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Title

Using, ^{68}Ga-PSMA-11 PET/CT for therapy response assessment in patients with metastatic castration-resistant prostate cancer: an application of EAU/EANM recommendations in clinical practice.

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Running Title

PSMA PET/CT for therapy assessment

ABSTRACT

For patients with metastatic castration-resistant prostate cancer (mCRPC), no reliable biomarkers are currently available that predict therapeutic response or assist in treatment selection and sequencing. Using the recent European Association of Urology and European Association of Nuclear Medicine (EAU/EANM) recommendations, we aimed to (1) compare response assessment between prostate-specific membrane antigen (PSMA) positron emission tomography combined with computed tomography (PET/CT) and conventional imaging (CI) in mCRPC patients starting a first-line treatment with novel hormonal agents (NHA), and (2) perform a sequential comparative analysis of PSMA PET/CT-derived parameters after 4 and 12 weeks of therapy. **Methods**: Eighteen mCRPC patients who started NHA and underwent ^{68}Ga-PSMA-11 PET/CT before therapy initiation (baseline), at week 4 (W4) and week 12 (W12), in addition to CI (bone scintigraphy, CT) at baseline and W12, were retrospectively included. PET/CT images were quantitatively analyzed for maximum and mean standardized uptake value and total PSMA-ligand positive total lesion (PSMA-TL). Comparative analysis of PET/CT-derived parameters was performed, and patients were classified with non-progressive disease (non-PD) or progressive disease (PD) according to ^{68}Ga-PSMA-11 PET/CT, PSA and CI criteria. **Results**: Treatment response was evaluable by ^{68}Ga-PSMA-11 PET/CT in 16/18 (89%) patients compared to 11/18 (61%) by CI. At W12, patients with PD by ^{68}Ga-PSMA-11 PET/CT already met progression criteria at W4 (n = 5/16) and substantial agreement was observed between the W4 and W12 (κ = 0.74) ^{68}Ga-PSMA-11 PET/CT. Nonetheless, 2/16 (13%) patients were wrongly classified with PD due to a flare phenomenon on PSMA PET/CT, which disappeared at W12. **Conclusion**: Volumetric assessments of ^{68}Ga-PSMA-11 PET/CT imaging can improve response evaluation in NHA-treated patients with mCRPC. Although early response assessments at W4 need to be approached with caution due to flare, ^{68}Ga-PSMA-11 PET/CT imaging at 4

and 12 weeks revealed a substantial agreement in the therapy response assessment, which warrants further investigation to distinguish PD from flare at W4 and help improve our understanding of resistance to therapy.

Keywords

mCRPC, prostate cancer, tumor quantification, PSMA PET/CT, flare

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INTRODUCTION

Although new imaging modalities using radionuclides have become available to e.g., evaluate tumor burden, a practical tool for improved staging and clinical decision-making in metastatic castration-resistant prostate cancer (mCRPC) is urgently needed. In current clinical practice, therapy response assessment by means of conventional imaging (CI), encompassing computed tomography (CT) and bone scintigraphy (BS), is typically performed after 12-16 weeks of therapy. However, CI has limited sensitivity and specificity for small lymph node and bone metastases, especially at low prostate-specific antigen (PSA) levels (*1-2*). Due to its higher accuracy, prostate-specific membrane antigen (PSMA) positron emission tomography combined with CT (PET/CT) has gained momentum in staging and recurrence localization compared to CI (*3-5*). Recently, the EAU (European Association of Urology) in collaboration with EANM (European Association of Nuclear Medicine) recruited a panel of international experts to reach a consensus statement for the use of PSMA PET/CT in assessing therapy response for patients with metastatic disease (*6*). However, semi-quantitative parameters that should be used for PSMA PET/CT interpretation were not clearly defined. Moreover, the expert panel raised awareness for potential "tumor flare" phenomena following the initiation of androgen deprivation therapy and discouraged the use of PSMA PET/CT within 12 weeks to avoid misinterpretation of potential flare as progressive disease (PD). As PSMA imaging is more widely used in clinical practice, understanding the factors underlying PSMA expression modulation is becoming increasingly important. Interestingly, other factors than exposure to androgen deprivation therapies, such as DNA damage response genes defect (*7*) or activation of the PI3K-Akt pathway (*8*), may modulate PSMA expression. Thus, PSMA PET/CT imaging may indirectly reflect underlying molecular biology and, besides a prognostic tool, also serve as a predictive biomarker prior to biochemical progression and/or PD on CI (*8-11*). Consequently,

exploring response endpoints by PSMA PET/CT might improve clinical decision-making, e.g., treatment intensification for oligoresistant or oligoprogressive lesions to delay disease progression (*11-13*). The present work evaluated ^{68}Ga-PSMA-11 PET/CT for the baseline assessment and monitoring of treatment response in a retrospective series of patients with mCRPC starting a first-line treatment with a novel hormonal agent (NHA). Additionally, therapy response by ^{68}Ga-PSMA-11 PET/CT at 12 weeks was compared to the earlier response obtained at 4 weeks and individual analysis of ^{68}Ga-PSMA-11 PET/CT-derived parameters using the proposed criteria from the expert-based consensus was performed.

METHODS

Patients

From a large internal database, files from mCRPC patients who started a first-line treatment by NHA between January 2018 and May 2021 at the University Hospital of Liège (Belgium) were retrospectively extracted and reviewed. Additional inclusion criteria comprised patients having undergone ^{68}Ga-PSMA-11 PET/CT before NHA initiation (baseline), at week 4 (W4 ± 7 days) and week 12 (W12 ± 7 days) along with CI at baseline and W12; having histologically confirmed prostate adenocarcinoma; having progressive castration-resistant disease, as defined by castrate levels of testosterone (< 1.7 nmol/L) and clinical, biological and/or radiographic progression, conform to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (*14*); and having documented evidence of metastatic disease (on CI and/or ^{68}Ga-PSMA-11 PET/CT) prior to NHA initiation. Patients who did not respect all inclusion criteria were excluded. This study was approved by the Institutional Review Board of the University Hospital of Liège and written informed consent was obtained from all patients.

^{68}Ga-PSMA-11 PET/CT

^{68}Ga-PSMA-11 PET/CT images were analyzed by a nuclearist (15-year experience including 7 years with PSMA PET/CT) blinded to the clinical data and BS results, using MIM Software (version 7.0.5, Cleveland, Ohio, USA). ^{68}Ga-PSMA-11 radiolabeling was performed as previously described (*15*). Image acquisition and tumor volume delineation technique are summarized in the Supplementary Data (*16-19*). The following semi-quantitative variables were extracted for each patient: maximum SUV of the hottest lesion (SUV_{max}), total PSMA-ligand positive tumor volume (PSMA-TV), mean SUV of PSMA-TV (SUV_{mean}) and total PSMA-ligand positive total lesion (PSMA-TL, the product of SUV_{mean} and PSMA-TV) (*20-21*). Following the EAU/EANM recommendations, the parameters used to assess therapy response for tracer uptake and tumor volume were SUV_{max} and PSMA-TL, respectively.

Conventional Imaging

CT (chest-abdomen-pelvis) and BS images were analyzed according to PCWG3 recommendations (*14*) by a nuclearist and a radiologist (10-year experience), also blinded to the clinical data and ^{68}Ga-PSMA-11 PET/CT results. To enable therapy response assessment, patients needed to have measurable disease defined as the presence of bone lesions on BS and/or at least one measurable lesion on CT according to RECIST v1.1 (*2*).

All retrospective images interpretations (^{68}Ga-PSMA-11 PET/CT and CI) were compared to the protocols issued prospectively as part of the follow-up: if discordances were observed, another nuclearist and radiologist, blinded to the clinical and imaging data, were to interpret the images to reach a consensus majority (two versus one).

Therapy Response Assessment

Therapy response by ^{68}Ga-PSMA-11 PET/CT and CI were assessed using EAU/EANM PSMA PET/CT (*6*) and PCWG3 (*2*,*14*) criteria, respectively (Table 1). The clinical response rate after 4 weeks (^{68}Ga-PSMA-11 PET/CT) and 12 weeks (^{68}Ga-PSMA-11 PET/CT, CI) of therapy was defined between patients with progressive disease (PD) and non-progressive disease (non-PD), calculated by adding the number of patients with complete response (CR), partial response (PR) and stable response (SR). Biochemical response was defined according to the PCWG3 criteria and patients without PSA progression were classified with non-PD.

Statistical Analyses

Categorical variables were described using relative frequencies (%). Mean ± standard deviation (SD), median, range and interquartile range (IQR) were used to describe normally and non-normally distributed data. The primary outcome measure of PSMA PET/CT response endpoints were reported as changes at 4 and 12 weeks, by means of waterfall plots. The percentage change of PSA, SUV_{max}, SUV_{mean} and PSMA-TL between baseline and W4/W12 was calculated using the following formula:

$$Change\ from\ baseline\ (\%) = 100\left(\frac{New\ value}{Baseline\ value} - 1\right)$$

Additionally, the proportion of patients categorized with non-PD versus PD using PSA or CI-driven response endpoints at 4-12 weeks were reported and compared to ^{68}Ga-PSMA-11 PET/CT response rates. Co-occurrence between W4 ^{68}Ga-PSMA-11 PET/CT and W12 ^{68}Ga-PSMA-11 PET/CT, PSA and CI response categories were tested using Cohen's kappa coefficient (κ). All statistical tests were performed in RStudio (version 1.1.463), with a two-sided *p*-value <0.05 as being considered as statistically significant.

RESULTS

Patients And Imaging

From our database, 165 patients with mCRPC starting a first-line treatment by NHA were extracted. A total of 144 patients were first excluded because ^{68}Ga-PSMA-11 PET/CT was not performed or not at the required timepoints. Out of the 21 remaining patients, 3 were further excluded: 2 patients were registered as mCRPC by the clinician, but no metastatic disease was detected by neither CI nor ^{68}Ga-PSMA-11 PET/CT at the time of NHA initiation, and 1 patient was found to have started his NHA therapy with 1 month delay, consequently, the imaging no longer fitted the inclusion criteria. Overall, 18 patients could be included for further analysis (Supplementary Figure 1, Table 2). PET/CT scans were performed 76.5 ± 14.8 minutes (mean ± SD) after intravenous injection of 154 ± 6.6 MBq (mean ± SD) of ^{68}Ga-PSMA-11. Median time intervals between NHA initiation and baseline ^{68}Ga-PSMA-11 PET/CT, BS and CT-scan were 10 (IQR 6–27), 5 (IQR 4–10) and 5 (IQR 4–12) days, respectively. Follow-up ^{68}Ga-PSMA-11 PET/CT scans at 4 and 12 weeks from NHA initiation were performed after a median time interval of 29 (IQR 28–29) and 85 days (IQR 85–85), respectively. BS and CT-scan at W12 were both performed at a median time interval of 86 days (IQR 86–86 and 86–87, respectively). No disagreement was observed in the prospective and retrospective image interpretations.

Baseline Assessment Of Tumor Burden And PCWG3 Clinical Subtypes

At baseline, ^{68}Ga-PSMA-11 PET/CT detected metastatic disease in all 18 patients (100%), whereas CI identified 14/18 (78%) patients with metastases. Overall, baseline tumor burden quantification (Supplementary Table 1) and subsequent therapy response assessment by ^{68}Ga-PSMA-11 PET/CT could be performed in 16/18 patients. Two patients were non-evaluable by PSMA PET; for one (UPN7), parameters could not be extracted as his PSMA-avid lesions

were below the fixed volume threshold for delineation, and for the other (UPN19), his unique residual lung nodule - highly suspicious given the diagnosis of biopsy-confirmed PC lung metastases 3 years prior to the study - was CT-visible but did not show PSMA tracer uptake. Individual imaging data are listed in Supplementary Figure 2.

Finally, we determined the PCWG3 clinical subtypes using CI and ^{68}Ga-PSMA-11 PET/CT (*14*,*22*). In 14/18 (78%) patients, ^{68}Ga-PSMA-11 PET/CT and CI resulted in concordant PCWG3 subtypes. ^{68}Ga-PSMA-11 PET/CT upstaged 4/18 (22%) patients from non-metastatic by CI to nodal involvement. Moreover, 3 patients considered oligometastatic by CI were upstaged to polymetastatic (UPN5, UPN18 and UPN20) by ^{68}Ga-PSMA-11 PET/CT.

Comparison Of Therapy Response Assessment At Week 12

Based on PSA values at W12, 17/18 (89%) and 1/18 (6%) patients were classified with non-PD and PD, respectively (Supplementary Table 2). Patients with undetectable metastatic disease at baseline by CI (n = 4/18) still showed no lesions at W12.

Overall, 16/18 (89%) patients remained to have measurable disease by ^{68}Ga-PSMA-11 PET/CT, which allowed for treatment response assessment in a larger proportion of patients compared to CI (11/18 [61%]). The non-evaluable patients by CI either had no metastases (4/18 [22%]) or non-measurable disease (3/18 [17%]) (Table 3). Among patients with CI-evaluable disease, 4/18 (22%) patients had RECIST v1.1-measurable disease, and in 7/18 (39%) patients, response assessment was BS-driven due to non-measurable disease on CT (2/18 [11%]) or bone-only disease (5/18 [28%]).

In patients with CI- and ^{68}Ga-PSMA-11 PET/CT-evaluable disease at W12 (n = 11), we observed discordances between imaging techniques in the response categorization for 4/11 (36%) patients (Table 3). Three patients categorized with PD by ^{68}Ga-PSMA-11 PET/CT were

responding to therapy according to CI, and one patient was categorized with PD by CI but not by ^{68}Ga-PSMA-11 PET/CT. The latter (UPN21) demonstrated a 38% increase in the sum of largest diameter of liver metastases at W12 despite a 42% decline in PSA from baseline. Distinction between true progression or size-progression related to necrosis will be clarified with follow-up. Overall, treatment response according to CI, ^{68}Ga-PSMA-11 PET/CT and PSA change were concordantly categorized in 5/11 (46%) patients. Discordant results were observed in 6/11 (55%) patients with PD on either CI and/or ^{68}Ga-PSMA-11 PET/CT despite a PSA response in all but one patient (UPN16). Individual patient data may be found in Supplementary Table 2.

Next, changes in ^{68}Ga-PSMA-11 PET/CT-derived parameters at W12 were compared to baseline (Figure 1A) and concordances in response categorization according to each parameter was investigated (Supplementary Table 3A). PSMA-TL was concordant with tracer uptake (SUV_{max} and SUV_{mean}) and with the appearance of ≥ 2 new lesions in the majority of cases (88%, n = 14/16), whereas the latter was concordant with SUV_{max} in only 12/16 patients (75%).

Early Therapy Response Assessment At Week 4 Using PSMA PET/CT Compared To Week 12

At W4, 17/18 (94%) patients were classified with PSA non-PD whereas 1/18 (6%) patients showed PSA PD (Supplementary Table 2). Similar to W12, 16/18 (89%) patients were ^{68}Ga-PSMA-11 PET/CT-evaluable at W4. Although only a fair agreement was observed in the response categorization between ^{68}Ga-PSMA-11 PET/CT at W4 and CI/PSA at W12, substantial agreement ($\kappa = 0.74$, $p < 0.005$) was observed between ^{68}Ga-PSMA-11 PET/CT at W4 and W12 (Supplementary Table 4). Overall, 7/16 (44%) patients were classified with PD at W4 versus

5/16 (31%) at W12. Importantly, the 5 patients with PD at W12 according to ^{68}Ga-PSMA-11 PET/CT, already fulfilled PD criteria at W4.

When comparing each ^{68}Ga-PSMA-11 PET/CT-derived parameter at W4 and W12, a higher number of discordant results was observed at W4, especially between PSMA-TL and SUV_{max} (Supplementary Table 3). At W4, 4/16 (25%) patients demonstrated a > 30% increase in SUV_{max}, which sustained till W12 in only 1 patient (UPN12). This flare phenomenon led to incorrectly classifying 2 patients (UPN2, UPN17) as progressive at W4 (Figure 1B). For both patients, this flare phenomenon resolved by W12 and patients were classified with non-PD (Figure 1A). Finally, on the contrary of SUV_{max}, SUV_{mean} showed little modifications at W4 (IQR -1.0% to +10.8%) and showed no discordances between W4 and W12. It was only significant in UPN1 who was confirmed progressive at W12.

DISCUSSION

Despite EAU/EANM consensus statements on PSMA PET/CT response assessment criteria (*6*), recommendations or guidelines on which segmentation algorithm and/or PSMA PET/CT-derived parameter(s) to be used are lacking. Various thresholding techniques also exist for PET image segmentation, such as using fixed thresholds, mostly SUV_{max} > 3, or relative thresholds (e.g., 40-45% of the SUV_{max} of the selected lesion) (*16-18,23*). Here, we applied a combined fixed SUV_{max} > 3 and lesion-volume threshold > 0.5ml to select and delineate PSMA-positive lesions. Although potential misinterpretation of background foci as small lesions was avoided in this way, it underestimated the number of liver metastases in 2/16 (12.5%) patients due to the difficulties in delineating lesions from the intense normal liver background activity. Combining liver-based and relative thresholds to limit image sampling errors and compensate spillover effect might also overcome the liver background-lesion discrimination issue (*20-21*).

Moreover, as low-dose CT may underestimate small visceral lesions that can also be PSMA-negative (*24*), PSMA imaging should be combined with a thin-slice contrast-enhanced CT to optimize tumor burden enumeration and monitoring.

In contrast to tracer intensity of uptake, volumetric parameters were most adequate to assess treatment response using the EAU/EANM PSMA PET/CT criteria in our dataset, and the least influenced by the flare phenomenon. (Supplementary Table 3). The underlying mechanism behind PSMA "flare" post androgen deprivation therapy is poorly understood. Similar to BS tumor flare definitions (*25*), the increase in SUV_{max} on ^{68}Ga-PSMA-11 PET/CT may also lead to a concomitant increase in PSMA-TV (and thus, PSMA-TL) due to activity spillover or emergence of previously invisible or non-significant lesions at baseline and result in misinterpretation of PD, which is why the EAU/EANM did not recommend PSMA PET/CT imaging before 12 weeks. The volumetric changes associated with a flare phenomenon may be significant but remain transitory, e.g., UPN17 for whom the increase in SUV_{max} by 54% at W4 lead to the appearance of 4 new lesions and an increase in PSMA-TL by 163%. By W12, the SUV_{max} decreased by 70% (i.e., 16% lower than baseline), the previously observed new lesions disappeared completely and PSMA-TL decreased by 49% from baseline (Figure 1).

When comparing PSMA PET/CT at W4 and W12 we made three observations : (1) An increase in SUV_{max} at W4 with a decrease in PSMA-TL, with or without new lesions, was confirmed at W12 to be linked to a flare phenomenon (e.g. UPN2, UPN14), (2) New lesions at W4 without a > 30% increase in SUV_{max}, independently of PSMA-TL, were confirmed progressive at W12 (e.g. UPN1, UPN13), and (3) when both SUV_{max} and PSMA-TL increase at W4, with or without new lesions, PD cannot be distinguished from flare (e.g., UPN12, UPN17). Thus, defining PD based on SUV_{max} alone does not seem feasible and SUV_{max} should always be evaluated in combination with the other parameters to limit misinterpretation of flare as PD.

Although at early time points SUV_{max} may hint the nuclearist on the presence of a flare phenomenon, no flare was observed after W12 and SUV_{max} at W12 did not change therapeutic response evaluation in our cohort.

Furthermore, it should be reminded that the EAU/EANM recommendations on the use of uptake thresholds based on the PET response criteria in solid tumors (PERCIST) were arbitrarily chosen as these have only been validated for ^{18}F-FDG PET. Even though tracer uptake in PSMA imaging does not reflect direct metabolic activity, the modified PERCIST criteria were shown to perform better than morphological criteria such as RECIST in metastatic PC, as molecular changes appear earlier than morphological ones (*26*). Although the aim of this study was not to validate PERCIST criteria in PSMA imaging, we observed that caution should be taken when using those criteria especially for early imaging. Indeed, changes in tracer uptake are not synonymous of PD but rather seem to reflect biomolecular changes leading to modifications in PSMA expression, as seen by the heterogeneous responses at the patient-level, and further highlighting the fact that additional data are needed to enlighten us on the mechanisms of PSMA expression and tracer uptake. Besides flare, the modulation of PSMA expression may also reflect intrinsic tumor tissue modifications conferring potential treatment resistance (*10*). In our data, the 5/16 (31%) patients with PD at W12 according to PSMA PET/CT already met progression criteria at W4. Two of those patients had PD according to CI (UPN12, UPN13), and one patient had PSA progression (UPN16).

Using these EAU/EANM recommendations, patients with non-PD may be further subdivided between SR, PR and CR depending on the reduction in both SUV_{max} and PSMA-TL (Table 1). These criteria may however need to be revised, as the extent of reduction in SUV_{max} and volumetric parameters seem rarely comparable (Figure 1). For example, at W12, 4/11 patients would be classified with PR (>30% reduction in both SUV_{max} and volumetric

parameters) and 7/11 patients would be classified with SR even though 5/7 achieved a significant >30% reduction in PSMA-TL. Data is also lacking on the thresholds that should be used, especially to define PD. For example, in the current recommendations PD may be defined by an increase in 30% of tumor volume, but the recently proposed RECIP criteria have set a lower threshold of 20% and have found these parameters to carry prognostic value after ^{177}Lu-PSMA therapy (*27*). Moreover, on the contrary of PERCIST, RECIP do not include tracer uptake modifications to evaluate response to ^{177}Lu-PSMA therapy. Nonetheless, this parameter could be of potential use to improve patient stratification before therapy initiation and was recently shown to predict higher likelihood of response to ^{177}Lu-PSMA therapy than cabazitaxel (*28*).

The integration of minimal-invasive molecular biomarkers, such as circulating tumor DNA (ctDNA), with novel imaging might facilitate in the discrimination between PD and flare and guide therapeutic intervention at early response assessment timepoints. As shown in a recent work, ctDNA does not seem to rise in patients presenting with PSA or bone flare on CI (*29*). Additionally, the introduction of PSMA PET/CT in mCRPC might improve disease control rates by identifying oligo-resistant/-progressive lesions, which could be subjected to e.g., metastasis-directed therapy, whilst preserving the antitumoral effect of the systemic agent on the responsive lesions (*12-13*).

Overall, molecular imaging parameters have the potential to act as predictive biomarkers of response to treatment, but whether modifying treatment plan according to them improves patient outcome is yet to be determined in larger prospective trials. The main limitation of this study was the small number of patients that were retrospectively included, in addition to the absence of validated criteria for interpretation of PSMA PET/CT scans and delineation method.

CONCLUSION

Volumetric assessments of PSMA PET/CT imaging can improve metastasis detection and image-based response assessment in NHA-treated patients with mCRPC. At early imaging timepoints flare phenomena can be observed, typically denoted by a SUV_{max} increase, which resolves by week 12. Overall, although early response assessments at W4 need to be approached with caution, our comparative analysis of PSMA PET/CT imaging at 4 and 12 weeks revealed a substantial agreement in the therapy response assessment, which warrants further investigation to distinguish PD from flare at W4.

KEY POINTS

QUESTION: Is the use of EAU/EANM recommendations on PSMA PET/CT feasible for therapy assessment of mCRPC patients and can early imaging detect resistance to treatment?

PERTINENT FINDINGS: EAU/EANM recommendations improve PSMA imaging reporting and evaluation of NHA-treated mCRPC patients, but caution should be taken when interpreting SUV_{max} on early imaging. Early PSMA uptake modifications occur as early as 4 weeks post-therapy and revealed substantial agreement with the imaging at week 12.

IMPLICATIONS FOR PATIENT CARE: Early imaging may contribute to improving therapy selection and sequencing in the mCRPC context. Adding biological biomarkers may provide further insight on the biology behind PSMA expression and help distinguish early progressive disease from flare.

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29.Conteduca V, Wetterskog D, Scarpi E, et al. Plasma tumor DNA as an early indicator of treatment response in metastatic castration-resistant prostate cancer. *Brit J Cancer*. 2020;123:982–987.

GRAPHICAL ABSTRACT

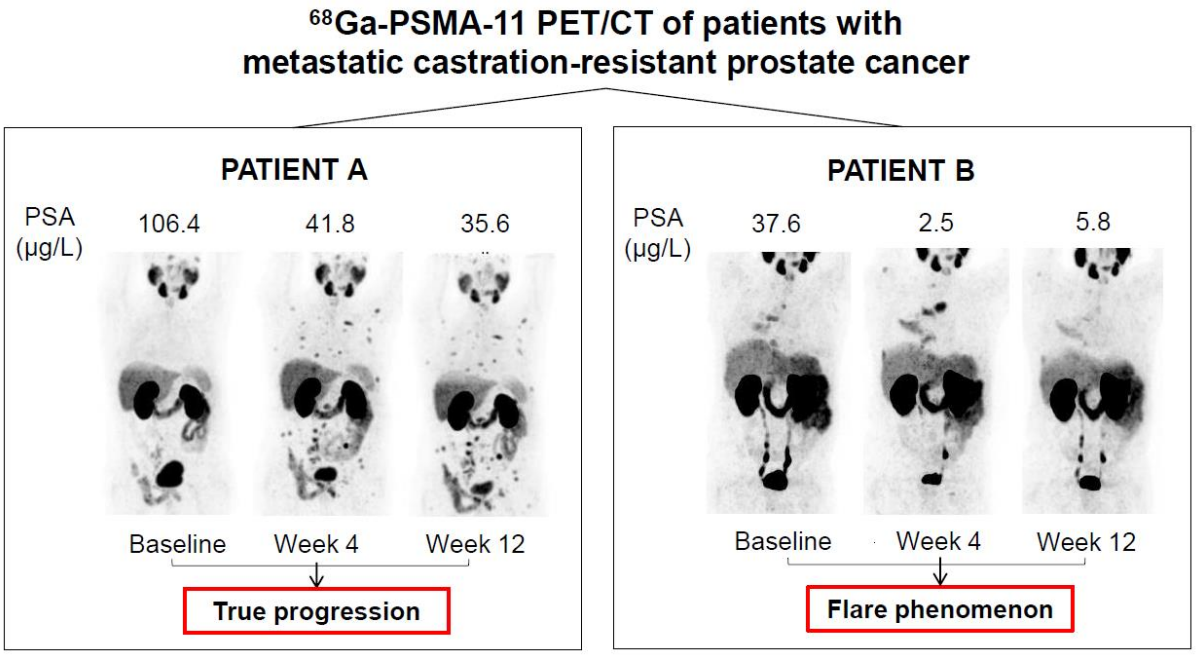
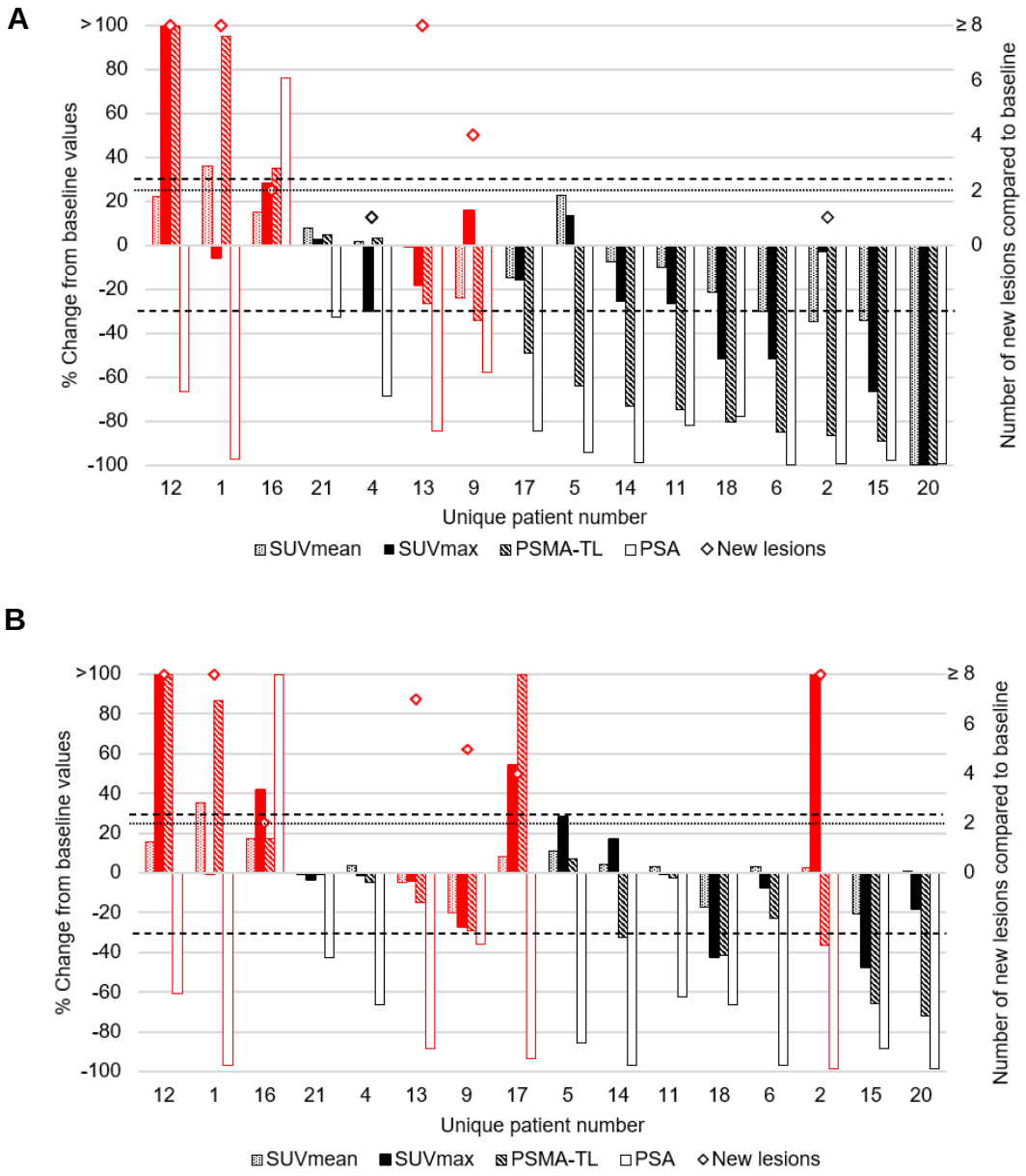


FIGURE 1: Waterfall plots of changes in PSMA PET/CT parameters (SUV_{mean}, SUV_{max}, PSMA-TL, PSA and the number of new lesions) at W12 (Figure 1A) and W4 (Figure 1B) in comparison to baseline PSMA PET/CT (*n* = 16), stratified according to PSMA-TL and therapy response assessment (i.e., non-PD in black and PD in red, as defined in Table 1).



The ± 30% cut-off is represented by the horizontal dashed line. The *n* = 2 lesions cut-off is represented by the dotted line. Patients in Figure 1B are presented in the same order as Figure 1A.

TABLE 1: Therapy response assessment criteria based on imaging.

		NON-PROGRESSIVE DISEASE			PROGRESSIVE DISEASE
		Complete Response (CR)	**Partial Response (PR)**	**Stable Response (SR)**	**(PD)**
PCWG3 imaging response criteria	**CT** (*2*)	Disappearance of all lesions	Decrease of ≥ 30% in the sum of target lesions (without new lesions or non-target lesions progression)	Not meeting the criteria for PR, CR or PD	Increase of ≥ 20% in the sum of target lesions, or unequivocal progression of non-target lesions or appearance of new lesions
	BS (*14*)	Disappearance of all suspicious lesions	No new lesion or appearance of < 2 new lesions		Appearance of at least ≥ 2 new lesions confirmed on subsequent scan
EAU/ EANM PSMA response criteria	**PSMA PET/CT** (*6*)	Disappearance of any lesion with tracer uptake	Reduction of uptake and tumor PET volume by > 30%	Change in uptake and tumor PET volume by ± ≤ 30%, without evidence of new lesions	Increase of uptake or tumor PET volume by > 30% And/or appearance of ≥ 2 new lesions (with or without CT change)

TABLE 2: Patient characteristics at study entry.

Characteristics	Value * (*n* = 18 patients)
Mean age (±SD)	73.1 (±6.1) years
Median PSA at baseline (IQR)	8.04 (5.96–24.8) ng/ml
Median time between initiation of first-generation ADT and mCRPC status (IQR)	47.5 (27.0–79.0) months
Patients with prior local treatment RP only RP + ePLND Exclusive RT only ePLND + aborted RP + RT	14 (78%) 4 (22%) 3 (17%) 5 (28%) 2 (11%)
Type of prior systemic therapy before resistance to castration First-generation ADT Upfront chemotherapy	 16 (89%) 2 (11%)
ISUP grade group V.8.0 at time of diagnosis Grade 1 Grade 2 Grade 3 Grade 4 Grade 5 Unknown	 2 (11%) 2 (11%) 3 (17%) 6 (33%) 4 (22%) 1 (6%)
First-line treatment initiated for mCRPC Enzalutamide (160mg daily) Abiraterone (1000mg daily)	 17 (94%) 1 (6%)

RP = Radical Prostatectomy, ePLND = extended Pelvic Lymph Node Dissection, RT = radiotherapy, ISUP = International Society of Urological Pathology.

* Values are reported as numbers of patients with percentages in brackets, unless otherwise indicated.

TABLE 3: Therapy response assessment at week 12 according to PCWG3 CI, biochemical (PSA) and EAU/EANM PSMA PET/CT response criteria.

Unique Patient number	CI	PSA	PSMA PET/CT
7	*NE_0*	Non-PD	*NE_{nt}*
11	*NE_0*	Non-PD	Non-PD
14	*NE_0*	Non-PD	Non-PD
6	*NE_0*	Non-PD	Non-PD
5	*NE_{nm}*	Non-PD	Non-PD
18	*NE_{nm}*	Non-PD	Non-PD
19	*NE_{nm}*	Non-PD	*NE_{nt}*
1	Non-PD†	Non-PD	PD
4	Non-PD†	Non-PD	Non-PD
9	Non-PD†	Non-PD	PD
15	Non-PD†	Non-PD	Non-PD
16	Non-PD†	PD	PD
2	Non-PD††	Non-PD	Non-PD
17	Non-PD††	Non-PD	Non-PD
20	Non-PD††	Non-PD	Non-PD
12	PD†	Non-PD	PD
13	PD†	Non-PD	PD
21	PD††	Non-PD	Non-PD

NE = Not Evaluable (NE_0 if no metastasis were detected since baseline, NE_{nm} if no measurable lesion was visible on CT and without bone lesions on BS, NE_{nt} if lesions visible but non-evaluable by PSMA imaging).

† Patients for which response assessment was BS-driven.

†† Patients with measurable lesions according to RECIST v1.1.

SUPPLEMENTARY DATA

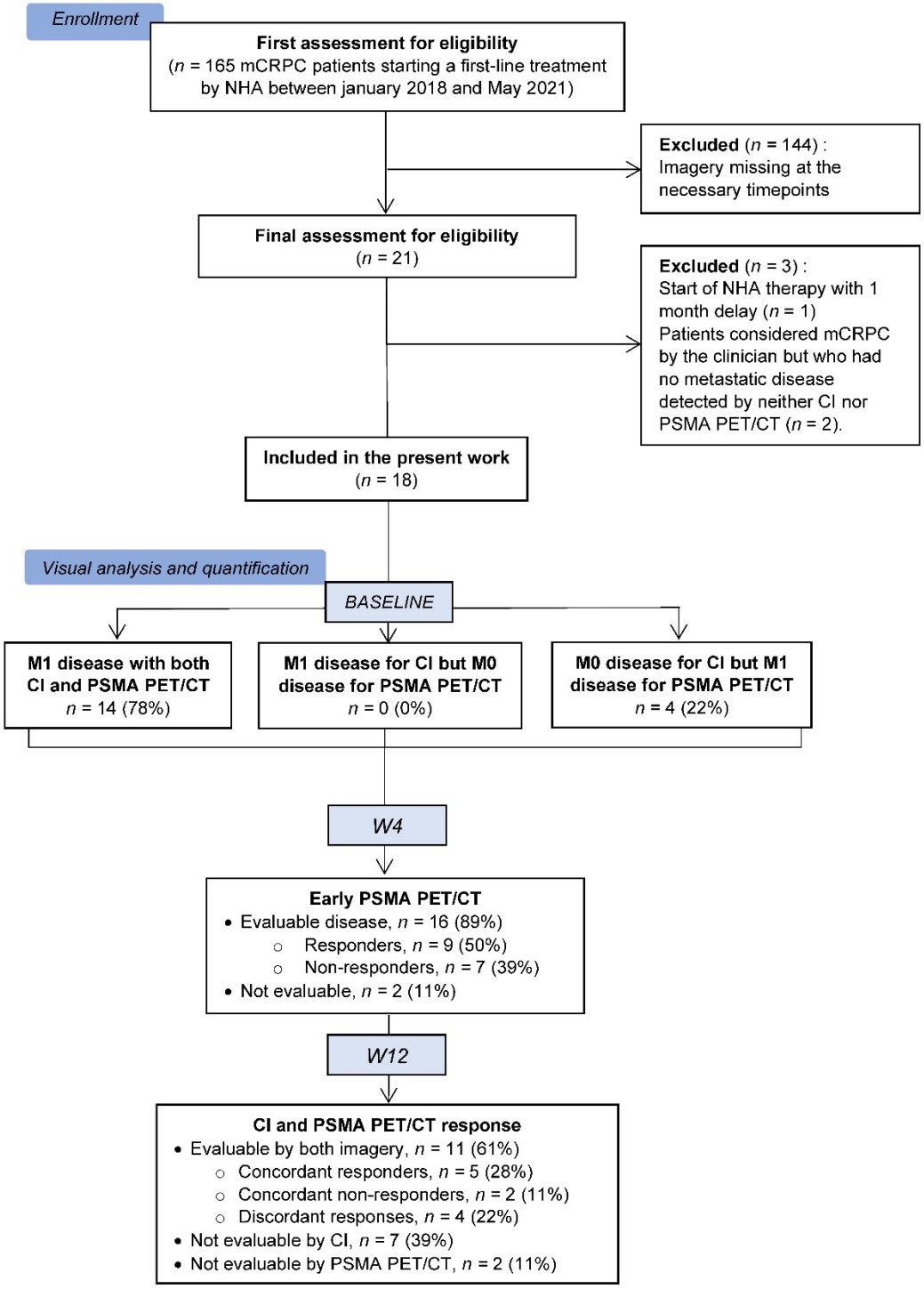
^{68}Ga-PSMA-11 PET/CT Image Acquisition and Tumor Volume Delineation

Whole-body scans from cranial base to the upper femur were acquired in a GEMINI TF Big Bore or a GEMINI TF 16 PET scanner (Philips Medical Systems, Cleveland, OH, USA), for which ^{68}Ga crosscalibration was performed. A low dose CT (3-mm slice thickness, tube voltage 120 kV) was performed for PET images attenuation correction, followed by a PET emission scan of 60 to 120s per bed position (depending on the patient's body mass index with bed overlap of 50%). Additionally, a thin-slice thoraco-abdomino-pelvic CT without injection of intravenous contrast agent was performed (1-mm slice thickness, tube voltage 120 kV). Reconstruction of PET images was done with standard 4 x 4 x 4 mm³ voxels using iterative list mode time-of-flight algorithm. Corrections for attenuation, dead-time, random and scatter events were applied. PSMA PET/CT images were initially analysed by an experienced nuclear medicine physician who was blinded to the clinical data. A positive lesion was defined as an area of focal uptake above the background level at a typical location of PC metastasis, with or without underlying CT abnormality.

Whole-body PSMA-positive tumor volume delineation was performed using a semi-automatic lesion delineation workflow at baseline, W4 and W12. A volume of interest including the whole body was manually selected. Then, a fully automated preselection of PSMA-positive prostate cancer (PC) lesions was applied to delineate lesions with an absolute standardized uptake value (SUV) threshold set at 3.0, as previously described (*16-18*). Additional lesion thresholds were applied: > 0.5 ml to avoid small non-PC lesions and < 500ml to avoid the automated delineation of the liver, kidneys, bowels, and retroperitoneal para-aortic lymph nodes as a single volume and limit large manual organ removal errors. For PSMA-positive para-aortic lymph nodes that were overlooked by this technique, an additional volume of interest centered on the para-aortic region was manually set and lymph nodes were then delineated using the same thresholds (SUV > 3.0 and volume > 0.5 ml). The observer used a clearing option to manually remove areas of known physiological uptake (*19*).

SUPPLEMENTARY FIGURES

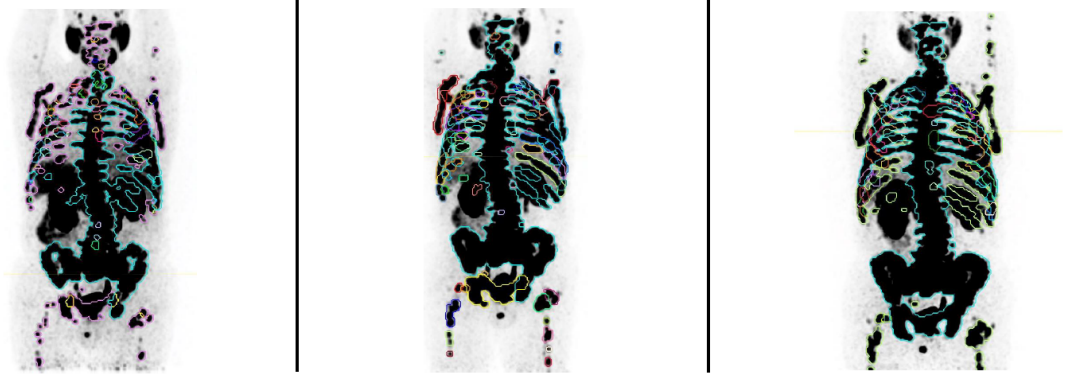
Supplementary Figure 1: Consort flow diagram.



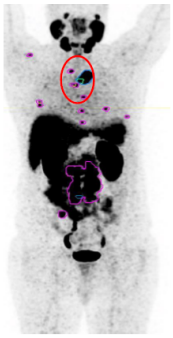
M1 = metastatic disease, M0 = no metastatic disease.

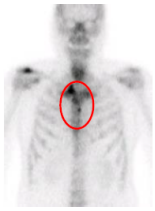
Supplementary Figure 2: Individual data from PSMA PET/CT-evaluable patients (n = 16) at baseline, week 4 and week 12. Each subpart of the figure corresponds to one patient, as denoted by their unique patient number (UPN) in the upper left corner and includes: a table, PSMA PET/CT maximal intensity projections (MIP) with the overall delineated tumor volume (shown by multiple-colored contours) and for some patients, relevant images from conventional imaging. Color coding in the tables is as follows: red if criterion fits PD definition, green if criterion fits non-PD definition. All images are shown with a SUV scale of 0 – 5 if not otherwise specified on the figure itself.

UPN1	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	300.9	10.3	-96.6	8.3	-97.2
PSMA-TL	17649.7	32920.1	+86.5	34457	+95.2
SUV_{max}	30.1	30.1	-0.13	28.4	-5.78
SUV_{mean}	6.32	8.55	+35.3	8.61	+36.2
New lesions from baseline		9		11	
Metastasis location PSMA PET/CT Conventional imaging	 Bone only Bone only	 Bone only -		 Bone only Bone only	

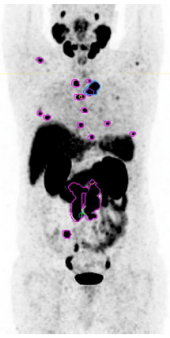


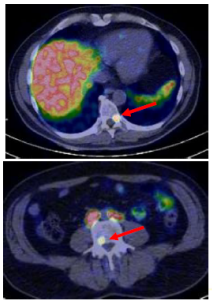
UPN2	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	7.83	0.11	-98.6	0.03	-99.6
PSMA-TL	2298.5	1456.4	-36.6	302.8	-86.8
SUV_{max}	30.9	63.8	+106.4	30.1	-2.55
SUV_{mean}	9.3	9.5	+2.27	6.01	-35.0
New lesions from baseline		9		1	
Metastasis location PSMA PET/CT Conventional imaging	Bone + lymph nodes Bone + lymph nodes	Bone + lymph nodes -		Bone + lymph nodes Bone + lymph nodes	



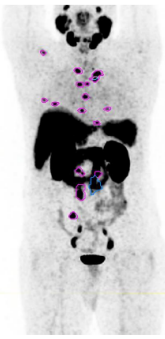


Only 4 metastatic lesions were described on bone scintigraphy (right) versus 16 bone lesions on PSMA PET/CT (left).

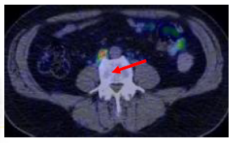




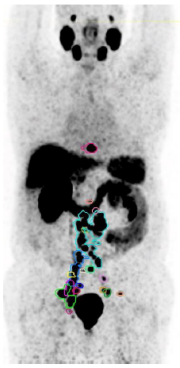
Examples of new bone lesions (arrows) appearing due to flare on PSMA PET/CT.



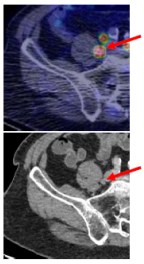
Disappearance of the small bone lesion (arrow) that appeared after a flare phenomenon at W4 on PSMA PET/CT.

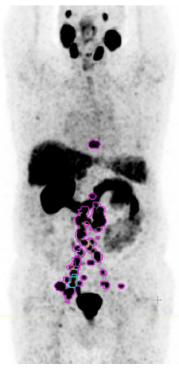


UPN4	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	29.0	9.8	-66.2	9.03	-68.8
PSMA-TL	1982.9	1891.5	-4.61	2049.0	+3.33
SUV_{max}	215.4	212.8	-1.20	151.2	-29.8
SUV_{mean}	10.6	11.01	+3.67	10.8	+1.88
New lesions from baseline		0		1	
Metastasis location PSMA PET/CT Conventional imaging	Bone + lymph nodes Bone + lymph nodes	Bone + lymph nodes -		Bone + lymph nodes Bone + lymph nodes	

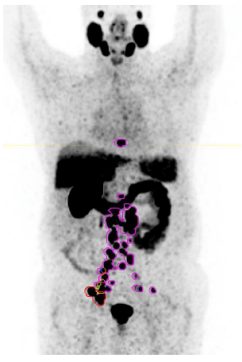


Example of an infracentimetric pathological lymph node (arrow) on PSMA PET/CT (upper image) versus CT (lower image).

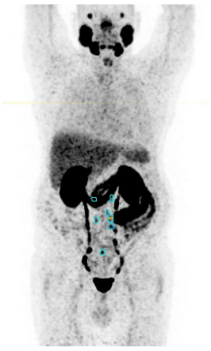
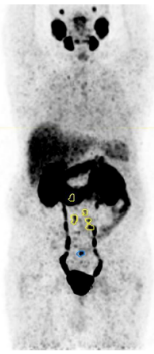
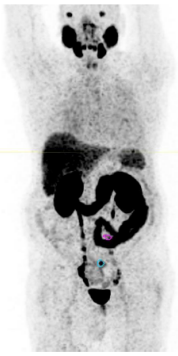




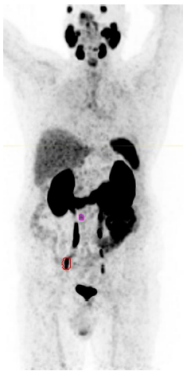
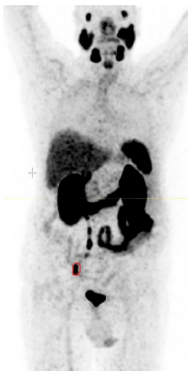
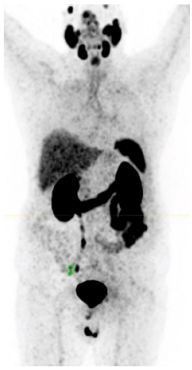
Only 2 supracentimetric lymph nodes were described as pathological on CT versus >20 on PSMA PET/CT.



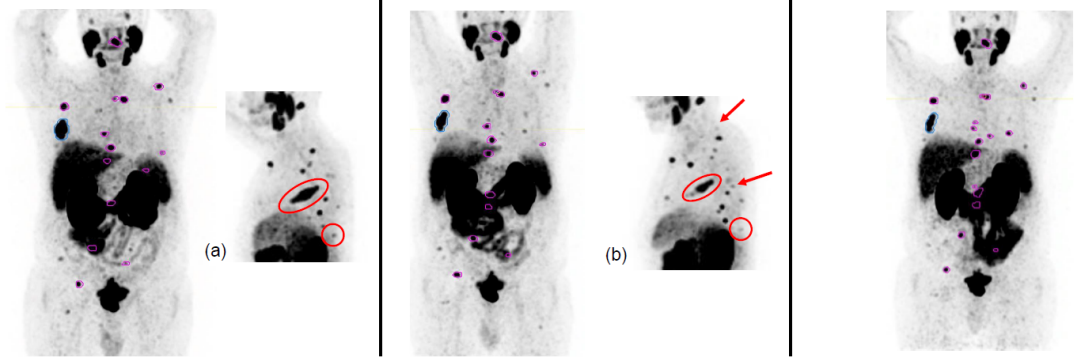
UPN5	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	3.06	0.45	-85.3	0.18	-94.1
PSMA-TL	38.0	40.6	+6.85	13.8	-63.8
SUV_{max}	8.31	10.7	+28.4	9.49	+14.2
SUV_{mean}	3.98	4.41	+10.8	4.88	+22.6
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes No measurable lesion	Lymph nodes -		Lymph nodes No measurable lesion	

UPN6	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	8.06	0.27	-96.7	0.01	-99.9
PSMA-TL	38.4	29.6	-23.1	5.72	-85.1
SUV_{max}	10.5	9.75	-7.14	5.01	-52.3
SUV_{mean}	5.14	5.31	+3,31	3.58	-30.4
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes No metastasis	Lymph nodes -		Lymph nodes No metastasis	

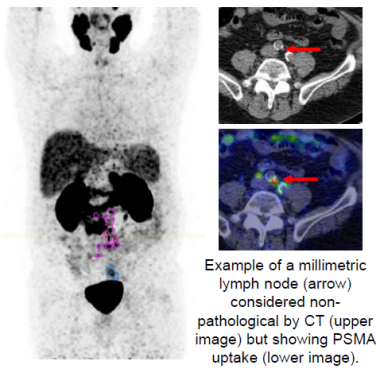




UPN9	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	58.5	37.6	-35.8	24.6	-57.9
PSMA-TL	612.1	433.0	-29.3	402.0	-34.3
SUV_{max}	37.8	27.4	-27.3	43.6	+15.5
SUV_{mean}	9.13	7.31	-19.9	6.96	-23.8
New lesions from baseline		5		4	
Metastasis location PSMA PET/CT Conventional imaging	Bone + lymph nodes Bone only	Bone + lymph nodes -		Bone + lymph nodes Bone only	

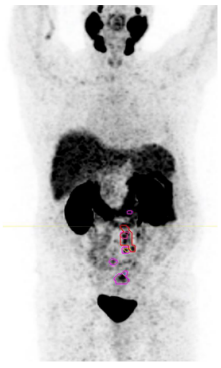


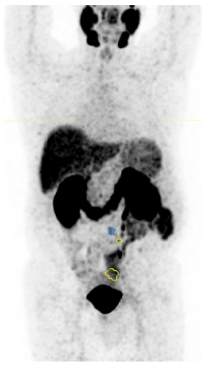
MIP side views were added for clarity (a, b). In comparison to baseline (a), new lesions (arrows) are appearing at W4 (b) while other lesions seem to respond to therapy (circles).

UPN11	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	6.65	2.50	-62.4	1.21	-81.8
PSMA-TL	103.73	101.1	-2.53	26.0	-74.9
SUV_{max}	8.38	8.32	-0.72	6.13	-26.9
SUV_{mean}	4.06	4.19	+3.20	3.66	-9.85
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes No metastasis	Lymph nodes -		Lymph nodes No metastasis	

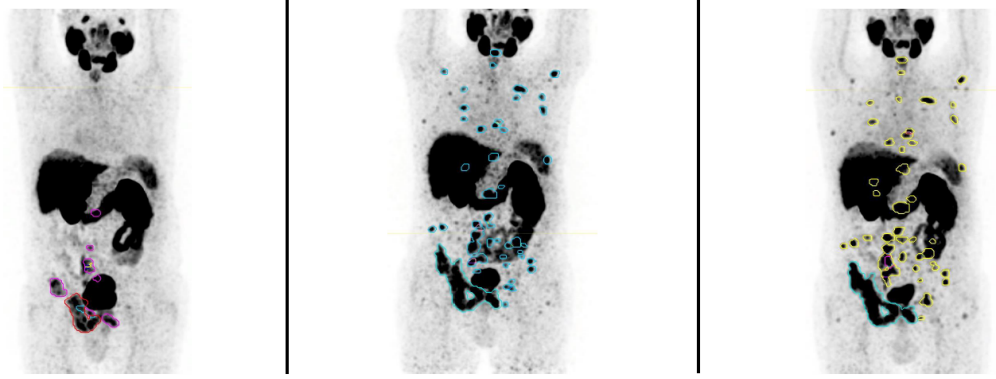


Example of a millimetric lymph node (arrow) considered non-pathological by CT (upper image) but showing PSMA uptake (lower image).

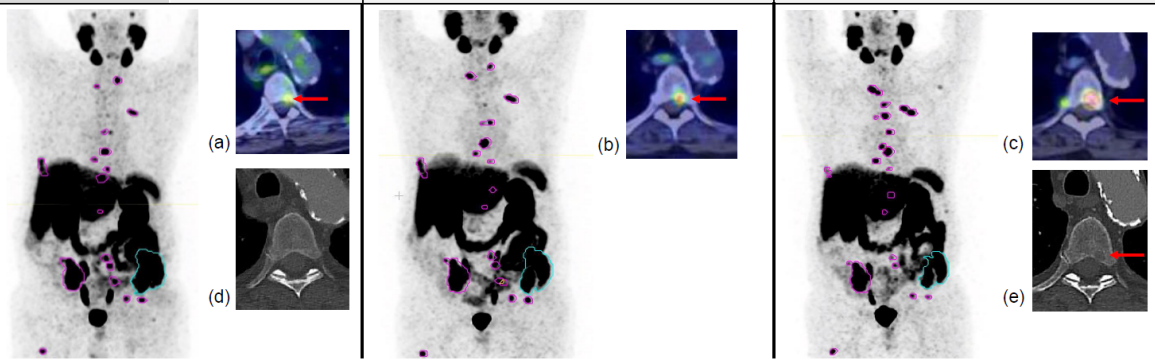




UPN12	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	106.4	41.8	-60.7	35.6	-66.6
PSMA-TL	683.32	2047.8	+199.7	2566.0	+275.5
SUV_{max}	11.0	26.7	+143.7	24.2	+120.8
SUV_{mean}	4.52	5.21	+15.3	5.53	+22.4
New lesions from baseline		>20		>20	
Metastasis location PSMA PET/CT Conventional imaging	Bone and lymph nodes Bone only	Bone and lymph nodes -		Bone and lymph nodes Bone only	

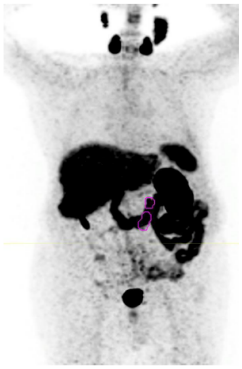
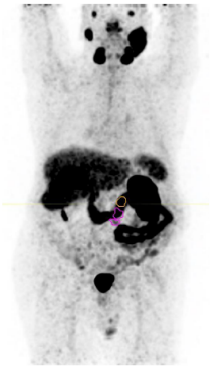
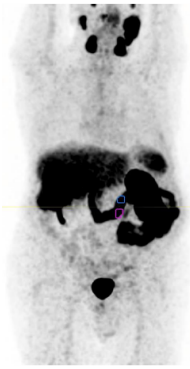


UPN13	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	12.47	1.44	-88.5	1.92	-84.6
PSMA-TL	2421.8	2056.6	-15.1	1779.5	-26.5
SUV_{max}	53.1	50.8	-4.24	43.8	-17.5
SUV_{mean}	8.69	8.26	-4.95	8.68	-0.12
New lesions from baseline		7		9	
Metastasis location PSMA PET/CT Conventional imaging	Bone + lymph nodes Bone only	Bone + lymph nodes -		Bone + lymph nodes Bone only	

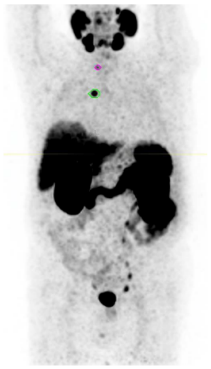
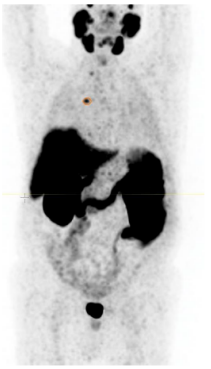
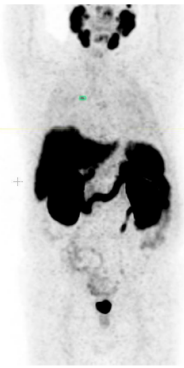


Evolution of a small bone lesion (arrow) that was detected on PSMA PET/CT at baseline (a), week 4 (b) and week 12 (c) but neither by CT (d) nor BS. The latter appeared as an osteolytic bone metastasis on CT only after 12 weeks (e).

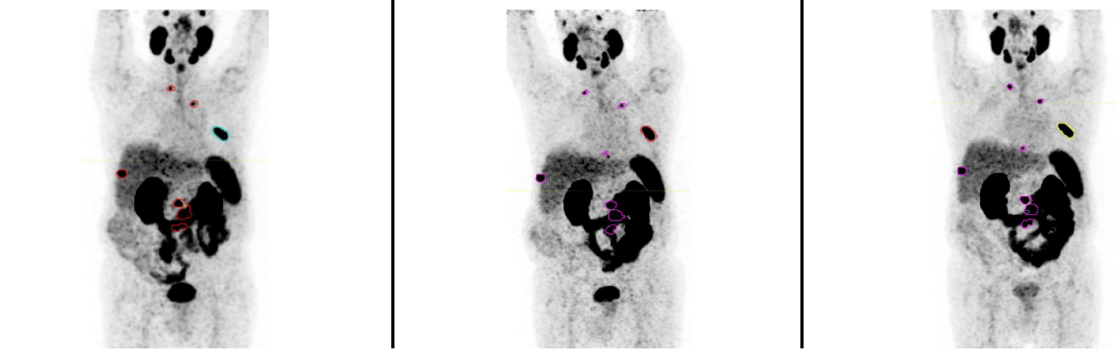
UPN14	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	3.21	0.10	-96.9	0.03	-99.1
PSMA-TL	51.9	35.16	-32.3	13.8	-73.5
SUV_{max}	8.26	9.68	+17.2	6.1	-26.2
SUV_{mean}	4.16	4.33	+4.09	3.84	-7.69
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes No metastasis	Lymph nodes -		Lymph nodes No metastasis	

UPN15	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	1.92	0.22	-88.5	0.04	-97.9
PSMA-TL	24.4	8.28	-66.04	2.59	-89.4
SUV_{max}	13.2	6.93	-47.3	4.36	-66.9
SUV_{mean}	5.6	4.46	-20.4	3.67	-34.5
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Bone Bone	Bone -		Bone Bone	

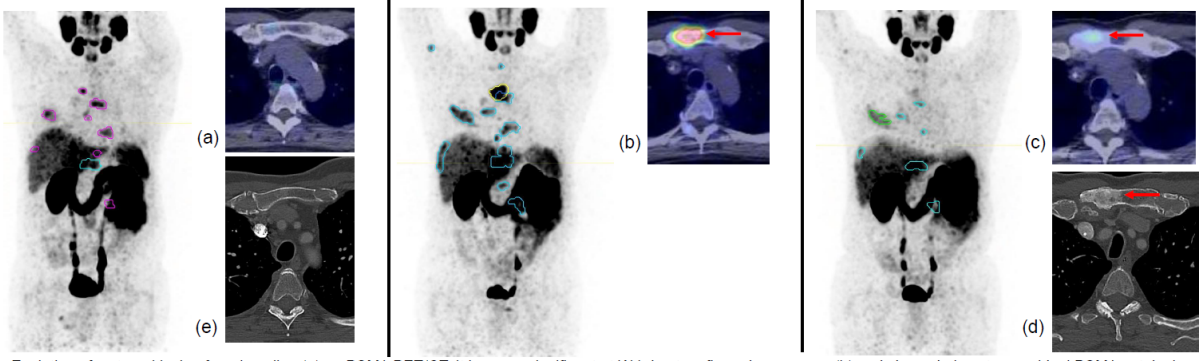




UPN16	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	8.02	27.5	+242.6 *	14.1	+75.9
PSMA-TL	807.5	945.4	+17.1	1090.2	+35.0
SUV_{max}	78.6	111.4	+41.7	100.6	+27.9
SUV_{mean}	13.8	16.2	+17.1	15.9	+14.8
New lesions from baseline		2		2	
Metastasis location PSMA PET/CT Conventional imaging	 Bone Bone		 Bone -		 Bone Bone



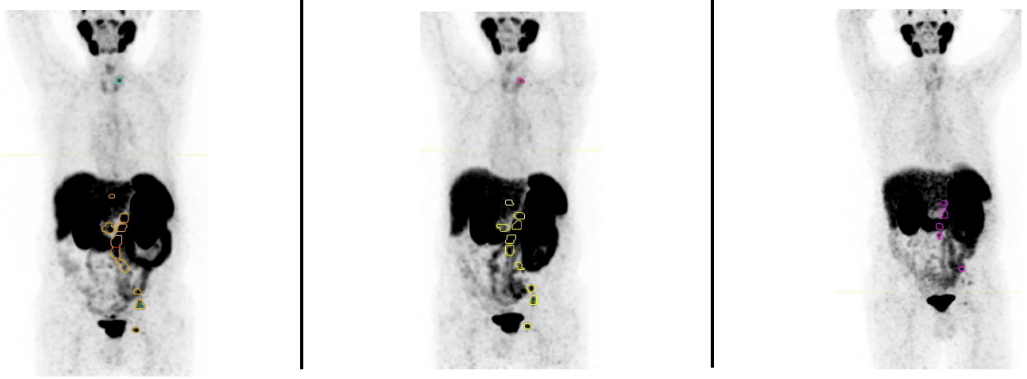
*For this patient, PSA value at week 4 may have been influenced by a concomitant pneumonia requiring a hospitalization at the same time-point. At the later time-points, PSA kept increasing in comparison to baseline (+76% at week 12, +142% at week 20 and +262% at week 24).

UPN17	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	37.6	2.54	-93.2	5.84	-84.5
PSMA-TL	233.0	612.3	+162.8	118.3	-49.2
SUV_{max}	7.50	11.6	+54.3	6.3	-16.0
SUV_{mean}	4.16	4.50	+8.17	3.55	-14.7
New lesions from baseline		4		0	
Metastasis location PSMA PET/CT Conventional imaging	 Bone + visceral Bone + visceral		 Bone + visceral -		 Bone + visceral Bone + visceral

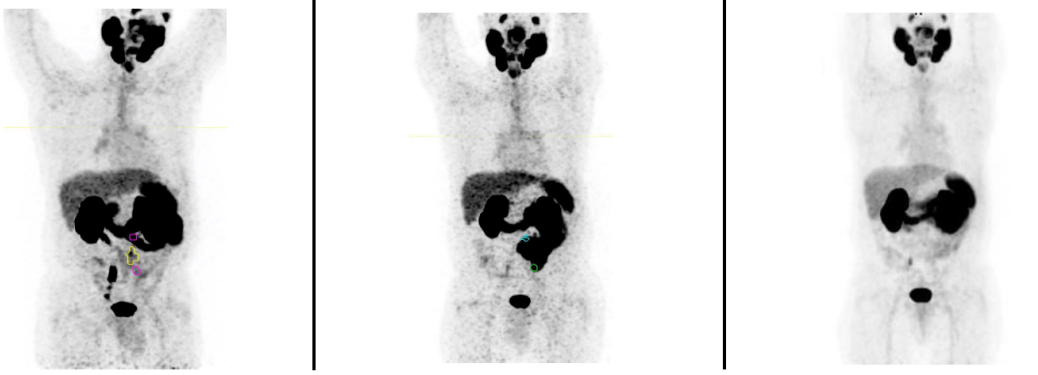


Evolution of a sternal lesion from baseline (a) on PSMA PET/CT. It became significant at W4 due to a flare phenomenon (b) and showed almost no residual PSMA uptake by week 12 (c). On CT, a sclerotic bone lesion appeared at week 12, as denoted by the arrow (d). Corresponding baseline CT image is shown for comparison (e).

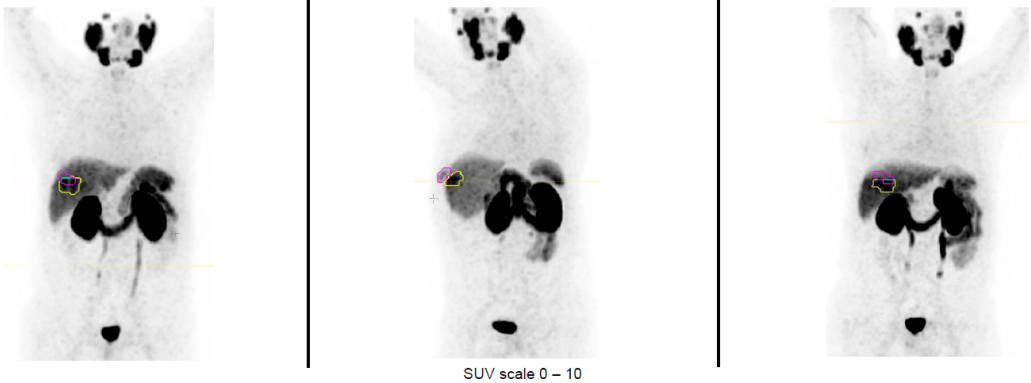
UPN18	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	6.17	2.08	-66.3	1.36	-78.0
PSMA-TL	158.0	92.3	-41.5	30.5	-80.7
SUV_{max}	14.6	8.42	-42.5	7.06	-51.8
SUV_{mean}	5.1	4.22	-17.3	4.00	-21.6
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes No measurable lesion	Lymph nodes -		Lymph nodes No measurable lesion	



UPN20	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	5.89	0.08	-98,6	0.02	-99.7
PSMA-TL	23.8	6.62	-72.2	0.00	-100.0
SUV_{max}	6.25	5.14	-17.8	0.00	-100.0
SUV_{mean}	3.65	3.67	+0.55	0.00	-100.0
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	Lymph nodes Lymph nodes	Lymph nodes -		Lymph nodes Lymph nodes	



UPN21	Baseline	Week 4		Week 12	
	Values	Values	% change from baseline	Values	% change from baseline
PSA (ng/ml)	3.51	2.01	-42.7	2.37	-32.5
PSMA-TL	210.3	209.5	-0.40	220.3	+4.76
SUV_{max}	14.4	13.9	-3.34	14.8	+2.99
SUV_{mean}	7.72	7.64	-1.04	8.33	+7.90
New lesions from baseline		0		0	
Metastasis location PSMA PET/CT Conventional imaging	 Bone + visceral Bone + visceral	 Bone + visceral -		 Bone + visceral Bone + visceral	



SUV scale 0 – 10

SUPPLEMENTARY TABLES

Supplementary Table 1: Quantitative measurements extracted from PSMA PET/CT (n = 16). Results are expressed with median values (IQR).

		Baseline	W4	W12
PSMA parameters	SUV_{max}	13.8 (8.4–32.6)	12.7 (9.4–35.3)	12.1 (6.1–33.5)
	PSMA-TV	43.5 (11.8–160.0) ml	42.9 (8.9–158.4) ml	29.9 (3.4–98.9) ml
	SUV_{mean}	5.4 (4.2–8.8)	5.3 (4.4–8.3)	5.2 (3.7–8.4)
	PSMA-TL	221.7 (48.6–1101.3)	321.2 (39.2–1565.2)	169.3 (13.8–1262.5)

Supplementary Table 2: Change in PSMA PET/CT parameters, PSA values and conventional imaging in comparison with baseline (*n = 18*). Patients with PD and non-PD are highlighted by a red and green background, respectively.

	WEEK 4					WEEK 12					
UPN	SUV_{max} (%)	PSMA-TL (%)	New lesions on PSMA PET/CT	PSA change (%)	PET response	SUV_{max} (%)	PSMA-TL (%)	New lesions on PSMA PET/CT	PSA change (%)	PET response	CI response
7 *	*n.a.*	*n.a.*	*n.a.*	-52	*n.a.*	*n.a.*	*n.a.*	*n.a.*	-65	*n.a.*	*n.a.*
19 *	*n.a.*	*n.a.*	*n.a.*	-98	*n.a.*	*n.a.*	*n.a.*	*n.a.*	-100	*n.a.*	*n.a.*
1	-0	+87	9	-97	PD	-6	+95	11	-97	PD	Non-PD
2	+106	-37	9	-99	PD	-3	-87	1	-100	Non-PD	Non-PD
9	-27	-29	5	-36	PD	+16	-34	4	-58	PD	Non-PD
12	+144	+200	>20	-61	PD	+121	+276	>20	-67	PD	PD
13	-4	-15	7	-89	PD	-18	-27	9	-85	PD	PD
16	+42	+17	2	+243 †	PD	+28	+35	2	+76	PD	Non-PD
17	+54	+163	4	-93	PD	-16	-49	0	-85	Non-PD	Non-PD
4	-1	-5	0	-66	Non-PD	-30	+3	1	-69	Non-PD	Non-PD
5	+28	+7	0	-85	Non-PD	+14	-64	0	-94	Non-PD	*n.a.*
6	-7	-23	0	-97	Non-PD	-52	-85	0	-100	Non-PD	*n.a.*
11	-1	-3	0	-62	Non-PD	-27	-75	0	-82	Non-PD	*n.a.*
14	+17	-32	0	-97	Non-PD	-26	-74	0	-99	Non-PD	*n.a.*
15	-47	-66	0	-89	Non-PD	-67	-89	0	-98	Non-PD	Non-PD
18	-43	-42	0	-66	Non-PD	-52	-81	0	-78	Non-PD	*n.a.*
20	-18	-72	0	-99	Non-PD	-100	-100	0	-100	Non-PD	Non-PD
21	-3	0	0	-43	Non-PD	+3	+5	0	-33	Non-PD	PD

Values are listed as whole numbers for clarity. UPN = Unique Patient Number, n.a. = not applicable.

* These two patients were non-evaluable by PSMA PET/CT (PN19 with a unique PSMA-negative lung nodule; PN7 with a small positive node but below the thresholds for tumour volume delineation).

† For this patient, PSA value at week 4 may have been influenced by a concomitant pneumonia requiring a hospitalization at the same time-point. At the later time-points, PSA kept increasing in comparison to baseline (+76% at week 12, +142% at week 20 and +262% at week 24).

Supplementary Table 3: Concordance between PSMA PET/CT parameters at week 12 (Supplementary Table 3A) and week 4 (Supplementary Table 3B) in the evaluable patients (n = 16). Patients in Table 3B are displayed in the same order as patients in Table 3A. For clarity, patients with PD are highlighted by a red background and those with non-PD by a green background.

A

Unique patient number	≥ 2 new lesions	PSMA-TL	SUV_{max}	SUV_{mean}
1	PD	PD	Non-PD	PD
12	PD	PD	PD	Non-PD
16	PD	PD	Non-PD	Non-PD
9	PD	Non-PD	Non-PD	Non-PD
13	PD	Non-PD	Non-PD	Non-PD
2	Non-PD	Non-PD	Non-PD	Non-PD
4	Non-PD	Non-PD	Non-PD	Non-PD
5	Non-PD	Non-PD	Non-PD	Non-PD
6	Non-PD	Non-PD	Non-PD	Non-PD
11	Non-PD	Non-PD	Non-PD	Non-PD
14	Non-PD	Non-PD	Non-PD	Non-PD
15	Non-PD	Non-PD	Non-PD	Non-PD
17	Non-PD	Non-PD	Non-PD	Non-PD
18	Non-PD	Non-PD	Non-PD	Non-PD
20	Non-PD	Non-PD	Non-PD	Non-PD
21	Non-PD	Non-PD	Non-PD	Non-PD

B

Unique patient number	≥ 2 new lesions	PSMA-TL	SUV_{max}	SUV_{mean}
1	PD	PD	Non-PD	PD
12	PD	PD	PD	Non-PD
16	PD	Non-PD	PD	Non-PD
9	PD	Non-PD	Non-PD	Non-PD
13	PD	Non-PD	Non-PD	Non-PD
2	PD	Non-PD	PD	Non-PD
4	Non-PD	Non-PD	Non-PD	Non-PD
5	Non-PD	Non-PD	Non-PD	Non-PD
6	Non-PD	Non-PD	Non-PD	Non-PD
11	Non-PD	Non-PD	Non-PD	Non-PD
14	Non-PD	Non-PD	Non-PD	Non-PD
15	Non-PD	Non-PD	Non-PD	Non-PD
17	PD	PD	PD	Non-PD
18	Non-PD	Non-PD	Non-PD	Non-PD
20	Non-PD	Non-PD	Non-PD	Non-PD
21	Non-PD	Non-PD	Non-PD	Non-PD

Supplementary Table 4: Contingency tables of patients with non-PD versus PD between PSMA PET/CT at week 4 and conventional imaging, PSA and PSMA PET/CT at week 12.

		PSA (W12)		PSMA PET/CT (W12)		Conventional imaging (W12)	
		PD	**Non-PD**	**PD**	**Non-PD**	**PD**	**Non-PD**
PSMA PET/CT (W4)	**PD**	1	4	5	2	2	3
	Non-PD	0	11	0	9	1	5
		n = 16 κ = 0.256, *p* = 0.13		*n = 16* κ = 0.738, *p* < 0.01		*n = 11* κ = 0.241, *p* = 0.39	