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^{177}Lu-PSMA SPECT Quantitation at 6 Weeks (dose 2) Predicts Short Progression Free Survival for Patients Undergoing Lu PSMA I&T Therapy.

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ABSTRACT

Background: ^{177}LuPSMA is an effective treatment in metastatic castrate-resistant prostate cancer (mCRPC). Our ability to assess response rates and adjust treatment may be improved using predictive tools. This study aimed to evaluate change in ^{177}Lu-PSMA-SPECT quantitative parameters to monitor treatment response.

Methods: 127 men with progressive mCRPC previously treated with androgen signaling inhibition (99%) and chemotherapy (71%) received a median 3 (IQR 2-5) doses Lu PSMA I&T 8 GBq (IQR 8-8.5). Imaging included ^{68}Ga-PSMA-11 PET-CT (SUVmax >15 at a single site and >10 at all sites > 2cm), diagnostic CT, and ^{177}Lu-SPECT/CT (Lu-SPECT) vertex to mid-thigh (24 hours following treatment). Lu-SPECT quantitative analysis was undertaken at cycle-1 (baseline) and 2 (week 6) of treatment. Clinical and biochemical results were assessed to evaluate PSA progression free (PSA-PFS) and overall survival (OS).

Results: 58% (74/127) had PSA reduction > 50%. The median PSA-PFS was 6.1 months [95%CI 5.5-6.7] and OS 16.8 months [95% CI 13.5-20.1]. At time of analysis 41% (52/127) were deceased. 76% (96/127) had analyzable serial ^{177}Lu-SPECT/CT imaging at baseline and week-6. SPECT-total tumor volume (SPECT-TTV) was reduced between baseline and week-6 in 74% (71/96, median -193 (IQR -486 to -41). Any increase in SPECT-TTV between baseline and week-6 was associated with significantly shorter PSA-PFS (HR 2.5 (95%CI 1.5-4.2) p 0.0008) but not OS. Median PSA-PFS in those with an increase in SPECT-TTV was 3.7 months (95%CI 2.8-6.8), compared to 6.7 months (95%CI 5.8-10.6) with no increase in SPECT-TTV. An increase in SPECT-TTV greater than 20% was also associated with PSA-PFS (HR 1.9 (95%CI 1.2-3.0) p

0.008), but less significantly than any change in SPECT-TTV. There was a significant difference in PSA-PFS between patients with both increased PSA and SPECT-TTV vs. those patients with reduced SPECT-TTV and PSA (median 2.8 vs. 9.0 months $p < 0.0001$).

Conclusion:

Increasing PSMA SPECT-TTV on quantitative ^{177}Lu-SPECT/CT predicts short progression free survival and may play a future role as an imaging response biomarker, identifying when to cease or intensify Lu-PSMA therapy.

INTRODUCTION

^{177}LuPSMA is an effective therapy in metastatic castrate resistant prostate cancer although treatment resistance and short response duration remains common (*1-4*). The ability to monitor early responses to ^{177}LuPSMA therapy may improve patient outcomes by enabling treatment escalation, change in treatment, or a treatment 'holiday', dependent on imaging results. Interim and serial ^{68}Ga-HBEDD-PSMA-11 PET/CT (^{68}Ga-PSMA) has recently been shown to be predictive of progression free survival with PSMA targeted radionuclide therapy (*5*). Quantitative ^{177}Lu-single photon emission computed tomography/CT (Lu-SPECT) imaging following each ^{177}LuPSMA dose may also be valuable in response monitoring in addition to providing dosimetric information. Increased tumor volume on Lu-SPECT at dose 3 (week 12) has been shown to predict early disease progression with ^{177}LuPSMA therapy (*6*) This study aimed to determine if quantitative parameters on the week 6 Lu-SPECT imaging 24 hours post ^{177}LuPSMA therapy predicted treatment response and progression free survival.

MATERIALS AND METHODS

Men with metastatic castrate-resistant prostate cancer (mCRPC) treated clinically with ^{177}Lu-PSMA-I&T were enrolled into a retrospective registry. Enrolled men were treated at a single centre with ^{177}LuPSMA-I&T at 6 weekly intervals until disease progression/ change in treatment. Information on prior treatment, years since diagnosis, biochemical and haematological parameters were all collected. Patients were followed up post treatment to document PSA progression free survival and overall survival. Lu-

PSMA SPECT 24 hours following each treatment was undertaken for quantification of disease burden. St Vincent's Hospital institutional review board approved this retrospective study and the requirement to obtain informed consent was waived (HREC) 2022/ETH00924.

Screening

Men underwent screening ^{68}Ga-PSMA PET/CT, bone scan and CT of the chest, abdomen, and pelvis. Men were eligible if they had a Standardized Uptake Value (SUV) maximum > 15 on ^{68}Ga-PSMA PET at ≥ 1 site, SUVmax >10 at all measurable sites of disease not impacted by partial voluming, and no sites of soft tissue disease on contrast CT without corresponding ^{68}Ga-PSMA uptake. ECOG 1-3 were eligible for treatment. A minimum eGFR 35 mls/min, Hb >70 g/L, platelets > 70 (10^9/unit).

Treatment

Men received treatment with ^{177}LuPSMA-I&T at 6-week intervals (median doses 3 (IQR 2-5)) between May 2018 - April 2022. A median 8 GBq (IQR 7.5-8). ^{177}LuPSMA-I&T was administered via slow intravenous injection. Dexamethasone 8mg orally was administered day 1 for each dose to minimise pain flare and vomiting (*7,8*). Bloods were routinely collected at 3-weekly intervals to assess toxicity/adverse events and biochemical response. Prior treatments and date of diagnosis were documented as was PSA progression free survival and overall survival. Clinical protocol included 6 doses Lu-PSMA 6 weekly, with multidisciplinary clinical decision dictating duration of treatment

based on evidence of disease progression or exceptional response. Patients were followed up post cessation of treatment to confirm clinical outcomes.

^{177}LuPSMA-I&T PSMA-I&T precursor (ABX/Huayi) in sodium acetate buffer was added to non-carrier added ^{177}Lu-$LuCl_3$ according to institutional production protocol. Radiochemical purity determined using high-pressure liquid chromatography and thin-layer chromatography.

Imaging procedures and analysis

Screening ^{68}Ga-PSMA PET/CT were performed in all patients prior to consideration for treatment. All patients treated had Lu-SPECT (vertex to mid thighs) acquired 24 hours after ^{177}Lu-PSMA-I&T injection, with the 24-hour time-point determined based on the TheraP trial protocol (*8*). SPECT imaging was undertaken with a Discovery 670 system (GE Healthcare, Milwaukee, USA) and a Tandem NM/CT 870 DR (GE Healthcare, Milwaukee, USA) with the following parameters: medium energy collimators, 3 bed positions, 60 projections over 360 degrees with an acquisition time of 10 seconds per frame, 128 x 128 matrix and 4.42 x 4.42 mm^2 pixel size. An energy window centered on 208 keV +/- 10% with a 165 keV +/- 6.5 % scatter window were used. A non-contrast low dose CT scan was performed immediately after using the following parameters: pitch = 1, tube voltage of 120 kV, automatic mAs control (reference mAs 90), slice thickness of 3.7mm, matrix of 512 x 512, field of view of 40cm. For quantitation, the required SPECT calibration was performed on both cameras with a cylindrical phantom (for determination of sensitivity factor and conversion from counts to units of activity) and CT attenuation correction was performed using a CIRS CT-to-ED phantom by MIM Software (Inc, Cleveland, USA). For images acquired on the Discovery

670, SPECT projection images were reconstructed with an iterative Ordered Subset Estimation Maximum algorithm that used 4 iterations and 10 subsets using SPECTRA Quant™ (MIM Software, Inc, Cleveland, USA). No pre- or post-reconstruction filters were applied. CT-based attenuation correction, Dual Energy Window Scatter Correction, collimator-based Resolution Recovery, and quantitative conversion to SUV were performed during the reconstruction. Images acquired on the Tandem NM/CT 870 DR were processed using the same reconstructive parameters on the GE Smart Console for quantitation. Diagnostic contrast CT chest, abdomen and pelvis was undertaken at each treatment cycle to assess for non-PSMA avid visceral disease progression.

Quantitative analysis

Lu-SPECT were analysed semi-quantitatively utilising MIM (LesionID™, MIM Software Inc., Cleveland, US) software and a standardised semi-automated workflow to delineate regions of interest with a minimum SUVmax cut-off of 3 and lesion size ≥ 0.5mm. All lesions identified quantitatively were manually reviewed and physiologic activity removed. Whole body quantitation derived total tumour volume (TTV), SUVmax and SUVmean (*9*).

Statistical Analyses

We measured PSA decline from baseline (≥50% (PSA50)) at any time-point, PSA progression-free survival (PSA-PFS) as defined by PCWG3 criteria (PSA progression defined as a rise of PSA ≥2), and overall survival (OS) (*10,11*). The Kaplan-

Meier method was used to characterise time-to-event endpoints and estimate medians (presented with 95%CIs). We correlated changes in SPECT-TTV, SPECT-PSMA intensity, clinical and biochemical parameters with time-to-event outcomes, using univariable and multivariable Cox proportional hazards regression models (*12,13*). Variables included increase in SPECT-TTV, SUVmax, SUVmean, PSA and radiographic progression. P-values below 5% were considered significant. Analyses were performed using R (version 4.0.5).

RESULTS

Patient Characteristics

127 men underwent Lu-PSMA I&T therapy between May 2019- April 2022. All men had mCRPC, 99% (126/127) had prior ASI and 70% (89/127) prior docetaxel. Mean age was 75 years (70-80) (Table 1). Patients received a median of 3 doses up to a maximum 10 (IQR 2-5). 7% (9/127) had received prior Lu-PSMA-617 on trial. 58% (74/127) had PSA reduction > 50% (PSA50). Median PSA-PFS 6.1 months (IQR 4.9-8.4 months) [95% CI 5.5-6.7 months] and OS 16.8 months (IQR 6.3-14.9 months) [95% CI 13.5-20.1 months]. At time of analysis 41% (52/127) were deceased.

SPECT Quantitation

76% (96/127) men had analysable baseline and week-6 Lu-SPECT data. Lu-SPECT quantitation measures at baseline and week-6, including SPECT-TTV, SUVmax and SUVmean are summarized in Table 2. On the baseline Lu-SPECT, median SUVmean was 8.8 (IQR 7-12), SUVmax 60 (35-88) and SPECT-TTV 411 mLs (128-

1169). SPECT-TTV was reduced between baseline and week 6 in 74% (71/96, median -193 (IQR -486 to -41) and increased in 25% (24/96), median 103mL (IQR 42 - 196). SUVmax was increased in 24% (23/96) and SUVmean increased in 22% (21/96).

Patient Outcomes:

Lu-SPECT

Baseline: SPECT-TTV (dose 1) was not significantly associated with PSA-PFS or OS (Table 2). SUVmean measured on dose 1 Lu-SPECT was significantly associated with PSA-PFS as a continuous variable (HR 0.90 (95% CI 0.85-0.96) p 0.0009), but not with OS (HR 0.94 (95%CI 0.9-1.0). When stratified by SUVmean > 7 on dose 1 Lu-SPECT, patients with SUVmean > 7 had median PSA-PFS 6.8 (95%CI 6-9) vs. 3.0 (95%CI 2.6-6) months in those with SUVmean < 7. SUVmean > 7 was significantly associated with longer PSA-PFS (HR 2.7 (95%CI 1.6-4.4), p<0.001) and OS (HR 2.1 (95%CI 1-4), p=0.03).

Week 6: Any increase in SPECT-TTV between baseline and week-6 was associated with significantly shorter PSA-PFS (HR 2.5 (95%CI 1.5-4.2) p 0.0008) but not OS. Median PSA-PFS in those with an increase in SPECT-TTV was 3.7 months (95%CI 2.8-6.8), compared to 6.7 months (95%CI 5.8-10.6) for those with no increase in SPECT-TTV (Figure 1). An increase in SPECT-TTV greater than 20% was also associated with PSA-PFS (HR 1.9 (95%CI 1.2-3.0) p 0.008), but less significantly than any change in SPECT-TTV. Increase in SUVmax and SUVmean were both associated with PSA-PFS

(HR 1.8 (95%CI 1.0-3.1) p 0.04) and (HR 2.1 (95%CI 1.2-3.8) p 0.01) respectively, but not OS (Table 3).

Biochemical

23% (22/96) patients demonstrated a rise in PSA by Week-6. A PSA rise was associated with significantly shorter PSA-PFS (HR 4.0 (95%CI 2.3-6.9) p < 0.0001) and worse OS (HR 2.4 (95%CI 1.1-5.1) p 0.02). Baseline LDH > 1.5 x ULN was associated with worse PSA-PFS (HR 2.3 (95%CI 1.3-4.1) p 0.006, as was ALP > 1.5 x ULN with both PSA PFS and OS (HR 1.8 (95%CI 1.1-3.0) p 0.03 and HR 2.2 (95%CI 1.1-4.5) p 0.04 respectively). Baseline haemoglobin was associated with neither PSA-PFS nor OS (Table 2).

Combination Biomarkers

In the 25 patients with SPECT-TTV progression at week-6, 44% (11/25) had no concurrent PSA progression (median PSA-PFS 3.7 months (95%CI 2.8-4.7), and 14 men had both PSA and SPECT TTV progression at week 6 (median PSA-PFS 2.8 months (95%CI 1.4-4.7) (Figure 2). There was a significant difference in PSA-PFS between patients with both increased PSA and SPECT-TTV vs. those patients with reduced SPECT-TTV and PSA (median 2.8 months vs 9.0 months p < 0.0001).
71 men had reduced SPECT-TTV by week 6. 11% (8/71) men had a reduction in SPECT-TTV and PSA progression (median PSA-PFS 2.7 months (95%CI 1.4-4.8). Of these, 2/8 had new PSMA negative hepatic lesions identified on diagnostic CT and 2/8 had new small volume lesions identified on SPECT, despite a drop in SPECT-TTV.

SPECT Multivariable Analysis

Both baseline SPECT SUVmean >7 and Δ SPECT-TTV were found to be independently predictive for PSA-PFS, while Δ SUVmean and Δ SUVmax were not (Table 4).

DISCUSSION

This study has demonstrated that change in tumour volume on Lu-SPECT between baseline and 6-weeks of ^{177}LuPSMA-617 therapy is predictive of short progression free survival. Furthermore, the combination of increased SPECT-TTV and a PSA rise at 6 weeks, identified a subgroup of men at high risk of poor response to Lu-SPECT therapy who may benefit from either a change in therapy or addition of appropriate combination treatments that may have synergistic benefit in conjunction with Lu-PSMA. Identifying effective response biomarker combinations such as early PSA rise and SPECT-TTV, that provide strong information as early as 6 weeks into treatment is a big step towards being able to tailor treatment strategies to individual patients, thereby personalising and improving outcomes.

^{177}LuPSMA has proven an effective therapy for mCRPC with randomised trials demonstrating improved OS and high PSA response rates compared to standard of care therapies (*2,3*). However, responses can be heterogenous and a proportion of men with suitable ^{68}Ga-PSMA PET screening results may have limited treatment responses. At the same time, combination trials with ^{177}LuPSMA are underway to investigate whether combining ^{177}LuPSMA with other agents may deepen and prolong responses (NCT04419402, NCT03658447, NCT03874884) (*7,14*). Imaging biochemical and

clinical interim response biomarkers will be critical in personalising treatments to optimise longer term treatment responses to PSMA targeted radionuclide therapy, and conversely stopping treatment early to mitigate opportunity cost if other treatment options are available.

RECIP criteria has recently been proposed for response assessment using a 12-week PSMA/PET scan (*5*). RECIP uses PET/CT quantification to derive volume and intensity scores utilising a combination of a 20% increase in PSMA PET TTV and new lesions to determine disease progression. A recent analysis of the LUPIN trial has found a week-12 LuPSMA-SPECT is also predictive of treatment response (*6*). This study has confirmed this predictive value, also finding that LuPSMA-SPECT predicts PFS earlier in treatment (6 weeks) without the need for an additional ^{68}Ga-PSMA PET scan. This has significant cost and availability advantages worldwide, with few countries having approved ^{68}Ga-PSMA PET/CT for response assessment. Additionally, the current analysis found that only 4/96 patients had new lesions not identified by an increase in SPECT-TTV, 2/4 of these being new PSMA negative hepatic lesions not evident on PSMA SPECT/CT. More work is required to determine if the presence of new lesions on PSMA imaging should be a requirement in classifying disease progression or if increased tumour volume in conjunction with biochemical parameters is sufficient.

Currently accepted response biomarkers in mCRPC include a sequential rise in PSA (*15*), and RECIST/ PCWG3 criteria progression on diagnostic CT and bone scan (*16*). Heterogeneity of PSA expression in mCRPC may limit its predictive value in a proportion of men (*17*). This is reflected in the fact that 25% of the men in this study who had an increase SPECT-TTV did not have a concurrent PSA rise at 6 weeks. This is

similar to the 21% identified in a previous SPECT-TTV study and the 14% demonstrating ^{68}Ga-PSMA PET progression prior to PSA progression by Gafita et al (*5,6*). RECIST progression requires serial imaging to determine progression on PCWG3 criteria, limiting its value as an early response biomarker for treatment adjustment. Ongoing evaluation is required to determine if response evaluation criteria should be modified to include Lu-SPECT, although diagnostic CT will remain important in identifying PSMA negative progression.

Screening PSMA and 18F-FDG PET parameters have demonstrated strong prognostic value for LuPSMA therapy (*18,19*). In the TheraP trial, patients with high PSMA SUVmean >10 have an excellent PSA 50 RR (*18*). SUVmean is an indirect measure of PSMA expression heterogeneity, which impacts treatment effectiveness, but cannot assess radiation sensitivity. However, Δ SPECT- TTV may provide individual information on radiation sensitivity, measuring tumour volume reduction to treatment. This study found that both the screening SUVmean (SPECT) and Δ SPECT-TTV were independently predictive of PSA-PFS, raising the possibility of developing effective imaging response nomograms as early as 6 weeks into treatment.

Previous work has identified baseline PSMA and biochemical parameters that predict early treatment failure for patients undergoing Lu PSMA therapy (*20*). A novel component of this study is the evaluation of baseline PSMA SPECT parameters in addition to the change in SPECT between baseline and the 6-week therapy. This study demonstrates that baseline PSMA predictive biomarkers can be derived from SPECT in addition to baseline PET imaging. This may be valuable in instances where PSMA PET is not widely available.

This study relied on quantitation of SPECT data rather than visual assessment. This reliance on quantitation for effective predictive and response biomarkers in molecular imaging is increasing, including the highly valuable SUVmean on screening ^{68}Ga-PSMA PET for ^{177}LuPSMA therapy (*18,19,21*). However, quantitation is not standard of care and is time intensive to undertake. Further work needs to be done both to streamline quantitation for widespread adoption into routine practice (*9*).

There are several limitations to this study. This is a single centre retrospective analysis of a clinical treatment program. While PSA and survival data was rigorously collected, obtaining routine RECIST/ PCWG3 bone scan criteria for radiographic progression was not possible. Additionally, ^{177}Lu-SPECT quantitative measures can vary significantly between centres and systems and these findings require validation in other clinical databases and quantitative programs (*22*). This study only evaluated the first 2 SPECT data timepoints quantitatively, and examination of subsequent time points could provide more comprehensive information on the value of Lu-SPECT. Finally, further research is necessary to better define appropriate volume cut-offs for significant increase in SPECT-TTV that should be used to identify disease progression. This will require trials with larger patient numbers and outcome data.

CONCLUSION

Increasing PSMA- SPECT-TTV on quantitative ^{177}Lu-SPECT/CT predicts short progression free survival and may play a future role as an imaging response biomarker, identifying when to cease or intensify Lu-PSMA therapy.

DISCLOSURE STATEMENT

The investigator-initiated study was sponsored by St Vincent's Hospital and was supported by a Cancer Institute NSW prostate translational research grant.

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AMJ – Advisory Role: Institutional funding – Novartis.

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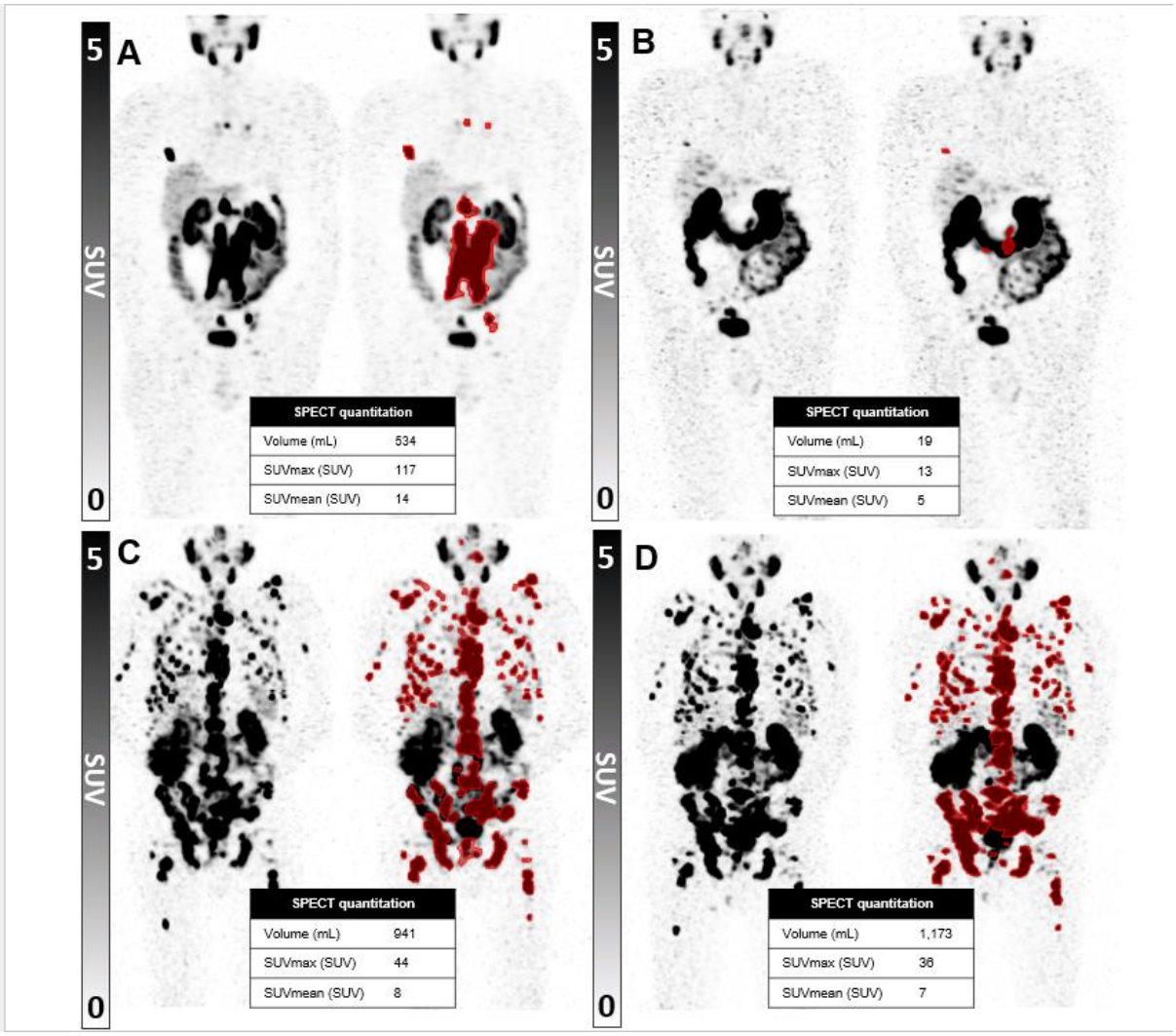
KEY POINTS

Question: Is there value in SPECT imaging of patients post Lutetium therapy?

Pertinent Findings: Week-6 Lu-SPECT change in tumor volume is predictive of short progression free survival and may have potential to as a response biomarker.

Implications for Patient Care: Lu-SPECT has potential as an imaging response biomarker and may assist in the management of men with metastatic castrate resistant prostate cancer undergoing ^{177}Lu PSMA therapy.



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341 Figure 1: A reduction between SPECT-TTV from baseline (A) and week-6 (B) in a
342 patient with a PSA-PFS 14 month. Image (C) demonstrates a patient with increased
343 SPECT-TTV at 6 weeks (D) and a PSA-PFS 2.0 months.

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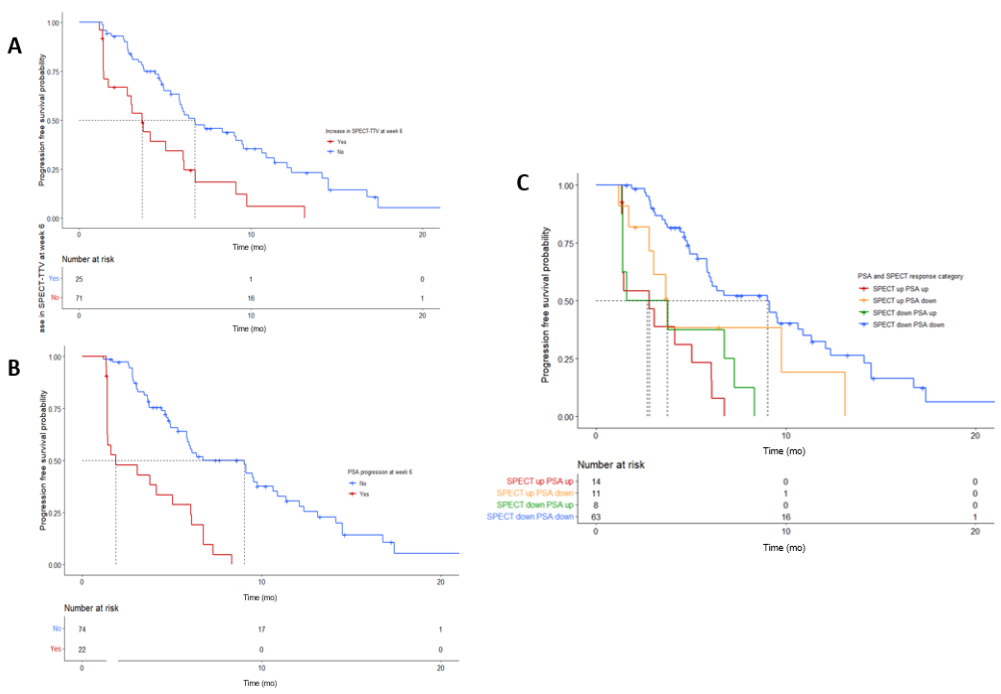
Fig 2



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346 Figure 2: Kaplan Meier curves for PSA-PFS in patients with any increase (red) versus
347 reduced (blue) SPECT-TTV (A), rise in PSA at 6-weeks (red) versus reduced PSA at 6-
348 weeks (blue)(B) and a combination of reduced SPECT-TTV and reduced PSA (blue),
349 rising PSA and reduced SPECT-TTV (green), rising SPECT-TTV and reduced PSA
350 (yellow), and rising PSA with rising SPECT-TTV (red) (C).

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352

TABLE 1: Patient Characteristics

Characteristic	N=127
Age (years)	75 (70-80)
Years since diagnosis	6 (3-9)
Prior Systemic treatments	
LHRH agonist/antagonist	100% (127/127)
Chemotherapy	70% (89/127)
Docetaxel	70% (89/127)
Cabazitaxel	35% (44/127)
Androgen Signalling Inhibitor (ASI)	99% (126/127)
PSA	76 (26.7-258.5)
LDH	242 (211-301)
Platelets	220 (177-271)
Haemoglobin	116 (103-127)
Sites of Disease	
Bone	97% (93/96)
Lymph nodes	47% (45/96)
Visceral	20% (19/96)

TABLE 2: Baseline Predictive Biomarkers

	PSA-PFS	OS
SPECT SUVmean	0.90 (0.85-0.96) [0.0009]	0.94 (0.9-1.0) [0.06]
SPECT SUVmean < 7	2.7 (1.6-4.4) [0.00003]	2.1 (1-4) [0.03]
SPECT TTV	1.0 (0.99-1.0) [0.17]	1.0 (0.99-1.001) [0.1]
Haemoglobin (> 100)	0.59 (0.32-1.1) [0.09]	0.92 (0.39-2.1) [0.83]
ALP (> 1.5 ULN)	1.8 (1.1-3.0) [0.03]	2.2 (1.1-4.5) [0.04]
LDH (> 1.5 ULN)	2.3 (1.3-4.1) [0.006]	1.8 (0.85-4.0) [0.12]

HR (95% CI) [*p*]

TABLE 3: Univariable Analysis of Response Biomarkers (Baseline to 6-week SPECT)

	PSA PFS	OS
Δ SPECT-TTV	2.5 (1.5-4.2) [0.0008]	1.2 (0.6-2.7) [0.57]
Δ SPECT SUV_{mean}	2.1 (1.2-3.8) [0.01]	1.7 (0.7-4.0) [0.2]
Δ SPECT SUV_{max}	1.8 (1.0-3.1) [0.04]	1.3 (0.6-2.8) [0.6]
Δ PSA	4.0 (2.3-6.9) [0.0001]	2.4 (1.1-5.1) [0.02]

HR (95% CI) [*p*]

TABLE 4: Multivariable analysis of SPECT Parameter for PSA-PFS and OS

	PSA PFS	OS
ΔSPECT-TTV	1.9 (1.1-3.3) [**0.03**]	0.85 (0.3-2.2) [0.7]
Δ SUVmax	1.0 (0.5-2.3) [0.9]	0.76 (0.2-2.6) [0.7]
Δ SUVmean	1.2 (0.5-2.8) [0.7]	1.3 (0.3-6.0) [0.70]
SUVmean < 7 (baseline)	2.4 (1.2-4.6) [**0.01**]	2.4 (0.9-6.1) [0.07]

HR (95% CI) [*p*]

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Graphical Abstract

^{177}Lu-PSMA SPECT Quantitation at 6 Weeks (dose 2) Predicts Short Progression Free Survival for Patients Undergoing ^{177}LuPSMA-I&T Therapy.