Journal of Nuclear Medicine, published on April 14, 2022 as doi:10.2967/jnumed.121.263072

Novel framework for treatment response evaluation using PSMA-PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): an international multicenter study

Andrei Gafita[1,2], Isabel Rauscher[2], Manuel Weber[3], Boris Hadaschik[4], Hui Wang[2], Wesley R. Armstrong[1], Robert Tauber[5], Tristan R. Grogan[6], Johannes Czernin[1], Matthew B. Rettig[7], Ken Herrmann[3], Jeremie Calais[1], Wolfgang A. Weber[2], Matthias R. Benz[1], Wolfgang P. Fendler[3*], Matthias Eiber[2*]

[1]Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, USA
[2]Department of Nuclear Medicine, Technical University Munich, Klinikum rechts der Isar, Munich, Germany
[3]Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany
[4]Department of Urology, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany
[5]Department of Urology, Technical University Munich, Klinikum rechts der Isar, Munich, Germany
[6]Department of Medicine Statistics Core, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California
[7]Department of Urology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California.
* joint senior authorship

Corresponding author: Andrei Gafita, MD
Ahmanson Translational Theranostics Division,
Department of Molecular and Medical Pharmacology,
David Geffen School of Medicine,
University of California, Los Angeles
200 Medical Plaza, Suite B114-61,
Los Angeles, CA 90095
Phone: +1 (310) 825-3617
E-mail: agafita@mednet.ucla.edu

Abstract: 328 words

Manuscript: 2746 words

Running Title: RECIP criteria

Key Words: metastatic castration-resistant prostate cancer; radionuclide treatment; PSMA PET; interim PET; ^{177}Lu-PSMA

ABSTRACT

Purpose: To develop a novel framework for Response Evaluation Criteria In PSMA-PET/CT (RECIP) 1.0 and a composite response classification which combines responses by PSA measurements and by RECIP 1.0 (PSA+RECIP).

Methods: This was an international, multicenter, retrospective study. 124 men with mCRPC who underwent ^{177}Lu-PSMA therapy and received PSMA-PET/CT at baseline (bPET) and at interim at 12 weeks (iPET) were included. Pairs of bPET and iPET were interpreted by consensus among three blinded readers for appearance of new lesions. Tumor lesions were segmented and total PSMA-positive tumor volume (PSMA-VOL) was obtained. Appearance of new lesions and changes in PSMA-VOL were combined to develop RECIP 1.0, which was defined as: complete response (RECIP-CR: absence of any PSMA-ligand uptake on iPET), partial response (PSMA-PR: decline ≥30% in PSMA-VOL and no appearance of new lesions), progressive disease (RECIP-PD: increase ≥20% in PSMA-VOL and appearance of new lesions), stable disease (RECIP-SD: any condition but RECIP-PR or RECIP-PD). Changes in PSA levels at 12 weeks by PCWG3 were recorded. Responses by PSA+RECIP were defined as: response (PSA decline ≥50% or RECIP-PR/CR) and progression (PSA increase ≥25% or RECIP-PD). Study's primary outcome measure was the prognostic value of RECIP 1.0 for overall survival (OS). Secondary outcome measure was the prognostic accuracy (C-index) of PSA+RECIP *vs* PSA responses.

Results: Patients with progressive disease (RECIP-PD; n=39; 8.3 mo) had shorter OS compared to patients with stable disease (RECIP-SD; n=47; 13.1 mo; p<0.001) and to those with partial response (RECIP-PR; n=38; 21.7 mo; p<0.001). PSA+RECIP had superior C-indices in identifying responders and progressors compared to PSA only: 0.65 *vs* 0.62 (p=0.028) and 0.66 *vs* 0.63 (p=0.044), respectively.

Conclusions: PSMA-PET/CT by RECIP 1.0 is prognostic for OS and can be used as a response biomarker to monitor early efficacy of ^{177}Lu-PSMA in men with mCRPC. PSA+RECIP may be used as a novel composite endpoint in mCRPC clinical trial design.

INTRODUCTION

In metastatic prostate cancer, treatment response is typically evaluated using conventional imaging (CT and bone scan) according to the Prostate Cancer Working Group Criteria 3 (PCWG3) guidelines. The prostate-specific membrane antigen (PSMA)-targeted PET/CT (PSMA-PET/CT) is a novel imaging technique which showed greater detection accuracy compared to conventional imaging in patients with high-risk primary prostate cancer (*1*). The U.S. Food and Drug Administration approved [^{68}Ga]Ga-PSMA-11 PET/CT for different clinical settings in men with prostate cancer (*2*). However, there is little evidence for the prognostic value of PSMA-PET/CT for response assessment in men with advanced prostate cancer (*3*,*4*). In our clinical experience using PSMA-PET/CT for response evaluation of systemic mCRPC treatments, a decrease in total disease burden can coincide with appearance of new lesions. This scenario referred to as *heterogeneous response* often leaves the treating physician in a clinical dilemma (*5*). Considering the rapidly evolving era of targeted treatments for mCRPC, accurate and early response assessment is urgently needed, but standardized response evaluation criteria for PSMA-PET imaging have not been developed yet.

[^{177}Lu]Lu-PSMA (^{177}Lu-PSMA) is a small molecule inhibitor that binds with high affinity to the prostate-specific membrane antigen (PSMA) and delivers beta radiation. The randomized TheraP trial demonstrated superior PSA responses and progression-free survival for [^{177}Lu]Lu-PSMA-617 vs. cabazitaxel (*6*). In the phase III VISION trial, [^{177}Lu]Lu-PSMA-617 prolonged overall survival and imaging-based progression-free survival when added to standard of care in patients with metastatic castration-resistant prostate cancer (mCRPC)(*7*).

This study had two key objectives: first, to develop a standardized framework for Response Evaluation Criteria In PSMA-imaging (RECIP) 1.0 in men with mCRPC who undergo ^{177}Lu-PSMA; second, to develop a composite response classification which combines PSA measurements and PSMA-PET/CT responses by RECIP 1.0 (PSA+RECIP).

METHODS

Patients and Study Design

In this international multicenter study, men with mCRPC treated with [^{177}Lu]Lu-PSMA-I&T or [^{177}Lu]Lu-PSMA-617 between December 10, 2014 and July 19, 2019 at the Technical University Munich, University of California Los Angeles, and University Hospital Essen were retrospectively

screened for inclusion. Eligible patients had received PSMA-PET/CT at baseline (bPET) and after two cycles of treatment (interim PET/CT [iPET]), received same PET radiotracer at bPET and iPET, and had survival data available. ^{177}Lu-PSMA was administered by intravenous injection of 6.0–8.5 GBq at 6–8 weekly intervals. Treatment was continued up to a maximum of 4 or 6 cycles in absence of progression and lack of severe toxicity according to the treating physician. The bPET were performed within ten weeks prior treatment. The iPET were performed at 12±2 weeks following treatment initiation and 5±1 weeks after second treatment cycle. Treatment protocols are detailed in Supplemental, Treatment Protocol (*8-13*). Serum PSA measurements were also collected at baseline and at 12±2 weeks. Changes in PSA levels at 12 weeks relative to baseline were recorded and categorized according to PCWG3 criteria: response (≥50% decrease) and progression (≥25% increase) (*14*).

The primary outcome measure of this study was the prognostic value of RECIP 1.0 for overall survival (OS). The secondary outcome measure was the prognostic ability of PSA+RECIP *vs* PSA only (Study design; Figure 1).

All patients gave written informed consent to undergo clinical PSMA-PET/CT. The retrospective analysis was approved by the Ethics Committee of each participating site (TUM 115/18S, UCLA IRB #20-000954, UKE 19-8570-BO) which waived the necessity for study specific consent. Of note, the patient population used in this publication to develop RECIP was used to compare different criteria for response assessment in mCRPC (submitted manuscript: JNUMED /2021/263073).

Imaging Acquisition

Images were obtained following application of PSMA-ligands that were synthesized as described previously (*15,16*). Patients received an average±SD of 126±4 and 317±9 MBq [^{68}Ga]Ga-PSMA-11 and [^{18}F]rhPSMA-7/7.3, respectively, via intravenous bolus. Image acquisition was started following 71±6 minutes after tracer injection. Data from the CT scan were used for attenuation correction. Images were acquired using Siemens Biograph mCT (n=115) and Siemens Biograph 64 (n=9) scanners. All images were obtained in accordance with the EANM guidelines (E-PSMA) for treatment monitoring in patients with mCRPC, ensuring harmonized quantification (*17*). Standard, vendor-provided image reconstructions were used. The institutional applied reconstruction parameters are summarized in the Supplementary Table 1. Paired bPET and

iPET were performed using the same PET/CT scanner and following same image reconstruction protocol.

Image Analysis

PET/CT datasets from each participating site were anonymized and centralized.

Changes in tumor burden. The PSMA-positive tumor lesions on bPET and iPET were annotated centrally by a nuclear medicine physician (AG) using the semi-automatic qPSMA software (Fig. 2). Segmentation workflow, time required for segmentation and inter-user reliability were described previously (*18*). Description of the workflow for tumor segmentation is provided in the Supplementary Figure 1. The total PSMA-positive tumor volume (PSMA-VOL) was extracted. Percentage changes of PSMA-VOL on iPET relative to bPET were calculated. Cut points for categorization of partial response (PSMA-VOL_PR; 10%, 20%, 30%, 40%, and 50% decrease) and progressive disease (PSMA-VOL_PD; 10%, 20%, 30%, 40%, and 50% increase) were evaluated. The cutoff (%) with the highest prognostic accuracy for OS was further used for definition of PSMA-VOL_PR and PSMA-VOL_PD.

New Lesions. Pairs of bPET and iPET were read independently by three nuclear medicine physicians (IR, MB, MW), which were blinded to outcome data and not involved in study design. Each reader was provided with full anonymized PET/CT datasets and was asked to assess the scans for appearance of new lesion(s) following pre-defined criteria (Table 1). Disagreement between readers was solved in consensus sessions.

Development of Response Evaluation Criteria In PSMA-imaging (RECIP) 1.0

Responses in PSMA-VOL were tested in conjunction with appearance of new lesions for associations with OS. We hypothesized that (i) patients with PSMA-VOL_PR without new lesions have superior OS compared to patients with PSMA-VOL_PR and new lesions, (ii) patients with PSMA-VOL_PD and new lesions have worse OS compared to patients with PSMA-VOL_PD without new lesions. Based on our hypothesis, RECIP 1.0 was developed and designed to classify patients into four categories: complete response (RECIP-CR), partial response (RECIP-PR), progressive disease (RECIP-PD), and stable disease (RECIP-SD)(Table 1). Associations of RECIP responses on iPET with OS were evaluated. Further, RECIP responses on iPET were combined with PSA responses at 12 weeks to develop a novel composite response classification

(PSA+RECIP). Definitions of all three response classifications are given in Table 1. The prognostic ability of PSA, RECIP, and PSA+RECIP responses for OS was evaluated.

Statistical Analysis

Values are reported as average (SD) or median (interquartile range [IQR]) for continuous variables and as number and percentage for categorical variables. OS was estimated using the Kaplan-Meier method. The associations between appearance of new lesions, changes in PSMA-VOL, and RECIP with OS were evaluated using univariate cox regression analyses. The hazard ratio (HR), its 95% confidence interval (95%CI), and the corresponding p-values were derived. Appearance of new lesions and PSMA-VOL were tested separately and in combination to identify combined criteria with highest associations with OS. The prognostic ability of PSA, RECIP, and PSA+RECIP classification systems was assessed using the Harrell's concordance index (C-index) (*19*). Comparisons (p-values) of C-indices were computed using the '*concordance'* function, which estimates the variance-covariance matrix between the correlated (repeated measure) c-indices (*20*). The agreement between readers in identifying new lesions on iPET was evaluated by Fleiss kappa (κ) ('*KappaM*' package) (*21*). Analyses were performed using R software version 3.4. A $p<0.05$ was considered statistically significant.

RESULTS

From October 1, 2019 to December 18, 2019, retrospective data from 287 men with mCRPC were screened. Of these, 124 (43%) met the eligibility criteria and were included (CONSORT diagram; Supplementary Figure 2). 115 (93%) of 124 patients were treated under compassionate access programs, while nine (7%) were enrolled in a phase II clinical trial (NCT03042312). Baseline characteristics are summarized in Table 2. Overall, 453 cycles of ^{177}Lu-PSMA were administered with a median of 4 cycles (IQR, 2-5). The median follow-up for survivors was 26.6 months (IQR, 23.0-36.3) and 113 (91%) of 124 patients had deceased at last follow-up. The cutoff date for follow-up was August 19, 2020. The median OS was 13.5 months (95%CI, 11.6-15.4). Eighty-nine (72%) patients received [^{68}Ga]Ga-PSMA-11 PET/CT, while 35 (28%) received [^{18}F]PSMA-rh7/7.3 PET/CT scans. The median time between bPET and treatment initiation was 3.2 weeks (IQR, 2.2-5.0), while the median time between treatment initiation and iPET was 11.5 weeks (IQR, 10.5-13.3).

Associations of Appearance of New Lesion with Overall Survival

Based on the consensus reads, 72 (58%) patients had appearance of at least one new lesion on iPET. Of these, 9 (13%) patients had new lesions on both PET and CT images. No new lesion was noticed on CT images only. Sixty-six (53%), 14 (11%), 24 (19%) and 12 (10%) of 124 patients had appearance of new bone, pelvic nodal, distant nodal, and visceral metastases, respectively. Appearance of at least one new lesion on iPET was associated with poor OS (HR 2.32; 95%CI, 1.57-3.42; p<0.001) (Fig. 3A). Results of independent reads in assessing new lesions are provided in the Supplementary Figure 3. Substantial agreement among all three readers in identifying new lesions was noticed in 95 (77%) of 124 patients (κ=0.69).

Associations of Changes in Tumor Volume with Overall Survival

The median change in PSMA-VOL on iPET relative to bPET was -2.2 % (IQR, -39.8, +46.2). The C-indices for each cut point for definition of response and progression are provided in the Supplementary Table 2. A cutoff of +20% had the highest prognostic value for PSMA-VOL_PD with OS (c-index: 0.64). Cutoffs of -20% and -30% had the highest but similar prognostic value for PSMA-VOL_PR with OS (c-index: 0.62) and the -30% cutoff was chosen to minimize the impact of measurement errors / biological variability. Stable disease (PSMA-VOL_SD) was defined as either <30% decrease or <20% increase in PSMA-VOL.

OS was significantly superior in men with PSMA-VOL_PR (HR 0.29; 95%CI, 0.19–0.45; p<0.001) or PSMA-VOL_SD (HR 0.35; 95%CI, 0.20–0.58; p<0.001) compared to men with PSMA-VOL_PD (Fig. 3B). Sixteen (31%) of 52, 16 (59%) of 27, and 40 (89%) of 45 patients with PSMA-VOL_PR, PSMA-VOL_SD, and PSMA-VOL_PD had appearance of new lesions on iPET (Fig. 3C).

Establishment of RECIP and Associations with Overall Survival

RECIP-CR. Absence of any PSMA-ligand uptake on iPET was not observed.

RECIP-PR. Men with PSMA-VOL_PR and no evidence of new lesions had superior OS compared to men with PSMA-VOL_PR and appearance of new lesions (HR 0.50; 95%CI, 0.25–0.93; p=0.039). On this basis, definition of RECIP-PR was maintained.

RECIP-PD. Men with PSMA-VOL_PD and appearance of new lesions had inferior OS compared to men with PSMA-VOL_PD but no evidence of new lesions (HR 4.50; 95%CI, 1.36–14.90; p=0.014)(Supplementary Fig. 4). On this basis, definition of RECIP-PD was maintained. A case example of a patient with RECIP-SD is presented in the Supplementary Figure 5.

OS was superior in men with RECIP-PR (n=38; HR 0.17; 95%CI, 0.10-0.28; p<0.001) or RECIP-SD (n=47; HR 0.30; 95%CI, 0.18-0.48; p<0.001) compared to men with RECIP-PD (n=39). RECIP-PR was associated with superior OS compared to RECIP-SD (HR 0.56; 95%CI, 0.35–0.90; p=0.017) (Fig. 4A). A waterfall plot displays the relationship between RECIP responses and PSA changes (Fig. 4B). The RECIP 1.0 classification method is summarized in Table 3.

Prognostic ability of PSA, RECIP and PSA+RECIP classifications for overall survival

Response. The C-index of response by PSA: 0.63 (95%CI, 0.58-0.66) was similar to RECIP: 0.63 (95%CI, 0.59-0.67; p=0.830) and inferior compared to the PSA+RECIP: 0.66 (95%CI, 0.62-0.70; p=0.028). Of 76 patients without a PSA response at 12 weeks, 10 (13%) had RECIP-PR on iPET and had a superior OS compared to those without RECIP-PR (HR 0.33; 95%CI, 0.15-0.73; p=0.006; Fig. 5A).

Progression. The C-index of progression by PSA: 0.62 (95%CI, 0.57-0.67) was similar compared to RECIP: 0.65 (95%CI, 0.60-0.69; p=0.210) and inferior compared to the PSA+RECIP: 0.65 (95%CI, 0.61-0.70; p=0.044). Of 84 patients without a PSA progression at 12 weeks, 12 (14%) had RECIP-PD on iPET and had an inferior OS compared to those without RECIP-PD (HR 3.33; 95%CI, 1.75-6.35; p<0.001; Fig. 5B).

DISCUSSION

Efficacy of ^{177}Lu-PSMA and other systemic treatments of mCRPC is currently evaluated using conventional imaging (bone scan + CT by PCWG3 criteria (*14*)) which may not accurately assess responses, especially for bone metastases which are present in ~90% of mCRPC patients. PSMA-PET/CT demonstrated higher detection rate compared to conventional imaging (*1*), however, its prognostic role for treatment monitoring has not been established. Criteria for monitoring tumor response in PET imaging were described previously for ^{18}F-FDG PET (PERCIST (*22*)), but PSMA-PET and ^{18}F-FDG PET image fundamentally different properties of

the tumor tissue (PSMA expression and glucose metabolism, respectively). Thus, PERCIST is not applicable for PSMA-PET imaging.

We developed RECIP 1.0 as the first evidence-based framework for response evaluation in prostate cancer using PSMA-PET imaging. Two criteria have been previously proposed for the same purpose, however, these proposals included clinical information and were not based on multicenter validation (*23*,*24*). Compared to PERCIST which uses measurements of individual lesions, RECIP 1.0 quantifies changes in total tumor volume capturing the entire extent of disease. Binary PCWG3 classifies patients into PD *vs* non-PD but lack to capture response by subcategorizing non-PD into CR, PR or SD. Despite identification of progressors may suffice in clinical practice, the objective response rate is commonly used in clinical trials as an endpoint to determining drug's efficacy (*25*). To enable assessment of tumor objective response rate, RECIP 1.0 was designed to distinguish true responders from patients with stable disease. Of note, heterogeneous response of individual metastatic lesions is quite common during treatment of advanced mCRPC (*5*), which was confirmed in our patient population, i.e. 13% of the patients had appearance of new lesions despite a response in tumor burden. These patients were classified by RECIP 1.0 as having stable disease and had a different survival outcome compared to true responders who have no sign of progression (i.e. appearance of new lesions) and to true progressors with both increase in tumor burden and appearance of new lesions (median OS: 13.1 vs. 21.7 vs. 8.3 months, respectively).

PSA response (≥50% decrease) is commonly used in phase II clinical trials of mCRPC as primary endpoint to estimate antitumor activity. Our composite response classification system (PSA+RECIP) demonstrated a superior prognostic accuracy for OS compared to PSA measurements only, highlighting the potential benefit of combining PSA and RECIP responses into a composite efficacy endpoint for clinical trials of mCRPC. Advantages of using composite endpoints include higher statistical precision and efficiency, i.e. smaller sample size (which enables less costly trials and lower rates of treatment-related side effects) and shorter follow-up (which can enable a faster availability of the results). Nevertheless, design and implementation of such endpoints can be challenging and hence requires caution (*26*). In comparison to PSA measurements, PSMA-PET/CT offers additional information about metastatic site and pattern of spread as well as potential bone complications (e.g. spinal cord compression or fractures). This is

highly relevant for the clinical management of patients when adjuvant treatments can be considered, e.g. emergency surgery, radiation or other metastasis directed therapies.

Nomograms to predict outcome after ^{177}Lu-PSMA using baseline patient and tumor characteristics were developed previously (*27*). The number of PSMA-positive metastases on pre-therapeutic PSMA-PET/CT was used as a surrogate marker of tumor volume for easier clinical implementation. Notably, the present analysis investigated dynamic changes in tumor burden during treatment. In this setting, changes in number of lesions are of limited use and quantitative measurements of tumor burden are essential for accurate response evaluation.

Clinical use of PSMA-PET/CT often lacks the ability to quantify whole-body disease burden because of high disease burden in metastatic settings. To enable quantitative assessment of total disease burden during treatment different vendors are currently developing software tools. For this retrospective study we used qPSMA for semiautomatic extraction of total tumor volume (*18*). It is in-house developed and is freely available for widespread use. Other dedicated segmentation software might also be used and are expected to be available in the coming future to enable clinical implementation of PSMA-PET/CT as a quantitative imaging biomarker in practice and trials (*28-30*). The prognostic value of interim PSMA-PET/CT by RECIP is optimal (C-index: 0.65-0.70). The limited prognostic value of RECIP might be caused by an artificial decrease in PSMA-expression because of dedifferentiation and not by a true decrease in tumor size.

The major limitations of this study are the lack of a prospective validation of RECIP criteria and an external validation of their threshold definition. Repeatability thresholds for tumor SUV measurements for ^{68}Ga-PSMA-11 PET/CT were determined previously, however, tumor volumes were not included in the analysis (*31*). Another limitation of the study is that we can only report the prognostic, but not the predictive value of RECIP since we did not analyze data from a randomized trial powered for outcome. Future randomized studies monitoring tumor response with PSMA-PET/CT are warranted to determine whether higher rates of PSMA response to a drug translate into a better clinical outcome. Also, this study could not compare the prognostic ability of RECIP vs. PCWG3 criteria, since bone scans were not included in the clinical workup of ^{177}Lu-PSMA radionuclide therapy at all institutions. Another limitation is that that different PSMA-PET radiotracers were used in this study, albeit consistent within patients. Further, the iPET was performed at 4-6 weeks after second cycle of treatment which could impact both the ability for disease regression to be observed and also impact opportunity for development of new lesions.

Last, progression-free survival data was not included as a secondary endpoint because clinical assessment was not uniformly performed and/or performed at consistent timepoints across the patients. Strengths of the study include the multicentric setting, a large patient population and long-term follow-up survival data.

Our study has important clinical implications. First, it demonstrates the prognostic role of interim PSMA-PET/CT as a response biomarker to monitor efficacy of ^{177}Lu-PSMA and possibly other mCRPC systemic therapies. Following positive outcome of the VISION registration trial (*7*), approval of ^{177}Lu-PSMA is imminent. Early and accurate treatment response assessment by PSMA-PET/CT may identify non-responders early in the course of treatment and consequently decrease overtreatment and guide these patients to more effective therapies. Our interim timepoint at 12 weeks for early response evaluation is in line with PCWG2 recommendations for mCRPC and with EANM procedure guidelines for ^{177}Lu-PSMA therapy (*13*,*32*). End-treatment response evaluation using PSMA-PET may also provide useful information whether patients who completed the maximum number of ^{177}Lu-PSMA are candidates for a treatment rechallenge (*33*). However, only a subgroup of patients respond well and complete all cycles (i.e. 39/124 [31%] of our patients) and therefore such analysis is limited by sample size. Further, there is currently no consensus among specialists on the maximum number of ^{177}Lu-PSMA cycles. Second, RECIP 1.0 was developed as a potential powerful tool to determine imaging responses and better assess heterogeneous response. Third, our findings suggest the added value of PSMA-PET/CT imaging to PSA measurements in evaluating treatment efficacy which may aid to higher precision and patient outcome of mCRPC trials.

CONCLUSION

RECIP 1.0 was developed as an evidence-based novel framework to assess tumor response early in the course of the treatment in mCRPC using PSMA-PET/CT. PSA+RECIP is proposed as a novel composite efficacy endpoint for clinical trials of mCRPC. PSMA-PET/CT can be used as a response biomarker to monitor early efficacy of ^{177}Lu-PSMA and potentially to other mCRPC treatments. Validation of the findings in a prospective setting is warranted.

FINANCIAL SUPPORT

This study was partly funded by the Prostate Cancer Foundation (grant 21YOUN18). AG is supported by the Prostate Cancer Foundation (grant 21YOUN18), UCLA Jonsson Comprehensive Cancer Center fellowship award and Dr. Christiaan Schiepers postdoctoral fellowship award. BH received financial support from the German Research Foundation (DFG HA 5160/5-1). JCa is supported by the Prostate Cancer Foundation (grant 20YOUN05 and 19CHAL02) and the Society of Nuclear Medicine and Molecular Imaging (2019 Molecular Imaging Research Grant for Junior Academic Faculty). WPF received financial support from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grant FE1573/3-1 / 659216), Mercator Research Center Ruhr (MERCUR, An-2019-0001), IFORES (D/107-81260, D/107-30240), Doktor Robert Pfleger-Stiftung, and Wiedenfeld-Stiftung/Stiftung Krebsforschung Duisburg. HW received financial support from the China Scholarship Council (CSC).

CONFLICT OF INTEREST

ME reports prior consulting activities for Blue Earth Diagnostics Ltd., Novartis, Telix, Progenics, Bayer, Point Biopharma and Janssen and a patent application for rhPSMA. BH reports personal fees and non-financial support from Bayer, personal fees and non-financial support from BMS, personal fees and non-financial support from AstraZeneca, personal fees from Pfizer, personal fees and non-financial support from Lightpoint medical, Inc, personal fees from ABX, personal fees and non-financial support from Janssen, all outside the submitted work. JCa reports prior consulting activities outside of the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, IBA Radiopharma, Janssen Pharmaceuticals, POINT biopharma, Progenics Pharmaceuticals, Radiomedix and Telix Pharmaceuticals. JCz is a founder, board member, and holds equity in Sofie biosciences and Trethera Therapeutics. Intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. JCz was a consultant for Endocyte Inc. (VISION trial steering committee), Actinium Pharmaceuticals and Point Biopharma outside of the submitted work. KH reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from

IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Bain Capital, personal fees from MPM Capital outside the submitted work. WPF reports fees from BTG (consultant), Calyx (consultant), RadioMedix (image review), Bayer (speakers bureau), and Parexel (image review) outside of the submitted work. WAW was on advisory boards and received compensation from Bayer, Blue Earth Diagnostics, Endocyte, ITM, RayzeBio, and Pentixapharm. He has received research support from BMS, Imaginab, Ipsen and Piramal. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: How can be developed a framework to evaluate efficacy of 177Lu-PSMA using PSMA-PET/CT imaging?

PERTINENT FINDINGS: RECIP 1.0 classification method was developed and has prognostic value for overall survival.

IMPLICATIONS FOR PATIENT CARE: RECIP 1.0 was developed as the first evidence-based novel framework to assess tumor response in mCRPC using PSMA-PET/CT.

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GRAPHICAL ABSTRACT

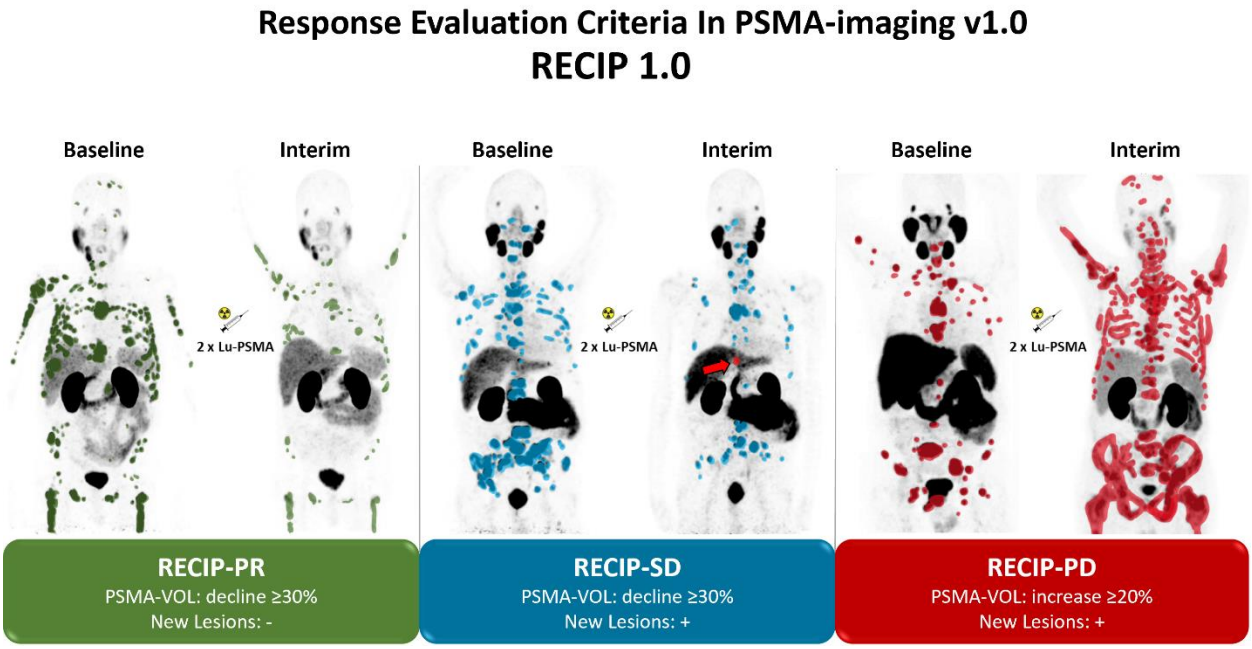


Figure 1. Study Design. Patients who received a baseline PSMA-PET/CT, were treated with at least two cycles of LuPSMA, subsequently received an interim PSMA-PET/CT and had available survival data were included in this analysis. Tumor segmentation on both scans was performed using qPSMA software and changes in total PSMA-positive tumor volume (PSMA-VOL) were calculated. Three independent readers interpreted the scans for appearance of new lesion and disagreement was solved by consensus reading. Changes in PSMA-VOL and consensus read results of appearance of new lesions were combined to develop Response Evaluation Criteria In PSMA-imaging (RECIP). Serum PSA levels at baseline and at interim were collected and changes were recorded. PSA and RECIP responses were combined to develop a composite response classification (PSA+RECIP). Prognostic ability for overall survival of PSA+RECIP *vs* PSA only were tested.

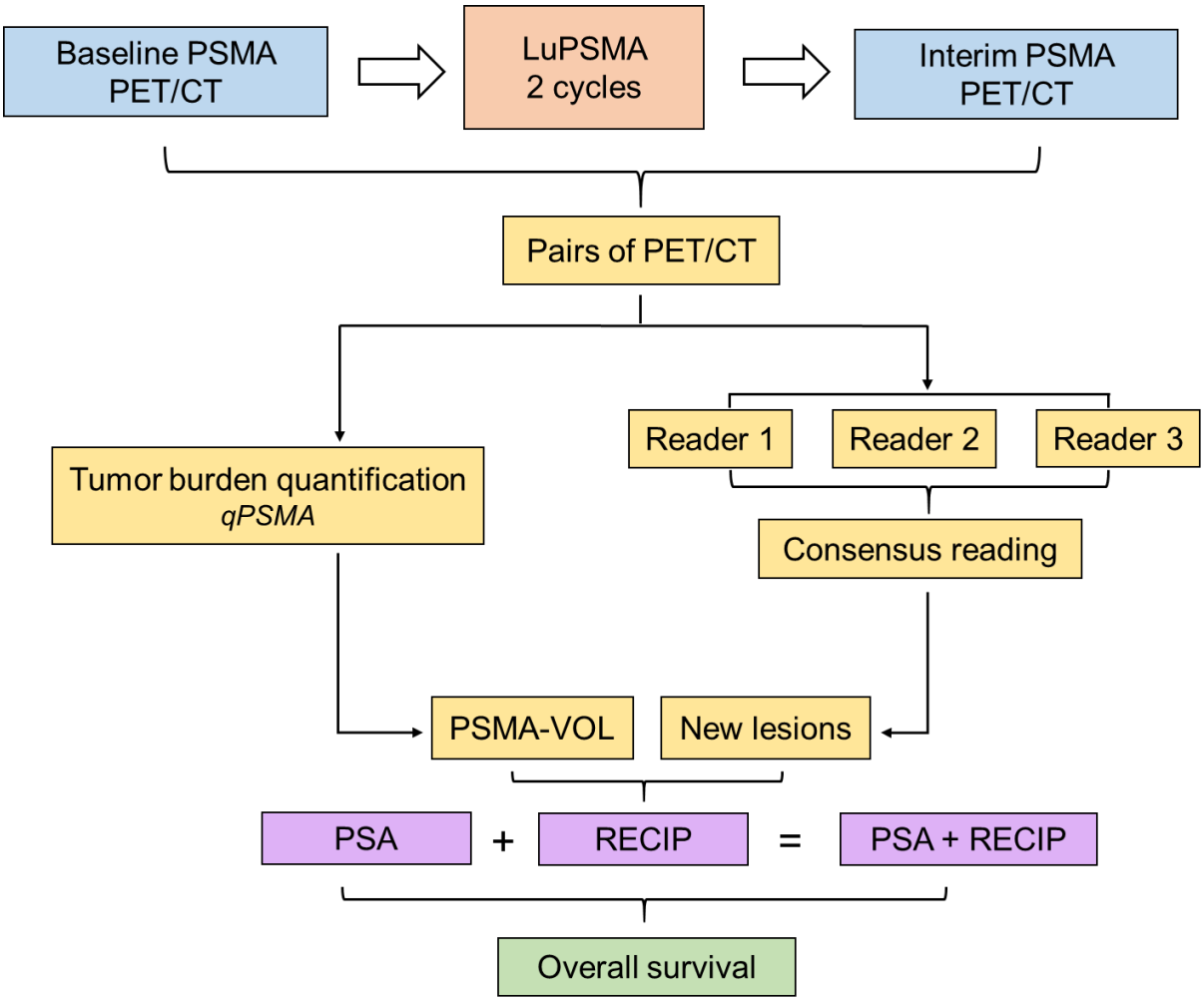


Figure 2. Changes in tumor burden. Semiautomatic quantitative assessment of ^{68}Ga-PSMA-11 PET/CT imaging using qPSMA software. Tumor lesions on paired baseline (bPET) and interim (iPET) ^{68}Ga-PSMA-11 PET/CT scans were segmented. Manual adjustments were performed when necessarily. Whole-body PSMA-positive tumor volume (PSMA-VOL) was extracted. DICOM images **(A, C)** are uploaded by the user and semiautomatic tumor segmentation **(B, D)** of bone (red color), lymph nodes (green color), and visceral (orange color) metastases is obtained.

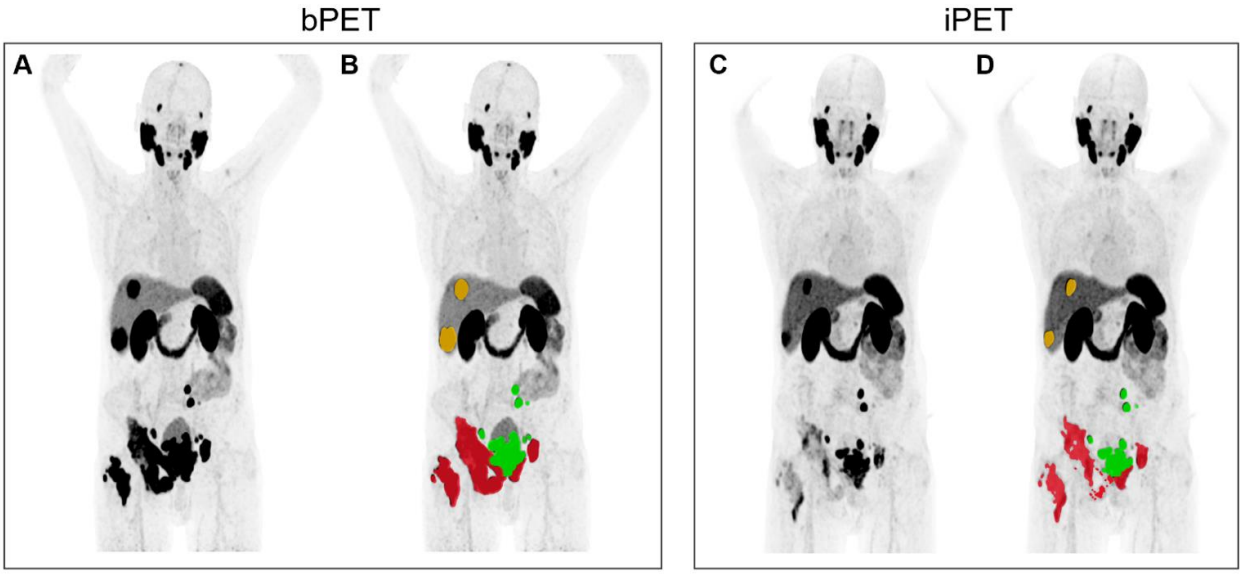


Figure 3. The Kaplan-Meier plot depicts the associations between appearance of new lesions **(A)** and response according to PSMA-VOL by qPSMA **(B)** with overall survival**.** The curves were truncated after 50 months of follow-up due to low number of patients at risk. The waterfall plot depicts the relation between changes in total PSMA-positive tumor volume (PSMA-VOL) and appearance of new lesions (NL) on PSMA-PET **(C)**. Asterisks indicate an increase >100% in the PSMA-VOL changes.

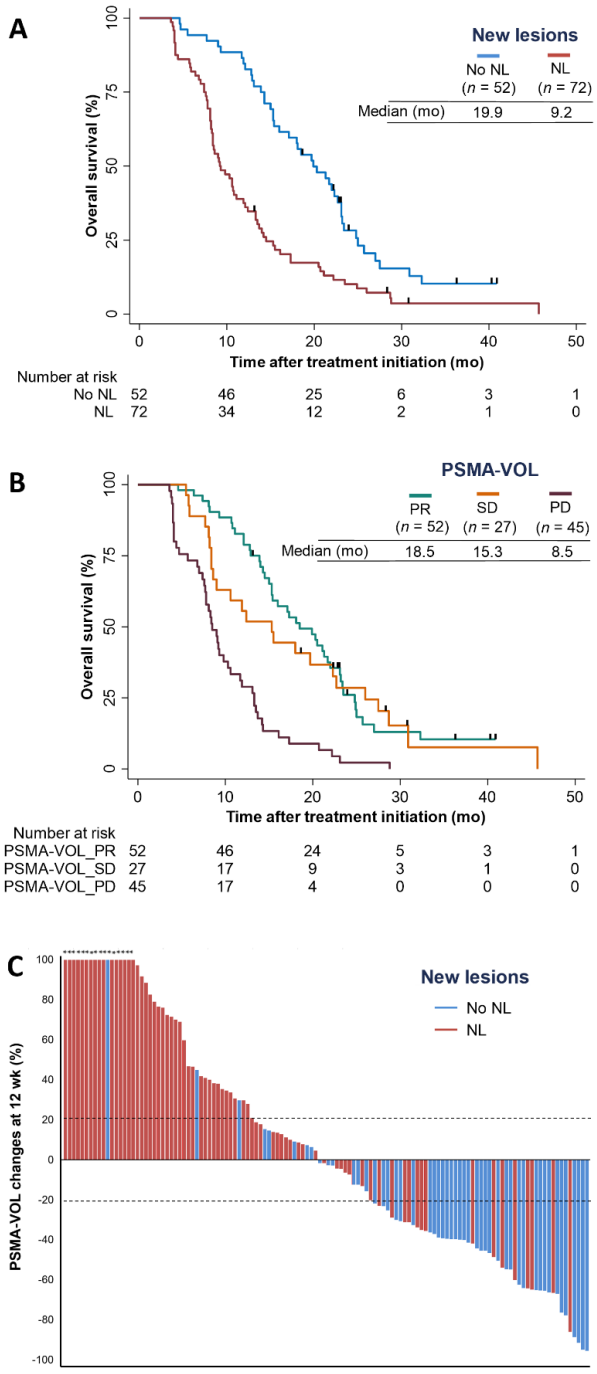
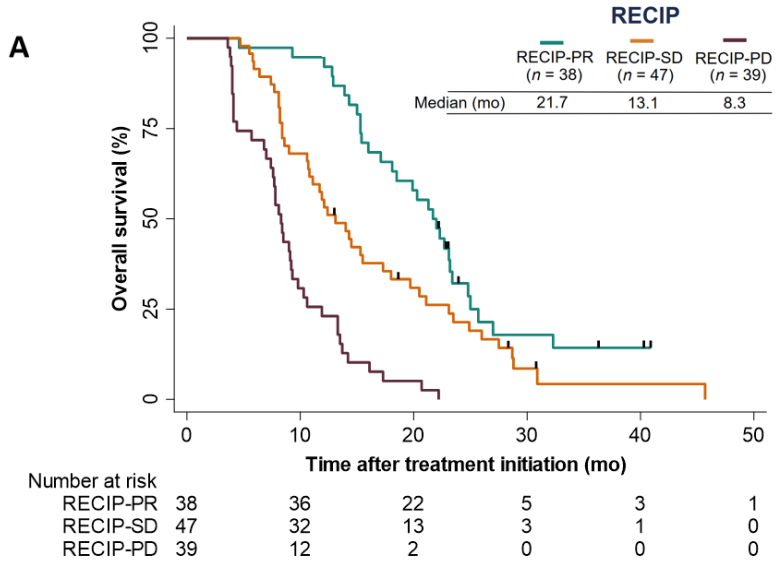


Figure 4. Kaplan-Meier plot shows the associations of imaging response according to RECIP with overall survival **(A)**. The curves were truncated after 50 months of follow-up due to low number of patients at risk. The waterfall plot depicts the relation between changes in PSA levels and imaging response according to RECIP **(B)**. Asterisks indicate an increase >100% in the PSA changes.



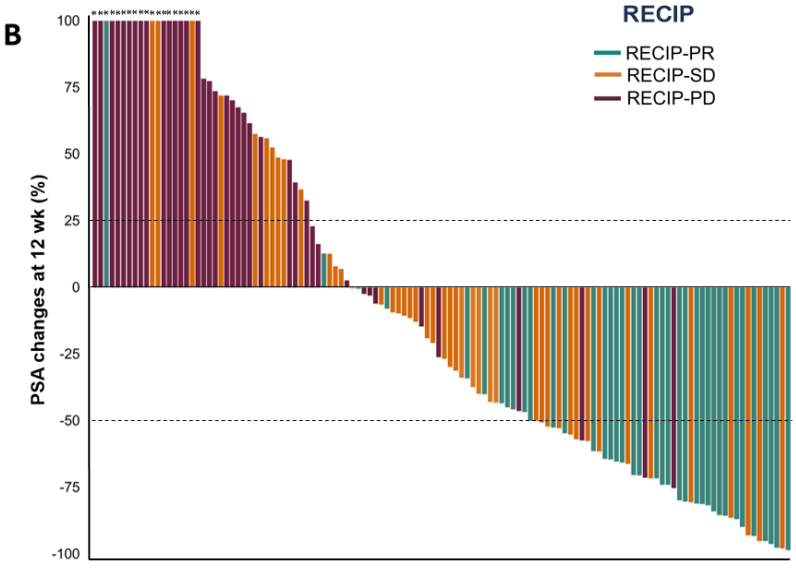


Figure 5. Kaplan-Meier plot shows the associations with OS of response vs. non-response in PSMA-PET/CT according to RECIP (RECIP-PR vs. no RECIP-PR) in patients without PSA response **(A)** and of progression vs. non-progression in PSMA-PET/CT according to RECIP (RECIP-PD vs. no RECIP-PD) in patients without PSA progression **(B)**.

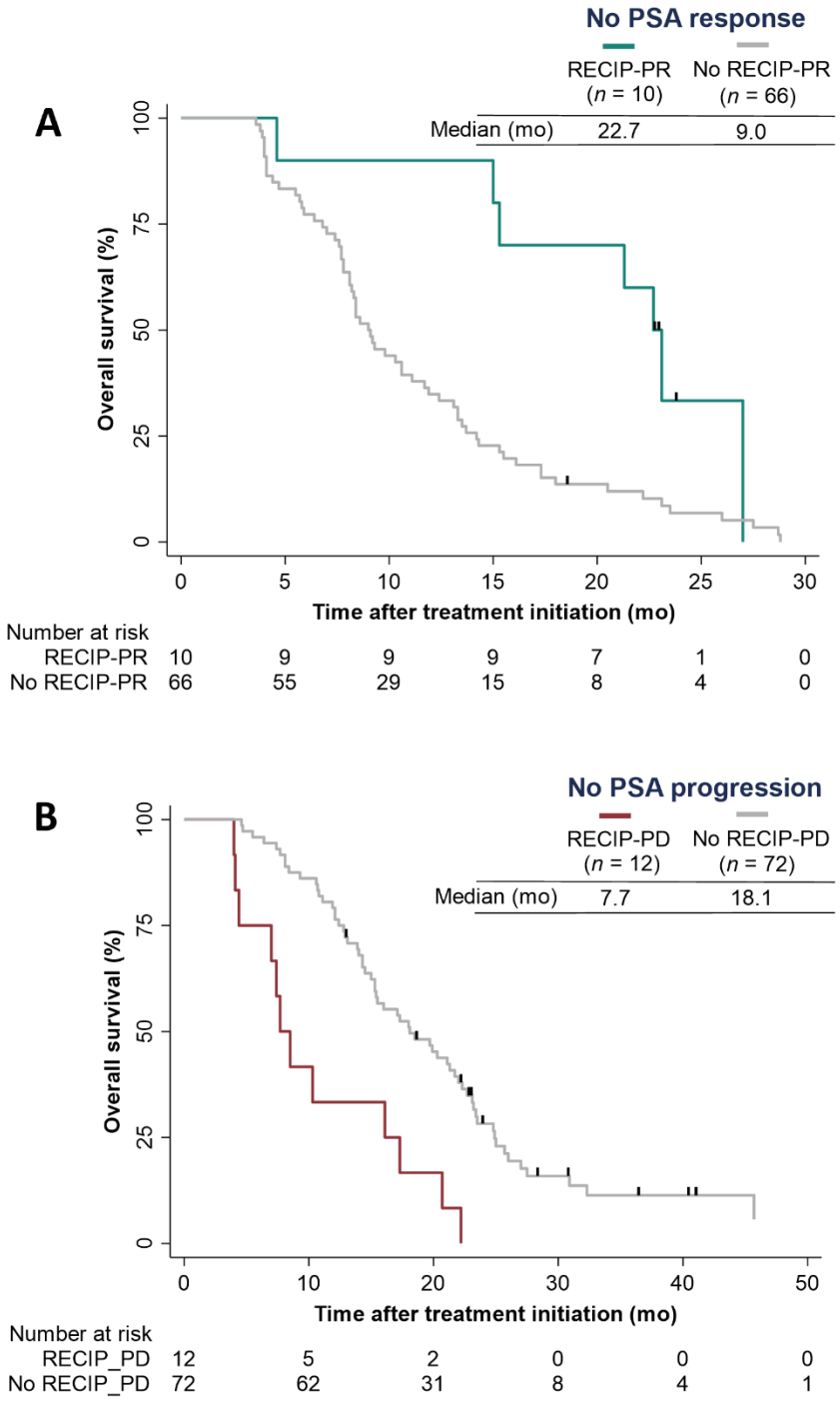


Table 1. Definitions of Criteria.

Criteria	Definition
New Lesions	
NL	Appearance of at least one new PSMA-positive lesion on iPET, which was defined as: • Any new focal uptake of PSMA-ligand higher than the surrounding background • Each tumor SUVmax > mean liver SUV
RECIP	
RECIP-CR	Absence of any PSMA-uptake on iPET
RECIP-PR	PSMA-VOL_PR without appearance of new lesions
RECIP-PD	PSMA-VOL_PD with appearance of new lesions
RECIP-SD	Not sufficient decline in PSMA-VOL to qualify for PSMA-VOL_PR *or* PSMA-VOL_PR with appearance of new lesions *or* Not sufficient increase in PSMA-VOL to qualify for PSMA-VOL_PD *or* PSMA-VOL_PD without appearance of new lesions
Response Classifications	
PSA	*Response:* ≥50% decrease *Progression:* ≥25% increase
RECIP	*Response:* RECIP-PR *Progression:* RECIP-PD
PSA+RECIP	*Response:* PSA ≥50% decrease or RECIP-PR / RECIP-CR *Progression:* PSA ≥25% increase and/or RECIP-PD

	All patients (N = 124)
Age (years)	73 (67-76)
Time since diagnosis of prostate cancer (years)	6 (4-11)
Gleason score at diagnosis*	
<8	36 (32%)
≥8	75 (68%)
M status at diagnosis	
M0	75 (60%)
M1	49 (40%)
Primary treatment	
Prostatectomy ± lymphadenectomy	70 (56%)
Local radiotherapy	12 (10%)
Systemic treatment	42 (34%)
PSA (ng/ml)	139 (37-427)
Lactate dehydrogenase (U/l)	286 (223-408)
Total alkaline phosphatase (U/l)	125 (81-250)
Hemoglobin (g/dl)	9.9 (11.3-12.7)
ECOG performance status	
0	31 (25%)
1	83 (67%)
2	10 (8%)
Previous mCRPC treatments	
Docetaxel	98 (79%)
Cabazitaxel	20 (16%)
Previous chemotherapy	99 (80%)
Abiraterone	111 (90%)
Enzalutamide	78 (63%)
Androgen-signaling-targeted inhibitors	123 (99%)
Radium-223	24 (19%)
Prior lines of mCRPC systemic treatment	
1	9 (7%)
≥2	115 (93%)
≥3	71 (57%)
≥4	33 (27%)
Sites of disease on PSMA-PET	
Bone	114 (92%)
Nodal	101 (81%)
Bone + Nodal	92 (74%)
Visceral	32 (26%)
Bone + Nodal + Visceral	27 (22%)

Table 2. Patient characteristics.
Data are median (interquartile range) or n (%);
Abbreviations: PSA, prostate-specific antigen; ECOG, Eastern Cooperative Oncology Group; PSMA, prostate-specific membrane antigen.
*Data missing for 13 patients.

Table 3. RECIP 1.0 Criteria.

RECIP-CR	Absence of any PSMA-uptake on follow-up PET scan
RECIP-PR	>30% decrease in PSMA-VOL without appearance of new lesions
RECIP-PD	>20% increase in PSMA-VOL with appearance of new lesions
RECIP-SD	<30% decrease in PSMA-VOL with/without appearance of new lesions *or* ≥30% decrease in PSMA-VOL with appearance of new lesions *or* <20% increase in PSMA-VOL with/without appearance of new lesions *or* ≥20% increase in PSMA-VOL without appearance of new lesions

SUPPLEMENTAL

Treatment Protocol

Patients were treated either under a compassionate use protocol or in a phase II clinical trial (NCT03042312). For patients treated under compassionate access programs, ^{177}Lu-PSMA was offered according to the German S3-guideline for prostate cancer (*1*), in accordance with the updated Declaration of Helsinki, paragraph-37 "Unproven Interventions in Clinical Practice," and in accordance with The German Medicinal Products Act, AMG §13 2b, including priority of all approved treatments (without contraindications) and confirmation of the indication by both a nuclear medicine physician and an expert in urology or oncology. Synthesis and radiolabeling of [^{177}Lu]Lu-PSMA-I&T and [^{177}Lu]Lu-PSMA-617 was locally performed as reported previously (*2-5*) The labelled product was produced, tested, and released under Good Manufacturing Practice (GMP) conditions as a sterile and ready to use solution for infusion. ^{177}Lu-PSMA was administered by intravenous injection. Oral hydration or administration of 500-1000 ml NaCL was performed. ^{177}Lu-PSMA was administered by intravenous injection of 6.0–7.4 GBq of ^{177}Lu-PSMA at 6–8 weekly intervals. Treatment was continued up to a maximum of 4 or 6 cycles in patients with absence of progression and lack of severe toxicity according to the treating physician. All patients underwent a screening PSMA-PET/CT within ten weeks of treatment. Hematological measurements and clinical laboratory assessments were done within 24 hours before each drug injection. All treatments were performed in accordance with international procedure guidelines for radionuclide therapy with ^{177}Lu-PSMA (*6*).

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Supplementary Figure 1. Workflow for tumor annotations.

Tumor measurements will be based on visual identification of tumor lesions with increased radioligand uptake on PET and SUV-based volumetry. A software with PET volume measurement capability will be used to determine the total PSMA-positive tumor volume (PSMA-VOL).

A. The SUV-based tumor segmentation will be performed using the following workflow:

- SUV uptake greater than 3 within the skeleton will be considered malignant and annotated as bone lesion
- SUV uptake greater than SUVthr_st (liver background) outside the skeleton will be considered malignant and annotated as soft-tissue lesion

SUVthr_st is calculated using the following formula: $\mathrm{SUV}_{\mathrm{thr\_st}} = \frac{4.30}{\mathrm{SUV}_{\mathrm{mean}}} \times (\mathrm{SUV}_{\mathrm{mean}} + \mathrm{SD})$, where

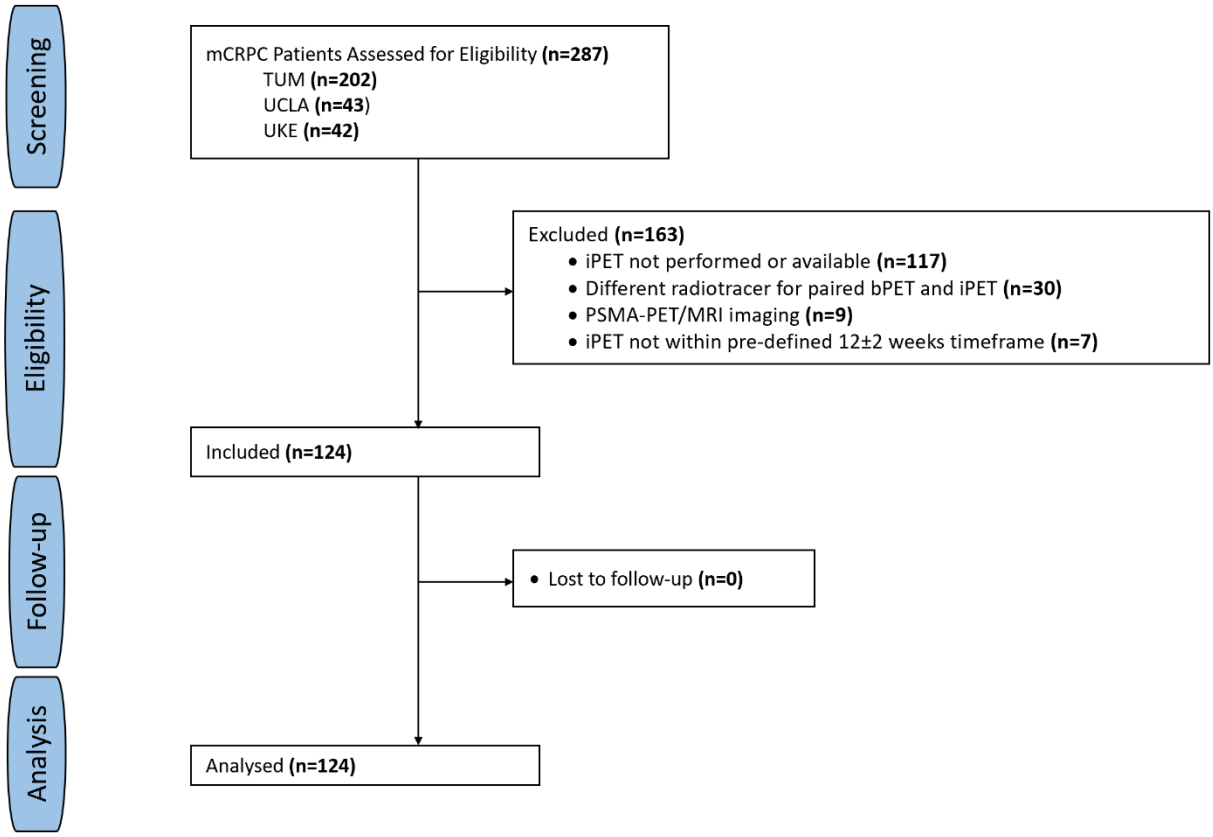
SUVmean = Average in the center of the right liver lobe (3 cm sphere or cube)

SD = Standard deviation of SUVmean in the center of the right liver lobe (3 cm sphere or cube)

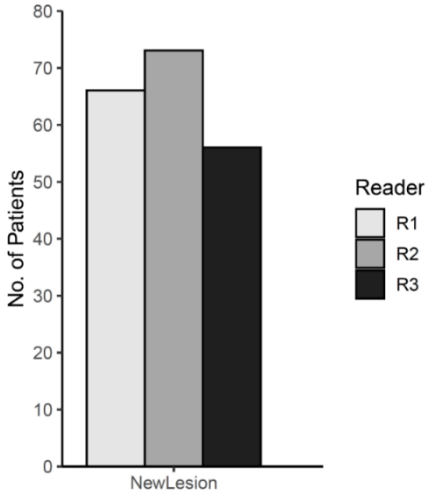
- Manual corrections can be made, whenever necessarily

B. After the whole-body malignant radioligand uptake is annotated, the volume of all voxels annotated as malignant are summed to obtain the PSMA-VOL (ml).

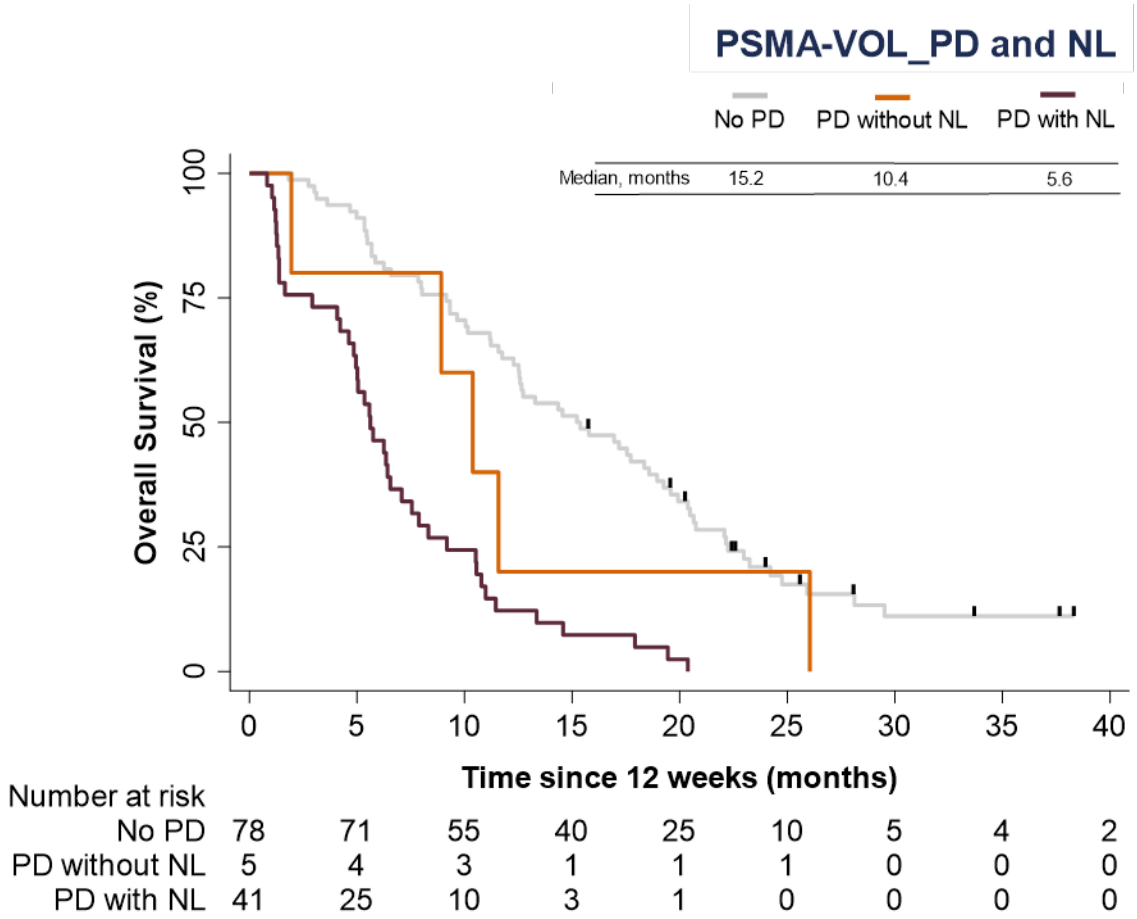
Supplementary Figure 2. CONSORT diagram.



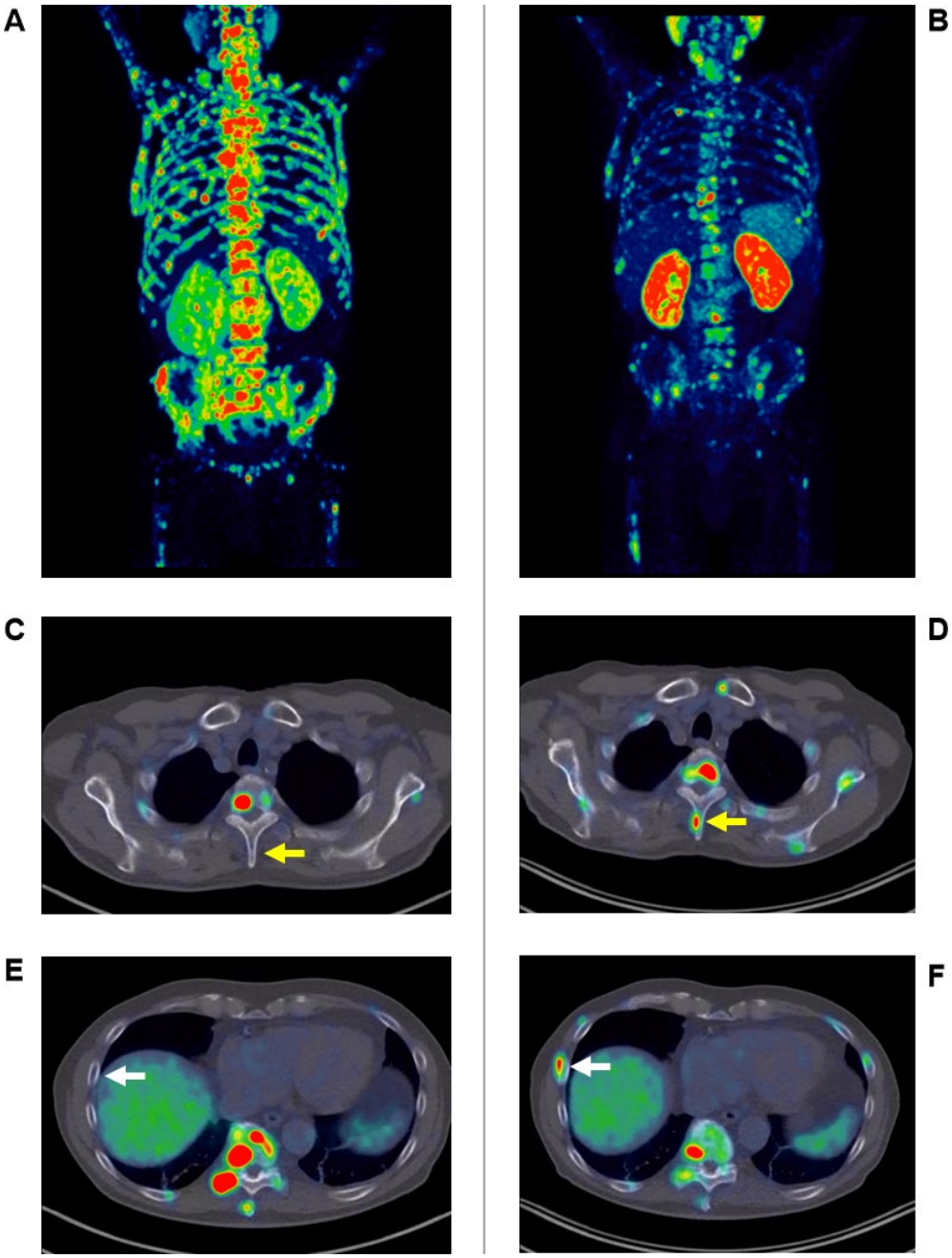
Supplementary Figure 3. Results of independent reads for appearance of new lesions on interim PET/CT. Reader 1, 2, and 3 identified 66 (53%), 73 (59%), and 56 (45%) patients with new lesions, respectively.



Supplementary Figure 4. The Kaplan-Meier plot depicts the relation between progressive disease in PSMA-VOL and occurrence of new lesions with overall survival.



Supplementary Figure 5. Case Example. An 83-y/o chemo-naïve mCRPC patient previously treated with abiraterone and enzalutamide and not eligible for chemotheray was referred for ^{177}Lu-PSMA treatment. The baseline PSMA-PET revealed nodal lesions and diffuse bone marrow involvement with a total PSMA-VOL of 3716 ml **(A).** After two cycles of treatment, the interim PSMA-PET images showed a significant response in PSMA tumor burden with a PSMA-VOL of 1328 ml (-64% decline relative to baseline) **(B)**. However, interim scan also revealed multiple new bone lesions, e.g. in bone spine (yellow arrow; **C, D**) and right rib (white arrow; **E, F**), which categorized the patient to PSMA-SD according to RECIP. The PSA levels decreased from 2183 ng/ml at baseline to 45 ng/ml at interim (-98% decline) and subsequently to a nadir of 31.7 ng/ml (-99% maximum decline). The patient received a total of six cycles of LuPSMA. The overall survival was 12 months.



Supplementary Table 1. Overview of the applied reconstruction parameters.							
No. Pts.	**Center**	**PET/CT system**	**Matrix Size**	**Recon-struction algorithm**	**Point-Spread-Functions**	**Pixel size (mm)**	**EANM/SNMMI Guideline**
N=104	TUM	Siemens, Biograph mCT	200x200	PSF-TOF (3i, 21s)	Yes	4.06x4.06	Yes
N=9	UCLA	Siemens, Biograph 64	200x200	OSEM3D (2i, 24s)	No	4.06x4.06	Yes
N=13	UKE	Siemens, Biograph mCT	200x200	PSF-TOF (3i, 21s)	Yes	4.06x4.06	Yes

Supplementary Table 2. Prognostic accuracy of different PSMA-VOL cutoffs

	Cutoff	C-index	95%CI
Partial Response	10%	0.61	0.56 – 0.65
	20%	0.62	0.57 – 0.66
	30%	**0.62**	**0.57 – 0.66**
	40%	0.59	0.54 – 0.63
	50%	0.57	0.53 – 0.62
Progressive Disease	10%	0.62	0.57 – 0.66
	20%	**0.64**	**0.59 – 0.68**
	30%	0.62	0.57 – 0.66
	40%	0.59	0.55 – 0.63
	50%	0.59	0.55 – 0.63