The Prognostic Value of Posttreatment ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT in Metastatic Castration-Resistant Prostate Cancer Treated with ^{177}Lu-PSMA-617 and NOX66 in a Phase I/II Trial (LuPIN)

Sarennya Pathmanandavel[1–3], Megan Crumbaker[2–4], Andrew Nguyen[1,4], Andrew O. Yam[2–4], Peter Wilson[5], Remy Niman[5], Maria Ayers[1], Shikha Sharma[1], Peter Eu[6], Andrew J. Martin[7], Martin R. Stockler[7], Anthony M. Joshua[2–4,8], and Louise Emmett[1,3,4,8]

[1]*Department of Theranostics and Nuclear Medicine, St. Vincent's Hospital, Sydney, New South Wales, Australia;* [2]*Kinghorn Cancer Centre, St. Vincent's Hospital, Sydney, New South Wales, Australia;* [3]*Garvan Institute of Medical Research, Sydney, New South Wales, Australia;* [4]*St. Vincent's Clinical School, University of New South Wales, Sydney, New South Wales, Australia;* [5]*MIM Software, Inc., Cleveland, Ohio;* [6]*Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [7]*NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia; and* [8]*Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia*

^{177}Lu-PSMA-617 therapy has shown high prostate-specific antigen (PSA) response rates in men with metastatic castration-resistant prostate cancer. However, early treatment resistance is common. This LuPIN substudy aimed to determine the prognostic value of posttreatment quantitative PET for PSA progression-free survival (PFS) and overall survival (OS) with ^{177}Lu-PSMA-617 therapy. **Methods:** Fifty-six men with progressive metastatic castration-resistant prostate cancer were enrolled in the LuPIN trial and received up to 6 doses of ^{177}Lu-PSMA-617 and a radiation sensitizer (NOX66). ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT, diagnostic CT, and bone scanning were performed at study entry and exit. Quantitative analysis tracked change in total tumor volume (TTV) and SUV. Univariable and multivariable analyses were conducted to examine the association of change in TTV (continuous and >30%), SUV_{max}, PSA, and radiographic progression with PSA PFS and OS. **Results:** All men (37/56) who underwent both screening and posttreatment molecular imaging were analyzed; 70% (26/37) had a PSA response of more than 50%. Median PSA PFS was 8.6 mo, and median OS was 22 mo. Clinical progression had occurred at trial exit in 54% (20/37). In response to treatment, a reduced PSMA SUV_{max} was demonstrated in 95% (35/37) and a reduced PSMA TTV in 68% (25/37). An increase in PSMA TTV by at least 30% was associated with worse OS (median, 10.2 vs. 23.6 mo; $P = 0.002$). Change in PSMA SUV_{max} was not associated with PSA PFS or OS. ^{18}F-FDG SUV_{max} was reduced in 51% (18/35) and ^{18}F-FDG TTV in 67% (22/35). An increased ^{18}F-FDG SUV_{max} was associated with worse OS (median, 20.7 vs. 25.7 mo; $P < 0.01$). An ^{18}F-FDG TTV increase by more than 30% was associated with a short PSA PFS (median, 3.5 vs. 8.6 mo; $P < 0.001$) but not OS. Both PSA and radiographic progression were associated with shorter OS (median, 14.5 vs. 25.7 mo [$P < 0.001$] and 12.2 vs. 23.6 mo [$P = 0.002$]). On multivariable analysis, only increased PSMA TTV and PSA progression remained independently prognostic of OS (hazard ratio, 5.1 [95% CI, 1.5–17.1; $P = 0.008$] and 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}Lu-PSMA-617 therapy, independent of ^{18}F-FDG PET parameters, PSA, or radiographic progression. Further research into the value of posttreatment PET as an imaging biomarker is warranted.

Key Words: metastatic prostate cancer; theranostics; lutetium-PSMA; prognosis; therapy response

J Nucl Med 2023; 64:69–74
DOI: 10.2967/jnumed.122.264104

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

In this study, we aimed to determine whether changes in total tumor volume (TTV) and SUV on both ^{68}Ga-PSMA PET and ^{18}F-FDG PET correlate with clinical outcomes in a prospective trial of treatment with ^{177}Lu-PSMA-617.

MATERIALS AND METHODS

This was an imaging substudy of the LuPIN trial. The LuPIN trial is a prospective single center, phase I/II dose escalation and expansion trial of combining ^{177}Lu-PSMA-617 with NOX66. The study enrolled men with

Received Mar. 5, 2022; revision accepted Jun. 13, 2022.
For correspondence or reprints, contact Sarennya Pathmanandavel (sarennya@gmail.com).
Published online Jun. 23, 2022.

metastatic castration-resistant prostate cancer previously treated with both at least 1 line of taxane chemotherapy and 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 written informed consent.

Screening

Men with progressive metastatic castration-resistant prostate cancer, based on either conventional imaging (CT and bone scanning) or a rising serum concentration of PSA based on Prostate Cancer Working Group 3 criteria (*13*), were eligible for screening. The men underwent screening with ^{18}F-FDG PET and ^{68}Ga-PSMA PET, bone scanning, and CT of the chest, abdomen, and pelvis. Patients were eligible if they had an SUV_{max} of more than 15 on ^{68}Ga-PSMA PET at 1 or more sites, an SUV_{max} of more than 10 at all measurable sites, and no ^{18}F-FDG PET avidity without corresponding PSMA uptake. All men with ^{68}Ga-PSMA PET and ^{18}F-FDG PET at both baseline and after treatment were included in this substudy.

Study Treatment

All men received up to 6 doses of ^{177}Lu-PSMA-617 at 6-wk intervals, with 3 dose-escalated cohorts of NOX66. NOX66 was provided as a dose-appropriate suppository taken from days 1 to 10 after each ^{177}Lu-PSMA-617 injection. All cohorts were administered 7.5 GBq of ^{177}Lu-PSMA-617 on day 1 via a slow intravenous injection. The PSMA-617 precursor (AAA Novartis) was radiolabeled to no-carrier-added ^{177}Lu-chloride according to the 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 400-, 800-, and 1,200-mg doses per a dose escalation protocol (*11*).

Imaging Procedures and Acquisition

^{68}Ga-PSMA PET and ^{18}F-FDG PET were performed at baseline (screening) and after treatment (6 wk after completing all 6 cycles or when treatment ceased earlier because of clinical progression). ^{68}Ga-HBEDD-CC PSMA-11 was produced on-site in a manner compliant with good-laboratory-practice procedures using a TRASIS automated radiopharmacy cassette. ^{18}F-FDG was produced off-site commercially under good-manufacturing-practice–compliant conditions. Radiopharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with a 2.0 MBq/kg dose of ^{68}GaPSMA-11 and a 3.5 MBq/kg dose of ^{18}F-FDG, with matched imaging parameters (dose, time after injection, and imaging protocols) for each patient. All PET/CT imaging was undertaken using a Phillips Ingenuity time-of-flight PET/64-slice CT scanner. An unenhanced low-dose CT scan was performed 60 min after tracer injection. Immediately after CT scanning, a whole-body PET scan was acquired for 2 min 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 after treatment.

Imaging Analysis

All ^{68}Ga-PSMA and ^{18}F-FDG PET scans (screening and after treatment) were analyzed semiquantitatively by a nuclear medicine physician using MIM Software and a standardized semiautomated workflow to delineate regions of interest with a minimum SUV cutoff of 3 for ^{68}Ga-PSMA PET and an SUV cutoff equal to the blood pool mean intensity plus 1.5 SDs for ^{18}F-FDG PET. All lesions identified quantitatively were manually reviewed and physiologic uptake or scatter removed. Whole-body quantitation derived total metabolic tumor volume, SUV_{max}, and SUV_{mean} for both ^{18}F-FDG PET and ^{68}Ga-PSMA PET (MIM Software) (*14*). A nuclear medicine physician visually assessed both the quantified and the nonquantified PET images to identify potential sites of ^{18}F-FDG PET–positive/^{68}Ga-PSMA PET–negative progressive disease between the screening and posttreatment scans.

Statistical Analyses

We measured PSA declines from baseline (absolute and ≥50%) at any time point, PSA PFS as defined by Prostate Cancer Working Group 3 criteria, radiographic progression defined by RECIST 1.1 and Prostate Cancer Working Group 3 criteria, and 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 last known to be event-free (at which point the observation was censored).

A 2-sided exact binomial 95% CI was calculated for PSA response rates. The Kaplan–Meier method was used to characterize time-to-event endpoints and estimate medians (presented with 95% CIs). We correlated changes in TTV, SUV_{max}, and SUV_{mean} for ^{68}Ga-PSMA PET and ^{18}F-FDG PET 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. Thirty-seven of 56 (66%) men on the LuPIN trial had both baseline screening and posttreatment imaging (6 wk after completion of 6 cycles of treatment, or earlier if the trial was exited because of clinical progression). Of these, 68% (25/37) had posttreatment imaging after completing all 6 cycles of ^{177}Lu-PSMA-617 plus NOX66, 3% (1/37) after 5 cycles, 14% (5/37) after 4 cycles, 14% (5/37) after 3 cycles, and 3% (1/37)

TABLE 1
Patient Characteristics

Characteristic	Substudy data
Age (y)	68 (65–74)
Eastern Cooperative Oncology Group performance status	
0 or 1	32 (86%)
2	5 (14%)
PSA at screening (μg/L)	91 (41.3–380)
Hemoglobin (reference range, 130–180 g/L)	122 (112–131)
Alkaline phosphatase (reference range, 30–100 U/L)	124 (83–359)
Prior systemic treatments	
Luteinizing hormone-releasing hormone agonist/antagonist	37 (100%)
Chemotherapy	37 (100%)
Docetaxel	37 (100%)
Cabazitaxel	34 (92%)
Androgen signaling inhibitor	37 (100%)
Cycles of ^{177}Lu-PSMA-617 administered	6 (4–6)
Exit diagnostic CT and bone scan	34 (92%)

Qualitative data are absolute counts and percentage; continuous data are median and interquartile range.

TABLE 2
Univariable Cox Regression Analysis for Association with PSA PFS and OS

	OS			PSA PFS		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Increase in PSMA TTV (L)	6.2	2.0–19.2	0.002	2.9	1.4–6.1	0.01
Increase in PSMA SUV_{max} at trial exit	1.9	0.2–14.4	0.56	1.3	0.3–5.6	0.71
Increase in ^{18}F-FDG TTV (L)	2.7	1.1–6.2	0.02	3.1	1.4–6.8	0.005
Increase in ^{18}F-FDG SUV_{max} at trial exit	3.0	1.2–7.3	0.02	3.0	1.4–6.4	0.01
PSA progression at trial exit	5.8	2.1–16.1	<0.001	5.0	2.3–10.7	<0.001
Radiographic progression at trial exit	5.4	1.8–16	0.003	4.4	1.6–12	0.004

after 2 cycles. Nineteen of 56 (34%) did not have exit imaging because of illness (12/19), travel restrictions (3/19), or unknown reasons (3/19).

Clinical Outcomes

The median reduction in PSA was 77% (interquartile range, 34%–92%), and 70% (26/37) of patients had a PSA response of more than 50%. With a median follow-up of 26 mo, the median PSA PFS was 8.6 mo (95% CI, 5.6–11.6) and the median OS was 22 mo (95% CI, 18.6–25.6). PSA or clinical progression had occurred in 54% (20/37) at the time of exit imaging, whereas 46% (17/37) had no PSA progression after the full 6 cycles of treatment. At exit, 92% (34/37) had conventional imaging (CT and bone scanning). 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 PSA PFS and OS (Table 2).

^{68}Ga-PSMA PET Quantitation

Quantitative ^{68}Ga-PSMA PET SUV_{max} and SUV_{mean} were reduced in 95% of men independently of whether they had PSA progression at the time of exit imaging (absolute change in PSMA SUV_{max}: median, −26 [interquartile range, −40 to −13]; absolute change in PSMA SUV_{mean}: median, −3 [interquartile range, −5 to −2]). There was no correlation between an increase in PSMA SUV_{max} and either PSA PFS or OS (Table 2).

The median change in PSMA TTV was −0.64 liters (interquartile range, −0.29 to +0.07). PSMA TTV was increased in 32% (12/37). Any increase in PSMA TTV was associated with shorter PSA PFS (hazard ratio [HR], 2.9 [95% CI, 1.4–6.1]; $P = 0.01$) and OS (median, 12.2 vs. 25.5 mo; HR, 6.2 [95% CI, 2.0–19.2]; $P < 0.01$) (Fig. 1). An increase in PSMA TTV by at least 30% was significantly associated with worse OS (HR, 6.0 [95% CI, 1.9–19.2]; $P = 0.002$), whereas association with PSA PFS was not significant (Fig. 2).

All 12 patients with an increasing PSMA TTV had an SUV_{max} of more than 15 at trial exit (above trial entry criteria), compared with 52% (13/25) of those with a reduced PSMA TTV.

^{18}F-FDG PET Quantitation

Analysis of screening and posttreatment ^{18}F-FDG PET demonstrated that 51% (18/35) had a reduced ^{18}F-FDG SUV_{max} (median absolute change, 0.1; interquartile range, −4 to +1) and that 66% (23/35) had a reduced ^{18}F-FDG SUV_{mean} (median absolute change, −0.4; interquartile range, −1 to +0.4) in response to treatment. An increase in ^{18}F-FDG SUV_{max} 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]; $P = 0.02$).

The median change in ^{18}F-FDG TTV was −0.01 liters (interquartile range, −0.05 to +0.02). ^{18}F-FDG TTV was increased in

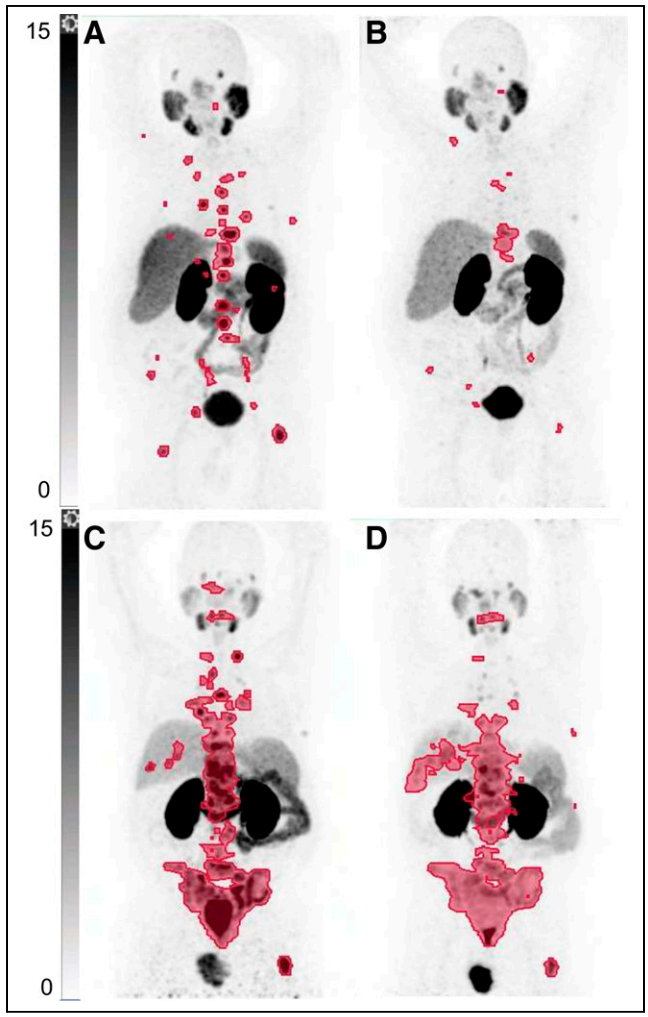

FIGURE 1. (A and B) Quantitative analysis for patient with reduced PSMA TTV between baseline (A) and after treatment (B). (C and D) Quantitative analysis for progressing patient at baseline (C) and after treatment (D). In patients with high-volume disease, it can be difficult to visually identify extent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

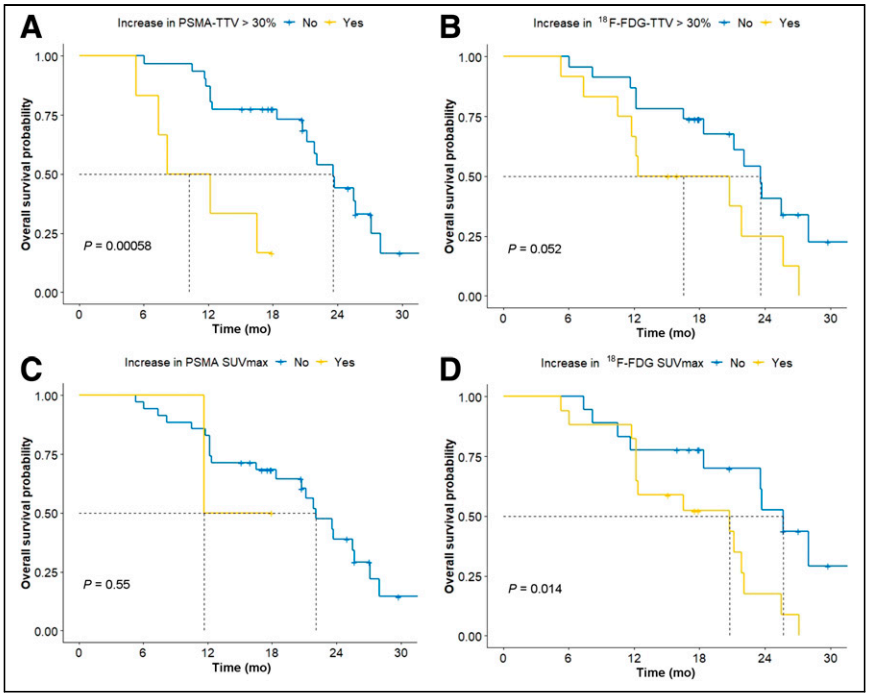

FIGURE 2. Kaplan–Meier curves for OS stratified by increase in PSMA TTV ≥ 30% from baseline (A), increase in ^{18}F-FDG TTV ≥ 30% from baseline (B), increase in PSMA SUV_{max} from baseline (C), and increase in ^{18}F-FDG SUV_{max} from baseline (D).

37% (13/35) at trial exit. Any increase in ^{18}F-FDG TTV was associated with worse PSA PFS (HR, 3.1 [95% CI, 1.4–6.8]; $P = 0.005$) and OS (median, 16.2 vs. 23.1 mo; HR, 2.7 [95% CI, 1.1–6.2]; $P = 0.02$). An increase in ^{18}F-FDG TTV by at least 30% was significantly associated with worse PSA PFS (HR, 2.7 [95% CI, 1.2–6.0]; $P = 0.01$) but was not significantly associated with OS (Fig. 2).

No ^{18}F-FDG–positive/^{68}Ga-PSMA PET–negative progressive sites were identified in this cohort at the time of exit imaging. One patient had a significant increase in ^{18}F-FDG–avid volume at 1 site, whereas PSMA tumor volume and SUV_{max} were reduced (Fig. 3).

Molecular Response Patterns and Patient Outcomes

Multivariable analysis including change in PSMA TTV, ^{18}F-FDG TTV, and ^{18}F-FDG SUV_{max}, 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 3.5 [95% CI, 1.1–10.9; $P = 0.03$], respectively) (Table 3).

DISCUSSION

This study has found that increasing TTV on posttreatment ^{68}Ga-PSMA PET identifies early disease progression and shorter OS independently of PSA, raising its potential for use as a prognostic biomarker. Metastatic castration-resistant prostate cancer is characterized by phenotypic and molecular heterogeneity, with marked PSMA heterogeneity previously demonstrated at both an imaging and a cellular level (*9,10*). Although the VISION and TheraP trials have found high treatment responses and improved quality-of-life parameters, the duration of treatment responses with ^{177}Lu-PSMA-617 remains limited. Identifying effective predictive and 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 ^{18}F-FDG PET, reduced PSMA SUV_{max} or SUV_{mean} occurred in almost all patients in response to ^{177}Lu-PSMA-617 therapy and was not predictive of either treatment response or OS. This lack of correlation between change in PSMA SUV_{max} or SUV_{mean} and treatment outcomes has previously been shown. Kurth et al. found that PSMA intensity decreased in both clinically responding and progressing patients (*7,16*). Grubmüller et al. also found no correlation between change in whole-body PSMA SUV_{mean} and OS in an analysis of posttreatment ^{68}Ga-PSMA PET after ^{177}Lu-PSMA-617 therapy. This lack of prognostic value of change in PSMA SUV_{mean} and SUV_{max} with PSMA-targeted therapy is not unexpected. ^{177}Lu-PSMA-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 for change in PSMA SUV_{mean} and SUV_{max} is important to highlight, as we intuitively use reduction in intensity (^{18}F-FDG PET) to denote treatment response with systemic therapy (*17*). We need to think differently when developing ^{68}Ga-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 Gafita et al. and Grubmüller 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 at least 30% was associated with poor OS, supporting the inclusion of this metric in the ^{68}Ga-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 SUV_{max} of more than 15, significantly higher than in patients without progressive disease, and above a range at which PSMA-targeted therapy is expected to be effective. This finding may indicate that radiation resistance is an important mechanism of treatment failure. Further evaluation in conjunction with genetic analysis may help identify optimal treatment combinations in patients who currently have a limited treatment response to ^{177}Lu-PSMA-617 alone.

^{18}F-FDG PET was undertaken both at screening and at trial exit, with ^{18}F-FDG PET screening parameters previously shown to be predictive of OS in this study cohort and other ^{177}Lu-PSMA-617 trials (*1,12,19*). Although we found that an increase in ^{18}F-FDG SUV_{max} and ^{18}F-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 (^{18}F-FDG PET–positive/^{68}Ga-PSMA PET–negative) was low, with only 1 patient having a significant increase in ^{18}F-FDG–avid volume at 1 site, whereas PSMA TTV was reduced.

RECIST progression is the 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

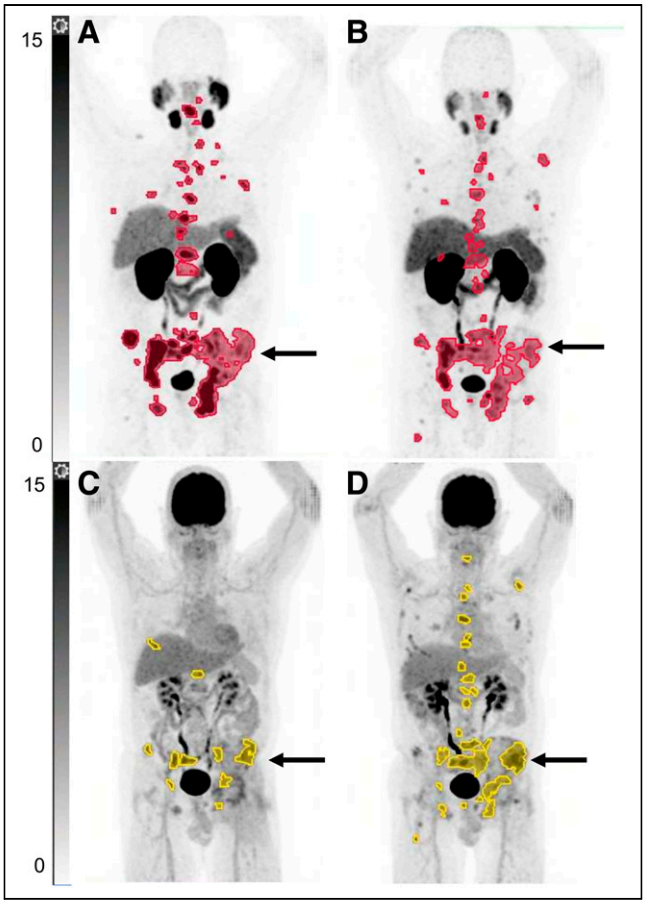

FIGURE 3. Quantitative analysis of baseline and posttreatment PSMA and ^{18}F-FDG PET images from same patient: baseline ^{68}Ga-PSMA PET (A), posttreatment ^{68}Ga-PSMA PET (B), baseline ^{18}F-FDG PET (C), and posttreatment ^{18}F-FDG PET (D). Arrows indicate lesion in iliac bone that reduced in volume and intensity on ^{68}Ga-PSMA PET but increased in volume and intensity of ^{18}F-FDG PET.

study exit. The promising prognostic value for molecular imaging parameters suggests that more work needs to be done validating PET for treatment response in metastatic castration-resistant prostate cancer, potentially as an alternative to CT and bone scanning currently used in Prostate Cancer Working Group 3 criteria.

This study had several limitations. Its small sample size made 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.

TABLE 3
Multivariable Cox Regression Analysis for Association of Clinical and Imaging Parameters with OS

Variable at trial exit	HR	95% CI	*P*
Increase in PSMA TTV	5.1	1.5–17.1	0.008
Increase in ^{18}F-FDG TTV	1.04	0.4–2.9	0.93
Increase in ^{18}F-FDG SUV_{max}	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

Additionally, selection of patients for this analysis was biased toward those well enough to complete posttreatment imaging, explaining the higher rate of at least 50% PSA decline and longer OS in this subset of patients than previously published for the trial. The interval between screening and posttreatment imaging was variable, with 32% exiting the trial early because of clinical progression.

Finally, PET quantitation software remains of limited availability and time-intensive to achieve accurate results. Further automation in quantitation is required to minimize the time required to derive reproducible results, in addition to harmonization and validation of quantitative methods. Nevertheless, the prognostic value of quantified PSMA TTV in this study suggests 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}Lu-PSMA-617 therapy, independently of ^{18}F-FDG parameters, PSA, or radiographic progression. Further research into the value of posttreatment PET as an imaging biomarker is warranted.

DISCLOSURE

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. Louise Emmett has an advisory role with Noxopharm, receives trial support from Novartis and Astellas, and receives grant funding support from St. Vincent's Clinic Foundation. Anthony Joshua has an advisory role with Noxopharm Limited and receives institutional funding from Novartis. Peter Wilson and Remy Niman are salaried employees of MIM Software, Inc. No other potential conflict of interest relevant to this article was reported.

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.

KEY POINTS

QUESTION: What are the imaging findings on ^{68}Ga-PSMA PET and ^{18}F-FDG PET after ^{177}Lu-PSMA-617 therapy, and do changes in tumor volume, SUV_{max}, or SUV_{mean} correlate with clinical outcomes?

PERTINENT FINDINGS: In this LuPIN substudy, any increase in PSMA TTV and PSA progression at study exit were independently prognostic of OS.

IMPLICATIONS FOR PATIENT CARE: Change in tumor volume on ^{68}Ga-PSMA PET after ^{177}Lu-PSMA-617 therapy provides information for clinicians on patient survival and may help them make clinical decisions on timing and type of next treatments.

REFERENCES

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

2. Morris MJ, De Bono JS, Chi KN, et al. Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION) [abstract]. *J Clin Oncol.* 2021;39(suppl):LBA4.
3. Emmett L, Subramaniam S, Joshua A, et al. ENZA-p trial protocol: a randomised phase II trial using PSMA as a therapeutic target and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901). *BJU Int.* 2021;128:642–651.
4. 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.
5. Prasad V, Huang K, Prasad S, Makowski MR, Czech N, Brenner W. In comparison to PSA, interim Ga-68-PSMA PET/CT response evaluation based on modified RECIST 1.1 after 2nd cycle is better predictor of overall survival of prostate cancer patients treated with ^{177}Lu-PSMA. *Front Oncol.* 2021;11:578093.
6. Gafita A, Weber W, Tauber R, Eiber M. Predictive value of interim PSMA PET during Lu-PSMA radioligand therapy for overall survival in patients with advanced prostate cancer [abstract]. *J Nucl Med.* 2019;60(suppl 1):73.
7. Grubmüller B, Senn D, Kramer G, et al. Response assessment using ^{68}Ga-PSMA ligand PET in patients undergoing ^{177}Lu-PSMA radioligand therapy for metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2019;46:1063–1072.
8. 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.
9. Current K, Meyer C, Magyar CE, et al. Investigating PSMA-targeted radioligand therapy efficacy as a function of cellular PSMA levels and intratumoral PSMA heterogeneity. *Clin Cancer Res.* 2020;26:2946–2955.
10. Paschalis A, Sheehan B, Riisnaes R, et al. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. *Eur Urol.* 2019;76:469–478.
11. Crumbaker M, Pathmanandavel S, Yam AO, et al. Phase I/II trial of the combination of ^{177}lutetium prostate specific membrane antigen 617 and idronoxil (NOX66) in men with end-stage metastatic castration-resistant prostate cancer (LuPIN). *Eur Urol Oncol.* 2021;4:963–970.
12. Pathmanandavel S, Crumbaker M, Yam AO, et al. ^{177}Lu-PSMA-617 and idronoxil in men with end-stage metastatic castration-resistant prostate cancer (LuPIN): patient outcomes and predictors of treatment response in a phase I/II trial. *J Nucl Med.* 2022;63:560–566.
13. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34:1402–1418.
14. Niman R, Buteau JP, Kruzer A. Turcotte Ã, Nelson A. Evaluation of a semi-automated whole body PET segmentation method applied to diffuse large B cell lymphoma [abstract]. *J Nucl Med.* 2018;59(suppl 1):592.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45: 228–247.
16. Kurth J, Kretzschmar J, Aladwan H, et al. Evaluation of [^{68}Ga]Ga-PSMA PET/CT for therapy response assessment of [^{177}Lu]Lu-PSMA radioligand therapy in metastasized castration refractory prostate cancer and correlation with survival. *Nucl Med Commun.* 2021;42:1217–1226.
17. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma.* 2009;50:1257–1260.
18. Fanti S, Hadaschik B, Herrmann K. Proposal for systemic-therapy response-assessment criteria at the time of PSMA PET/CT imaging: the PSMA PET progression criteria. *J Nucl Med.* 2020;61:678–682.
19. Ferdinandus J, Violet J, Sandhu S, et al. Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [^{177}Lu]-PSMA-617. *Eur J Nucl Med Mol Imaging.* 2020;47:2322–2327.
20. Brown LC, Sonpavde G, Armstrong AJ. Can RECIST response predict success in phase 3 trials in men with metastatic castration-resistant prostate cancer? *Prostate Cancer Prostatic Dis.* 2018;21:419–430.