European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:2322–2327
https://doi.org/10.1007/s00259-020-04723-z

SHORT COMMUNICATION

Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [177Lu]-PSMA-617

Justin Ferdinandus[1,2] · John Violet[3] · Shahneen Sandhu[4,5] · Rodney J. Hicks[2,5] · Aravind S. Ravi Kumar[2,5] · Amir Iravani[2,5] · Grace Kong[2,5] · Tim Akhurst[2,5] · Sue Ping Thang[2] · Declan G. Murphy[5,6] · Scott Williams[3,5] · Michael S. Hofman[2,5]

Received: 11 December 2019 / Accepted: 10 February 2020 / Published online: 5 March 2020

Abstract

Purpose We analysed quantitative biomarkers derived from both baseline whole-body imaging and blood serum to identify prognostic markers in patients treated within the lutetium-177 prostate-specific membrane antigen (LuPSMA) phase 2 trial.

Methods PET image analysis was carried out using whole-body segmentation quantifying molecular tumour volume (SUV > 3 threshold for PSMA, SUV > liver+2sd for fluorodeoxyglucose (FDG) including SUVmax and SUVmean. For baseline bone scans, EXINI bone scan index (BSI) was used to calculate the percentage of involved bone. Baseline alkaline phosphatase (ALP), lactate dehydrogenase (LDH), prostate specific antigen (PSA) and PSA doubling time were also used in this analysis. We used univariate cox regression analysis and log-rank comparison with optimised cut-offs to find suitable biomarkers prognostic of overall survival from time of enrolment.

Results This analysis identified FDG-positive tumour volume (FDGvol; HR 2.6; 95% CI, 1.4–4.8), mean intensity of PSMA-avid tumour uptake (PSMAmean; HR 0.89; 95% CI, 0.8–0.98), bone scan index (BSI; HR 2.3; 95% CI, 1.2–4.4), ALP (HR 1.1; 95% CI, 1–1.2) and LDH (HR 1.2; 95% CI, 1–1.5) as biomarkers prognostic of overall survival.

Conclusions In addition to established biomarkers, both FDG and PSMA PET/CT parameters have prognostic significance for survival in men undergoing LuPSMA therapy.

Keywords Prostate specific membrane antigen · PSMA · Theranostics · Prognostic markers · FDG · Radioligand therapy · Prostate cancer

This article is part of the Topical Collection on Oncology–Genitourinary

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00259-020-04723-z) contains supplementary material, which is available to authorized users.

✉ Michael S. Hofman
michael.hofman@petermac.org

[1] Department of Nuclear Medicine, University Hospital Essen, Essen, Germany

[2] Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[3] Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[4] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[5] Sir Peter MacCallum Department of Oncology, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC, Australia

[6] Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Introduction

The lutetium 177 prostate-specific membrane antigen (LuPSMA) trial (ANZCTR, No. 12615000912583), a prospective, single-centre, non-randomised Phase II trial demonstrated a PSA response rate greater than 50% in 64% and low toxicity in men receiving ^{177}Lu-PSMA-617 (LuPSMA) for metastatic castrate-resistant prostate cancer (mCRPC) [1, 2]. These results are consistent with several retrospective studies [3, 4]. For screening, patients underwent both 2-deoxy-2-[18F]fluoro-D-glucose PET/CT (FDG-PET) and ^{68}Ga-PSMA-11 PET/CT (PSMA-PET). The baseline PET scans characterised individual patient phenotype and was used for patient selection. In an earlier report, we documented the poor outcome of the patients that were deemed ineligible on the basis of low PSMA expression or sites of PSMA-negative FDG-positive disease [5]. In contrast, little is known about the prognostic value of baseline imaging in patients undergoing LuPSMA therapy and this is of relevance given the

heterogeneous outcomes in mCRPC. Previous studies have shown that higher levels of serum alkaline phosphatase (ALP), rising serum lactate dehydrogenase (LDH), second line chemotherapy and presence of visceral metastases were associated with poor survival [4, 6]. Here, we aim to evaluate the prognostic value of baseline imaging or blood biomarkers in patients enrolled in the LuPSMA trial.

Methods

Patients

We analysed baseline data of 50 patients with mCRPC who had mostly progressed after chemotherapy and novel androgen therapies. They received up to four cycles of LuPSMA on trial; 15 patients received further retreatment with LuPSMA upon disease progression after prior response (see Supplementary Table 1 for baseline characteristics and Supplementary Fig. 1 for study schema). Methodology and patient outcomes have been detailed previously [1, 2]. Forty-three of the 50 patients had died at the time of analysis. With median follow-up of 31.4 months, median overall survival was 13.3 months (95% CI 10.5–18.7); no patients were lost to follow-up.

Imaging and serum biomarkers

All patients underwent baseline PSMA-PET, FDG-PET and planar ^{99m}Tc-bone scan imaging. Quantitative bone scan index (BSI) was determined using EXINI software (Lundt, Sweden) by a single experienced physician. On PSMA-PET and FDG-PET, we determined SUVmax, SUVmean and total molecular volume (TMV) of disease following semi-automated tumour segmentation (MIM Software, Ohio, USA). Tumour was delineated based on SUV > 3 for PSMA-PET and SUV > SUVmean-liver +2 standard deviations (PERCIST definition) for FDG-PET. The whole-body threshold tool was used to define all activity above these limits and normal organ uptake was then erased using the 3D brush tool. Contouring was performed by two experienced nuclear medicine physicians (MH, SPT). Baseline serum biomarkers for analysis included lactate dehydrogenase (LDH), alkaline phosphatase (ALP), prostate specific antigen (PSA) and PSA doubling time (PSADT).

Statistical analysis

Univariate cox regression for continuous variables was applied to assess prognostic value for overall survival (OS). A p value ≤ 0.05 was regarded as significant. We further determined a cut-off value for all significant parameters from regression analysis using a cut-off finder. Survival data for the resulting subgroups is presented using Kaplan-Meier-curves and log-rank-comparison. R-statistics was used for statistical analysis.

Results

Analysis identified FDG-positive molecular tumour volume (FDGvol; HR 2.6, 95% CI, 1.4–4.8), mean intensity of PSMA tumour uptake (PSMAmean; HR 0.89, 95% CI, 0.8–0.98), BSI (HR 2.3;95% CI, 1.2–4.4), ALP (HR 1.1;95% CI: 1–1.2) and LDH (HR 1.2;95% CI,: 1–1.5) as potential biomarkers prognostic of overall survival (see Table 1 and Fig. 1). The determined cut-off values were mostly within the second

Table 1 Cox regression of baseline biomarkers LuPSMA trial

	Biomarker	*N*	Median	Lower quartile	Upper quartile	HR interval	HR (95% CI)	P*cox regression*	Optimal cut-off
Imaging	PSMAmax	50	50, 1	37, 6	70, 8	1 SUV	0.99 (0.99–1)	0.18	
	PSMAmean	50	8, 4	6, 9	10, 2	1 SUV	0.89 (0.8–0.98)	0.02	10.55
	PSMAvol [ml]	50	1047, 8	485, 5	1934, 7	1 L	1.2 (0.96–1.6)	0.1	
	FDGmax	50	12, 6	8, 7	18, 2	1 SUV	1 (0.98–1)	0.7	
	FDGmean	50	4, 7	3, 8	5, 6	1 SUV	1 (1–1)	0.8	
	FDGvol [ml]	50	248, 2	46, 1	686, 8	1 L	2.6 (1.4–4.8)	0.002	207
	BSI [%]	46	4, 1	1, 2	6, 7	10%	2.3 (1.2–4.4)	0.012	5.4
Serum	LDH [U/L]	39	268, 0	222, 5	318, 5	100 U/L	1.2 (1–1.5)	0.011	240.5
	ALP [U/L]	50	130, 5	86, 0	208, 0	100 U/L	1.1 (1–1.2)	0.035	126.5
	PSA [μg/L]	50	189, 8	76, 6	896, 9	100 [μg/L]	1 (0.98–1)	0.5	
	PSADT [months]	50	2, 6	1, 8	3, 7	1 month	1 (1–1)	0.1	

PSMAmax, maximum tumour uptake on PSMA-PET; *PSMAmean*, mean tumour uptake on PSMA-PET; *PSMAvol*, volume of disease [ml] on PSMA-PET; *FDGmax*, maximum tumour uptake on FDG-PET; *FDGmean*, mean tumour uptake on FDG-PET; *FDGvol*, volume of disease [ml] on FDG-PET; *BSI*, EXINI bone scan index [%]; *LDH*, lactate dehydrogenase [U/L]; *ALP*, alkaline phosphatase [U/L]; *PSA*, prostate specific antigen [μg/L]; *PSADT*, prostate specific antigen doubling time [months]

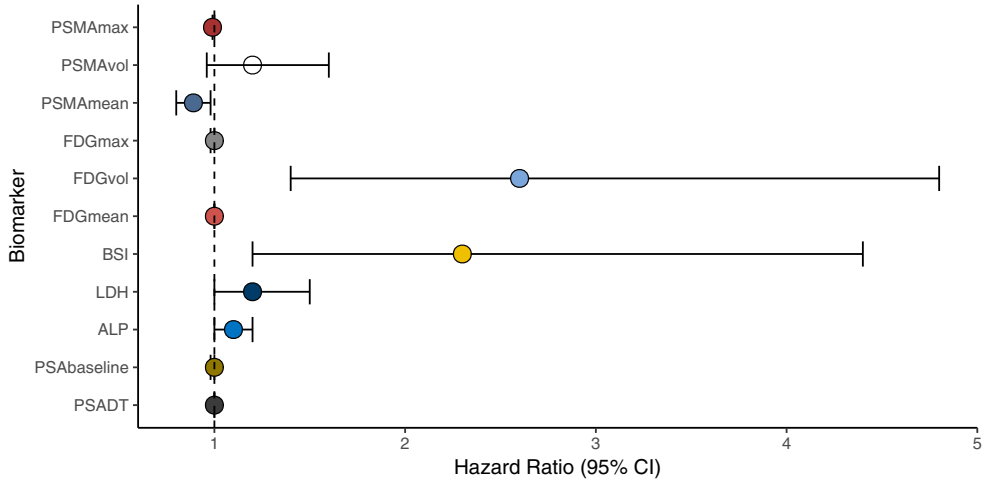

Fig. 1 Hazard ratios (95% CI) of imaging and serum biomarkers in univariate regression. Figure 1 shows the hazard ratios and 95% confidence intervals of patients within the LuPSMA stratified by baseline predictors from imaging or serum bloods. PSMAmax, = Maximum tumour uptake on PSMA-PET;, PSMAmean, = mean tumour uptake on PSMA-PET;, PSMAvol, = volume of disease [ml] on PSMA-PET;, FDGmax, = maximum tumour uptake on FDG-PET;, FDGmean, = mean tumour uptake on FDG-PET;, FDGvol, = volume of disease [ml] on FDG-PET;, BSI, = EXINI bone scan index [%];, LDH, = lactate dehydrogenase [U/L];, ALP, = alkaline phosphatase [U/L];, PSA, = prostate specific antigen [µg/L];, PSADT, = prostate specific antigen doubling time [months]

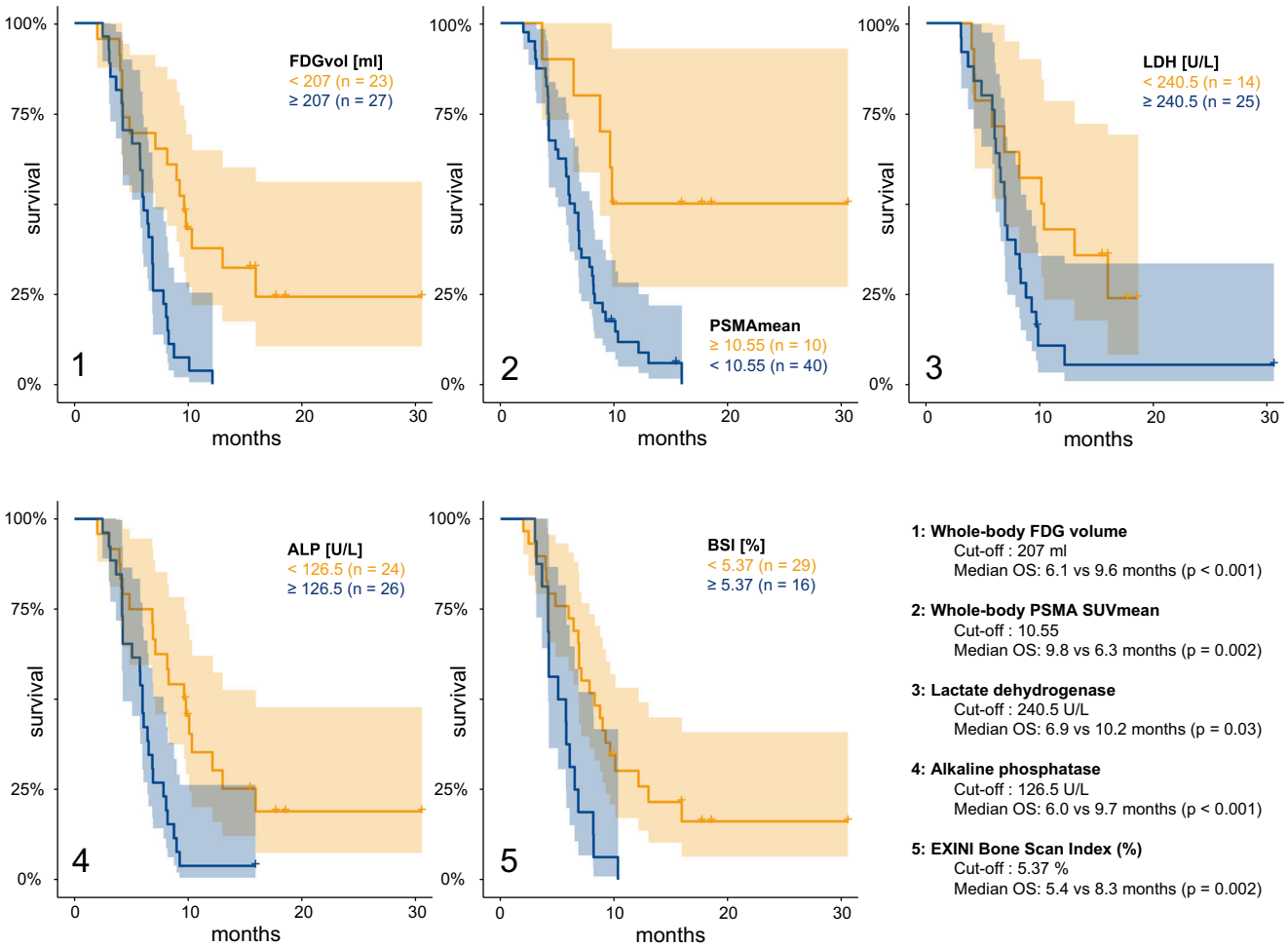

Fig. 2 Kaplan-Meier survival curves of patients within the LuPSMA stratified by significant baseline predictors from imaging or serum bloods identified by Cox regression and their respective cut-offs

and third quartile. Only PSMAmean displayed a cut-off value in the fourth quartile, indicating longer survival for a select group of patients with particularly high intensity of uptake in all sites of disease in PSMA-PET scans. Interestingly, neither the intensity of FDG tumour uptake (FDGmean) nor the volume of PSMA-positive molecular tumour volume (PSMAvol) were prognostic. Prostate specific antigen levels and doubling time were not prognostic. Figure 2 shows Kaplan-Meier-curves for the subgroups divided by the proposed biomarkers and their cut-off-values.

Discussion

In a theranostic setting, molecular imaging enables whole-body characterisation of the prostate cancer phenotype. The strength of FDG-PET as a biomarker in this setting is several-fold. First, in conjunction with PSMA-PET, it identifies sites of disease that are FDG-positive but PSMA image negative and may not be amenable to targeting by LuPSMA. Second, in contrast to some biomarkers, it is not limited to osseous sites of disease (such as ALP and BSI). And third, it uniquely provides a measure of tumour glycolysis, increased in aggressive tumour subtypes. Imaging biomarkers also enable a new opportunity for targeted biopsies to characterise biological and molecular heterogeneity of individual patients' disease.

This study reveals that high-intensity tumour uptake on PSMA-PET identifies a cohort with long survival undergoing LuPSMA therapy. While FDG-PET, BSI, ALP and LDH are prognostic for most patients with mCRPC, high intensity of PSMA uptake may represent a unique biomarker for predicting response to LuPSMA therapy. Previously, we have reported that uptake intensity on PSMA-PET correlates with delivered radiation dose [Gy] in patients treated with LuPSMA, as well as PSA response at 12 weeks [7].

Fizazi et al. associated high ALP with decreased progression-free survival (PFS) and OS in a large cohort of patients receiving chemotherapy for mCRPC [8]. Together with previous findings from retrospective studies, our results support that this association is also applicable to patients receiving LuPSMA therapy. Along with ALP, BSI is one of two known bone-metabolism markers prognostic of OS [9].

Jadvar et al. reported on the prognostic value of summarised SUVmax in FDG-PET in 87 mCRPC patients [10]. Patients with high SUVmax had decreased survival. Our present analysis confirms that FDG-PET is prognostic of survival in patients treated with LuPSMA. Patients with low volumes of FDG avid disease had a longer OS than other patients (6.1 vs 9.6 months, $p < 0.001$). In contrast, the volume of tumour burden on PSMA PET/CT was not prognostic. Accordingly, we infer in this setting of PSMA-avid advanced prostate cancer, the volume of aggressive disease defined by

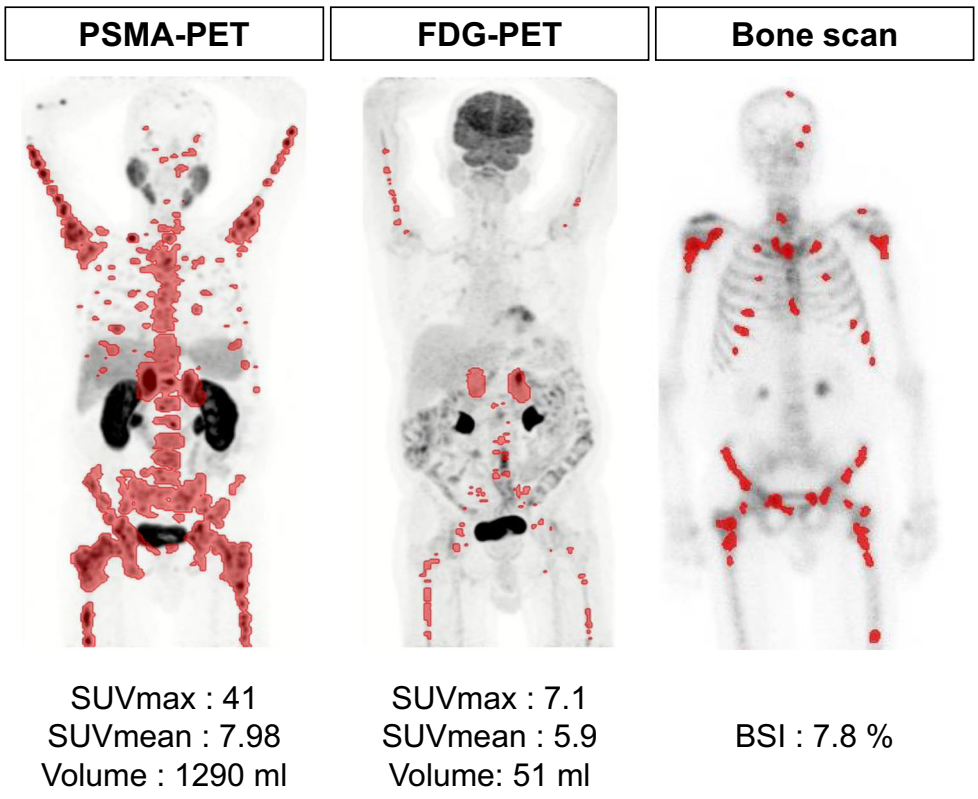

Fig. 3 Baseline imaging in a patient enrolled in our trial. This case demonstrates that despite widespread PSMA-positive disease only a fraction is FDG-positive. Furthermore, automated bone scan analysis only detected a small portion of bone metastases. Regions of interest are coloured in red

FDG has a much higher impact on patient outcome than the volume of PSMA-avid disease which is effectively targeted by the therapy. This should encourage histopathologic comparison of FDG-positive versus negative metastases in future studies to better understand molecular drivers of aggressive phenotype. Figure 3 demonstrates the different tumour burdens in one patient before undergoing LuPSMA. FDG-avidity is heterogeneous across different sites of disease and should therefore be considered when obtaining histologic correlation.

A primary limitation of our study is the sample size which did not enable valid multivariate regression analysis. Although our clinical protocol listed analysis of baseline biomarkers as an exploratory endpoint, we did not pre-define the methods for imaging analysis. Our thresholds for PET imaging analysis and use of BSI were selected after commencing the study. As such, these results must be interpreted as exploratory rather than definitive. We will further evaluate the predictive and prognostic utility of PET imaging parameters in our randomised study of cabazitaxel [11].

In summary, this analysis demonstrates that quantitative biomarkers derived from imaging including the volume of FDG-avid disease and intensity of PSMA-avid disease, as well as conventional blood biomarkers identify patients with a poorer prognosis undergoing PSMA-directed radionuclide therapy.

Acknowledgements EXINI quantitative bone analysis was kindly performed by Dr. Lars Edenbrandt. MH is supported by a Clinical Fellowship from the Peter MacCallum Foundation. For the clinical study, Lutetium-177 was kindly supplied by the Australian Nuclear Science and Technology Organisation ANSTO, Sydney, Australia) and PSMA-617 from Advanced Biochemical Compounds (ABX, Radeberg, Germany) and Endocyte (a Novartis company). MH additionally acknowledges grant support from Movember Australia, Prostate Cancer Foundation (PCF), the Prostate Cancer Foundation of Australia (PCFA), US Department of Defence and the Victorian Cancer Agency (VCA).

Compliance with ethical standards

Conflict of interest MH is the chair of the ANZUP TheraP Study which receives research support from Prostate Cancer Foundation of Australia (PCFA) and Endocyte (a Novartis company). Unrelated to this work, he has received honorarium and travel support from Janssen, Ipsen and Sanofi Genzyme. RJH is supported by a National Health and Medical Research Foundation Practitioner Fellowship and receives research support from the Neuroendocrine Tumor Research Foundation (NETRF), Clarity Pharmaceuticals and Ipsen. He holds stock in Telix Pharmaceuticals. SS reports a consulting or advisory role for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Astra Zeneca, Janssen and Roche; and research funding from research support from the Movember Australia, Prostate Cancer Foundation (PCF), the Victoria Cancer Agency (VCA), Endocyte, Astra Zeneca, Amgen, Bristol-Myers Squibb and Merck Sharp & Dohme.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Peter Mac ethics committee (approval date: 26 August 2015) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This trial is registered with the Australian New Zealand Clinical Trials Registry, number 12615000912583. This article does not contain any studies with animals performed by any of the authors. The study was investigator-initiated and sponsored by the Peter MacCallum Cancer Centre, Melbourne, Australia. All patients signed written informed consent prior to participation in the study. The authors are responsible for the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review and approval of the manuscript. MSH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, 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;19:825–33. https://doi.org/10.1016/S1470-2045(18)30198-0.
2. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. 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. J Nucl Med. 2019. https://doi.org/10.2967/jnumed.119.236414.
3. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schafers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med. 2016. https://doi.org/10.2967/jnumed.116.183194.
4. Heck MM, Tauber R, Schwaiger S, Retz M, D'Alessandria C, Maurer T, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with (177)Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol. 2019;75:920–6. https://doi.org/10.1016/j.eururo.2018.11.016.
5. Thang SP, Violet J, Sandhu S, Iravani A, Akhurst T, Kong G, 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. 2019;2:670–6. https://doi.org/10.1016/j.euo.2018.11.007.
6. Kessel K, Seifert R, Schafers M, Weckesser M, Schlack K, Boegemann M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving (177)Lu-PSMA-617. Theranostics. 2019;9:4841–8. https://doi.org/10.7150/thno.35759.
7. Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, 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;60:517–23. https://doi.org/10.2967/jnumed.118.219352.
8. Fizazi K, Massard C, Smith M, Rader M, Brown J, Milecki P, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration-resistant prostate cancer. Eur Urol. 2015;68:42–50. https://doi.org/10.1016/j.eururo.2014.10.001.
9. Armstrong AJ, Anand A, Edenbrandt L, Bondesson E, Bjartell A, Widmark A, et al. Phase 3 assessment of the automated bone scan index as a prognostic imaging biomarker of overall survival in men with metastatic castration-resistant prostate cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol. 2018;4:944–51. https://doi.org/10.1001/jamaoncol.2018.1093.
10. Jadvar H, Desai B, Ji L, Conti PS, Dorff TB, Groshen SG, et al. Baseline 18F-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J

Nucl Med. 2013;54:1195–201. https://doi.org/10.2967/jnumed.112.114116.
11. Hofman MS, Emmett L, Violet J, Zhang A Y, Lawrence NJ, Stockler M, et al. TheraP: a randomized phase 2 trial of (177) Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). BJU Int. 2019;124(Suppl 1):5–13. https://doi.org/10.1111/bju.14876.

Data sharing The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.