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Impact of different PSMA PET-based eligibility criteria on outcome of [^{177}Lu]Lu-PSMA radioligand therapy using [^{18}F]rhPSMA-7/[^{18}F] rhPSMA-7.3 (Flotufolastat)

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Abstract

Background [^{177}Lu]Lu-PSMA radioligand therapy (RLT) is key in treating metastatic castration-resistant prostate cancer (mCRPC). Various PSMA agents and eligibility criteria for [^{177}Lu]Lu-PSMA RLT have been described. We retrospectively assessed applicability and outcomes using Blue Earth Therapeutics' (BET) phase I study criteria with [^{18}F]rhPSMA-7 and Flotufolastat ([^{18}F]rhPSMA-7.3), comparing them to VISION trial-based PSMA PET/CT criteria. Patients eligible for [^{177}Lu]Lu-PSMA RLT, as assessed by an interdisciplinary board, were retrospectively stratified into four groups based on whether their PSMA PET scans with Flotufolastat met BET (B + /B-) and/or VISION (V + /V-) criteria. Outcome parameters like PSA response, PSA progression-free survival (PSA-PFS), and overall survival (OS) were compared, and reasons for (in-)eligibility by BET or VISION were analyzed.

Results In total, 191 mCRPC patients from our institutional database were included, of which 138 underwent [^{18}F] rhPSMA-7.3 and 53 [^{18}F]rhPSMA-7. 161 (84.3%) met both criteria (V + /B +), 13 (6.8%) were ineligible (V-/B-), and 17 (8.9%) met VISION but not BET criteria (V + /B-). No patient was BET-eligible without also fulfilling VISION criteria. Of the 30 patients excluded by BET criteria, 17 (56.7%) lacked the "majority" tumor volume criterion; 10/13 (76.9%) excluded by VISION had visceral metastases with lower PSMA expression than the liver. In the subgroups V + /B +, V + /B-, and V-/B-, a PSA response > 50% was present in 62/157 (39.5%), 2/17 (11.8%), and 0/13 (0%) patients, respectively. V + /B + patients had the significantly longest PSA-PFS compared to V + /B- and V-/B- (PSA-PFS: 4.3 months (95% CI 3.4 – 5.2) vs. 1.5 months (95% CI 1.4 – 1.6) vs. 2.8 months (95% CI 0.0 – 6.5), p = 0.002) and a trend towards longer OS (14.9 vs. 13.1 vs. 7.7 months, p = 0.065).

Conclusion Multiple similarities between BET and VISION eligibility criteria (V + /B +) prior to [^{177}Lu]Lu-PSMA RLT were observed, with the majority of patients fulfilling both. Positivity in both criteria was associated with the best outcome.

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Data from our pilot cohort suggest that the criteria for BET's phase I trial select patients more strictly for [^{177}Lu]Lu-PSMA RLT than VISION criteria, while OS did not significantly differ between the three different groups.

Key points

- Pertinent findings: The majority of patients fulfilled both BET and VISION eligibility criteria prior to [^{177}Lu]Lu-PSMA RLT and were associated with the best outcome while there was a mismatch in 8.9% of the cases. Our data suggest that criteria for BET's phase I trial select patients more strictly for [^{177}Lu]Lu-PSMA RLT than VISION criteria. Further prospective trials will evaluate the most appropriate criteria for study eligibility prior to [^{177}Lu]Lu-PSMA RLT.
- Implications for patient care: Applying BET eligibility criteria prior [^{177}Lu]Lu-PSMA RLT selects patients more strictly for [^{177}Lu]Lu-PSMA RLT than VISION criteria.

Keywords PSMA therapy, [^{18}F]rhPSMA-7.3, Eligibility, VISION, [^{177}Lu]Lu-rhPSMA-10.1, Prostate cancer

Introduction

[^{177}Lu]Lu-PSMA radioligand therapy (RLT) has become a cornerstone for patients with metastatic castration-resistant prostate cancer (mCRPC) [1–3]. [^{177}Lu]Lu-PSMA RLT is highly effective with low toxicity [2, 4, 5] and was also recently FDA-approved in mCRPC prior to first-line chemotherapy [6]. Patients who receive [^{177}Lu]Lu-PSMA RLT usually undergo prior PET imaging to determine target expression for treatment suitability and agents such as [^{68}Ga]Ga-PSMA-11, [^{18}F]rhPSMA-7.3 (POSLUMA®), and [^{18}F]DCFPyL (Pylarify®) are commonly used to screen for sufficient PSMA-ligand uptake [7]. However, according to the SNMMI/EANM guidelines, all PSMA agents are suitable for selecting patients for [^{177}Lu]Lu-PSMA RLT [8]. To date, the PET-based criteria used to select patients are frequently inconsistent in clinical routine and often even differ between prospective clinical trials.

In 2021, the VISION trial, a multicenter randomized phase III study involving 831 patients with mCRPC, assessed the effectiveness of [^{177}Lu]Lu-PSMA-617 plus standard of care compared to standard of care alone. Before treatment, patients underwent [^{68}Ga]Ga-PSMA-11 PET/CT imaging to confirm PSMA-positive status and were only admitted to therapy if they fulfilled a set of PSMA PET-based criteria. The trial findings demonstrated significantly longer overall survival (OS) and radiographic progression-free survival (rPFS) for patients receiving [^{177}Lu]Lu-PSMA-617 than the standard of care alone [2].

[^{177}Lu]Lu-rhPSMA-10.1 is another therapeutic PSMA-targeting agent that has shown promising results for treating mCRPC [9–11]. It has already been demonstrated in patients treated with up to 6 cycles that [^{177}Lu]Lu-rhPSMA-10.1 displays moderately low toxicity and encouraging declines in PSA levels [10, 11]. This agent is currently being explored in a prospective, multicenter, non-randomized trial by Blue Earth Therapeutics (NCT05413850, Registration Date: 20/05/2022). Patients in this trial undergo a Flotufolastat PET scan prior to therapy to assess treatment eligibility, and are required to present with at least one PET/CT-visible lesion with a PSMA expression score higher than liver uptake. They are excluded from therapy if they show any of the following: lymph node > 10 mm short axis and uptake ≤ blood pool, bone metastasis with soft tissue component with uptake ≤ blood pool, visceral metastasis > 10 mm long axis and uptake ≤ liver, or majority of all metastases (based on a visual assessment) ≤ liver.

Considering the frequently high cost of [^{177}Lu]Lu-PSMA RLT and the sometimes limited benefit, careful patient selection is important to optimize the average benefit per patient. It has been demonstrated that PSMA PET/CT-related findings, such as specific types of metastases (i.e., visceral metastases), low SUVs in PSMA PET, or PSMA-negative tumor lesions, are predictive factors linked to unfavorable treatment outcomes and responses to [^{177}Lu]Lu-PSMA RLT [12–15]. For that reason, the 2021 TheraP trial, based on previous findings [16], excluded patients with FDG-positive/PSMA-negative (discordant) lesions from RLT to optimize response rates [17]. However, it is also known that patients with lower PSMA expression, which would not have been eligible for the VISION trial, can respond to [^{177}Lu]Lu-PSMA RLT [18]. Based on advice from the FDA to broaden access to novel [^{177}Lu]Lu-PSMA agents for patients, including those with low PSMA-expressing tumors but also excluding patients with negative prognostic PET features, a new set of criteria has been developed for this [^{177}Lu]Lu-rhPSMA-10.1-based phase I trial (BET-PSMA-121).

In this study, we retrospectively assessed how the BET-PSMA-121 eligibility criteria align with those of the VISION trial, and whether these differences affect patient outcomes.

Material and methods

Patients

We reviewed data from our institutional database and included all patients who received [^{177}Lu]Lu-PSMA RLT with [^{177}Lu]Lu-PSMA-I&T from October 2017 to August

2021 and underwent imaging via ([^{18}F]rhPSMA-7 or Flotufolastat PET/CT with a median interval of 21 days prior to treatment (IQR: 12–34.5; range, 0–219). Patients treated at our institution were deemed eligible for therapy and discussed in an interdisciplinary tumor board. From this group, 191 consecutive patients were selected, all of whom had previously received second-line hormonal therapy and taxane-based chemotherapy. The retrospective analysis was approved by the Ethics Committee of the Technical University of Munich (permit number 2018–115) and is in accordance with the principles of the Declaration of Helsinki. The requirement to obtain informed consent for publication of the data was waived.

PET imaging

([^{18}F]rhPSMA-7 and Flotufolastat were synthesized according to Wurzer et al. [19]. The substance was administered to patients via an intravenous bolus, followed by an intravenous injection of diuretics (furosemide). The PET acquisition started approximately 60 min after the injection. All patients underwent examination on a Biograph mCT or a Biograph Vision scanner (Siemens Healthineers). A diagnostic CT scan was initially performed during the portal venous phase, 80 s after the intravenous injection of an iodinated contrast agent, followed by the PET scan. Each patient received a diluted oral contrast agent (300 mg of Telebrix; Guerbet). The PET scans were conducted in 3-dimensional mode, with an acquisition time of 3–4 min per bed position, or 1.1–1.5 mm/s using the flow technique. Emission data were adjusted for randoms, dead time, scatter, and attenuation and were iteratively reconstructed using ordered-subsets expectation maximization (4 iterations, 8 subsets), followed by a post-reconstruction smoothing Gaussian filter (5 mm full width at half maximum).

Table 1 Comparison of PET-based eligibility criteria of VISION vs. BET trial

	PET-based eligibility in BET's phase I/II trial	PET-based eligibility in VISION
Inclusion criterion	at least one lesion visible on the CT/MRI > liver uptake (1 lesion PSMA score ≥ 2)	≥ 1 PSMA-positive lesion in any organ of any size
Exclusion criterion	• Lymph node > 10 mm short axis with PSMA score 0 • Visceral metastasis > 10 mm long axis with PSMA score ≤ 1 • Bone metastasis with PSMA-negative soft tissue component with PSMA score 0 • Majority of tumor volume (based on qualitative visual assessment) from lymph node and/or bone lesions with PSMA score ≤1 ("majority criterion")	• Lymph node ≥ 2.5 cm short axis with PSMA score ≤ 1 • Visceral metastasis ≥ 1 cm with PSMA score ≤ 1 • Bone metastasis with PSMA-negative soft tissue component ≥ 1 cm defined by PSMA score ≤ 1

Image analysis and definition of PET eligibility

Metastatic patterns were assessed according to the miTNM classification [20, 21] (N1/M1a: presence of lymph node metastases; M1b: presence of bone metastases; and M1c: presence of visceral metastases), derived from ([^{18}F]rhPSMA-7 and Flotufolastat PET imaging, for every patient.

All patients were assessed by a board-certified nuclear medicine physician (with > 5 years of experience) to determine if they met (showcased by a "+") the imaging-based eligibility criteria for the BET (B) and the VISION trial (V), and stratified into four groups depending on their eligibility: 1) V + /B + , 2) V + /B-, 3) V-/B + , and 4) V-/B-. The criteria utilized for this analysis from BET and VISION are shown in Table 1. PSMA expression was described based on the miPSMA Expression Score [20], with 0 signifying a tracer uptake below blood pool, 1 ≥ blood pool but < liver, 2 ≥ liver but < parotid gland, and 3 ≥ parotid gland.

In short, VISION criteria exclude any patient who fulfills at least one of the following abnormalities with uptake ≤ liver (miPSMA score 0 or 1) in the baseline PET scan: lymph nodes ≥ 2,5 cm, solid organ/parenchymal metastases ≥ 1 cm, and/or bone metastases with soft tissue component ≥ 1 cm (Table 1).

BET criteria similarly exclude any patient with at least one of the following: lymph nodes > 1 cm with miPSMA score 0, bone metastases with negative (miPSMA score 0) soft tissue components, as well as visceral metastases > 1 cm and miPSMA score 0 or 1 (Table 1). Additionally, BET criteria exclude a patient when, based on a visual assessment by the assessing physician, the majority of lymph nodes and/or bone lesions exhibit PSMA levels ≤ liver (miPSMA score 0 or 1) ("majority criterion") (Table 1).

[^{177}Lu]Lu-PSMA-I&T RLT

[^{177}Lu]Lu-PSMA-I&T was synthesized and radiolabeled as reported by Weineisen et al. [22]. The preparation of [^{177}Lu]Lu-PSMA-I&T complied with good manufacturing practices and the German Medicinal Products Act (Arzneimittelgesetz §13 2b). In total, we administered 750 cycles of [^{177}Lu]Lu-PSMA RLT, with a median of 4 cycles per patient (ranging from 1 to 10 cycles). Treatment was discontinued in cases of radiographic and/or clinical signs of progression and/or severe toxicity. Patients received an intravenous treat ment with an average standard activity of 7.4 GBq of [^{177}Lu]Lu-PSMA-I&T every 5 to 16 weeks (median of 6 weeks), which could be slightly adjusted based on laboratory test results and tumor burden.

Outcome measures

PSA response and PSA progression

PSA levels and their relative change between cycles were assessed. According to the Prostate Cancer Clinical Trials Working Group 3 [23], a PSA response was defined as a PSA decline of at least 50% from baseline. PSA progression was defined as either a PSA increase of at least 25% and at least 2 ng/mL above the nadir following an initial PSA decline or a PSA increase of at least 25% and at least 2 ng/mL from baseline in cases with no PSA decline.

PSA progression-free survival

PSA-PFS was defined as the time from the first cycle of RLT to the time of PSA progression or until the time of death if progression had not been observed.

Overall survival

OS was defined as the time from initiation of RLT until death from any cause. Patients who were alive or lost to follow-up were censored at the last date they were known to be alive.

Statistical analysis

Kaplan–Meier graphs and t-tests were generated using SPSS Statistics, version 29.0.2.0 (IBM Corp.) for Mac. Other statistical calculations and waterfall plots were performed and generated via Microsoft Excel for Mac, version 16.92. All statistical tests were conducted for the entire cohort and after stratification by eligibility criteria. Kaplan–Meier tests were calculated for survival analyses. A p-value < 0.05 was rated as statistically significant. Cohen's κ calculations were performed with Microsoft Excel for Max, version 16.92, and agreement between sets of eligibility criteria was rated according to the benchmarks established by Landis & Koch, with $\kappa < 0.0$ signifying poor strength, 0.0–0.2 slight, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 substantial, and 0.81–1.0 almost perfect agreement [24].

Table 2 Baseline patient characteristics

Characteristic	*N (range)*
No. of patients	191
Age (y)	74 (37–91)
PSA (ng/mL)	70.9 (0.03–4830)
Prior systemic therapies for mCRPC	*N (%)*
Docetaxel	133 (69.6)
Cabazitaxel	24 (12.6)
Abiraterone	162 (84.8)
Enzalutamide	117 (61.3)
^{223}Ra	14 (7.3)
Site of metastasis	*N (%)*
Lymph node, overall (N1 + / M1a)	137 (71.7%)
Intrapelvic lymph node only (N1)	14 (7.3%)
Extrapelvic lymph node only (M1a)	28 (14.7%)
Both intra- and extrapelvic lymph nodes (N1 + M1a)	95 (49.7%)
Bone (M1b)	175 (91.6%)
Visceral (M1c)	59 (30.9%)

Results

Patient characteristics

A total of 191 patients with a median age of 74 years were analyzed. Patient characteristics and pre-treatments are presented in Table 2. Of the 191 patients, 138 (72.3%) underwent imaging via Flotufolastat, while the remaining 53 (27.7%) underwent [^{18}F]rhPSMA-7 PET/CT. A separate analysis of the Flotufolastat subcohort was performed and is included in the Supplementary Material. At baseline, loco-regional lymph node, distant lymph node, bone, and visceral metastases were present in 109 (57.1%), 123 (64.4%), 175 (91.6%), and 59 (30.9%) patients, respectively. The median durations of treatment and follow-up were 4 months (range, 0–35 months) and 12 months (range, 0–62 months), respectively. Two patients died shortly after the first cycle of [^{177}Lu]Lu-PSMA-I&T (three weeks and one month, respectively), and three other patients had missing follow-up data regarding their PSA, meaning that we could only assess PSA-PFS and PSA response for 186/191 patients (97.4%). As of June 2024, 162 patients (84.8%) have deceased.

Comparison of [^{177}Lu]Lu-PSMA RLT eligibility as assessed by VISION and BET criteria

1. V + /B + : A total of 161/191 patients (84.3%) were classified as eligible for both BET and VISION (V + /B +) (Supp. 1).
2. V + /B-: 17/191 (8.9%) qualified for VISION only, while 15/17 of them were BET-ineligible due to the majority of the metastases having less uptake than the liver ("majority criterion"), the other two patients had PSMA-negative lymph node metastases (> 10 mm short axis and uptake ≤ liver) (Fig. 1, Supp. 1).
3. V-/B-: 13/191 patients (6.8%) were ineligible using both sets of eligibility criteria (V-/B). 7/13 were excluded from both studies solely due to PSMA-negative visceral metastases (6/13 had low uptake according to BET, 1/13 was negative in BET), 2/13 solely due to PSMA-negative lymph nodes, and 1/13 because of PSMA-negative soft tissue component of bone metastases (Fig. 1). Two other patients simultaneously exhibited PSMA-negative visceral metastases (VISION + low uptake in BET) and fulfilled BET's majority criterion. One patient had both PSMA-negative visceral metastases (VISION + low in BET) as well as bone metastases

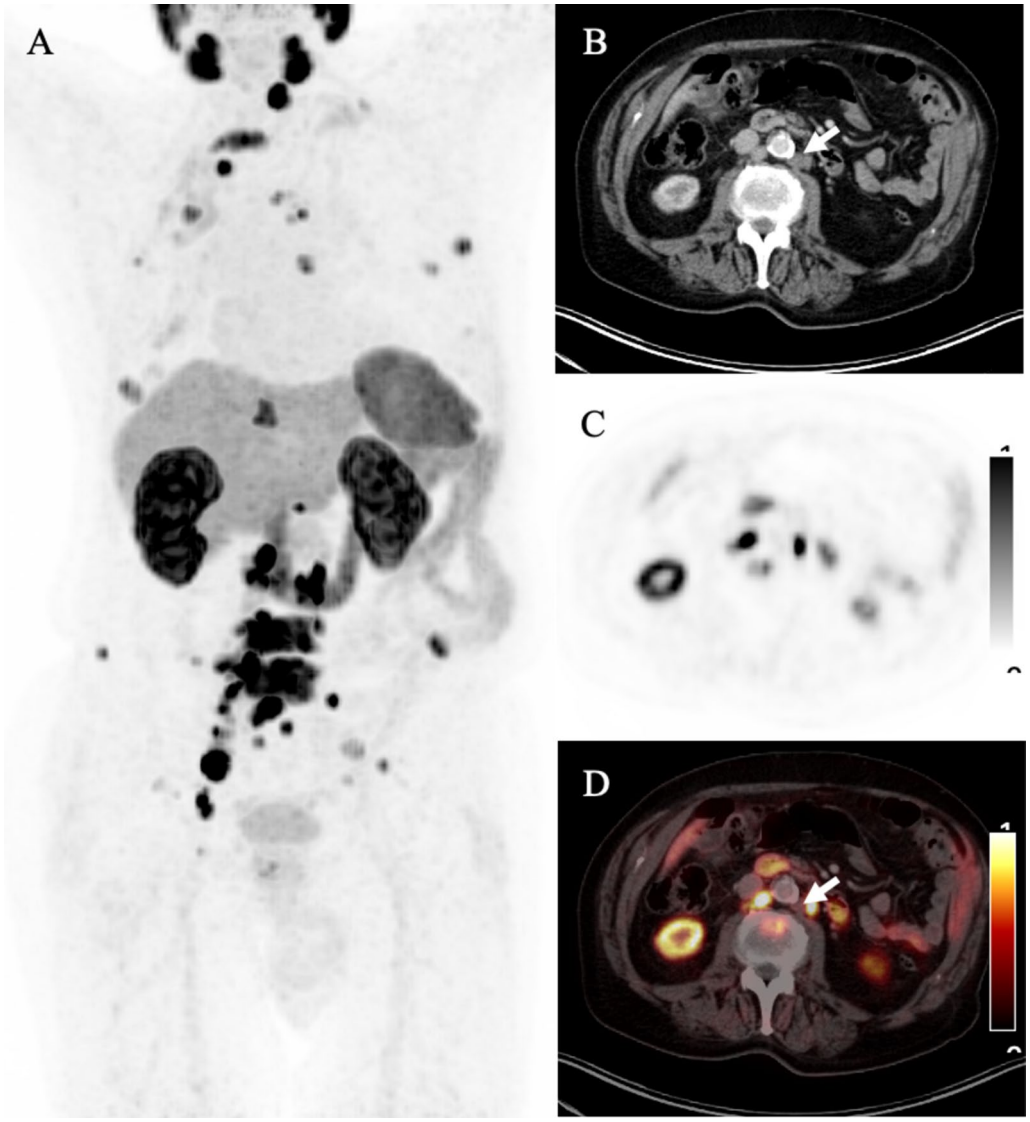


Fig. 1 Flotufolastat PET/CT images of a patient excluded from BET due to a PSMA-negative paraaortic lymph node metastasis. (**A**) MIP, (**B**) CT image, (**C**) PET scan, (**D**) CT scan with PET scan overlay. PSMA-negative lymph node metastasis visible in (B), but not in (**C**, **D**) (SUVmax 1.6), while the remaining metastases presented with a heterogenous PSMA expression (**A**). Due to the size < 2.5 cm of the lymph node (**B**), this patient was suitable according to VISION criteria (SUVmean liver: 5.0. SUVmean blood pool: 1.8)

with PSMA-negative soft tissue component in VISION (Supp. 2).

4. V-/B + : No patient was eligible based on BET criteria while ineligible by VISION's criteria.

Clinical outcomes

PSA response: PSA response and PSA-PFS could be assessed for 186/191 patients (97.4%). Out of the 186 patients, 107 (57.5%) exhibited an initial PSA decline, with 64 (34.4%) achieving a 50% reduction in PSA levels. In 77 cases (41.4%), PSA values increased under PSMA RLT; 74 patients (39.8%) exhibited 25% PSA progression. In two cases (1.0%), PSA values were stable after PSMA RLT.

In the subgroups V + /B + , V + /B-, and V-/B-, a > 50% PSA response was present in 62/157 (39.5%, 95% CI 31.8–47.6%), 2/17 (11.8%, 95% CI 1.5–36.4), and 0/13 (0%, 95% CI 0–24.7%) patients, respectively. The median time from baseline to assessment of PSA response was 73 days (IQR: 42–133; range: 0–1243 days). The median PSA change from baseline to final assessment (best response or progression) was -16% (IQR: -77.1% to 51.0%, range: -100 to + 5660%). A PSA waterfall plot illustrates the best PSA response across the subgroups and for the entire cohort (Fig. 2).

PSA-PFS: Median PSA-PFS for the entire cohort was 3.9 months (95 CI, 2.9–4.9 months). PSA-PFS differed significantly between the three groups with 4.3 months

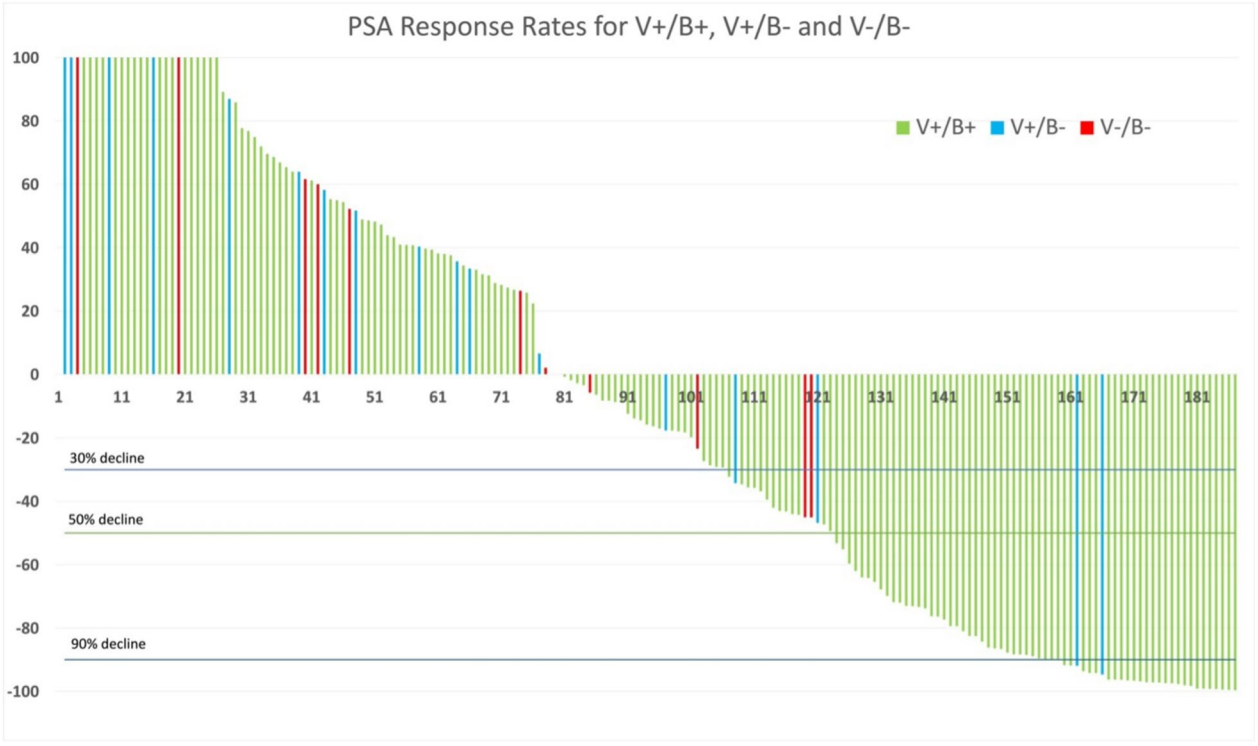


Fig. 2 Waterfall plot depicting best PSA response in percentage for each patient: In the subgroups V + /B + , V + /B-, and V-/B-, a > 50% PSA response was present in 62 of 157 (39.5%, 95% CI 31.8–47.6%), 2 of 17 (11.8%, 95% CI 1.5–36.4), and 0 of 13 (0%, 95% CI 0–26.5%) patients, respectively

Table 3 Endpoints by group

Entire cohort	*PSA PFS*	Median: 3.9 months (95% CI 2.9–4.9 months)
	OS	Median: 14.4 months (95% CI 12.8–16.0 months)
	PSA 50% decline	64/186 = 34.4% (95% CI 27.6–41.7%)
V + /B +	*PSA PFS*	Median: 4.3 months (95% CI 3.4–5.2 months)
	OS	Median: 14.9 months (95% CI 12.2–17.6 months)
	PSA 50% decline	62/157 = 39.5% (95% CI 318–47.6%)
V + /B-	*PSA PFS*	Median: 1.5 months (95% CI 1.4–1.6 months)
	OS	Median: 13.1 months (95% CI 9.2–17.0 months)
	PSA 50% decline	2/17 = 11.8% (95% CI 1.5–36.4%)
V-/B-	*PSA PFS*	Median: 2.8 months (95% CI 0.0–6.5 months)
	OS	Median: 7.7 months (95%CI 3.1–12.3 months)
	PSA 50% decline	0/12 = 0% (95% CI 0–26.5% (one-sided interval))

(95% CI, 3.4–5.2 months) vs. 1.5 months (95% CI, 1.4–1.6 months) vs. 2.8 months (95% CI 0.0–6.5 months) for the subgroups of V + /B + , V + /B- and V-/B-, respectively ($p = 0.002$). PSA-PFS was significantly prolonged between V + /B + vs. V + /B- ($p < 0.001$) but not between V + /B + vs. V-/B- and V + /B- vs. V-/B- ($p > 0.05$, each) (Table 3, Fig. 3).

OS: Median OS for the entire cohort was 14.4 months (95% CI, 12.8–16.0). For V + /B + , V + /B- and V-/B-, the OS was 14.9 months (95% CI, 12.2–17.6 months), 13.1 months (95% CI, 9.2–17.0 months), and 7.7 months (95% CI, 3.1–12.3 months), respectively, with a trend towards a prolonged OS for V + /B + compared to the two other groups ($p = 0.065$). V + /B + had a significantly prolonged OS compared to V-/B- ($p = 0.02$) with no significant differences between V + /B- vs. V-/B- ($p = 0.159$) and between V + /B + and V + /B- ($p = 0.782$) (Table 3, Fig. 4).

Cohen's κ

The overall agreement between the two trials' eligibility criteria was determined. For the complete cohort (161 eligible by both standards, 17 eligible only according to VISION, 13 completely ineligible), κ was moderate at 0.56.

Discussion

Certain (bio-)markers, including imaging-based ones such as PSMA-negative metastases, can predict a poorer response to [^{177}Lu]Lu-PSMA RLT [25]. To provide well-suited mCRPC patients with [^{177}Lu]Lu-PSMA therapy, there have been multiple attempts to develop ideal selection criteria prior to therapy [13, 14, 26–28], such as those from the VISION and BET trials. Considering the mixed responses to [^{177}Lu]Lu-PSMA therapy reported in

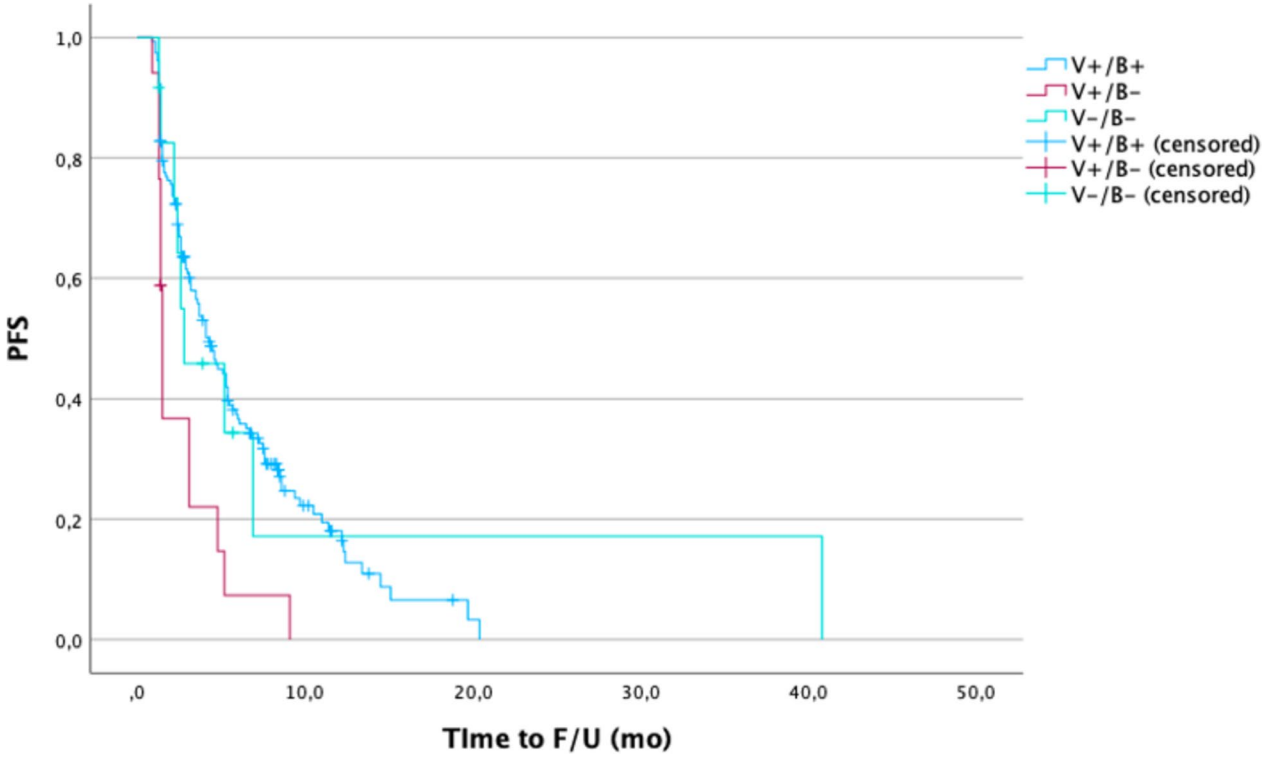


Fig. 3 Kaplan–Meier plots depicting PSA PFS in months by group: Median PSA-PFS for the entire cohort was 3.9 months (95 CI, 2.9–4.9 months). PSA-PFS differed significantly between the three groups with 4.3 months (95% CI, 3.4–5.2 months) vs. 1.5 months (95% CI, 1.4–1.6 months) vs. 2.8 months (95% CI 0.0–6.5 months) for the subgroups of V + /B + , V + /B- and V-/B-, respectively ($p = 0.002$). PSA-PFS was significantly prolonged between V + /B + vs. V + /B- ($p < 0.001$) but not between V + /B + vs. V-/B- and V + /B- vs. V-/B- ($p > 0.05$, each)

some patients, establishing optimal selection criteria is crucial to identify and offer RLT to those most likely to benefit.

The VISION trial excluded patients with metastases (visceral, bone with a soft tissue component, lymph node) expressing low PSMA levels (miPSMA score 0 or 1) from [^{177}Lu]Lu-PSMA RLT [2]. The BET trial introduced more detailed criteria, such as the majority criterion, which excludes patients in whom the majority of tumor volume shows less uptake than the liver, and is somewhat more permissive regarding lymph node metastases.

In this retrospective analysis, we applied both sets of election criteria to the same group of mCRPC patients to determine whether different eligibility thresholds identified different cohorts and influenced responses to therapy with [^{177}Lu]Lu-PSMA RLT.

Under VISION criteria, 174/191 patients (91.1%) were eligible, compared to 161/191 patients (84.3%) under BET. No patient in our cohort was included in BET but excluded from VISION (V-/B +). Most patients were eligible under both, which correlated with better OS and PFS outcomes, indicating that V + /B + effectively stratifies optimal candidates for [^{177}Lu]Lu-PSMA therapy.

The VISION exclusion criterion for bone metastases specifies "bone metastasis with PSMA-negative soft tissue component (uptake ≤ liver) ≥ 1 cm". BET's equivalent is similar but without the size limit, thus including VISION's criterion. For lymph nodes, BET defines them as "> 10 mm short axis with uptake ≤ blood pool," whereas VISION excludes lymph nodes only when "≥ 2.5 cm short axis with PSMA ligand uptake ≤ liver." Despite VISION's stricter uptake criterion, it allows patients with low-expressing lymph nodes < 2.5 cm, as their PSMA-expression is not a selection factor. BET's "majority criterion" was designed to include patients with low-expressing lesions in principle, but restrict against a predominant pattern of low-expressing disease.

We hypothesized a case in which a lymph node metastasis would meet BET but not VISION criteria (V-/B +), concluding that it would need to be > 2.5 cm in size with low but not negative tracer uptake (> blood pool and < liver). While possible, we did not observe this in our cohort. BET's criterion regarding visceral metastases is identical to VISION's. Overall, both trials exclude a similar number of patients (13 for VISION, 15 for BET) from therapy (V-/B-).

Of the 13 V-/B- patients, 7/13 were excluded solely due to PSMA-negative (PSMAscore ≤ 1) visceral metastases. Considering that V-/B- had the worst survival data of the three sub-groups, the criteria that led to V-/B- might

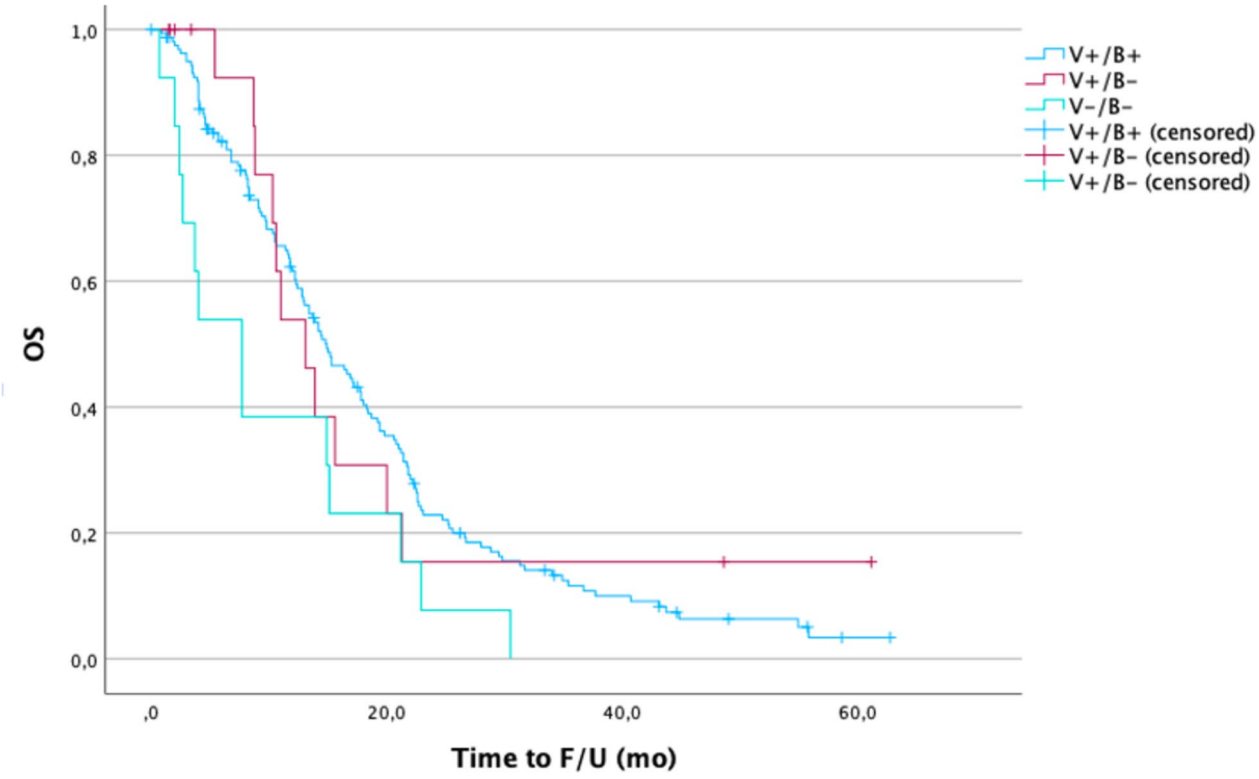


Fig. 4 Kaplan–Meier plots depicting median OS per group. Median OS for the entire cohort was 14.4 months (95% CI, 12.8–16.0). For V + /B + , V + /B-, and V-/B-, the OS was 14.9 months (95% CI, 12.2–17.6 months), 13.1 months (95% CI, 9.2–17.0 months), and 7.7 months (95% CI, 3.1–12.3 months), respectively, with a trend towards a prolonged OS for V + /B + compared to the two other groups (p = 0.065). V + /B + had a significantly prolonged OS compared to V-/B- (p = 0.02) with no significant differences between V + /B- vs. V-/B- (p = 0.159) and between V + /B + and V + /B- (p = 0.782)

be successful for the prediction of [^{177}Lu]Lu-PSMA RLT-ineligibility.

The remaining differences mostly involve the "majority criterion" in BET, which excludes 15/17 V + /B- patients; notably, two such patients responded with over 50% PSA decrease (92% and 95%), respectively. The remaining two V + /B- patients had PSMA-negative lymph nodes.

Since VISION does not use the majority criterion, the 15 aforementioned patients were classified as V + , reducing the total eligible population under BET's stricter rule. The V + /B- group showed the worst PSA-PFS but no significantly decreased OS; however, the small sample size limits the ability to draw definitive conclusions. Future prospective studies should assess whether the application of both criteria sets enhances prognostic accuracy in mCRPC patients.

In summary, BET's criteria, particularly due to the majority criterion, are more restrictive than VISION's within this cohort. Including the majority criterion and BET's lymph node criterion appears to exclude patients who would not profit from RLT. The requirements regarding visceral metastases are identical between the two sets, and the absence of size restrictions within BET's bone metastasis criterion had a limited impact compared to VISION's.

There are several limitations to our study. It was retrospective, leading to some uncertain data, such as missing follow-up PSA values. Treatment decisions were made clinically, so minor deviations from recommended eligibility criteria were at the discretion of the treating nuclear medicine physician. Since follow-up treatments after [^{177}Lu]Lu-PSMA RLT are unknown to us, they may also have impacted PSA-PFS. Additionally, the disproportionately small sizes of the V-/B- and V + /B- cohorts relative to V + /B + reduce our study's statistical power.

Differences in tracer uptake with various diagnostic tracers should also be noted. While 72% of our patients, like those in the BET patient cohort, underwent Flotufolastat PET scans, the VISION trial used [^{68} Ga]Ga-PSMA-11 for eligibility assessments. Although these tracers differ slightly in aspects such as half-life and imaging resolution, they are all considered appropriate for detecting PSMA-expressing prostate cancer as per guidelines. Furthermore, differences in outcomes may be attributable to our use of [^{177}Lu]Lu-PSMA-I&T, as opposed to VISION's use of [^{177}Lu]Lu-PSMA-617, and BET's use of [^{177}Lu]Lu-rhPSMA-10.1.

Lastly, the assessment of the PET/CT scans was conducted by a single experienced nuclear medicine physician, which represents a methodological limitation as

interobserver variability could not be assessed. This absence of an interobserver reliability assessment may have introduced bias in the PET eligibility classification. To reduce subjectivity and improve reproducibility, future studies should ideally employ multiple independent readers for image analysis.

Conclusion

Most patients fulfilled both BET and VISION eligibility criteria prior to [^{177}Lu]Lu-PSMA RLT (V + /B +) and were associated with the best patient outcomes. Our data suggest that the criteria for BET's phase I trial select patients more strictly for [^{177}Lu]Lu-PSMA RLT than VISION criteria, with a mismatch in 8.9% of cases between VISION and BET (V + /B-) criteria, while overall survival did not differ significantly between the three groups. The implementation of both criteria in prospective trials will further compare BET and VISION PET-based eligibility criteria.

Abbreviations

CT	Computer tomography
^{18}F	Fluoride-18
F/U	Follow-up
^{68} Ga	Gallium-68
^{177}Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
MRI	Magnet resonance imaging
MIP	Maximum intensity projection
OS	Overall survival
PET	Positron emission tomography scan
PFS	Progression-free survival
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
^{223}Ra	Radium-223, [^{223}Ra]Radium-chloride therapy
rh	Radiohybrid
RLT	Radioligand therapy
rPFS	Radiographic progression-free survival
SPECT	Single photon emission computed tomography
SUV	Standardized uptake value

Supplementary Information

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Supplemetary Material 1

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Author contributions

SG, TL, IR, TLo, TLa, TH, ME, LU and WW all contributed to the study conception and design. Data collection was performed by KH, SG, TH, TLa, and TLo. Data analysis was performed by SG. The first draft of the manuscript was written by SG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author, SG, upon reasonable request.

Declarations

Ethics approval and consent to participate

The analysis was approved by the Ethics Committee of the Technical University Munich (#2018–115) and is in accordance with the principles of the Declaration of Helsinki. The requirement to obtain informed consent was waived.

Consent for publication

Not applicable.

Competing interests

ME reports fees from Blue Earth Diagnostics Ltd. (consultant, research funding), Novartis/AAA (consultant), Telix (consultant), Bayer (consultant, research funding), RayzeBio (consultant), Point Biopharma (consultant) and Janssen Pharmaceuticals (consultant, speakers bureau), Parexel (image review) and Bioclinica (image review) outside the submitted work and a patent application for rhPSMA. WW is on the advisory boards and receives compensation from Blue Earth Diagnostics, ITG, and Pentixapharm. He has received research support from Blue Earth Diagnostics, BMS, and Pentixapharm. He is also an editor for EJNMMI. LU reports fees from Novartis (speaker), Telix (consultant) and Astellas Pharma Inc. (speaker) outside of the submitted work. No other potential conflicts of interest relevant to this article exist.

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