Journal of Nuclear Medicine, published on July 29, 2021 as doi:10.2967/jnumed.121.262552

# $^{177}$Lutetium-PSMA-617 and idronoxil (NOX66) in men with end-stage metastatic castration-resistant prostate cancer (LuPIN): Patient outcomes and predictors of treatment response of a Phase I/II trial.

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Running title: Phase I/II trial Lu-PSMA-617 and NOX66

Keywords: Metastatic prostate cancer, theranostics, lutetium-PSMA

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Total word count: 5162

Figures: 4

Tables: 4

Financial support: This investigator-initiated study was sponsored by St Vincent's Hospital Sydney and 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.

**ABSTRACT**

Background: $^{177}$Lutetium PSMA-617 (Lu-PSMA-617) is an effective therapy for metastatic castrate-resistant prostate cancer (mCRPC). However, treatment resistance occurs frequently and combination therapies may improve outcomes. We report the final safety and efficacy results of a phase I/II study combining Lu-PSMA-617 with idronoxil (NOX66), a radiosensitiser, and examined potential clinical, blood-based and imaging biomarkers.

Methods: 56 men with progressive mCRPC previously treated with taxane chemotherapy and novel androgen signaling inhibitor (ASI) were enrolled. Patients received up to six doses of Lu-PSMA-617 (7.5Gbq) day 1 in combination with NOX66 suppository days 1-10 each 6-week cycle. Cohort 1 (n=8) received 400mg NOX66, cohort 2 (n=24) received 800mg and cohort 3 (n=24) received 1200mg. $^{68}$Ga-PSMA and FDG PET/CT were performed at study entry and semi-quantitative imaging analysis was undertaken. Blood samples were collected for blood-based biomarkers including androgen receptor splice variant 7 expression. The primary outcomes were safety and tolerability; secondary outcomes included efficacy, pain scores and xerostomia. Regression analyses were performed to explore the prognostic value of baseline clinical, blood-based and imaging parameters.

Results: 56/100 men screened were enrolled (56%) with a screen failure rate of 26% (26/100) for PET imaging criteria. All men had received prior treatment with ASI and docetaxel, and 95% (53/56) had received cabazitaxel. 96% (54/56) patients received ≥2 cycles of combination NOX66 and Lu-PSMA-617, and 46% (26/56) completed six cycles. Common adverse events were anaemia, fatigue and xerostomia. Anal irritation attributable to NOX66 occurred in 38%. 48/56 had a reduction in prostate-specific antigen (PSA) (86%, 95% CI 74-94), 34/56 (61%, 95% CI 47-74) had a PSA reduction ≥50% (PSA50). Median PSA progression-free survival was 7.5 months (95% CI 5.9-9) and median overall survival 19.7 months (95% CI 9.5-30). Higher PSMA $SUV_{mean}$ correlated with treatment response, while higher PSMA tumour volume and prior treatment with ASI for less than 12 months were associated with worse overall survival.

Conclusions: NOX66 with Lu-PSMA-617 is a safe and feasible therapeutic strategy in men treated 3$^{rd}$ line and beyond for mCRPC. PSMA $SUV_{mean}$, PSMA avid tumour volume and duration of treatment with ASI were independently associated with outcome.

## INTRODUCTION

Metastatic castrate-resistant prostate cancer (mCRPC) is a lethal disease and treatment options remain limited. $^{177}$Lutetium-prostate-specific membrane antigen-617 (Lu-PSMA-617) is a radio-ligand therapy that targets prostate specific membrane antigen (PSMA), a receptor highly expressed on prostate cancer cells (*1*). Lu-PSMA-617 has shown promising results in prospective single-centre studies, the phase II TheraP trial and phase III VISION trial (*2-5*). However, secondary treatment resistance hinders longer term outcomes for many men (*2, 3, 6*).

Combination therapies may overcome resistance mechanisms and improve clinical outcomes. Idronoxil (NOX66) is a derivative of the flavonoid genistein that binds to external NADH oxidase 2 (ENOX2), a tumor specific enzyme that induces apoptosis and inhibits topoisomerase II. It has shown potential as a radiation sensitizer in prostate cancer (*7-9*). We hypothesized that combining NOX66 with Lu-PSMA-617 may improve treatment responses with minimal increase in toxicity.

Improving treatment response with targeted radionuclide therapy involves optimizing treatment responses through effective combinations, but also improving patient selection. Quantitative parameters on $^{68}$Ga-HBEDD-PSMA-11 (PSMA) and $^{18}$F-fluorodeoxyglucose (FDG) PET/CT have shown potential as predictive and prognostic biomarkers for Lu-PSMA-617 therapy (*6, 10-13*). Duration of prior treatments and other markers of treatment resistance, such as androgen receptor splice variant 7 (AR-V7) may also have prognostic utility (*11, 14, 15*). We report results of a trial of combination NOX66 and Lu-PSMA-617. Additionally, we evaluate the predictive and prognostic potential of blood-based markers, clinical factors and molecular imaging.

## MATERIALS AND METHODS

### Study Design

This is a prospective single-center phase I/II dose escalation/expansion trial of combination Lu-PSMA-617 and NOX66. St Vincent's Hospital institutional review board approved the study protocol (HREC/17/SVH/19, ACTRN12618001073291) and all patients provided informed written consent.

### Screening

Men with mCRPC experiencing progression on conventional imaging (computed tomography [CT] and bone scan) and/or a rising PSA based on Prostate Cancer Working Group 3 criteria (*16*), previously treated with at least one line of taxane chemotherapy (docetaxel, cabazitaxel) and at least one androgen signalling inhibitor (ASI; abiraterone and/or enzalutamide) were screened. All patients had adequate organ function (baseline haemoglobin ≥100g/L, platelet count ≥100 $x10^9$/L, estimated glomerular filtration rate ≥40mL/min), estimated life expectancy > 12 weeks and World Health Organization Eastern Cooperative Oncology Group performance status (ECOG) ≤ 2.

Men underwent screening with FDG and PSMA PET/CT, bone scan and CT. Men were eligible if they had an $SUV_{max}$ > 15 on PSMA PET at ≥ 1 site, an $SUV_{max}$ > 10 at all measurable sites and no FDG avidity without corresponding PSMA uptake (Figure 1).

### Study Treatment

All men received up to six cycles of Lu-PSMA-617 at 6 weekly intervals in combination with one of three doses of NOX66 (400mg, 800mg, 1200mg). NOX66 was administered via suppository on days 1-10 post each Lu-PSMA-617 injection. All cohorts were administered 7.5 GBq of Lu-PSMA-617 day 1 via slow intravenous (IV) injection. In addition, participants in cohort

1 (n=8) received 400mg NOX66. Following interim safety data reviews, the dose of NOX66 was escalated to 800mg in cohort 2 (n=24) and 1200mg for cohort 3 (n=24).

The PSMA-617 precursor (AAA Novartis) was radiolabelled to no-carrier-added $^{177}$lutetium chloride according to manufacturer's instructions by a qualified radio-pharmacist or radiochemist. Quality control tests for radionuclidic and radiochemical purity were performed using high-pressure liquid chromatography and thin-layer chromatography. NOX66 (Noxopharm Limited) was commercially produced.

**Imaging Procedures and Analysis**

$^{68}$Ga-HBEDD-CC PSMA-11 was produced on-site compliant with Good Laboratory Practice procedure using a TRASIS automated radio-pharmacy cassette. $^{18}$FDG was produced off site commercially. Radio-pharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with 2.0MBq/kg PSMA and 3.5 mBq/kg FDG, with identical 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, a whole-body PET scan was acquired for 2 minutes per bed position.

PET/CT scans were analysed semi-quantitatively using MIM software and a standardised semiautomated workflow to delineate regions of interest with a minimum $SUV_{max}$ cut-off 3 for PSMA and blood pool intensity + 1.5SD for FDG (*17*). Quantitation derived total metabolic tumour volume, standardised uptake value ($SUV_{max}$, $SUV_{mean}$) and total lesional activity for both FDG and PSMA (MIM software, Cleveland, USA).

**Study Endpoints**

Safety and tolerability were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) every 2 weeks during each 6-week cycle

until 6 weeks following the final study treatment. To assess efficacy, we measured PSA decline from baseline (absolute and ≥50% (PSA50)) at any time-point, PSA progression-free survival (PFS), and overall survival (OS). 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). Patient reported outcomes were measured day 1 of each cycle and during follow-up using the University of Michigan Xerostomia-Related Quality of Life Scale (XeQoLS) (*18*) and the Brief Pain Inventory-short form (*19*). Pain palliation was defined as a reduction ≥30% in the worst pain intensity score over the last 24 hrs observed at two consecutive evaluations (*20*).

**Clinical, Blood-based and Molecular Analysis**

Clinical information regarding initial diagnosis, Gleason score, previous lines of therapy and prior treatment responses were collected. Blood was prospectively collected for biomarkers including hemoglobin, platelets, alkaline phosphatase, albumin and PSA. Whole blood samples were collected at baseline, prior to cycle 3 and prior to cycle 6 for analysis of potential molecular biomarkers including AR-V7. AR-V7 analysis was performed using the method described by To et al (*21*).

**Statistical Analyses**

The study sample size was calculated to characterize the toxicity profile of the combination, based on the expectation that an adverse event with a true 5% incidence would be detected with 70% probability in a sample of N=24, and detected with over 90% probability in sample of N=56. All patients that received ≥ 1 cycle of study treatment were included in the safety and efficacy analyses. P-values below 5% were considered significant but interpreted cautiously. 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

(PSA PFS, OS) and estimate medians (presented with 95% CIs). The three NOX66 dose levels were compared in terms of adverse events, PSA50 and OS.

Cox proportional hazards regression, and logistic regression, were used to identify prognostic factors for time-to-event (PSA PFS, OS), and binary endpoints (PSA50), respectively. The covariates investigated included baseline clinical, blood-based and imaging parameters including tumor volume and intensity scores ($SUV_{max}$ and $SUV_{mean}$). In the absence of compelling evidence of a dose-response effect on PSA50, the cohorts were grouped, and prognostic analyses were performed on the grouped cohort.

We used the relaxed Lasso regression method to identify covariates for inclusion in a multivariable model (*22*). These were fitted in a standard multivariable Cox regression model to obtain conventional hazard ratios, 95% CIs and p-values.

All patients with worst pain score ≥ 4 were included in the analysis and changes in score between baseline, pre-cycle 3 and end of treatment were compared. Scores from the XeQoLS questionnaire were compared between baseline, pre-cycle 3 and end of treatment. A two-tailed paired t-test was used to assess for a change in scores. Analyses were performed using R (version 4.0.5) and SPSS (version 25).

## RESULTS

### Baseline Patient Characteristics

One hundred men were screened, of whom, 56 (56%) were enrolled between November 2017-February 2020. 26% were ineligible based on PET imaging criteria (13% low PSMA intensity disease, 13% due to sites with FDG/PSMA mismatch). Remaining screen fails (18%) were from clinical deterioration (6%), concurrent illness (3%), low hemoglobin (7%), or personal reasons (2%). Baseline characteristics are summarized in Table 1. All patients had prior treatment with at least one ASI and taxane chemotherapy with 95% (53/56) having two lines of

taxane chemotherapy. 66% (37/56) had ≥ 20 PSMA avid metastases. 88% (49/56) of men had metastases in bone, 55% (31/56) in lymph nodes and 19% (11/56) visceral metastases.

Due to small numbers in each NOX66 dose cohort, with Lu-PSMA-617 as the key treatment, we combined the three patient cohorts to report outcomes and for exploratory analysis of biomarkers of response and survival. Analysis of the 3 dose escalation cohorts of NOX66 did not reveal any statistical differences in adverse events, PSA response rate, PSA PFS or OS.

**Safety and Tolerability**

Adverse events were predominantly grade 1 (149/188; 79%). The most common toxicities were anemia (50/56; 89%), fatigue (36/56; 64%), and xerostomia (33/56; 59%) (Table 2). Anal inflammation due to NOX66 suppository occurred in 38% (21/56) with 27% (15/56) requiring topical treatment for anal inflammation. The rate of grade 1 anal inflammation was higher in cohort 3 (46%) compared to cohort 1 and 2 (25% and 21% respectively). Two men in cohort 2 and one man in cohort 3 required dose reduction or omission of NOX66. Four cases of grade 3 anemia were reported. There were no other significant differences in toxicities across the three cohorts and no grade 4-5 adverse events or treatment-related deaths occurred.

**Treatment Duration**

Participants received a median of 5 (IQR 3-6) cycles of Lu-PSMA-617 and NOX66. 96% (54/56) received ≥ 2 cycles and 46% (26/56) completed all 6 cycles. Of the 30 participants that ceased treatment prior to completing six cycles, 2 participants ceased due to exceptional responses, the other patients ceased treatment for progressive disease (46%, n=26), withdrawal of consent (2%, n=1) and inability to continue the study due to COVID-19 travel restrictions (2%, n=1). One participant ceased NOX66 due to grade 2 anal inflammation but continued Lu-PSMA-617. No participant ceased LuPSMA-617 due to toxicity.

**Treatment Response**

At a median follow-up of 21.8 months, PSA50 occurred in 61% (34/56, 95% CI 47-74%), while any decline in PSA occurred in 86% (48/56, 95% CI 74-94%). The waterfall plot of best PSA responses at any time-point is shown in Figure 2. At the time of this analysis, 91% (51/56) of participants have had PSA progression and 66% (37/56) are deceased. The median PSA PFS was 7.5 months (95% CI 5.9-9.0) (Figure 3A), and median OS 19.7 months (95% CI 9.5-30.0) (Figure 3B).

**Quality of Life**

95% (53/56) men completed baseline Brief Pain Inventory-short form assessment. The mean worst pain score at baseline was 4.21 (range 0-10, SD 2.99). 56% (29/52) men recorded a worst pain score ≥ 4, and of these, 41% (12/29) experienced pain palliation at any time-point.

Baseline XeQoLS assessment was completed by 48/56 (86%) men at baseline, with serial results at cycle 3 (48/56) and cycle 6 (26/48). There was no significant difference in XeQoLS scores between baseline and cycle 3, but a statistically significant difference between baseline and cycle 6 (p=0.04). There were no differences in XeQoLS scores between the three dose levels.

**Potential Prognostic Factors**

We performed exploratory univariable analysis to identify potential markers of PSA50 and overall survival.

*Quantitative PET imaging markers.* Comparative screening imaging characteristics are detailed in Table 1**.** Higher tumour volume on PSMA PET was associated with lower likelihood of achieving PSA50 (OR 0.41 (0.19-0.87), p=0.02) and shorter OS (HR 2.18 (1.36-3.51), p=0.001). PSMA $SUV_{mean}$ was associated with increased likelihood of achieving PSA50 (OR1.57 (1.12-2.19), p=0.008). Higher FDG avid tumour volume at baseline was associated

with worse OS (HR 3.02 (1.04-8.79) p=0.04). The presence of visceral metastases was also associated with worse OS (HR 2.35 (1.06-5.20, p=0.04).

*Impact of prior treatments on outcome.* The most common treatment immediately prior to enrolment on the trial was cabazitaxel (70%, 39/56). Receiving either chemotherapy or ASI immediately prior to the trial did not predict treatment response or survival. Similarly, duration of chemotherapy treatment did not predict a response to therapy. However, duration of treatment with ASI for more than 12 months was significantly associated with improved OS (HR 0.45 (0.22-0.91), p=0.03).

*Blood based markers.* Higher baseline haemoglobin was associated with higher odds of PSA50 (OR 1.05 (1.01-1.10), p=0.03) and improved OS (HR 0.96 (0.93-0.99), p=0.004). Other known prognostic markers including baseline alkaline phosphatase, PSA and use of opioid analgesia did not correlate with outcome.

35 patients had ARV7 assessed prior to cycle 1, of these 9 (26%) were ARV7 positive. 2 patients remained positive at cycle 3, and 2 patients became positive while on treatment. A total of 11 patients had ARV7 detected at any time point. Presence of ARV7 at any time point was not significantly associated with treatment response or survival.

*Multivariable Analysis of Potential Prognostic Factors.* A higher PSMA mean intensity score ($SUV_{mean}$) and lower PSMA tumour volume remained predictive of PSA50 (OR 1.61 (1.12-3.32), p=0.01 and OR 0.42 (0.18-0.94), p=0.04 respectively), while PSMA tumour volume predicted worse overall survival (HR 2.19 (1.38-3.46), p=0.001 respectively) (Figure 4). The only clinical parameter predictive of survival, was treatment with ASI for more than 12 months (HR 0.42 (0.20-0.87), p=0.02). Baseline FDG tumour volume, presence of visceral disease and haemoglobin did not remain independently predictive of outcome (Table 3 and 4).

## Discussion

PSMA targeted radionuclide therapy is emerging as a new treatment paradigm in men with mCRPC. The randomised TheraP trial demonstrated significantly improved treatment response (PSA50), progression free survival and quality of life parameters for Lu-PSMA-617 compared to cabazitaxel chemotherapy in mCRPC. However, while results from TheraP are encouraging, progression free survival remains short, with a median of 5.1 months (CI 3.4-5.7) (*4*). We postulate that deepening and prolonging responses to Lu-PSMA-617 therapy for men with mCRPC may be possible by targeting intracellular resistance mechanisms to maximise treatment effect. This study reports the results of a dose escalation trial of Lu-PSMA-617 with a radiation sensitiser (NOX66) and evaluates potential predictive markers of response to PSMA targeted therapy.

Treatment response rates to the Lu-PSMA-617 and NOX66 combination were high with a 61% PSA50 even though a majority of men in this trial had high volume disease, baseline anaemia, high baseline opiate requirements and 95% having undergone two lines of taxane therapy. Despite these high-risk features, the treatment response rate is in line with previous prospective single centre trials and the TheraP study (range 36-66%) (*2-4*). Further, PFS and OS were longer than those reported in previous studies with Lu-PSMA-617 and longer than those reported using alternative treatments post taxane chemotherapy (*3, 23*). These results are encouraging for men with ASI and taxane refractory mCRPC, but a randomised trial possibly with less stringent imaging enrolment criteria will be required to determine if this is due to the novel treatment combination, or patient selection.

NOX66 was included in the trial as a potential tumour specific radiation sensitiser that binds to external NADH oxidase 2 (ENOX2), a tumor specific enzyme inducing apoptosis and inhibiting topoisomerase II and demonstrating radiation sensitization in preclinical models (*7*).

We did not find an association between increasing dose of NOX66 and PSA50 or OS. However, the role of NOX66 in the study was as a radiation sensitiser, rather than a direct therapy effect, and it may be that either the lower dose of NOX66 was sufficient to induce radiation sensitivity, or the impact of NOX66 was limited. Safety of combination therapy with Lu-PSMA-617 and NOX66 has been previously reported for the first 2 cohorts of the LuPIN trial and is confirmed in this study (*24*).

Predictors of treatment response are important to further improve PSMA targeted therapy. Men were screened for this study with molecular imaging, with a requirement for an $SUV_{max}$ ≥15 on PSMA PET and no sites of FDG/PSMA PET mismatch. $SUV_{max}$ ≥15 has been previously reported to stratify men into responders and non-responders for Lu-PSMA-617 therapy (*2*). Hence it is not surprising that PSMA $SUV_{max}$ was not predictive of a treatment response in this study. However, PSMA $SUV_{mean}$ was an independent predictor of treatment response in this study, and previously (*10*). A relationship between higher $SUV_{mean}$ and improved clinical outcomes is biologically plausible. Intra- and inter-lesional heterogeneity of PSMA is common in mCRPC, and high heterogeneity of expression is likely to impact treatment response (*25*). $SUV_{mean}$ is likely a better indicator of lesional heterogeneity than $SUV_{max}$. Further, dosimetry studies have shown that $SUV_{mean}$ correlates with mean absorbed radiation dose and treatment response (*13*). While $SUV_{mean}$ requires quantitative analysis, its repeated association with treatment response suggests it may have a future role as a predictive biomarker for PSMA targeted radionuclide therapy.

PSMA tumour volume at baseline was the strongest independent predictor of treatment response and was also prognostic for overall survival. FDG tumour volume was also prognostic, but not independent of other variables. Essentially, men with higher tumour volumes responded poorly to treatment. This agrees with retrospective analyses of men undergoing Lu-PSMA-617

therapy (*12, 26*). It raises questions around timing of PSMA targeted therapy in men with mCRPC, suggesting that earlier referral for treatment upon prior treatment failure may both improve treatment responses and prolong survival.

Duration of response to prior therapies may help predict treatment response to PSMA targeted agents and overall survival. We found that men with shorter duration of response to ASI (<12 months) had worse overall survival, though it did not impact depth of treatment response. By contrast, duration of response to chemotherapy, or whether the patient received chemotherapy or ASI immediately prior to the trial, was not predictive of either survival or response.

This study enrolled a population of heavily pre-treated men with mCRPC, therefore the prognostic markers identified may not be generalisable to other stages of prostate cancer. Larger studies are needed to validate the prognostic markers identified in this study.

## CONCLUSION

Lu-PSMA-617 in combination with NOX66 is a safe treatment for heavily pre-treated men with mCRPC with encouraging results that warrant further evaluation. PSMA $SUV_{mean}$ and tumor volume merit further investigation as imaging markers of treatment response and survival.

## ACKNOWLEDGMENTS

We thank the patients, and the clinical trials teams at the Department of Theranostics and Nuclear Medicine and the Kinghorn Cancer Centre, St Vincent's Hospital for their support.

## 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.

EMK – Honoraria from Janssen, Ipsen, Astellas Pharma. Research Review, Consulting or Advisory Role: Astellas Pharma, Janssen, Ipsen. Research Funding: Astellas Pharma, AstraZeneca.

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

LE -Advisory Role: Noxopharm Limited. Trials support – Novartis, Astellas.

No other authors have declared any conflicts of interest.

## KEY POINTS

**Question:** Is combination therapy with Lu-PSMA-617 and NOX66 feasible and safe?

**Pertinent Findings:** This phase I/II dose escalation and expansion study found that the combination is feasible and potentially efficacious. Evaluation of clinical, blood-based and quantitative imaging markers identified PSMA $SUV_{mean}$, tumor volume and duration of prior treatment with androgen signaling inhibitor as potential prognostic markers.

**Implications for patient care:** Further randomized studies combining Lu-PSMA-617 and NOX66 are needed. Quantitative imaging markers correlate with treatment response and survival and should be explored further.

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**FIGURES**

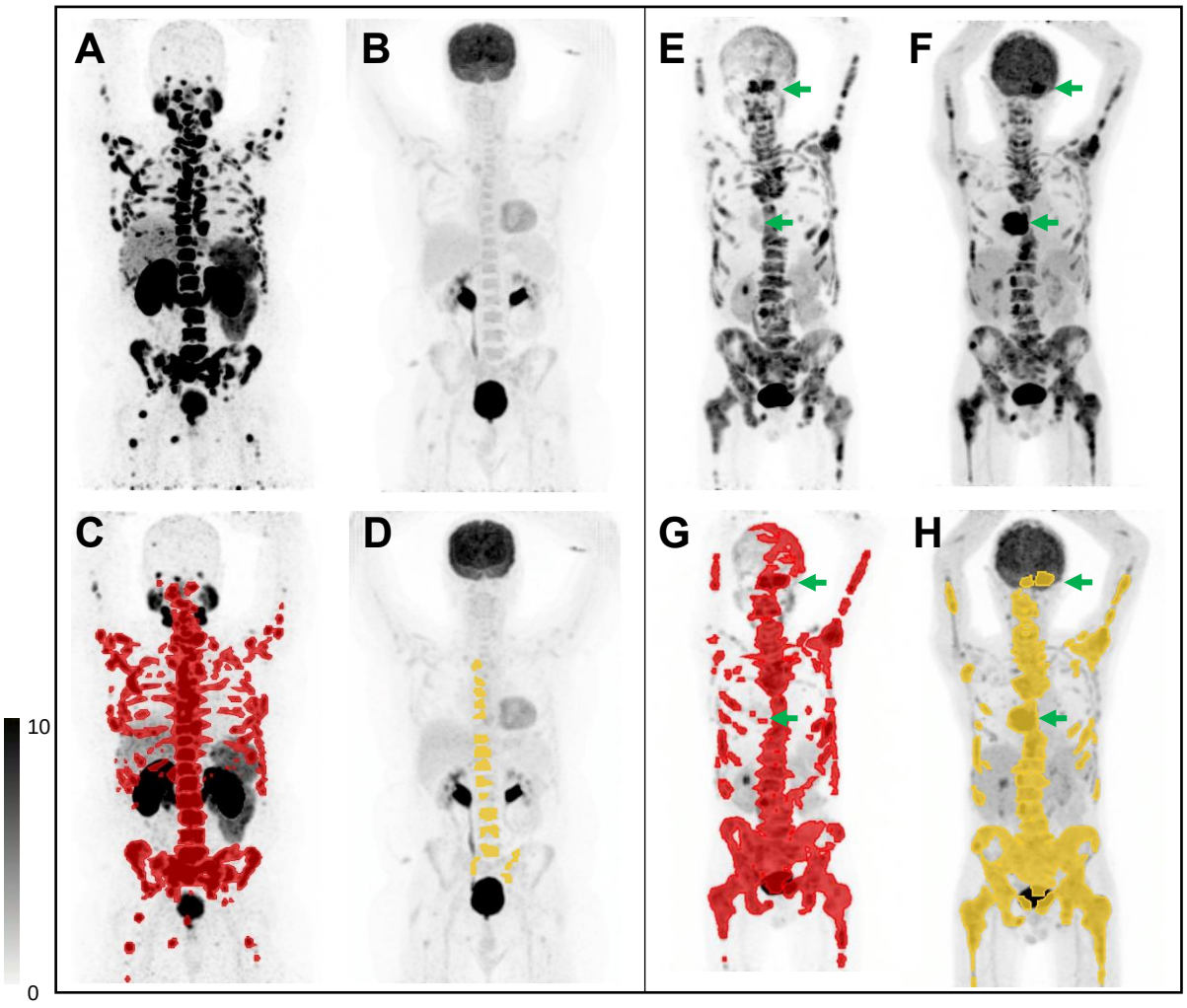


Figure 1. Left: This patient was eligible based on imaging with PSMA avid disease (A), and no sites of discordant FDG (B). Quantitative PSMA tumour volume (C) and FDG tumour volume (D) are shown. Right: This patient was ineligible on imaging with two sites indicated by green arrows with higher FDG avidity (F) than PSMA (E). Quantitative PSMA tumour volume (G) and FDG tumour volume (H) for this patient are shown.

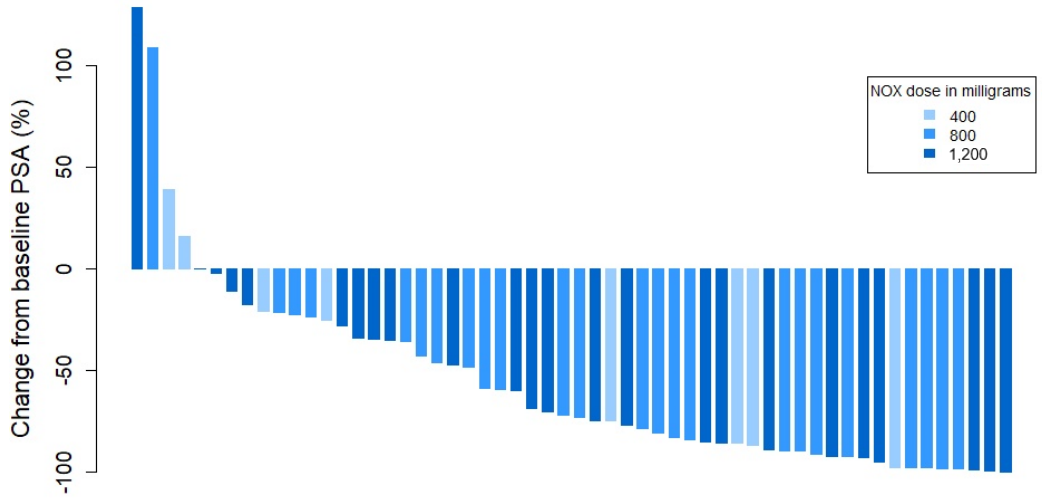


Figure 2. Waterfall plot of best PSA responses at any timepoint in maximum percentage change from baseline.

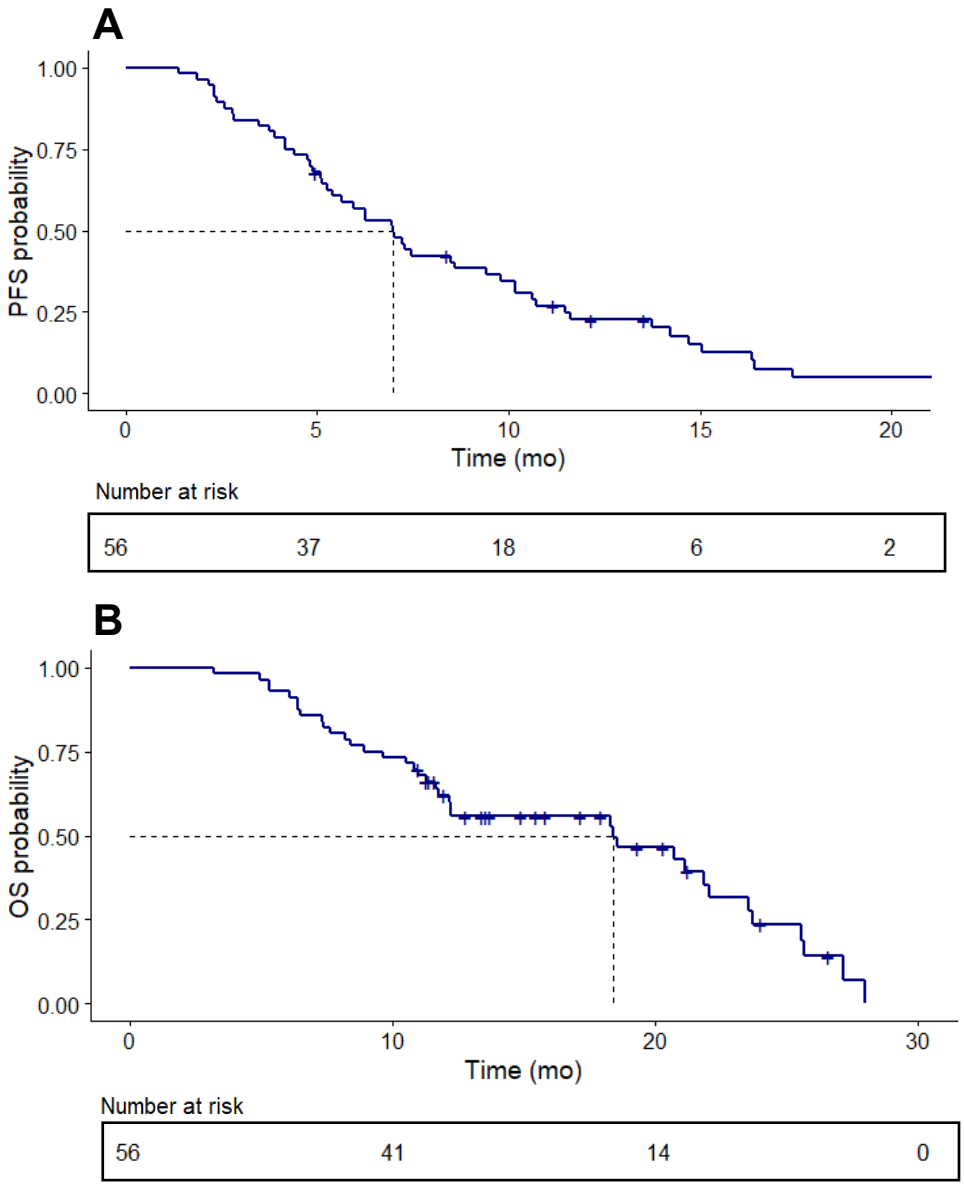


Figure 3. Kaplan-Meier curves for A: PSA Progression free survival, and B: Overall survival

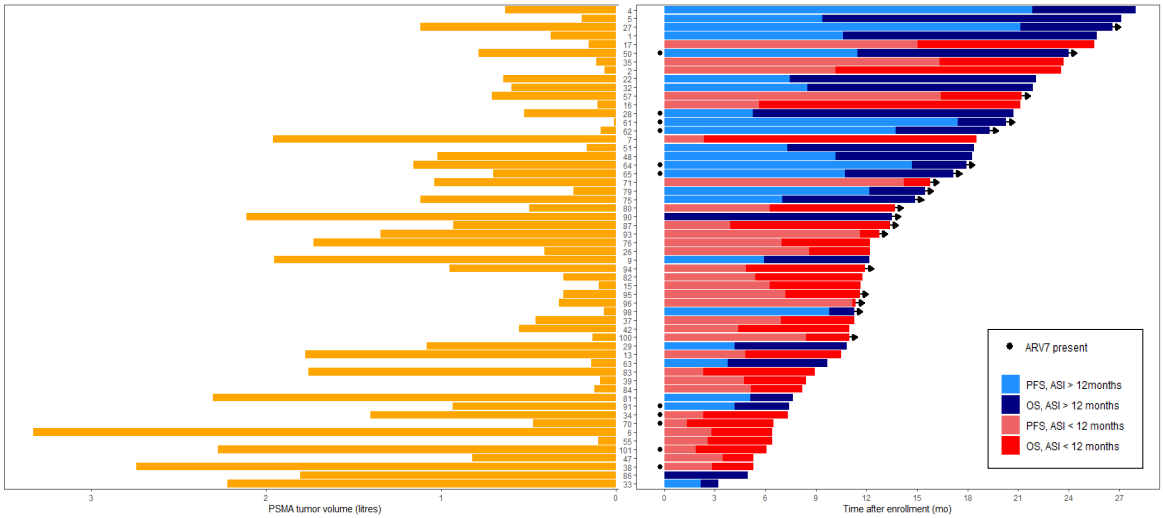


Figure 4. Graphical representation of important markers of overall survival. Right: The swimmer plot shows individual patient progression free and overall survival. Patients treated with ASI > 12 months are shown in blue, patients treated with ASI < 12 months are in red. Patients with ARV7 detected during the study are represented with an asterisk. Left: The graph shows the corresponding baseline tumour volume for each patient.

| Characteristic | N=56 |
|---|---|
| Age (years) | 69 (64-74) |
| **ECOG** | |
| 0 or 1 | 49 (88) |
| 2 | 7 (12) |
| PSA at C1 (ug/L) | 115 (46-476) |
| Haemoglobin (Normal Range 130-180 g/L) | 122 (110-131) |
| Alkaline Phosphatase (NR 30-100 U/L) | 113 (86-231) |
| Albumin (NR 36-52 g/L) | 38 (34-41) |
| De novo metastatic disease | 29 (52) |
| **Gleason Score** | |
| ≤ 7 | 9 (16) |
| 8-10 | 35 (63) |
| Unknown/Not Available | 12 (21) |
| **Prior Systemic treatments** | |
| LHRH agonist/antagonist | 56 (100) |
| Chemotherapy | 56 (100) |
| Docetaxel | 56 (100) |
| Cabazitaxel | 53 (91) |
| Other chemotherapy | 5 (9) |
| Androgen Signalling Inhibitor (ASI) | 56 (100) |
| Enzalutamide only | 27 (48) |
| Abiraterone only | 13 (23) |
| Abiraterone + Enzalutamide | 16 (29) |
| Clinical trial medication | 4 (7) |
| **PSMA PET** | |
| $SUV_{mean}$ | 8 (7-10) |
| $SUV_{max}$ | 39 (29-61) |
| Volume in litres | 0.64 (0.19-1.21-1206) |
| **FDG PET** | |
| $SUV_{mean}$ | 4(3-5) |
| $SUV_{max}$ | 8 (5-10) |
| Volume in litres | 0.07 (0.02-0.31) |
| **Disease Volume** | |
| < 20 metastases | 19 (33) |
| ≥ 20 metastases | 37 (66) |
| **Sites of Disease on PSMA PET** | |
| Bone | 49 (88) |
| Lymph Node | 31 (55) |
| Visceral | 12 (21) |

Table 1. Patient Characteristics. Numbers are presented as absolute counts (percentage) or median (interquartile range).

| Adverse event | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | All Grades (%) |
|---|---|---|---|---|
| Anemia | 31 (55) | 16 (29) | 4 (7) | 51 (91) |
| Xerostomia | 30 (54) | 3 (5) | 0 (0) | 33 (59) |
| Fatigue | 27 (48) | 8 (14) | 0 (0) | 35 (63) |
| Anal Inflammation | 18 (32) | 3 (5) | 0 (0) | 21 (38) |
| Nausea | 15 (27) | 0 (0) | 0 (0) | 15 (27) |
| Thrombocytopenia | 12 (21) | 3 (5) | 0 (0) | 15 (27) |
| Constipation | 11 (20) | 1 (2) | 0 (0) | 12 (21) |
| Neutropaenia | 5 (9) | 0 (0) | 0 (0) | 5 (9) |
| Pneumonitis* | 0 (0) | 1 (3) | 0 (0) | 1 (3) |

Table 2. Summary of common and therapeutically relevant adverse events (n=56).

| Variable | LASSO Odds ratio | Multivariable logistic regression Odds ratio (95% CI) [p-value] | Backward elimination model Odds ratio (95% CI) [p-value] |
|---|---|---|---|
| PSMA TV | 0.73 | 0.47 (0.20-1.09) [0.08] | 0.42 (0.18-0.94) [0.04] |
| PSMA $SUV_{mean}$ | 1.20 | 1.61 (1.10-2.34) [0.01] | 1.61 (1.12-2.32) [0.01] |
| Haemoglobin | 1.02 | 1.04 (0.99-1.10) [0.12] | NA |

Table 3. Final multivariable model for the association of baseline markers with PSA response ≥ 50% (PSA50)

| Variable | LASSO Hazard ratio | Multivariable Cox regression Hazard ratio (95% CI) [p-value] | Backward elimination model Hazard ratio (95% CI) [p-value] |
|---|---|---|---|
| PSMA TV | 1.67 | 2.05 (1.19-3.53) [0.009] | 2.19 (1.381-3.463) [0.001] |
| ASI > 12 months | 0.70 | 0.56 (0.24-1.31) [0.56] | 0.42 (0.202-0.869) [0.02] |
| FDG tumour volume (litres) | NA | 0.99 (0.25-3.98) [0.99] | NA |
| Haemoglobin | 0.99 | 0.98 (0.95-1.02) [0.30] | NA |
| Presence of visceral disease | 1.499 | 2.01 (0.89-4.53) [0.09] | NA |

Table 4. Final multivariable model for the association of baseline markers with overall survival

## GRAPHICAL ABSTRACT

**Final results of a phase I/II trial of the combination of 177Lutetium PSMA 617 and Idronoxil (NOX66)**