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The prognostic value of post-treatment PSMA and FDG PET/CT in metastatic, castration-resistant prostate cancer treated with 177LuPSMA-617 and NOX66 in a phase I/II trial (LuPIN).

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ABSTRACT

BACKGROUND

^{177}Lutetium PSMA-617 (^{177}LuPSMA-617) therapy has shown high prostate specific antigen (PSA) response rates in men with metastatic castration-resistant prostate cancer (mCRPC). However early treatment resistance is common. This LUPIN sub-study aimed to determine the prognostic value of post-treatment quantitative PET for PSA progression free (PSA-PFS) and overall survival (OS) with ^{177}LuPSMA-617 therapy.

METHODS

56 men with progressive mCRPC were enrolled in LuPIN trial and received up to 6 doses of ^{177}LuPSMA-617 and a radiation sensitizer (NOX66). ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT, diagnostic CT and bone scan were performed at study entry and exit. Quantitative analysis tracked change (Δ) in total tumour volume (TTV) and standardised uptake value (SUV). Univariable and multivariable analyses were conducted to examine the association of ΔTTV (continuous and > 30%), SUVmax, PSA and radiographic progression with PSA-PFS and OS.

RESULTS

All men (37/56) who underwent both screening and post treatment molecular imaging were analyzed. 70% (26/37) had a PSA response >50%, median PSA-PFS was 8.6 months and median OS 22 months. Clinical progression had occurred at trial exit in 54% (20/37). 95% (35/37) demonstrated reduced PSMA SUVmax and 68% (25/37) reduced PSMA-TTV in response to treatment. An increase in PSMA-TTV ≥30% was

associated with worse OS (median OS 10.2 vs 23.6 months, p 0.002). Change in PSMA-SUVmax was not associated with PSA-PFS or OS. FDG-SUVmax was reduced in 51% (18/35) and FDG -TTV in 67% (22/35). Increased FDG-SUVmax was associated with worse OS (median OS 20.7 vs. 25.7 months, p<0.01). Increased FDG-TTV > 30% was associated with short PSA-PFS (median PFS 3.5 vs 8.6 months, p<0.001) but not OS. Both PSA and radiographic progression were associated with shorter OS (median 14.5 vs 25.7 months, p<0.001, and 12.2 vs 23.6 months, p 0.002). On multivariable analysis, only increased PSMA-TTV and PSA progression remained independently prognostic of OS (HR 5.1 (95%CI 1.5-17.1), p 0.008 and HR 3.5 (95%CI 1.1-10.9), p 0.03 respectively).

CONCLUSION

Change in quantitative PSMA-TTV has strong potential as a prognostic biomarker with ^{177}LuPSMA-617 therapy, independent of FDG-PET parameters, PSA or radiographic progression. Further research into the value of post-treatment PET as imaging biomarker is warranted.

INTRODUCTION

^{177}Lutetium-PSMA-617 (^{177}LuPSMA-617) targeted therapy improved overall survival (OS) and progression-free survival (PFS) in metastatic, castration-resistant prostate cancer (mCRPC) when compared with to standard-of-care in the VISION trial and yielded a higher PSA-response rate and PSA-PFS than second-line chemotherapy with cabazitaxel in the TheraP trial (*1,2*). However, further work is needed to deepen treatment response and prolong survival. ^{68}Ga-PSMA-11 PET CT (PSMA-PET) and ^{18}F-fluorodeoxyglucose PET CT (FDG-PET) have been used as screening tools in prospective trials to select patients most likely to respond to ^{177}LuPSMA-617 targeted treatments (*1-4*). Less work has been done using molecular imaging to monitor treatment response to ^{177}LuPSMA-617 therapy. (*5-8*). Preclinical studies have confirmed that there is considerable inter-patient and intra-patient heterogeneity of PSMA expression (*9,10*). We hypothesized that an increase in uptake or tumor volume on PSMA-PET or FDG-PET might have potential as prognostic biomarker in men being treated with ^{177}LuPSMA-617.

In this study, we aimed to determine if changes in total tumour volume (TTV), and in standardized uptake value (SUV), on both PSMA-PET and FDG-PET, were correlated with clinical outcomes in a prospective trial of treatment with ^{177}LuPSMA-617.

MATERIALS AND METHODS

This is an imaging sub-study of the LuPIN trial. The LuPIN trial is a prospective, single centre, phase I/II dose escalation and expansion trial of combining ^{177}LuPSMA-617 with NOX66. The study enrolled men with mCRPC previously treated with both at

least one line of taxane chemotherapy, and with an androgen signaling inhibitor. The clinical results have been previously published (*11,12*). St Vincent's Hospital institutional review board approved the study protocol (HREC/17/SVH/19 ACTRN12618001073291) and all participants provided signed, written, informed consent.

Screening

Men with progressive mCRPC, based on either conventional imaging (computed tomography [CT] and bone scan) or a rising serum concentration of prostate specific antigen (PSA) based on Prostate Cancer Working Group 3 (PCWG3) criteria (*13*), were eligible for screening. Men underwent screening with FDG-PET and PSMA-PET, bone scan and CT of the chest, abdomen, and pelvis. Men were eligible if they had a SUVmax >15 on PSMA-PET at ≥ 1 site, an SUVmax >10 at all measurable sites, and no FDG-PET avidity without corresponding PSMA uptake. All men with PSMA-PET and FDG-PET at both baseline and post-treatment were included in this sub-study.

Study Treatment

All men received ^{177}LuPSMA-617 up to 6 doses at 6-week intervals with 3 dose escalated cohorts of NOX66. NOX66 was provided as a dose appropriate suppository taken from day 1-10 post each ^{177}LuPSMA-617 injection. All cohorts were administered 7.5 GBq of ^{177}LuPSMA-617 on day 1 via slow intravenous (IV) injection. The PSMA-617 precursor (AAA Novartis) was radiolabelled to no-carrier-added ^{177}lutetium chloride according to manufacturer's instructions. Quality control tests for radionuclide and

radiochemical purity were performed using high-pressure liquid chromatography and thin-layer chromatography. NOX66 suppositories were administered at 400mg, 800mg and 1200mg doses as per a dose escalation protocol (*11*).

Imaging Procedures and Acquisition

PSMA-PET and FDG-PET scans were performed at baseline (screening) and post-treatment (6 weeks after completing all 6 cycles or when treatment ceased earlier due to clinical progression). ^{68}Ga-HBEDD-CC PSMA-11 was produced on-site compliant with Good Laboratory Practice procedure using a TRASIS automated radio-pharmacy cassette. ^{18}F-FDG was produced off site commercially under good manufacturing practice-compliant conditions. Radio-pharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with 2.0 MBq/kg ^{68}GaPSMA-11 and 3.5 MBq/kg ^{18}F-FDG, with matched imaging parameters (dose, time post injection and imaging protocols) for each patient. All PET/CT imaging was undertaken using a Phillips Ingenuity TOF-PET/64 slice CT scanner. A non-contrast low dose CT scan was performed 60 minutes post tracer injection. Immediately after CT scanning, a whole-body PET scan was acquired for 2 minutes per bed position. The emission data were corrected for randoms, scatter, and decay.

Diagnostic contrast enhanced CT of the chest, abdomen, and pelvis, and a whole-body bone scan were performed at baseline and post-treatment.

Imaging Analysis

All PSMA and FDG PET/CT scans (screening and post-treatment) were analysed semi-quantitatively by a nuclear medicine physician using MIM Software and a standardised semi-automated workflow to delineate regions of interest with a minimum SUV cut-off of 3 for PSMA-PET and an SUV cut-off equal to blood pool mean intensity + 1.5 standard deviation for FDG-PET. All lesions identified quantitatively were manually reviewed and physiologic uptake or scatter removed. Whole body quantitation derived total metabolic tumour volume, SUVmax and SUVmean for both FDG-PET and PSMA-PET (MIM Software, Cleveland, USA) (*14*). A nuclear medicine physician undertook visual assessment of both the quantified and non-quantified PET images to identify potential sites of FDG-PET positive/PSMA-PET negative progressive disease between the screening and post-treatment scans.

Statistical Analyses

We measured PSA decline from baseline (absolute and ≥50% (PSA50)) at any time-point, PSA progression-free survival (PSA-PFS) as defined by PCWG3 criteria, radiographic progression defined by RECIST 1.1 and PCWG3 criteria and overall survival (OS) (*13,15*). Time-to-event endpoints (PSA-PFS and OS) were defined as the interval from the date of enrolment to the event date, or the date of last known to be event-free (at which point the observation was censored).

A two-sided exact binomial 95% confidence interval (CI) was calculated for PSA response rates. The Kaplan-Meier method was used to characterise time-to-event endpoints and estimate medians (presented with 95% CIs). We correlated changes in

PSMA-PET TTV, SUV max/mean and FDG-PET TTV, SUVmax/mean with time-to-event outcomes, using univariable and multivariable Cox proportional hazards regression models. P-values below 5% were considered significant. Analyses were performed using R (version 4.0.5) and SPSS (version 25).

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. 37/56 (66%) men on the LUPIN trial had both baseline screening and post-treatment imaging (6 weeks after completion of 6 cycles of treatment, or earlier if trial exit for clinical progression). Of these, 68% (25/37) had post-treatment imaging after completing all 6 cycles of ^{177}LuPSMA-617 + NOX66, 3% (1/37) after 5 cycles, 14% (5/37) after 4 cycles, 14% (5/37) after 3 cycles, and 3% (1/37) after 2 cycles. 19/56 (34%) did not have exit imaging due to being unwell (12/19), travel restrictions (3/19), and unknown reasons (3/19).

Clinical Outcomes

The median reduction in PSA was 77% (IQR 34-92%), and 70% (26/37) of patients had PSA response > 50%. With a median follow-up of 26 months, the median PSA-PFS was 8.6 months (95% CI 5.6 – 11.6) and median OS 22 months (95% CI 18.6-25.6).PSA or clinical progression had occurred in 54% (20/37) at the time of exit imaging, while 46% (17/37) had no PSA progression after the full 6 cycles of treatment. 92% (34/37) had conventional imaging (CT and bone scan) at exit. Radiographic progression at the time of exit imaging was identified in 18% (6/34). On univariable analysis, PSA progression

and radiographic progression at trial exit were also associated with significantly worse PFS and OS (Table 2).

PSMA-PET Quantitation

Quantitative PSMA-PET SUVmax and SUVmean were reduced in 95% of men independent of whether they had PSA progression at time of exit imaging (absolute change in PSMA SUVmax (median -26 IQR -40 to -13) and SUVmean (median -3, IQR -5 to -2)). There was no correlation between an increase in PSMA SUVmax with either PSA-PFS or OS (Table 2).

PSMA-TTV was increased in 32% (12/37). Any increase in PSMA-TTV was associated with shorter PSA-PFS (HR 2.9 (95%CI 1.4-6.1), p 0.01) and OS (median OS 12.2 vs 25.5 months, HR 6.2 (95% CI 2.0-19.2), p<0.01) (Figure 1). An increase in PSMA-TTV ≥30% was significantly associated with worse OS (HR 6.0 (1.9-19.2), p 0.002) while association with PSA-PFS was not significant **(**Figure 2**)**.

All 12 patients with increasing PSMA-TTV had an SUVmax > 15 at trial exit (above trial entry criteria), compared to 52% (13/25) of those with reduced PSMA-TTV.

FDG-PET Quantitation

Analysis of screening and post treatment FDG-PET demonstrated that 51% (18/35) had reduced FDG SUVmax (median absolute change 0.1, IQR -4 to +1) and 66% (23/35) had reduced FDG SUVmean (median absolute change -0.4, range -1 to +0.4) in response to treatment. An increase in FDG SUVmax was associated with

worse PSA-PFS (HR 3.0 (95%CI 1.4-6.4), p 0.01) and OS (HR 3.0 (95%CI 1.2-7.3), p 0.02).

FDG-TTV was reduced in 67% (22/35) at trial exit. Any increase in FDG-TTV was associated with worse PSA-PFS (HR 3.1 (95%CI 1.4-6.8), p 0.005) and OS (median OS 16.2 vs 23.1 months, HR 2.7 (95% CI 1.1-6.2) p 0.02). An increase in FDG-TTV ≥30% was significantly associated with worse PSA-PFS (HR 2.7 (95%CI 1.2-6.0) p 0.01) but not significantly associated with OS (Figure 2).

No FDG positive/PSMA negative progressive sites were identified in this cohort at the time of exit imaging. One patient had significant increase in FDG avid volume at one site, while PSMA tumor volume and SUVmax were reduced (Figure 3).

Molecular Response Patterns and Patient Outcomes

Multivariable analysis including change in PSMA-TTV, FDG-TTV, FDG SUVmax, as well as PSA progression and radiographic progression found that only PSMA-TTV and PSA progression remained independently prognostic of OS (HR 5.1 (95%CI 1.5-17.1), p 0.008 and HR 3.5 (95%CI 1.1-10.9), p 0.03 respectively) (Table 3).

DISCUSSION

This study has found that increasing TTV on post-treatment PSMA-PET identifies early disease progression and shorter OS independent of PSA, raising its potential for use as a prognostic biomarker. Metastatic castration-resistant prostate cancer is characterised by phenotypic and molecular heterogeneity with marked PSMA heterogeneity previously demonstrated at both an imaging and cellular level (*9,10*).

While the VISION and TheraP trials have found high treatment responses and improved quality of life parameters, duration of treatment responses with ^{177}LuPSMA-617 remain limited. Identifying effective predictive/prognostic biomarkers is critical to deepening and prolonging responses to PSMA targeted treatments with appropriate combinations and judicious treatment sequencing.

A second key finding in this study is that in contrast to FDG-PET, reduced PSMA SUVmax or SUVmean occurred in almost all patients in response to ^{177}LuPSMA-617 therapy and was not predictive of either treatment response or OS. This lack of correlation between change in PSMA SUVmax or SUVmean and treatment outcomes has been previously shown. Kurth et al found that PSMA intensity decreased in both clinically responding and progressing patients. (*7,16*). Grubmuller et al. also found no correlation between change in whole-body PSMA SUVmean and OS in an analysis of post treatment PSMA-PET following ^{177}LuPSMA-617 therapy. This lack of prognostic value of change in PSMA SUVmean with PSMA targeted therapy is not unexpected. ^{177}LuPSMA-617 preferentially targets highly PSMA expressing cells, leading to persistent populations of low PSMA expression disease that may be less responsive to treatment. The lack of predictive or prognostic value of change in PSMA SUVmean/max is important to highlight, as we intuitively use reduction in intensity (FDG-PET) to denote treatment response with systemic therapy (*17*). We need to think differently when developing PSMA-PET response criteria for PSMA targeted therapy.

Increasing PSMA-TTV was an independent predictor of PSA-PFS and OS in this study. Similar to Grubmuller et al and Gafita et al, we confirmed that an increase in quantitative PSMA-TTV is a poor prognostic factor for OS (*6,7*). An increase in PSMA-

TTV by ≥30% was associated with poor OS, supporting the inclusion of this metric in the PSMA PET Progression criteria (*18*). However, accurate assessment of change in TTV visually can be difficult, especially in high volume disease and quantitative PET analysis may become an important tool in PSMA targeted therapy.

We found that patients with an increase in PSMA-TTV at trial exit had a PSMA SUVmax >15, significantly higher than those patients without progressive disease, and above a range at which PSMA targeted therapy is expected to be effective. This may indicate that radiation resistance is an important mechanism of treatment failure. Further evaluation of this in conjunction with genetic analysis may help identify optimal treatment combinations in patients who currently have limited treatment response to ^{177}LuPSMA-617 alone.

FDG-PET was undertaken both at screening and trial exit, with FDG-PET screening parameters previously shown to be predictive of OS in this study cohort and other ^{177}LuPSMA-617 trials (*1,12,19*). Although we found an increase in FDG SUVmax and FDG-TTV was associated with poor OS in univariable analysis, they did not remain significant on multivariate analysis. Further, the incidence of discordant progressive lesions (FDG-PET positive/PSMA-PET negative) was low, with only one patient having a significant increase in FDG avid volume at one site, while PSMA-TTV was reduced.

RECIST criteria progression is standard of care for identifying progressive disease on imaging and has a strong correlation with OS in prostate cancer (*20*). However, RECIST progression was less prognostic than change in either PSMA-TTV or PSA progression at study exit. The promising prognostic value for molecular imaging parameters suggests that more work needs to be done validating PET for treatment

response in mCRPC, potentially as alternatives to CT and bone scan currently used in PCWG3 criteria.

This study has a number of limitations. Its small sample size makes it purely exploratory, and the findings will need to be validated in larger trials. The sample size also did not allow for a multivariable analysis incorporating other known prognostic factors.

Additionally, the patients in this analysis were biased towards those well enough to complete post-treatment imaging, explaining the higher PSA50 and longer OS in this subset of patients than previously published for the trial. The interval between screening and post-treatment imaging was variable, with 32% exiting the trial early due to clinical progression.

Finally, PET quantitation software remains of limited availability and time intensive to achieve accurate results. Further automation in quantitation is required to minimise the time required to derive reproducible results, in addition to harmonisation and validation of quantitative methods. Despite this, the prognostic value of quantified PSMA-TTV in this study suggest that investment in PET quantitation will yield significant clinical benefit.

CONCLUSION

Change in quantitative PSMA-TTV has strong potential as a prognostic biomarker with ^{177}LuPSMA-617 therapy, independent of FDG parameters, PSA or radiographic progression. Further research into the value of post treatment PET as imaging biomarkers is warranted.

FINANCIAL DISCLOSURES

The investigator-initiated study was sponsored by St Vincent's Hospital and was supported by a Cancer Institute NSW prostate translational research grant. Noxopharm Limited provided funding for drug and PET scans, AAA/Novartis provided PSMA-617 ligand.

LE -Advisory Role: Noxopharm. Trials support – Novartis, Astellas, grant funding support from St Vincent's Clinic Foundation

AMJ – Advisory Role: Noxopharm Limited. Institutional funding – Novartis.

PW, RN – salaried employees of MIM Software, Inc.

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KEY POINTS

Question: What are the imaging findings on PSMA and FDG PET following ^{177}LuPSMA-617 therapy, and do changes in tumour volume, SUVmax or SUVmean correlate with clinical outcomes?

Pertinent Findings: In this LuPIN sub-study, any increase in PSMA-TTV and PSA progression at study exit were independently prognostic of overall survival,

Implications for patient care: Change in tumour volume on PSMA PET following ^{177}LuPSMA-617 therapy provides information for clinicians on patient survival and may help clinical decisions in regard to timing and type of next treatments.

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FIGURES

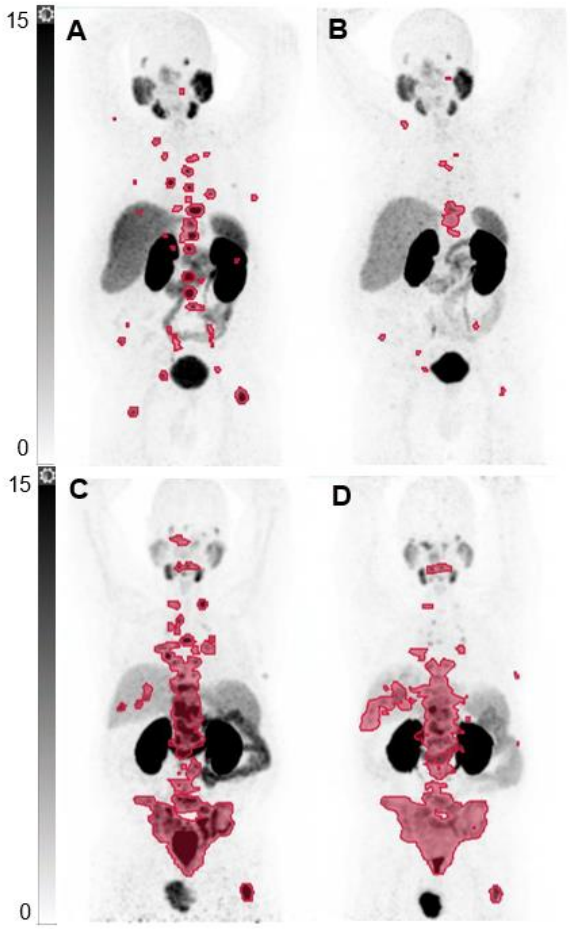


Figure 1. Quantitative analysis for a patient with reduced PSMA-TTV between baseline (A) and post-treatment (B). Quantitative analysis for a progressing patient at baseline (C) and post-treatment (D). In patients with high volume disease, it can be difficult to visually identify extent of volume change. In this second case, the volume increase is 25%.

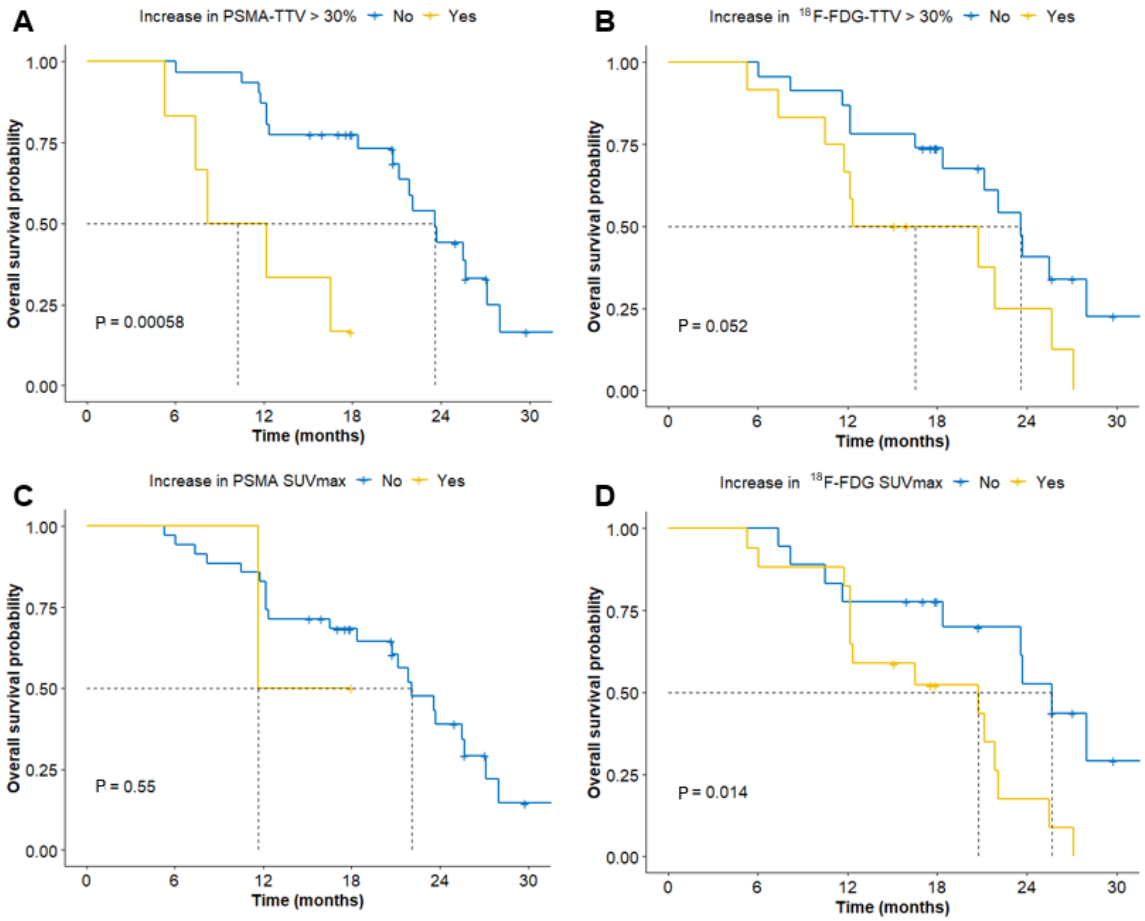


Figure 2. Kaplan-Meier curves for OS stratified by (A) Increase in PSMA-TTV ≥ 30% from baseline and (B) Increase in FDG-TTV ≥ 30% from baseline (C) Increase in PSMA SUVmax from baseline (D) Increase in FDG SUVmax from baseline.

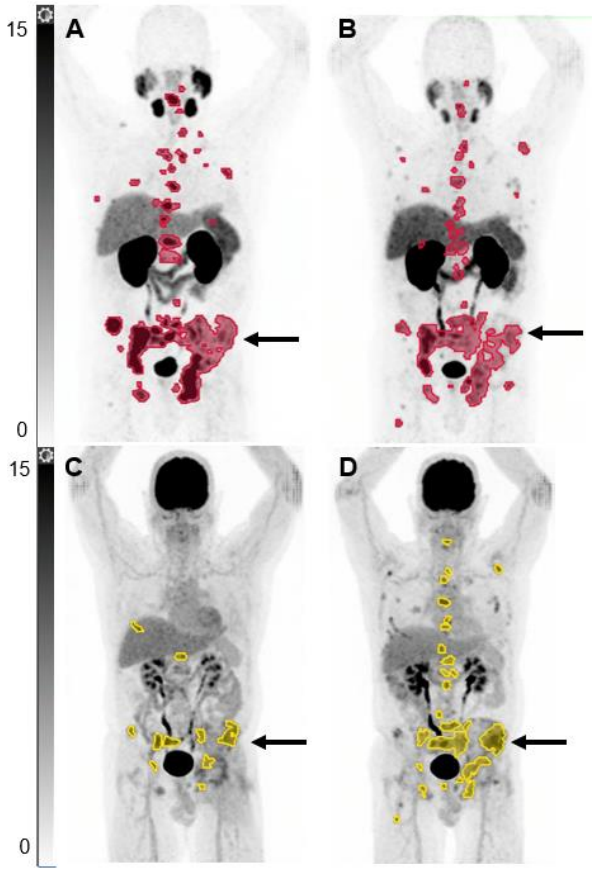


Figure 3. Quantitative analysis of baseline and post-treatment PSMA and FDG-PET from the same patient (A) baseline PSMA-PET (B) post-treatment PSMA-PET (C) baseline FDG-PET (D) post-treatment FDG-PET. Arrows indicate a lesion in iliac bone which reduced in volume and intensity on PSMA-PET, but increased in volume and intensity of FDG-PET.

TABLES

Patient Characteristics	Sub-study
Age (years)	68 (65-74)
ECOG	
0 or 1	32 (86)
2	5 (14)
PSA at screening (ug/L)	91 (41.3-380)
Haemoglobin (Normal Range 130-180 g/L)	122 (112-131)
Alkaline Phosphatase (NR 30-100 U/L)	124 (83-359)
Prior Systemic treatments	
LHRH agonist/antagonist	37 (100%)
Chemotherapy	37 (100%)
Docetaxel	37 (100%)
Cabazitaxel	34 (92%)
Androgen Signalling Inhibitor	37 (100%)
Cycles of ^{177}LuPSMA-617 administered	6 (4-6)
Exit diagnostic CT and bone scan	34 (92%)

Numbers are presented as absolute counts (percentage) or median (interquartile range).

Table 1. Patient characteristics.

Univariable analysis	**OS**	**PSA-PFS**
PSMA-TTV*	6.2 (2.0-19.2) [0.002]	2.9 (1.4-6.1) [0.01]
Increase in PSMA SUVmax †	1.9 (0.2-14.4) [0.56]	1.3 (0.3-5.6) [0.71]
FDG-TTV*	2.7 (1.1-6.2) [0.02]	3.1 (1.4-6.8) [0.005]
Increase in FDG SUVmax †	3.0 (1.2-7.3) [0.02]	3.0 (1.4-6.4) [0.01]
PSA progression †	5.8 (2.1-16.1) [<0.001]	5.0 (2.3-10.7) [<0.001]
Radiographic progression †	5.4 (1.8-16) [0.003]	4.4 (1.6-12) [0.004]

Hazard ratios are presented as HR (95%CI) [p value].
* increase in litres, continuous variable † at trial exit

Table 2. Univariable Cox regression analysis for association with PSA-PFS and OS.

TTV = total tumour volume

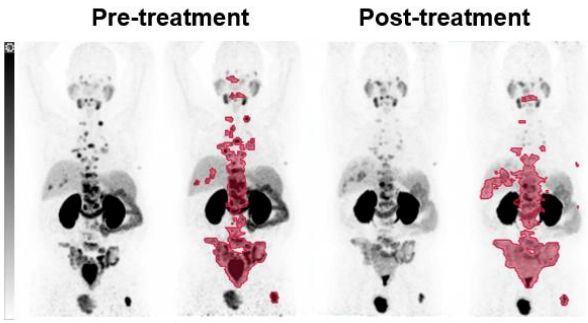
Variable	Hazard ratio
Increase in PSMA-TTV †	5.1 (1.5-17.1) [0.008]
Increase in FDG-TTV †	1.04 (0.4-2.9) [0.93]
Increase in FDG SUVmax †	1.3 (0.4-4.5) [0.67]
PSA progression†	3.5 (1.1-10.9) [0.03]
Radiographic progression†	1.8 (0.5-6.0) [0.36]

Hazard ratios are presented as HR (95%CI) [p value]. † at trial exit

Table 3. Multivariable Cox regression analysis for association of clinical and imaging parameters with OS. TTV = total tumour volume

GRAPHICAL ABSTRACT

Change in total tumor volume on serial quantitative PSMA PET is associated with overall survival with ^{177}Lu-PSMA-617 therapy



In patients with high volume disease, change in quantitative tumour volume can be difficult to assess visually.