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✉ Ken Herrmann | ken.herrmann@uk-essen.de

Associations between quantitative baseline ^{68}Ga-PSMA-11 PET parameters and ^{177}Lu-PSMA-617 efficacy in the PSMAfore study

Ken Herrmann,[1] Kim N Chi,[2] Johann S de Bono,[3] Karim Fizazi,[4] Oliver Sartor,[5] Xiao X Wei,[6] James Nagarajah,[7] Matthias Eiber,[8] Irene A Burger,[9] Phillip H Kuo,[10] Samson Ghebremariam,[11] Nisha Rajagopal,[12] Connie C Wong,[12] Shaheen Alanee,[13] Michael J Morris[14]

[1]University Hospital Essen, Essen, Germany; [2]University of British Columbia, Vancouver, BC, Canada; [3]The Institute of Cancer Research and Royal Marsden Hospital, London, UK; [4]Institut Gustave Roussy and Centre Oscar Lambret, Université Paris-Saclay, Paris, France; [5]Transformational Prostate Cancer Research Center LCMC Health, New Orleans, LA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Radboud University Medical Centre, Nijmegen, Netherlands; [8]Technical University of Munich, Munich, Germany; [9]Department of Nuclear Medicine, Cantonal Hospital Baden, Affiliated Hospital for Research and Teaching of the Faculty of Medicine of the University of Zurich, Baden, Switzerland; [10]City of Hope National Medical Center, Duarte, CA, USA; [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [12]Novartis Pharmaceuticals Corporation, Cambridge, MA, USA; [13]Novartis Pharmaceuticals Corporation, Detroit, MI, USA; [14]Memorial Sloan Kettering Cancer Center, New York City, NY, USA

KEY FINDINGS & CONCLUSIONS

- In PSMAfore, rPFS benefit of ^{177}Lu-PSMA-617 versus ARPI change was observed regardless of SUV_{mean} in patients with PSMA+ mCRPC.
  - Higher whole-body SUV_{mean} was associated with better outcomes, with no optimal cutpoints.
  - ^{177}Lu-PSMA-617 improved rPFS in both SUV_{mean} ≥ median and SUV_{mean} < median subgroups, but the benefit was more pronounced in the SUV_{mean} ≥ median subgroup.
  - SUV_{mean} was predictive of rPFS improvement with ^{177}Lu-PSMA-617 versus ARPI change.
  - Similar trends were observed in OS but results were likely confounded by the high rate of crossover.
- Higher PSMA+ TV was associated with worse outcomes both in patients receiving ^{177}Lu-PSMA-617 and in those receiving ARPI change.
  - PSMA+ TV was prognostic of rPFS regardless of treatment.
- Patients with soft tissue-only disease receiving ^{177}Lu-PSMA-617 appeared to have longer rPFS and OS than those with bone disease, and this was probably related to their higher SUV_{mean} and lower PSMA+ TV.
- These results are consistent with quantitative PSMA-PET analysis findings in VISION.

Scan to obtain:
- Poster

https://tinyurl.com/KenHerrmann2390P

Poster presented at European Society for Medical Oncology (ESMO) Congress 2025, held on 17–21 October 2025 in Berlin, Germany.

INTRODUCTION

- In the phase 3 VISION study, baseline quantitative positron emission tomography (PET) parameters were associated with efficacy outcomes.[1]
  - Whole-body mean standardized uptake value (SUV_{mean}) was the best predictor of [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) efficacy.
- In the phase 3 PSMAfore study, ^{177}Lu-PSMA-617 prolonged radiographic progression-free survival (rPFS) versus change of androgen receptor pathway inhibitor (ARPI) in taxane-naive adults with PSMA-positive (PSMA+) metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed once on a prior ARPI.[2]
  - Overall survival (OS) did not differ between arms at the final OS analysis (hazard ratio [HR] 0.91, 95% confidence interval [CI]: 0.72, 1.14) and was confounded by high crossover to the ^{177}Lu-PSMA-617 arm (141 [60.3%] of 234 patients assigned to ARPI change).[3]
- We assessed associations between baseline quantitative PSMA PET parameters and efficacy outcomes in PSMAfore.

METHODS

Overview of PSMAfore study design

- PSMAfore (NCT04689828) was an international, open-label, phase 3 trial in patients with PSMA+ mCRPC who had experienced disease progression once on a prior ARPI and were candidates for ARPI change.
- PSMA+ mCRPC was defined as ≥ 1 PSMA+ lesion and no exclusionary PSMA-negative lesions on centrally read baseline [^{68}Ga]Ga-PSMA-11 PET/computed tomography (CT) scans.
- Randomization was 1:1 to ^{177}Lu-PSMA-617 (7.4 GBq once every 6 weeks for 6 cycles) or ARPI change (abiraterone or enzalutamide); crossover from ARPI change to ^{177}Lu-PSMA-617 was allowed.

Quantitative PSMA PET analysis

- Quantitative PET parameters including SUV_{mean}, PSMA+ tumour volume (TV), maximum standardized uptake value (SUV_{max}), tumour load and presence of PSMA+ lesion (yes/no) were extracted for bone, lymph node, liver, soft tissue (non-liver parenchymal organs) and whole body.
- Four types of analyses were performed as follows.
  - **Multivariable analysis:** a Cox proportional hazards model was used to assess associations with rPFS and OS; associations with overall response rate (ORR) and prostate-specific antigen (PSA) response were assessed using logistic regression.
  - **Optimal cutpoint analysis:** an optimal cutpoint analysis was performed to identify the mean standardized uptake value (SUV_{mean}) that maximized HRs for the best rPFS or OS within a treatment arm.
  - **Analysis by median cutpoint:** efficacy outcomes were assessed in subgroups based on SUV_{mean} and PSMA+ TV medians using the stratified Cox model to estimate HR and 95% CI, and the Kaplan–Meier method to assess associations with rPFS and OS within the two treatment arms.
  - **Subgroup analyses:** using the Kaplan–Meier method, subgroup analyses were performed in patients with soft tissue-only disease and bone metastases.
- Associations with rPFS, ORR and PSA response were assessed using data from the third interim analysis (data cut-off: 27 Feb 2024).
- Associations with OS were assessed at the final OS analysis (data cut-off: 1 Jan 2025).
- All analyses were *post hoc* and non-inferential.

RESULTS

Baseline PET parameters and associations with outcomes

- Quality requirements for baseline PET/CT scans to be included in the present quantitative analysis were met for 455/468 randomized patients.
- Quantitative parameters were balanced between study arms.
- Elevated whole-body SUV_{mean} associated with improved rPFS only in the ^{177}Lu-PSMA-617 arm (not in the ARPI change arm or in the overall study population) (**Figure 1**).
  - A one-unit increase in SUV_{mean} was associated with a 9% decrease in the risk of an rPFS event in the ^{177}Lu-PSMA-617 arm.
- Elevated whole-body SUV_{mean} also associated with improved OS in both study arms and overall, and with ORR and PSA response in the ^{177}Lu-PSMA-617 arm and overall (not in the ARPI change arm) (**Figure 1**).
  - A one-unit increase in SUV_{mean} was associated with a 6% decrease in the risk of death, and 10% increases in the odds of an ORR or PSA response, in the overall study population.
- Increased whole-body PSMA+ TV was associated with worsened rPFS and OS in both study arms and overall (**Figure 1**).
  - A 100 mL increase in PSMA+ TV was associated with a 26.6% increase in the risk of an rPFS event and a 6.9% increase in the risk of death in the overall population.

Figure 1. Association of whole body quantitative ^{68}Ga-PSMA-11 PET parameters with efficacy outcomes

Parameter	rPFS			OS			ORR			PSA		
	T	C	O	T	C	O	T	C	O	T	C	O
SUV_{mean}	■			■		■	■		■	■		■
SUV_{max}												
PSMA+ TV	■	■	■	■	■	■					■	
Tumour load		■	■									

■ > 5% decrease in risk per unit ■ ≤ 5% decrease in risk per unit
■ > 5% increase in risk per unit ■ ≤ 5% increase in risk per unit

C, control arm only; O, overall (treatment + control arm); ORR, overall response rate; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; T, treatment arm only; TV, tumour volume.

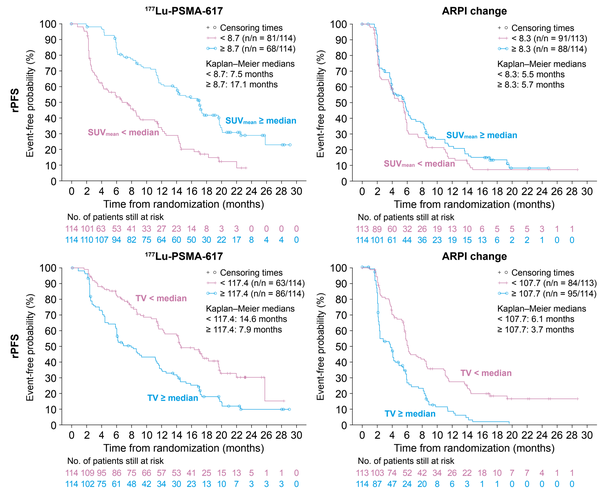
Cutpoint analysis

- No meaningful optimal cutpoint within the ^{177}Lu-PSMA-617 arm was identified that could separate patients into subgroups with longer or shorter rPFS or OS.

Radiographic progression-free survival

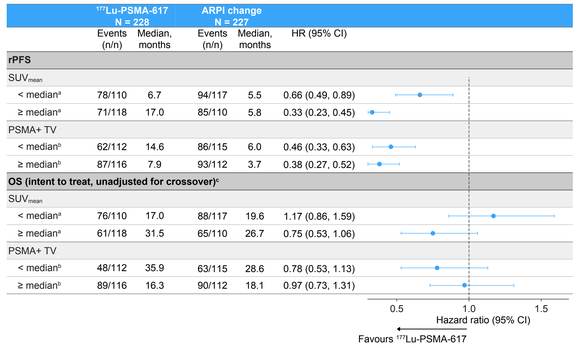
- rPFS was longer in the SUV_{mean} ≥ median versus the SUV_{mean} < median subgroup in the ^{177}Lu-PSMA-617 arm but not in the ARPI change arm (**Figure 2**).
  - ^{177}Lu-PSMA-617 improved rPFS versus ARPI change in both subgroups, but the benefit was more pronounced in the SUV_{mean} ≥ median subgroup than in the SUV_{mean} < median subgroup (**Figure 3**).
- rPFS was shorter in the TV ≥ median versus the TV < median subgroup across both treatment arms (**Figure 2**).
  - ^{177}Lu-PSMA-617 improved rPFS versus ARPI change in both subgroups, with similar benefits (**Figure 3**).

Figure 2. Kaplan–Meier analysis for rPFS by median SUV_{mean} and PSMA+ TV



ARPI, androgen receptor pathway inhibitor; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SUV_{mean}, mean standardized uptake value; TV, tumour volume.

Figure 3. rPFS and OS according to SUV_{mean} and PSMA+ TV medians

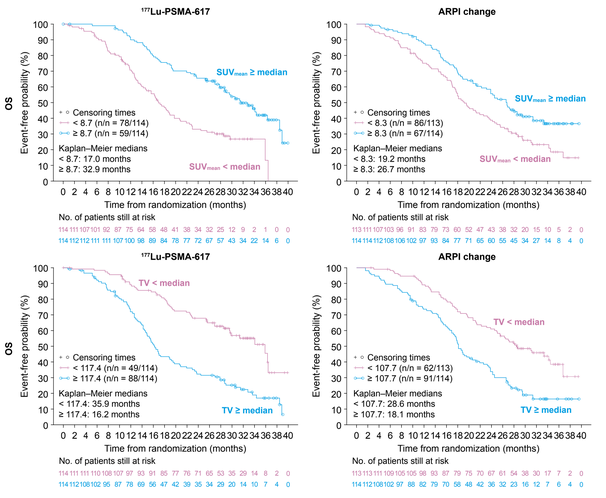


[a]8.4. [b]115.6 mL. [c]141/234 participants in the ARPI change arm crossed over.
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SUV_{mean}, mean standardized uptake value; TV, tumour volume.

Overall survival

- OS was longer in the SUV_{mean} ≥ median versus the SUV_{mean} < median subgroup in both treatment arms (**Figure 4**).
- OS was shorter in the TV ≥ median versus the TV < median subgroup in both treatment arms (**Figure 4**).
- OS did not differ between arms at the final OS analysis and is challenging to interpret because of the high crossover rate to the ^{177}Lu-PSMA-617 arm.
  - 95% CI for all subgroups overlapped 1 (**Figure 3**), consistent with no difference between arms.

Figure 4. Kaplan–Meier analysis for OS by median SUV_{mean} and PSMA+ TV

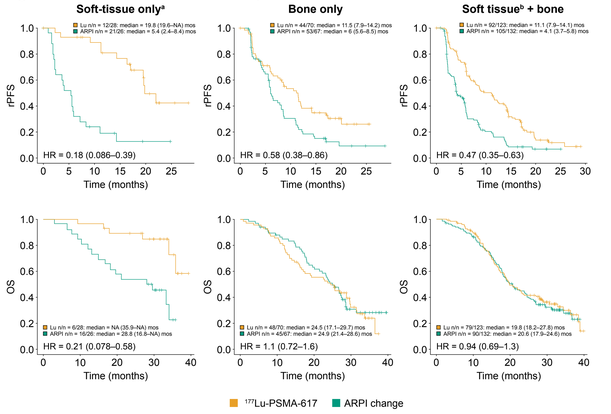


ARPI, androgen receptor pathway inhibitor; OS, overall survival; PSMA, prostate-specific membrane antigen; SUV_{mean}, mean standardized uptake value; TV, tumour volume.

Subgroup analyses in patients with soft tissue-only disease versus bone metastases

- Benefits of ^{177}Lu-PSMA-617 versus ARPI change were more pronounced in the subgroup of patients with soft tissue-only mCRPC than in those with bone-only disease (**Figure 5**).
  - Patients with soft tissue-only disease had a higher baseline SUV_{mean} (9.7 vs 7.8) and a lower PSMA+ TV (40 vs 84 mL) than those with bone-only disease.

Figure 5. rPFS and OS benefits in patients with soft tissue versus bone disease



[a]177Lu-PSMA-617 arm, n = 28 (25 lymph node-only, 3 liver metastases); ARPI change arm, n = 26 (25 lymph node-only, 2 liver metastases). [b]177Lu-PSMA-617 arm, n = 123 (92 lymph node-only, 7 liver metastases); ARPI change arm, n = 132 (101 lymph node-only, 8 liver metastases).
ARPI, androgen receptor pathway inhibitor; HR, hazard ratio; mo, month; NA, not available; OS, overall survival; PSMA, prostate-specific membrane antigen; TV, tumour volume.

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