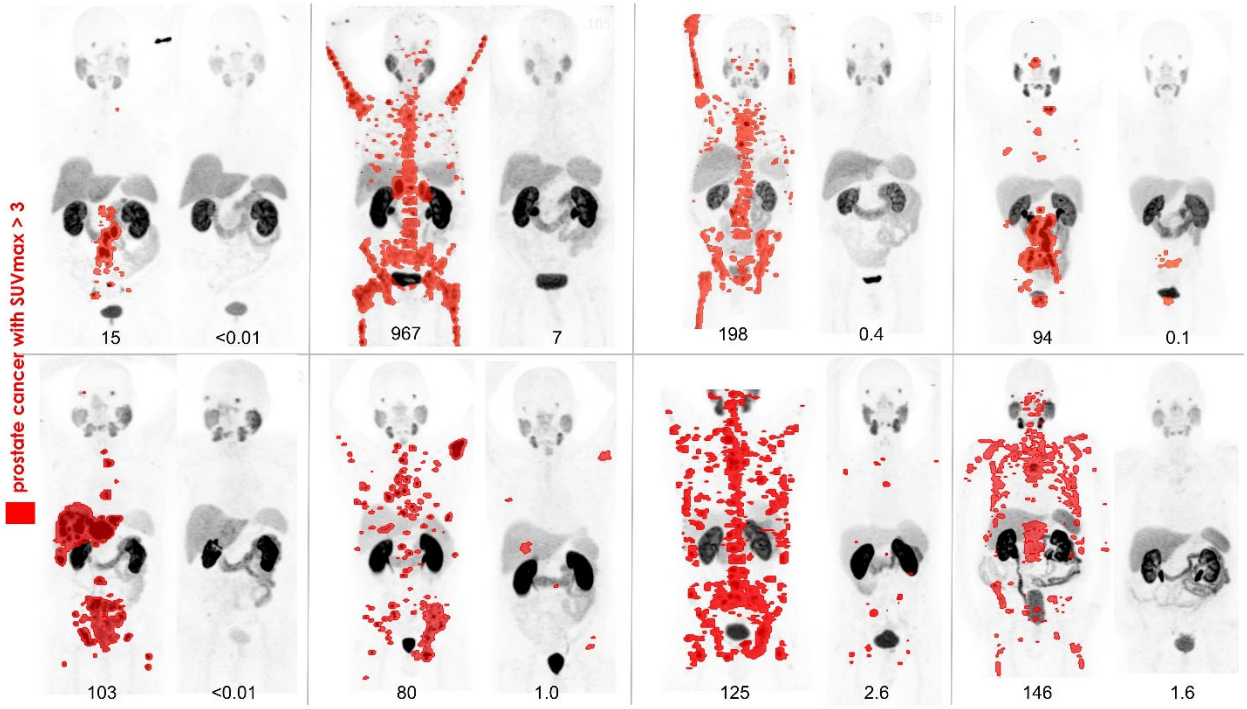


Figure 3: ^{68}Ga-PSMA-11 PET/CT before and 3 months after therapy in 8 patients with PSA declines ≥98% following LuPSMA therapy. Prostate cancer with SUV > 3 highlighted in red. Previously presented at the *Society of Nuclear Medicine and Molecular Imaging Scientific Meeting, Image of the Year 2018.*

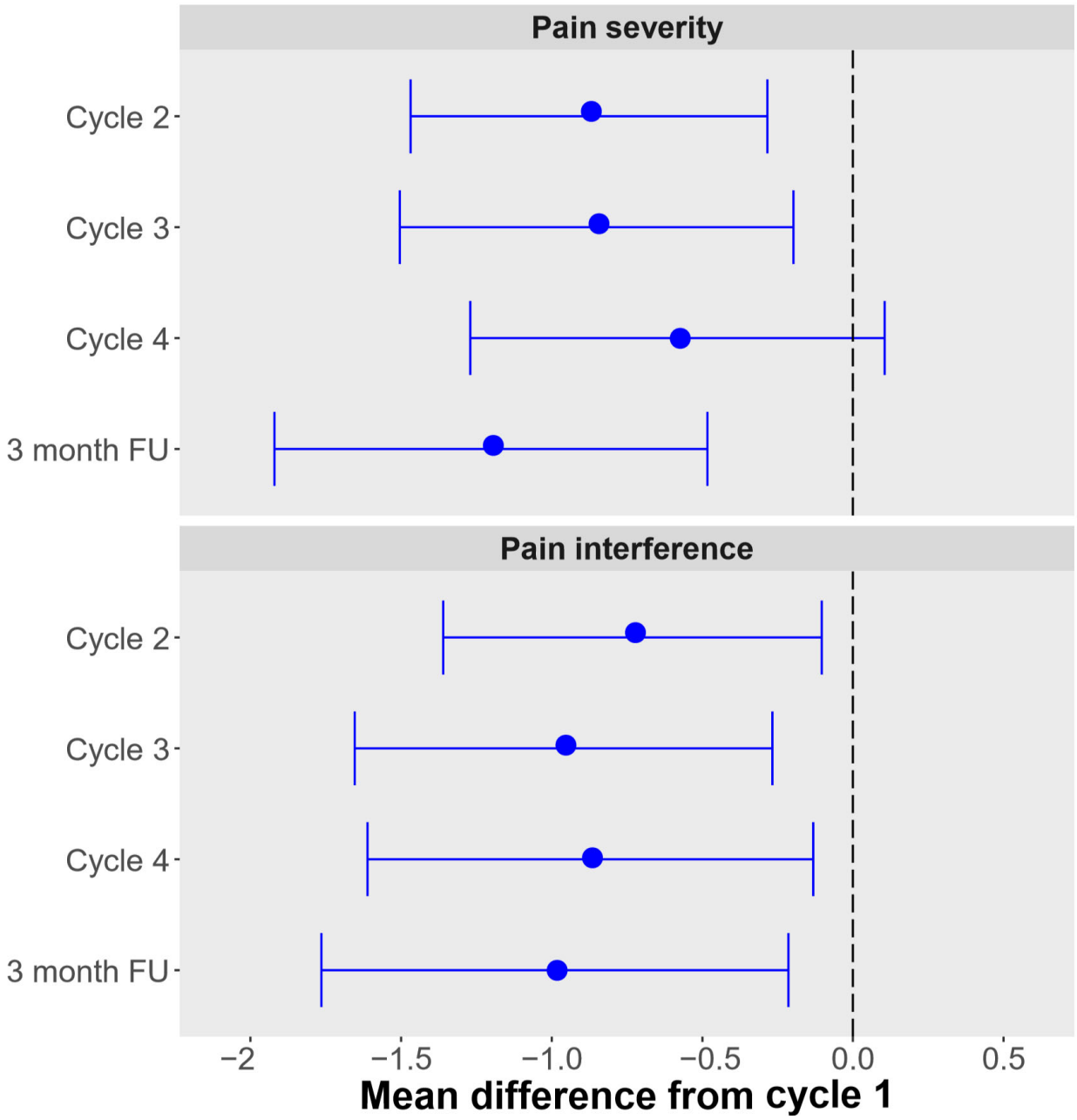


Figure 4: Brief pain index (BPI) scores compared to baseline with 95% confidence interval

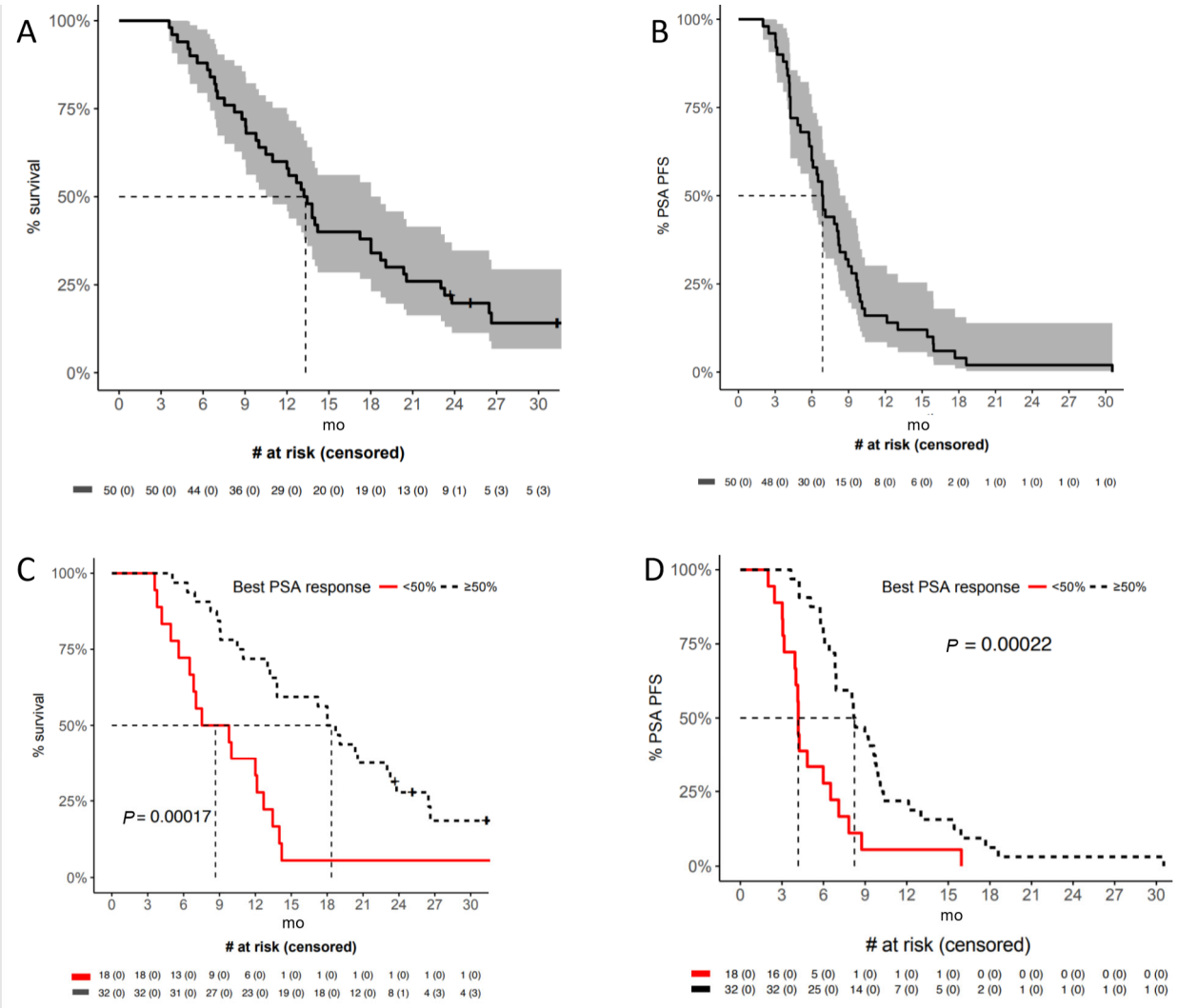


Figure 5: Kaplan-Meier Survival Curves: A) overall survival, B) PSA progression free survival (PFS), C) OS and D) PSA-PFS in patients with PSA decline ≥50% compared to PSA decline < 50%.

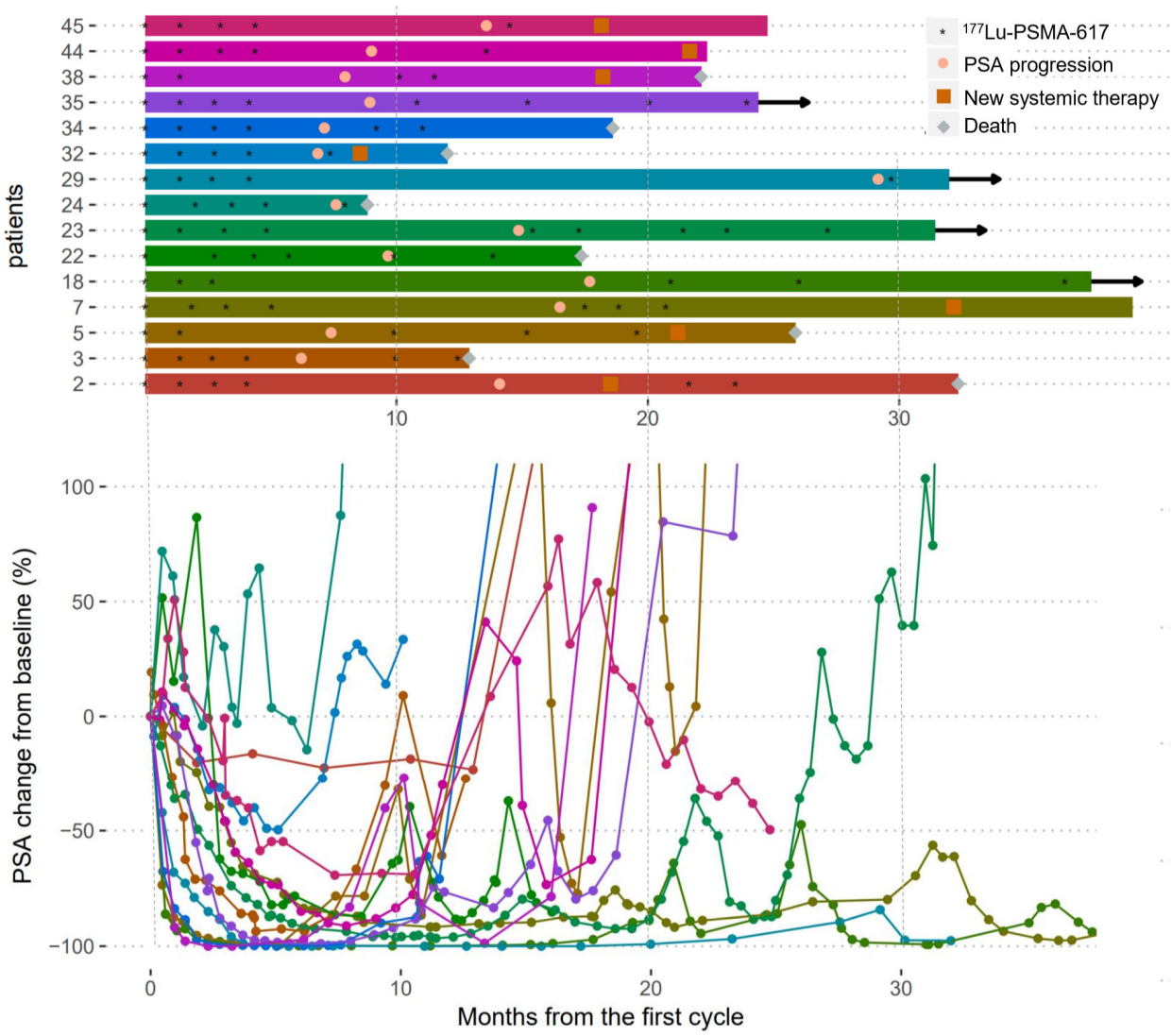


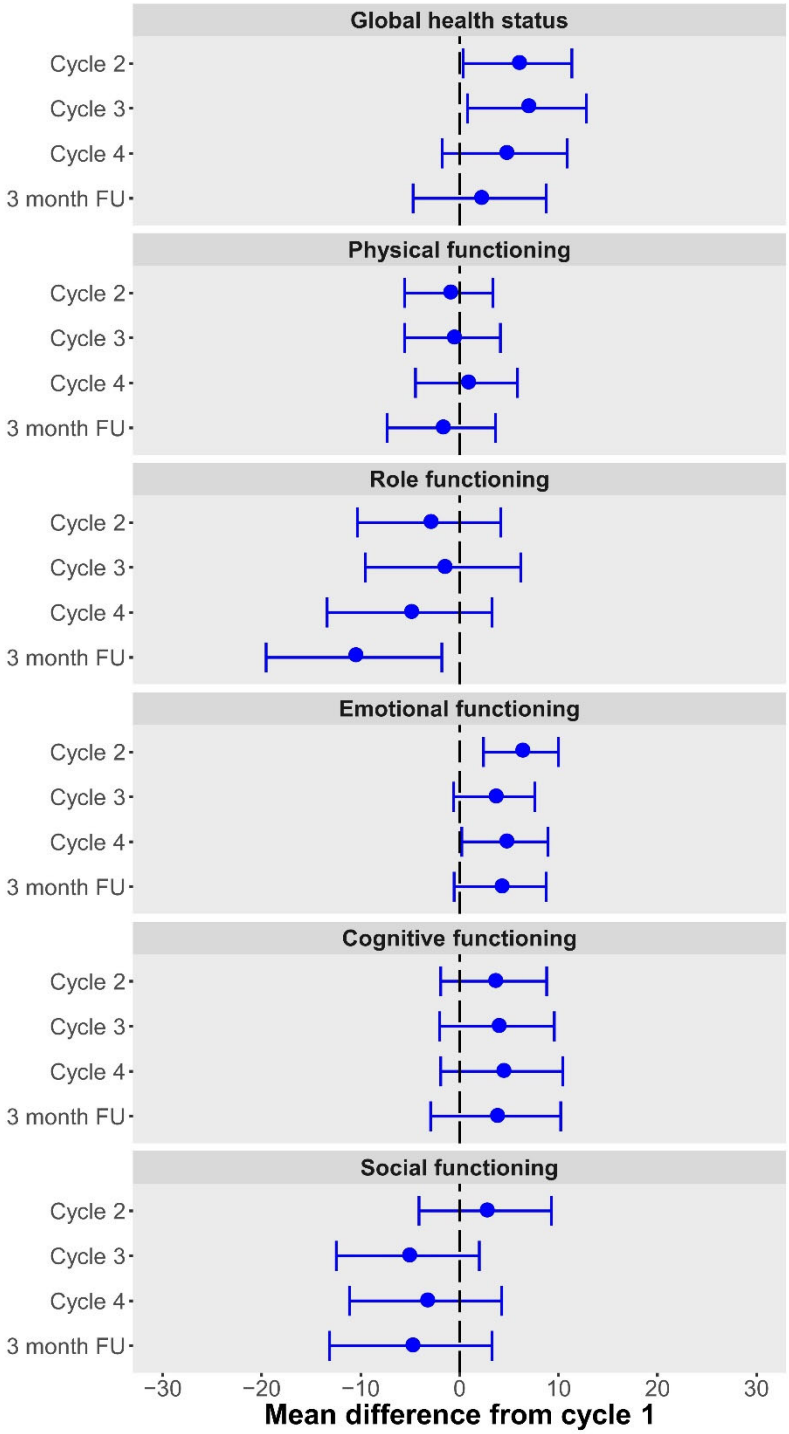
Figure 6: Outcomes of 15 Patients who received further LuPSMA. Top: swimmers plot of progress over time; black arrow: alive in follow-up. Bottom: corresponding spider plot of percentage PSA change over time compared to baseline.

SUPPLEMENTARY INFORMATION

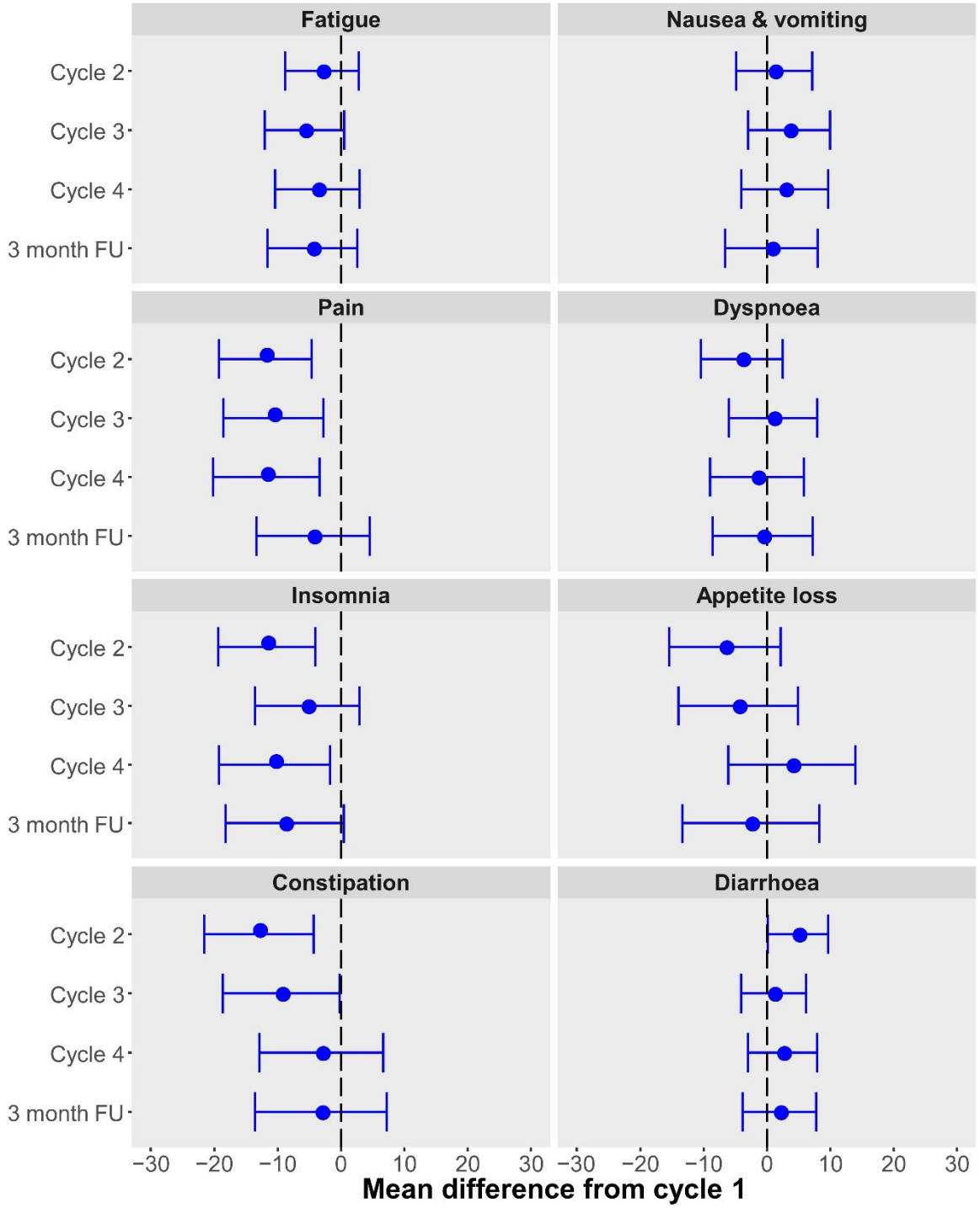
Supplementary Table 1: EORTC QLQ-C30 mean difference in scores from baseline

	Cycle 2 – Baseline		Cycle 3 – Baseline		Cycle 4 – Baseline		3 month FU – Baseline	
Number evaluable	46		37		30		26	
	mean (95% CI)	p-value	mean (95% CI)	p-value	mean (95% CI)	p-value	mean (95% CI)	p-value
Global health status	6 (0 to 11)	0.037	7 (1 to 13)	0.026	5 (-2 to 11)	0.155	2 (-5 to 9)	0.553
Functional scales								
Physical functioning	-1 (-6 to 3)	0.627	-1 (-6 to 4)	0.769	1 (-4 to 6)	0.789	-2 (-7 to 4)	0.506
Role functioning	-3 (-10 to 4)	0.400	-2 (-10 to 6)	0.672	-5 (-13 to 3)	0.233	-11 (-20 to -2)	0.019
Emotional functioning	6 (2 to 10)	0.001	3 (-1 to 8)	0.094	5 (0 to 9)	0.040	4 (-1 to 9)	0.084
Cognitive functioning	3 (-2 to 9)	0.204	4 (-2 to 10)	0.197	4 (-2 to 10)	0.173	4 (-3 to 10)	0.277
Social functioning	3 (-4 to 9)	0.445	-5 (-12 to 2)	0.154	-3 (-11 to 4)	0.380	-5 (-13 to 3)	0.238
Symptom scales / items								
Fatigue	-3 (-9 to 3)	0.309	-6 (-12 to 1)	0.071	-4 (-10 to 3)	0.272	-5 (-12 to 3)	0.210
Nausea and vomiting	1 (-5 to 7)	0.713	3 (-3 to 10)	0.287	3 (-4 to 10)	0.420	1 (-7 to 8)	0.856

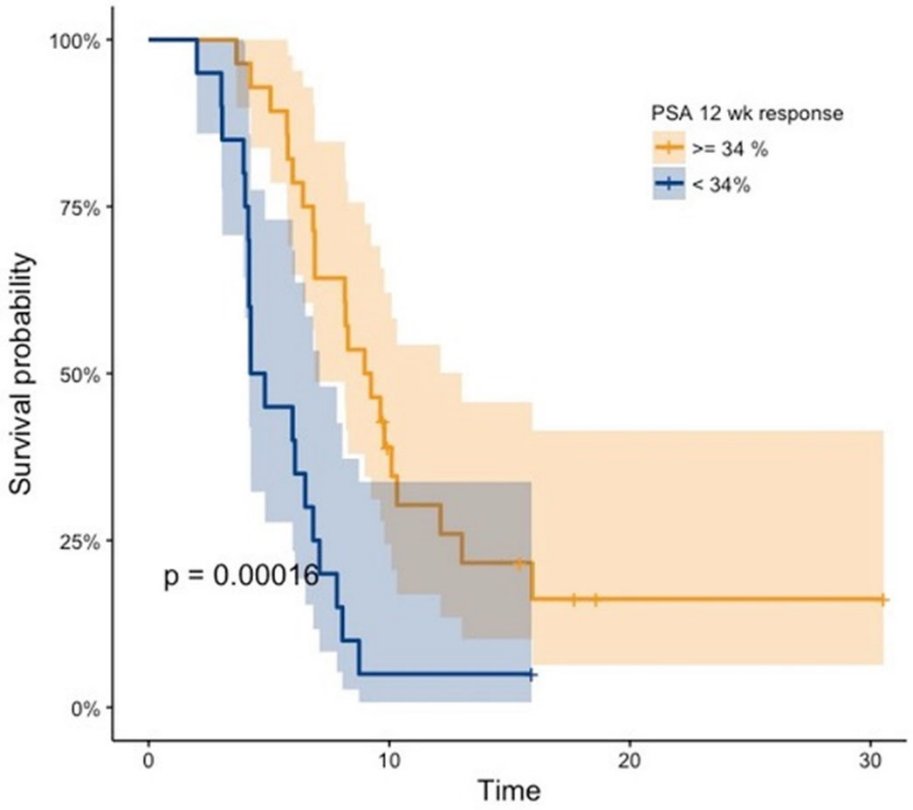
Pain	-12 (-19 to -5)	0.002	-11 (-19 to -3)	0.008	-12 (-20 to -3)	0.006	-4 (-13 to 5)	0.329
Dyspnoea	-4 (-10 to 2)	0.227	1 (-6 to 8)	0.785	-2 (-9 to 6)	0.677	-1 (-9 to 7)	0.862
Insomnia	-12 (-19 to -4)	0.003	-5 (-14 to 3)	0.201	-11 (-19 to -2)	0.019	-9 (-18 to 0)	0.061
Appetite loss	-7 (-15 to 2)	0.138	-5 (-14 to 5)	0.342	4 (-6 to 14)	0.439	-3 (-13 to 8)	0.638
Constipation	-13 (-22 to -4)	0.003	-9 (-19 to 0)	0.044	-3 (-13 to 7)	0.532	-3 (-14 to 7)	0.549
Diarrhoea	5 (0 to 10)	0.044	1 (-4 to 6)	0.695	2 (-3 to 8)	0.376	2 (-4 to 8)	0.509



Supplementary Figure 1: Health-related Quality of Life assessment using EORTC QLQ-C30

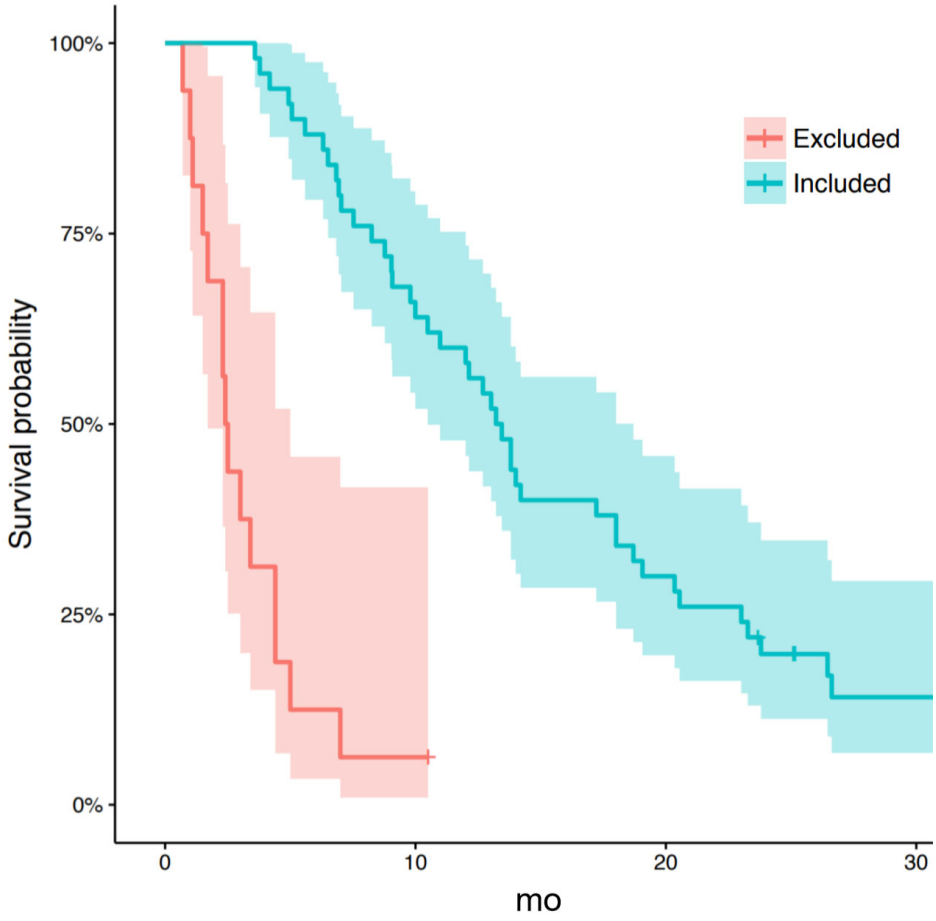


Supplementary Figure 2: Health-related Quality of Life assessment using EORTC QLQ-C30



Supplementary Figure 3: Kaplan-Meier Overall Survival Curve by PSA response at 12 weeks with optimal cut-off of 34%. Hazard ratio increases 1.088 per 10% (95% CI 1.049-1.129).

Supplementary Figure 4: Kaplan-Meier Overall Survival Curve in 16 patients who were excluded on the basis of low PSMA-expression or discordant FDG-avid disease compared to the 50 patients who were treated with 95% confidence interval shaded. Median OS was 2.5 months compared to 13.3 months.



The Journal of NUCLEAR MEDICINE

Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 (^{177}Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer

John Violet, Shahneen Sandhu, Amir Iravani, Justin Ferdinandus, Sue Ping Thang, Grace Kong, Aravind Ravi Kumar, Tim Akhurst, David Pattison, Alexis Beaulieu, Jennifer Mooi, Christina Guo, Victor Kalff, Declan G Murphy, Price Jackson, Peter Eu, Mark Scalzo, Scott Williams, Rod J Hicks and Michael S Hofman

J Nucl Med.
Published online: November 15, 2019.
Doi: 10.2967/jnumed.119.236414

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING