European Association of Urology

Real-world Outcomes and Predictive Biomarkers for [177]Lutetium Prostate-specific Membrane Antigen Ligand Treatment in Metastatic Castration-resistant Prostate Cancer: A European Association of Urology Young Academic Urologists Prostate Cancer Working Group Multi-institutional Observational Study

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Article info

Abstract

Background: The European Association of Urology guidelines include the lutetium-177 (^{177}Lu) PSMA-617 prostate-specific membrane antigen (PSMA) ligand as a therapy option for metastatic castration-resistant prostate cancer (mCRPC). A major challenge in clinical practice is to pursue a personalized treatment approach based on robust predictive biomarkers.
Objective: To assess the performance of ^{177}Lu PSMA in real-world practice and to elaborate clinical biomarkers for evaluating treatment responses.

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Design, setting, and participants: We conducted a retrospective observational study including 233 patients with mCRPC treated with ^{177}Lu PSMA in eight high-volume European centers.

Outcome measurements and statistical analysis: Baseline characteristics and clinical parameters during and after ^{177}Lu PSMA treatment were documented. Correlations to treatment response were analyzed using χ^2 and log-rank tests, with differences between groups with and without disease progression calculated using a Mann-Whitney U test. Univariate and multivariate-adjusted hazard ratios (HRs) were measured using Cox proportional hazards models.

Results and limitations: A prostate-specific antigen (PSA) decrease of $\geq$30% was observed in 41.7%, 63.5%, and 77.8% of patients after the first, second, and third treatment cycle, respectively. Restaging performed via PSMA positron emission tomography-computed tomography revealed that 33.7% of patients had an imaging-based response, including two patients with a complete response, while 13.4% had stable disease. The median time to progression was 5 mo and the median time until the start of a consecutive antineoplastic therapy was 8.5 mo. Of importance, a PSA decrease $\geq$30% after the first two cycles of ^{177}Lu PSMA (1 cycle: $p = 0.0003$; 2 cycles: $p = 0.004$), absolute PSA after the first three cycles (1 cycle: $p = 0.011$; 2 cycles: $p = 0.0005$; 3 cycles: $p = 0.002$), and a PSA doubling time >6 mo ($p = 0.009$) were significantly correlated to treatment response. Furthermore, gamma-glutamyl transferase $\leq$31 U/L at the start of ^{177}Lu PSMA therapy was correlated with 1.5 times higher risk of progression for patients without but not with visceral metastases ($p = 0.046$).

Conclusions: ^{177}Lu PSMA is an effective treatment option in mCRPC in the real-world setting. A PSA decrease $\geq$30% after the first two cycles is an early marker of response that can be easily implemented in clinical practice.

Patient summary: ^{177}Lu PSMA is a radioactive agent approved for treatment of advanced prostate cancer. We reviewed its use outside of clinical trials for patients treated at eight European centers. We found that ^{177}Lu PSMA is an effective treatment option in real-world practice. A PSA (prostate-specific antigen) decrease of $\geq$30% after the first two therapy cycles is an early indicator of response to treatment and can be used in personalizing treatments for patients.

1. Introduction

Treatment of metastatic prostate cancer has significantly shifted from androgen deprivation therapy (ADT) towards personalized treatment with the introduction of multiple innovative therapy options for both metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC). According to the current European Association of Urology (EAU) guidelines, mCRPC treatment is based on ADT plus either taxane-based chemotherapy (docetaxel, cabazitaxel), androgen receptor signaling inhibitors (ARSIs), PARP inhibitors as monotherapy or in combination with abiraterone acetate/prednisone, immunotherapy agents (sipuleucel-T, ipatasertib), or radium-233 for bone-dominant disease [1]. Of note, the current EAU guidelines recommend for the first time ^{177}Lu PSMA-617, a radioligand therapy based on the VISION trial, a randomized multicenter trial evaluating ^{177}Lu PMSA plus best standard of care (SOC) versus best SOC alone in men with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC [2]. VISION demonstrated significant improvement in both overall survival (OS) and radiographic progression-free survival (rPFS) in patients treated with ^{177}Lu PMSA [2]. However, cabazitaxel and olaparib

were excluded from SOC regimens, so patients could only be treated with ARSIs as SOC. Nevertheless, as a consequence of the study results, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved Pluvicto (^{177}Lu PSMA-617) for mCRPC previously treated with ARSIs and taxane chemotherapy. Furthermore, the prospective randomized TheraP trial recently demonstrated higher prostate-specific antigen (PSA) response rates and lower rates of grade 3–4 side effects among patients treated with ^{177}Lu PSMA-617 in comparison to cabazitaxel, highlighting the therapeutic strength of ^{177}Lu PSMA-617 [3].

Hence, a major challenge for clinicians is the selection of those patients who would best benefit from ^{177}Lu PSMA therapy and changing to alternative therapeutic strategies for nonresponders in order to pursue a personalized treatment approach [4]. While PSMA expression on PSMA positron emission tomography-computed tomography (PET-CT) is recognized as an imaging-based predictive biomarker, clinical biomarkers for easy and inexpensive therapy monitoring are still lacking. Therefore, the aim of the present multi-institutional observational study was to elucidate clinical biomarkers for evaluating treatment responses before and during ^{177}Lu PSMA therapy.

2. Patients and methods

An international, multicenter, retrospective observational study was conducted after approval from the local ethics committee (reference number 1140/2022). Clinical data for 233 patients with mCRPC treated with ^{177}Lu PSMA (different PSMA ligands) between January 2014 and June 2022 at eight high-volume European centers (Cologne, Mainz, Munich, Tübingen, Vienna, Padua, Lübeck/Kiel, and Innsbruck) were extracted from patient charts. As data were not 100% complete for every patient, the number of patients for whom data were available is included for each parameter in the tables.

Statistical analysis was performed using SPSS v26.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics were tabulated with descriptive statistics for the population. The median and interquartile range (IQR) are reported for continuous variables, and the frequency and percentage for categorical variables. Correlation between various parameters and clinical progression was tested using χ^2 and log-rank tests. To calculate the significance of differences between groups with and without disease progression, we used the Mann-Whitney U test. Univariate and multivariate adjusted hazard ratios (HRs) were calculated using Cox proportional hazards models. For adjustment in multivariate analysis, we included the following potentially statistically relevant parameters that were explored in calculations using a Mann-Whitney U test and χ^2 test: PSA decrease $\geq$30% after cycles 1–3, hemoglobin $\geq$10.4 g/l, visceral metastasis, gamma-glutamyl transferase (GGT) >31 U/l, and alkaline phosphatase (ALP) >220 U/l. All statistical tests were two-sided at a significance level of 0.05. Owing to the explorative nature of our study and the lack of prespecified statistical approach, we did not correct for multiple testing.

3. Results

3.1. Efficacy of ^{177}Lu PSMA ligand therapy

Data on PSA levels were collected after cycles 1–3 and at the end of treatment. After the first cycle, 41.7% of patients (n = 79) had a PSA decrease of $\geq$30% in comparison to the start of therapy. After the second and third cycles, 63.5% (n = 120) and 77.8% (n = 148), respectively, had a PSA decrease of $\geq$30%. At the end of ^{177}Lu PSMA therapy, the median PSA was 85 ng/ml, compared to 99.2 ng/ml before therapy, and 56% of the patients (n = 51) had a PSA doubling time (PSA-DT) of <6 mo, compared to 68.7% (n = 68) before ^{177}Lu PSMA treatment (Table 1). PSMA PET-CT was performed after a median of three cycles of ^{177}Lu PSMA and revealed an imaging response in 33.7% (n = 58), including two patients who experienced a complete response during therapy. According to Response Evaluation Criteria in Solid Tumors v2.0, 13.4% of patients (n = 23) were classified as having stable disease, while disease progression was observed in 52.9% (n = 91). With progression defined as fulfillment of two out of three criteria (clinical/symptomatic progression, PSA progression, and progress on imaging), 57.6% of the patients had progression during ^{177}Lu PSMA therapy, and 42.4% showed a response or at least had stable disease. The median time to progression (TTP) was 5 mo in the overall population (mean 8.3, IQR 9) with a median time of 8.5 mo (mean 31.8, IQR 15) until the start of the next antineoplastic therapy. Among those undergoing subsequent treatment, most patients (40.7%, n = 33) received chemotherapy, while 22.2% (n = 18) had ^{177}Lu PSMA rechallenge and 16% (n = 13) received an ARSI as next treatment. Some 20.9% (n = 17) of patients underwent experimental therapies or were included in clinical trials. For the group of patients treated with chemotherapy, 46.6% (n = 14) received cabazitaxel, 43.3% (n = 13) received docetaxel, and 10% (n = 3) received carboplatin. At the end of our study period, 48% of patients were alive, 48% had died from prostate cancer, and 4% had died from other causes.

Routine laboratory measurements revealed declines in median hemoglobin (from 11.6 to 10.5 g/l) and thrombocyte count (from 229 to 191 $\times$ 10^9/l) after therapy, while median GGT (from 31 to 36 U/l) and ALP (from 96 to 113 U/l) had increased. However, of importance, the Eastern Cooperative Oncology Group (ECOG) performance status did not significantly chance during therapy (ECOG 0–1: 95% before and 89.4% after ^{177}Lu PSMA therapy). Results for all parameters collected during and at end of treatment are listed in Table 1.

3.2. Baseline patient characteristics

Our population comprised 233 patients with mCRPC who received at least one cycle of ^{177}Lu PSMA therapy (median 3 cycles, IQR 2). Most patients (93.9%, n = 219) received up to six cycles of ^{177}Lu PSMA, while only 6% (n = 14) received up to 13 cycles in total (Supplementary Table 1). The median ^{117}Lu PSMA dose per patient was 22.7 GBq (mean 24.9, IQR 16.2). The median patient age at diagnosis was 64 yr (mean 63.3, IQR 11) and the median PSA at primary diagnosis was 29 ng/ml (Table 1). Some 58% of patients had de novo metastatic disease, of whom 73.6% were classified as having low-volume disease according to the CHAARTED criteria [5]. Of note, a significant proportion of patients were classified as D'Amico high risk at primary diagnosis, of whom 50% (n = 64) had International Society of Urological Pathology (ISUP) grade group 5, 26.5% (n = 34) had grade group 4, 13.2% (n = 17) had grade group 3, 7.8% (n = 10) had grade group 2, and 2.3% (n = 3) had grade group 1 disease. Some 91/190 patients (47.9%) underwent radical prostatectomy (RP) at when their disease was at the organ-confined stage, 14.7% (n = 28) had external beam radiation therapy (EBRT), 4.7% (n = 9) underwent RP followed by adjuvant EBRT, and 32.1% (n = 61) had received no previous local therapy. An antiandrogen or ADT monotherapy was used for primary systemic treatment in mHSPC in 54.3% (n = 94) of the patients, while 37.6% were treated with an ADT + ARSI combination (n = 65) and 8% (n = 14) with chemotherapy. Genetic testing was performed in 50/191 patients (26.1%) in our cohort, with genetic alterations found in 9.9% (n = 19; Supplementary Table 2).

Table 2 provides an overview of the baseline characteristics of the study population overall and by treatment response group. None of the baseline parameters were sig-

Table 1 – Clinical course and outcome after ^{177}Lu PSMA ligand therapy

Parameter	N	Overall cohort	Response/stable disease	Disease progression	p value[a]
PSA after cycle 1 (ng/ml)[b]	233	69.9 (365.6 ± 850)	31.7 (251.2 ± 506)	75.4 (394 ± 966)	**0.011**
PSA decrease after cycle 1	189				**0.00003**
≥30% (n)		79	48	31	
<30% (n)		110	33	77	
PSA after cycle 2 (ng/ml)[b]	210	40 (329.4 ± 794)	17 (167.2 ± 407.2)	80 (428.7 ± 996.9)	**0.0005**
PSA decrease after cycle 2	189				**0.004**
≥30% (n)		120	61	59	
<30% (n)		69	20	49	
PSA after cycle 3 (ng/ml)[b]	147	22.5 (229.8 ± 505.7)	10 (118.8 ± 287.8)	69.9 (342.9 ± 659.8)	**0.002**
PSA decrease after cycle 3	190				0.051
≥30% (n)		148	69	79	
<30% (n)		42	12	30	
PSA AET (ng/ml)[b]	189	85 (443.9 ± 920.4)	8 (153.7 ± 395)	169.9 (620.1 ± 1168)	**<0.000005**
PSA doubling time AET (mo)[b]	73	1.48 (74.2 ± 582)	−0.7 (9 ± 39.5)	1.66 (131.5 ± 789.3)	**0.012**
PSA doubling time AET	91				**0.009**
>6 mo (n)		40	16	24	
≤6 mo (n)		51	8	43	
ECOG performance status AET	132				0.620
ECOG 0 (n)		53	28	25	
ECOG 1 (n)		65	29	36	
ECOG 2–3 (n)		14	5	9	
Hemoglobin AET (g/l)[b]	202	10.5 (10.6 ± 5.6)	11.2 (10.7 ± 3.6)	10.5 (11 ± 6.6)	0.096
Thrombocytes AET (10⁹/l)[b]	202	191.5 (189.3 ± 94.2)	205.5 (200 ± 76.7)	204 (198.4 ± 105.2)	0.736
C-reactive protein AET (mg/dl)[b]	191	0.91 (3 ± 5.6)	0.23 (2.3 ± 6.55)	1.2 (2.9 ± 4.7)	**0.0001**
GGT AET (U/l)[b]	196	36 (85 ± 149.3)	23 (55.5 ± 94.6)	42 (88.5 ± 152.5)	**0.003**
Alkaline phosphatase AET (U/l)[b]	196	113 (223 ± 314.8)	82 (142 ± 199.9)	143 (239 ± 336)	**0.00006**
Metastasis on PSMA PET-CT AET	174				**< 0.001**
Lymph nodes (n)		14	10	4	
Bone (n)		29	19	10	
Visceral (n)		3	1	2	
Multiple (n)		128	48	80	
Findings on PSMA PET-CT	172				**<0.001**
Disease progression (n)		91	0	91	
Stable disease (n)		23	23	0	
Response (n)		56	55	1	
Complete response (n)		2	2	0	
Time to progression (mo)[b]	115	5 (8.3 ± 10.7)	6.5 (8.9 ± 6.9)	3 (7.9 ± 13.2)	**0.004**
Time to next therapy (mo)[b]	78	8.5 (31.8 ± 80.5)	12 (27 ± 45)	5 (36.3 ± 102)	0.160
Type of next therapy	81				
ARSI (n)		13	6	7	
Chemotherapy (n)		33	14	19	
[177]Lu PSMA rechallenge (n)		18	13	5	
Other (eg, clinical trial) (n)		17	6	11	
Cause of death	131				
Alive (n)		63	35	28	
Prostate cancer (n)		63	22	41	
Other (n)		5	1	4	

PSMA = prostate-specific membrane antigen; PSA = prostate-specific antigen; AET = at end of treatment; ECOG = Eastern Cooperative Oncology Group; ARSI = androgen receptor signaling inhibitor; GGT = gamma-glutamyl transferase; PET-CT = positron emission tomography-computed tomography.

[a] p value for correlation with progression after ^{177}Lu PSMA ligand therapy. Progression was defined as fulfillment of two of the following three criteria: clinical/symptomatic progression, PSA progression, and progression on imaging.

[b] Result presented as median (mean ± standard deviation).

nificantly associated with treatment response to ^{177}Lu PSMA.

3.3. Patient characteristics at the start of ^{177}Lu PSMA ligand therapy

At the start of therapy, median PSA was 99.2 ng/ml and 68.7% (n = 68) of patients had a PSA-DT of <6 mo. Some 75% (n = 140) had multiple metastases on PSMA PET-CT, while 14.9% (n = 28) had only osseous metastasis, 9.6% (n = 18) had only lymph node metastasis, 34% (n = 78) had visceral metastases, and 0.5% (n = 1) had a solitary visceral metastasis. Most patients were either asymptomatic (54.2%, n = 103) or had mild symptoms (35.2%, n = 67) and 54.6% (n = 83) had an ECOG performance status of 0

at the start of ^{177}Lu PSMA therapy. The time from castration resistance to the start of ^{177}Lu PSMA therapy did not differ between responders and nonresponders (p = 0.151).

The following clinical parameters previously described as potential biomarkers in small patient cohorts were assessed at the start and end of ^{177}Lu PSMA treatment: hemoglobin, thrombocytes, ALP, GGT, C-reactive protein (CRP), and lactate dehydrogenase (LDH) (Table 3) [4].

3.4. Evaluation of clinical parameters as biomarkers for treatment response

A PSA decrease of ≥30% after the first two cycles in comparison to the start of therapy was predictive for treatment response (p = 0.0003 after 1 cycle; p = 0.004 after 2 cycles;

Table 2 – Baseline characteristic of the study population and stratification by treatment success

	N	Overall cohort	Response/stable disease	Disease progression	p value[a]
PSA at pDx (ng/ml)[b]	233	29 (470 ± 2064)	30 (336.2 ± 1129.6)	27.5 (228.1 ± 894)	0.576
Age at diagnosis (yr)[b]	224	64 (63.8 ± 8.1)	63.8 (63.6 ± 7.11)	63.3 (62.5 ± 8.24)	0.390
Metastatic disease	176				0.236
Synchronous (n)		102	38	64	
Metachronous (n)		74	37	37	
Local prostate treatment	190				0.436
None (n)		61	29	32	
RP (n)		91	33	58	
EBRT (n)		28	14	14	
RPE + EBRT (n)		9	4	5	
Other (n)		1	1	0	
ISUP grade group	128				0.088
Grade group 1 (n)		3	2	1	
Grade group 2–3 (n)		27	9	18	
Grade group 4 (n)		34	14	20	
Grade group 5 (n)		64	24	40	
sTx for mHSPC	173				0.875
AA/ADT (n)		94	40	54	
ARSI + ADT (n)		65	28	37	
CTx + ADT (n)		14	5	9	
Volume of disease[c]	129				0.671
Low (n)		95	39	56	
High (n)		34	13	21	

PSA = prostate-specific antigen; pDx = primary diagnosis; RP = radical prostatectomy; EBRT = external beam radiation therapy; ISUP = International Society of Urological Pathology; sTx = systemic therapy; mHSPC = metastatic hormone-sensitive prostate cancer; AA = antiandrogen agent; ADT = androgen deprivation therapy; ARSI =androgen receptor signaling inhibitor; CTx = chemotherapy.
[a] p value for correlation with progression after ^{177}Lu prostate-specific membrane antigen ligand therapy. Progression was defined as fulfillment of two of the following three criteria: clinical/symptomatic progression, PSA progression, and progression on imaging.
[b] Result presented as median (mean ± standard deviation).
[c] Volume of disease according to the CHAARTED criteria.

Table 3 – Clinical parameters at the start of ^{177}Lu PSMA ligand therapy

	N	Overall cohort	Response/stable disease	Disease progression	p value[a]
ECOG PS	152		71	81	0.932
ECOG 0 (n)		83	40	43	
ECOG 1 (n)		62	29	33	
ECPG 2 (n)		7	2	5	
Symptoms	190				0.726
Asymptomatic (n)		103	46	57	0.726
Symptomatic (n)		87	35	52	
PSA DT (mo)[b]	91	3 (11.1 ± 60.4)	3.1 (21.7 ± 98.8)	2.7 (4.3 ± 3.9)	0.297
PSA DT	99				0.572
>6 mo (n)		31	14	17	
≤6 mo (n)		68	31	37	
PSA (ng/ml)[b]	233	99.2 (421.6 ± 977.5)	62.4 (353.9 ± 684)	109.1 (439.3 ± 1161.5)	0.176
Hemoglobin (g/l)[b]	233	11.6 (11 ± 5.6)	12.1 (10.7 ± 3.6)	11.6 (11.4 ± 7.3)	0.492
Thrombocytes (10^9/l)[b]	233	229 (241 ± 91)	239 (249.9 ± 71)	228 (241.1 ± 101.9)	0.130
LDH (U/l)[b]	204	239.5 (318.3 ± 255)	221 (266.5 ± 149.1)	237 (300 ± 209.1)	0.277
CRP (mg/dl)[b]	231	0.53 (13.1 ± 168)	0.35 (33 ± 284.3)	0.54 (2.1 ± 3.71)	0.220
GGT(U/l)[b]	228	31 (68.1 ± 162)	25 (43.9 ± 53.3)	30.5 (81.9 ± 218)	0.116
ALP (U/l)[b]	228	96 (174.5 ± 232)	91.5 (128.8 ± 128.3)	94 (178.6 ± 219.3)	0.113
mPC on PSMA PET-CT	187				0.343
Lymph nodes (n)		18	9	9	
Bone (n)		28	10	18	
Visceral (n)		1	0	1	
Multiple (n)		140	60	80	

ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; DT = doubling time; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein; LDH = lactate dehydrogenase; mPC = metastatic prostate cancer; PSMA = prostate-specific membrane antigen; PET-CT = positron emission tomography-computed tomography.
[a] p value for correlation with disease progression after ^{177}Lu PSMA therapy. Progression was defined as fulfillment of two of the following three criteria: clinical/symptomatic progression, PSA progression, and progress on imaging.
[b] Result presented as median (mean ± standard deviation).

$p = 0.051$ after 3 cycles). Furthermore, the absolute PSA level after all three therapy cycles was a statistically significant marker for therapy response ($p = 0.011$ after 1 cycle; $p = 0.0005$ after 2 cycles; $p = 0.002$ after 3 cycles).

In addition, absolute PSA-DT ($p = 0.012$) and especially a PSA-DT of <6 mo ($p = 0.009$) at the end of ^{177}Lu PSMA therapy were significantly correlated to disease progression. Patients with any PSA rise after the first cycle of ^{177}Lu PSMA

Table 4 – Parameters analyzed as potential biomarkers of disease progression using a χ^2 test for categorical variables or a Mann-Whitney U test for continuous variables

Parameter	p value
Volume of disease (high vs low)	0.671
Primary metastatic disease (yes vs no)	0.236
Location of metastasis (lymph nodes, bone, visceral, multiple)	0.343
Primary local treatment of the prostate (RP, EBRT, RP + EBRT, none, other)	0.436
Type of genetic alteration (BRCA1/2, TB53, PIK3CA, multiple)	0.371
Any positive genetic alteration (yes vs no)	0.513
Four or more cycles of ^{177}Lu PSMA ligand therapy (yes vs no)	0.724
Prostate-specific antigen doubling time ≤ 6 mo at the start of ^{177}Lu PSMA therapy (yes vs no)	1
Prostate-specific antigen ≥ 100 ng/ml at primary diagnosis (yes vs no)	0.663
International Society of Urological Pathology grade group (1–3 vs 4–5)	1
Any primary local treatment of the prostate (yes vs no)	0.352
Type of systemic treatment in mHSPC (ADT/AA, ARSI, chemotherapy)	0.875
Age >65 yr at the start of ^{177}Lu PSMA therapy (yes vs no)	0.185
ECOG performance status category (0 vs 1–3)	0.870
Hemoglobin ≥ 10.4 g/l (yes vs no)	0.345
Thrombocytes $>300 \times 10^9$/l (yes vs no)	0.746
Lactate dehydrogenase ≥ 225 U/l (yes vs no)	0.271
C-reactive protein >16 mg/dl (yes vs no)	1
Gamma-glutamyl transferase >31 U/l (yes vs no)	0.234
Alkaline phosphatase >220 U/l (yes vs no)	**0.048**
Asymptomatic vs symptomatic at the start of ^{177}Lu PSMA therapy	0.559
Prostate-specific antigen at diagnosis (in ng/ml)	0.653
International Society of Urological Pathology grade group (1–5)	0.924
ECOG performance status at the start of ^{177}Lu PSMA therapy	0.782
Prostate-specific antigen at the start of ^{177}Lu PSMA therapy	0.176
Prostate-specific antigen doubling time at the start of ^{177}Lu PSMA therapy	0.297

PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; EBRT = external beam radiation therapy; mHSPC = metastatic hormone-sensitive prostate cancer; ADT = androgen deprivation therapy; AA = antiandrogen agent; ARSI = androgen receptor signaling inhibitor; ECOG = Eastern Cooperative Oncology Group.
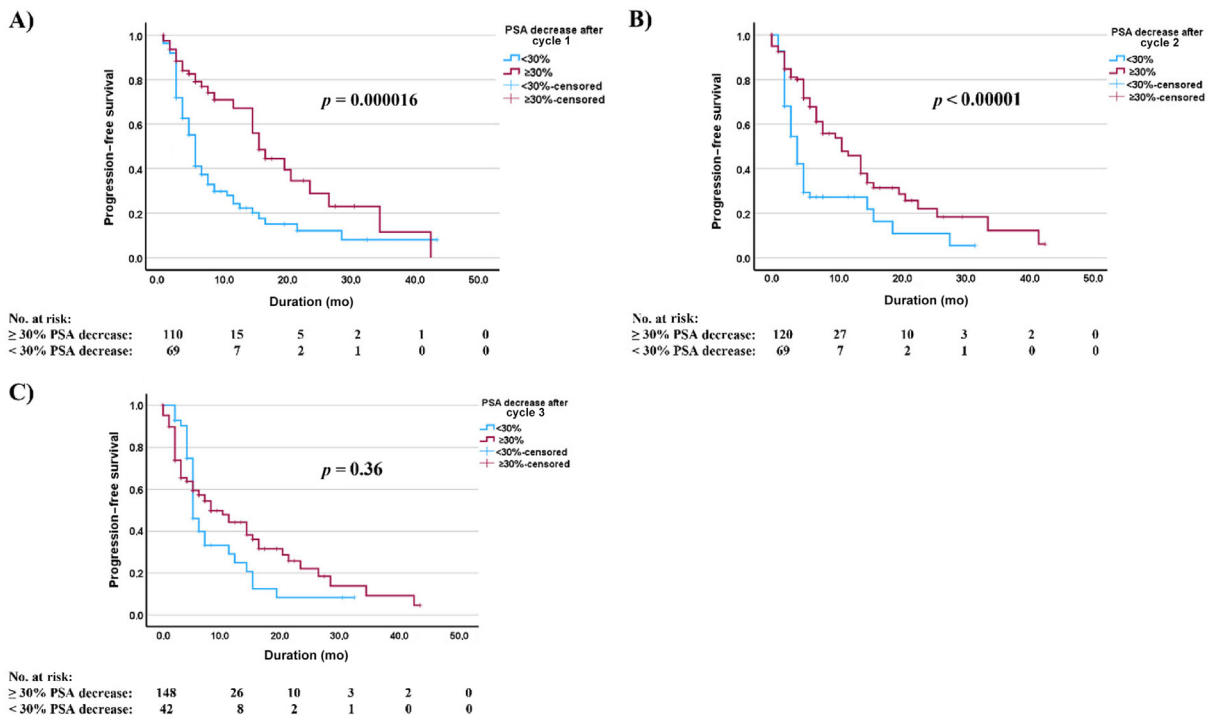

Fig. 1 – Progression-free survival for patients with a prostate-specific antigen (PSA) decrease of <30% versus ≥30% after (A) one, (B) two, and (C) three cycles of ^{177}Lu prostate-specific membrane antigen ligand therapy.
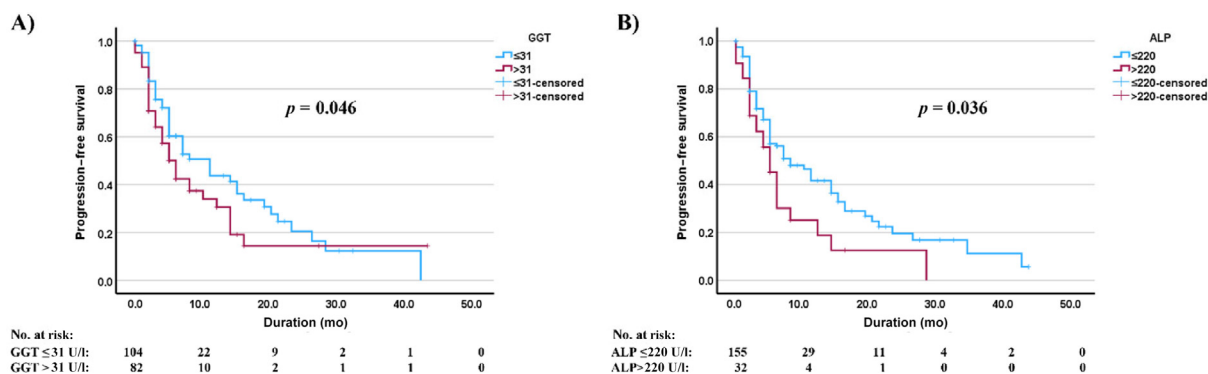
Fig. 2 – Progression-free survival for patients with (A) gamma-glutamyl transferase (GGT) of ≤31 versus >31 U/l and (B) alkaline phosphatase (ALP) of ≤220 versus 220 U/l at the start of therapy.

had more than twofold higher risk of progression (HR 2.1, 95% confidence interval [CI] 1.4–3.2; $p < 0.001$).

In addition, we found a statistically significant correlation between baseline ALP and treatment response (ALP cutoff level of >220 U/l), indicating that patients with higher baseline ALP were more likely to experience disease progression after ^{177}Lu PSMA ($p = 0.048$). Moreover, laboratory parameters including PSA, CRP, ALP, and GGT at the end of ^{177}Lu PSMA therapy were significantly associated with the risk of progression (Table 1).

In contrast to findings reported by other groups, volume of disease ($p = 0.671$), de novo versus recurrent metastatic disease ($p = 0.236$), site of metastases ($p=0.343$), primary local treatment of the prostate ($p = 0.436$), primary systemic therapy ($p = 0.216$), ISUP grade group ($p = 0.088$), number of ^{177}Lu PSMA cycles ($p = 0.506$), genetic status ($p = 0.513$), PSA-DT ≤6 mo ($p = 0.572$), PSA ≥100 ng/ml at treatment start ($p = 0.337$), symptomatic disease ($p = 0.733$), and ECOG performance status ($p = 0.472$) were not significantly correlated to treatment outcome in our cohort (Table 4).

Finally, we performed Kaplan-Meier analysis using the parameters and categories described above. In line with our previous calculations, a PSA decrease of ≥30% after the first and second cycles was statistically significantly correlated to treatment response over time (1 cycle: $p = 0.000016$; 2 cycles: $p < 0.00001$; Fig. 1A, B). A PSA decrease ≥30% remained statistically significant on multivariate analysis (1 cycle: HR 0.543, 95% CI 0.335–0.880; $p = 0.013$; 2 cycles: HR 0.503, 95% CI 0.319–0.793; $p = 0.003$), suggesting that PSA decrease is a robust early dynamic marker for treatment response. We included PSA decrease ≥30% after cycles 1–3, hemoglobin ≥10.4 g/l, GGT >31 U/l, and ALP >220 U/l in multivariate analysis. A PSA decrease of ≥30% after the third cycle was not statistically significant on Kaplan-Meier analysis (Fig. 1C; $p = 0.360$) or Cox regression (HR 1.172, 95% CI 0.733–1.874; $p = 0.507$).

As depicted in Figure 2, lower GGT (≤31 U/l; $p = 0.046$) and ALP (≤220 U/l; $p = 0.036$) at treatment start were significantly associated with a lower risk of progression during ^{177}Lu PSMA therapy. To further analyze the strength of these results, we performed multivariate analysis. Only

GGT >31 U/l at treatment start remained a statistically significant predictor (HR 1.546, 95% CI 1.016–2.353; $p = 0.042$), associated with 1.5 times higher risk of progression. When we also adjusted for the presence of visceral metastasis on primary PSMA PET-CT, GGT >31 U/l was no longer statistically significant (HR 1.431, 95% CI 0.906–2.259; $p = 0.124$).

4. Discussion

Radioligand therapy with ^{177}Lu PSMA is a recent FDA- and EMA-approved treatment modality rapidly gaining importance in the therapeutic landscape for mCRPC. Structured information on its clinical performance in the real-world setting is an unmet medical need. Here we present one of the largest international multicenter series assessing the efficacy and tolerability of ^{177}Lu PSMA, which also includes patients with disease characteristics that are underrepresented in registration trials (eg, ECOG performance status of 2 or 4, multiple systemic pretreatments).

In summary, our real-world data revealed a PSA decrease of ≥30% in 77.8% of our patients and an imaging response or stable disease in 47%. The median TTP was 5 mo, in comparison to 8.7 mo in the VISION trial; the reason for the difference might be that our cohort included heavily pretreated patients and patients with ECOG performance status of 2 or 3. In addition, >80% of men in our study had ISUP grade group 4 or 5 at primary diagnosis, reflecting the aggressive disease phenotype in our cohort. The multicenter nature of our retrospective observational study means that there were variations in the total number of cycles, cycle intervals, total activity, pretreatment imaging procedures (eg, additional fluorodeoxyglucose PET-CT), and even different ligands used for therapy. Of note, apart from luteinizing hormone–releasing hormone agonists/antagonists, none of the patients included in our trial received any additional systemic therapy that might further influence the therapy outcome.

Our data indicate that a PSA decrease of ≥30% after the first two cycles of ^{177}Lu PSMA is an early indicator of treatment response. This finding is in line with data from the REALTY study, which demonstrated that biochemical

response was a predictor of longer OS [6]. Similarly, other studies reported that a PSA decrease after the first two cycles of ^{177}Lu PSMA was a predictor for treatment response and longer OS [7–13]. While most biomarkers described in the literature are based on imaging tools (PSMA tumor load/intensity, tumor-to-liver ratio, bone scan indexes, and nomograms consisting of imaging markers), a PSA decrease after the first two treatment cycles seems to be a valid and robust alternative as an early dynamic clinical biomarker predictive for response that should be used in clinical decision-making [4,12,13].

Furthermore, we found that lower ALP ($\leq$220 U/l) was correlated to response to ^{177}Lu PSMA therapy, a finding previously observed in a smaller patient cohort by Ferdinandus and colleagues [14–16]. The Cologne group recently identified initial ALP $\leq$220 U/l as a key predictor for longer OS among patients treated with ^{177}Lu PSMA [17], further strengthening our findings. Another highly interesting result is that baseline GGT $\leq$31 U/l was significantly correlated to response. Similarly, an analysis of 52 patients demonstrated shorter survival for those with elevated GGT levels [18]. On multivariate analysis, only GGT $\leq$31 U/l remained statistically significant and was associated with 1.5 times greater risk of progression; ALP $\leq$220 U/l was no longer significant.

However, after accounting for the presence of visceral metastases as a potential confounding factor for GGT in relation to liver metastases, we found no association between GGT and disease progression, and therefore it cannot be validated as a biomarker for progression in this setting according to the current data set.

In contrast to others, our study did not reveal a significant correlation between baseline hemoglobin, LDH, CRP, or thrombocyte count and treatment response [9,15,19,20]. Other parameters such as age $\geq$65 yr at the start of treatment, disease symptoms, higher Gleason score, poor PS, and metastatic load also showed no correlation to response in our larger data set. One possible explanation and limitation of our study is that some of the other studies used OS for their calculations, while we used response and progression as endpoints [4]. Another limitation is that we can only report on changes in ECOG PS and not on side effects, treatment interruptions, or even dropout rates, which would be interesting from a real-world perspective. Furthermore, one limitation of our statistical analysis is that because of the explorative nature of our study and the lack of a prespecified statistical approach, we did not correct for multiple testing.

5. Conclusions

Our results confirm that ^{177}Lu PSMA ligand therapy is an effective treatment option in real-world practice. A PSA decrease $\geq$30% after the first two cycles is an early indicator of treatment response and should therefore be implemented in clinical practice. In addition, we identified baseline ALP $\leq$220 U/l and especially GGT $\leq$31 U/l as indicators of response to ^{177}Lu PSMA for patients without but not with visceral metastases.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.07.018.

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