

Early prostate-specific antigen changes and clinical outcome following ^{177}Lu -PSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer

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ABSTRACT

Background: Prostate-specific antigen (PSA) is widely used to monitor treatment response in patients with metastatic castration-resistant prostate cancer (mCRPC). However, PSA measurements are considered only after 12 wk of treatment. We aimed to evaluate the prognostic value of early PSA changes following ^{177}Lu -labelled prostate specific membrane antigen (LuPSMA) radionuclide treatment in mCRPC patients.

Methods: Men who were treated under a compassionate access program with LuPSMA at our institution and had available PSA values at baseline, at 6 wk after treatment initiation were included in this retrospective analysis. Patients were assigned to three groups based on PSA changes: 1) response: $\geq 30\%$ decline, 2) progression: $\geq 25\%$ increase and 3) stable: $< 30\%$ decline and $< 25\%$ increase. The co-primary endpoints were overall survival and imaging-based progression-free survival. The secondary end points were PSA changes at 12 wk and PSA flare-up.

Results: We identified 124 eligible patients with PSA values at 6 wk. A $\geq 30\%$ decline in PSA at 6 wk was associated with longer overall survival (median 16.7 mo; 95%CI 14.4–19.0) compared with patients with stable PSA (median: 11.8 mo; 95%CI 8.6–15.1; $p=0.007$) and progression (median: 6.5 mo; 95%CI 5.2–7.8; $p<0.001$). Patients with $\geq 30\%$ decline in PSA at 6 wk also had a reduced risk of imaging-based progression compared with patients with stable PSA (HR: 0.60; 95%CI 0.38–0.94; $p=0.02$), while patients with PSA progression had a higher risk of imaging-based progression compared with those

showing stable PSA (HR: 3.18; 95%CI 1.95–5.21; $p<0.001$). The percentage changes of PSA at 6 wk and 12 wk were highly associated ($r=0.90$; $p<0.001$). 29 of 31 (94%) patients who experienced early PSA progression at 6 wk achieved biochemical progression at 12 wk. Overall, only 1 of 36 (3%) patients with PSA progression at 6 wk achieved any PSA decline at 12 wk (1% of the entire cohort). Limitations of the study included its retrospective nature and the single center experience.

Conclusion: PSA changes at 6 wk after LuPSMA initiation are an early indicator of long-term clinical outcome. Patients progressing by PSA after 6 wk of treatment could benefit from a very early treatment switch decision. PSA flare-up during LuPSMA treatment is very uncommon. Prospective studies are now warranted to validate our findings and potentially inform clinicians earlier on the effectiveness of LuPSMA.

INTRODUCTION

Despite recent therapeutic advances, only one third of patients with metastatic castration-resistant prostate cancer (mCRPC) survive more than five years, with survival rates depending on known prognostic risk factors (1,2). Results on ¹⁷⁷Lu-labelled prostate specific membrane antigen (LuPSMA) radionuclide therapy of mCRPC have been reported in more than 1000 patients based on compassionate access programs in Germany and other countries (3). These results as well as encouraging efficacy in Phase II clinical trials (4,5) led to an ongoing Phase III clinical trial (VISION: NCT03511664). Reliable markers and early prognostic factors are urgently needed to support patient management decisions and to select the optimized therapy sequencing in mCRPC.

Since the introduction of serum prostate-specific antigen (PSA) screening in the 1980s (6), prostate cancer management has been guided by this biomarker. For mCRPC, a 30% and 50% decline in PSA after 12 wk of treatment have been consistently associated with longer survival (7-9). Similarly, a 25% PSA rise from baseline/nadir was associated with poor outcome (10,11). According to Prostate Cancer Working Group 3 (PCWG3) recommendations for mCRPC, PSA progression should not be determined in the first 12 wk of treatment because of possible late declines and flare reactions reported in patients treated with taxanes (12-14). However, previous reports found early PSA changes after 4 wk of treatment with abiraterone acetate and enzalutamide to be associated with overall survival, with flare reactions being uncommon (15,16). Insufficient data have been reported regarding the clinical outcome of early PSA changes in mCRPC patients treated with LuPSMA. The primary objective of this study was to evaluate the

association between PSA changes at 6 wk after treatment initiation and clinical outcome. The secondary objectives were to assess the frequency of PSA flare-up and the associations between PSA changes at 6 wk and 12 wk. We hypothesized that patients with an early 25% increase in PSA will also develop PSA progression at 12 wk.

MATERIALS AND METHODS

Patients Population and Treatment Regimen

Patients with progressive mCRPC treated with ^{177}Lu -PSMA-imaging&therapy (LuPSMA) at our institution under a compassionate access program (9) were considered. All patients provided written informed consent. The retrospective data analysis was approved by the medical ethics committee of the Technical University of Munich (reference number: 115/18S). Eligible patients had available serum PSA levels at baseline, after 6 wk of treatment, and survival data. When available, PSA measurements 12 wk after LuPSMA initiation were also extracted. Our institutional eligibility criteria for LuPSMA are provided in Supplementary Table 1. Intravenous treatment with 7.4 GBq of LuPSMA was applied every 6-8 weeks and was continued up to a maximum of six cycles in patients with absence of progressive disease and lack of severe toxicity according to the investigator. Progressive disease was defined as biochemical progression, imaging-based and/or clinical progression according to the PCWG3 criteria (12). In the case of biochemical progression earlier than 12 wk, the treatment continuation/discontinuation decision was made based on the available imaging, laboratory tests, and patient's

performance status. Patients who successfully completed the initial treatment ($\geq 50\%$ decline in PSA) were considered for further LuPSMA in a rechallenge setting, as recently described (17). Patients were evaluated using PSMA-targeted PET/CT at baseline and every two cycles.

End Points

The co-primary end points were overall survival and imaging-based progression-free survival. The secondary end points were PSA changes at 12 wk after LuPSMA initiation and PSA flare-up. The imaging-based progression-free survival was defined as the time between treatment initiation to the occurrence of imaging-based progression or death. Using a modified form of the PCWG3 criteria, imaging-based progression was defined as: 1) at least two new bone metastases in PSMA-targeted PET, 2) any new soft-tissue lesion in morphological imaging or PSMA-targeted PET and/or 3) soft-tissue progression on CT according to the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 (12). The percentage change in PSA from baseline at 6 and 12 wk was categorized as 1) response: $\geq 30\%$ decline, 2) progression: $\geq 25\%$ increase and 3) stable: $< 30\%$ decline and $< 25\%$ increase. A subanalysis defining PSA response as $\geq 50\%$ decline from baseline was performed. Evaluation of PSA changes was consistent with published consensus guidelines (PCWG3) (12). PSA flare-up was defined as an increase of at least 25% at 6 wk followed by any decline below baseline levels at 12 wk.

Statistical Analysis

Results are presented as the median and interquartile range (IQR) for continuous variables and as number and percentage for categorical variables. Kaplan-Meier analysis was used to estimate overall survival and imaging-based progression-free survival. The log-rank test was used to compare survival curves between groups of patients according to PSA changes at 6 and 12 wk time-points. Associations between PSA changes, radiological progression and survival were evaluated in univariable and multivariable Cox regression analyses. The multivariable Cox models included PSA changes after 6 wk as a categorical variable; clinical history: Gleason score at diagnosis, metastasis status at diagnosis, time since diagnosis of prostate cancer, chemotherapy status; baseline characteristics: presence of visceral metastases, ECOG performance status, pain status, PSA, lactate dehydrogenase, and alkaline phosphatase levels. Continuous variables with a non-normal distribution were log-transformed. Spearman's rho correlation coefficient r was calculated to evaluate the association between the percentage PSA decline at 6 and 12 wk. The association between PSA response at 6 and 12 wk as dichotomized variables (progression/non-progression) was assessed using Chi-Square and Relative Risk tests. Statistical analyses were performed using SPSS version 22 (IBM, NY, USA) and STATA version 15 (StataCorp LLC, TX, USA).

RESULTS

From 160 considered patients, we identified 124 consecutive patients who met the eligibility criteria. The first LuPSMA treatment was administered on December 2014 and

the last cycle on September 2018. Cut-off for follow-up was September 1, 2019; All patients had available PSA values at 6 wk at a mean time of 6.16 (95%CI 6.03-6.29) wk after treatment initiation. Of these, 115 patients had available PSA values at 12-wk at a mean time of 12.03 (95%CI 11.81-12.26) wk after treatment initiation. The study protocol is displayed in Figure 1. Baseline characteristics are summarized in Table 1; 96 (77%) patients had received previous chemotherapy, 20 (16%) had received second-line cabazitaxel, and all patients prior abiraterone or enzalutamide. Overall 429 cycles of LuPSMA were administered at a median of 3 (IQR: 2–5) cycles per patient. All patients received cycle 1 of LuPSMA, and 118 (95%), 61 (49%), and 28 (23%) patients received cycles two, four and six, respectively. The median number of treatment cycles was lower in patients with PSA progression after 6 wk of treatment compared to those who had stable PSA or PSA response: 2 (IQR 2-2) vs. 4 (IQR 2-5) vs. 4 (IQR 4-6) cycles; $p<0.001$, respectively. Twelve (10%) patients received further LuPSMA treatments in a rechallenge setting. The median follow-up was 23.4 (IQR 20.0–28.7) mo and 109 (88%) patients were deceased at last follow-up. The median overall survival was 13.4 (95%CI 11.1–15.6) mo and the median imaging-based progression-free survival was 3.3 (95%CI 2.0–4.6) mo.

PSA Changes at 6 wk and 12 wk

The median PSA changes at 6 wk was -11.8 (IQR -49.2 to 38.75) %, while at 12 wk was -12.8 (IQR -62.8 to 62.5) %. Fifty (40%) patients experienced $\geq 30\%$ decline in PSA at 6 wk after LuPSMA initiation, while 30 (23%) patients achieved $\geq 50\%$ decline in

PSA; 36 (29%) patients had PSA progression. At 12 wk, 50 (44%) patients experienced $\geq 30\%$ decline in PSA, while 39 (33%) achieved $\geq 50\%$ decline in PSA. Out of the 115 patients with PSA values available at both 6 and 12 wk time-points, 25 of 28 (89%) patients with an early $\geq 50\%$ PSA decline achieved biochemical response at 12 wk; 41 of 48 (85%) patients with an early $\geq 30\%$ PSA decline achieved $\geq 30\%$ PSA decline at 12 wk, whereas 29 of 31 (94%) patients with an early PSA progression experienced PSA progression at 12 wk (Table 2). The percentage changes of PSA at 6 wk and 12 wk were highly associated ($r=0.90$; $p<0.001$).

Out of the 36 patients with PSA progression at 6 wk, five underwent an additional imaging-based assessment at 6 wk (as previously described (18)) and discontinued the treatment due to progressive disease, while 29 of 31 (94%) patients had PSA progression at 12 wk. Of note, all these 29 patients experienced a progressive disease at 12 wk, which led to LuPSMA discontinuation. From the remaining two patients, one (3%) had stable PSA at 12 wk, while one (3%) patient showed $\geq 30\%$ decline in PSA at 12 wk. Overall, 1 of 36 (3%) patients with PSA progression at 6 wk, which represents 0.8% of the overall cohort, achieved a PSA decline below baseline levels at 12 wk. Patients with PSA progression at 6 wk had a higher likelihood to experience PSA progression at 12 wk compared to patients without early PSA progression (RR: 8.7; 95%CI 4.6-16.3; $p<0.001$). PSA progression at 6 wk had a sensitivity of 93.5% and specificity of 89.3% to predict biochemical progression at 12 wk.

Early PSA Changes and Overall Survival

In a landmark analysis at 6 wk, $\geq 30\%$ decline in PSA at 6 wk was associated with longer overall survival (median 16.7 mo; 95%CI 14.4–19.0) compared to stable PSA (median: 11.8 mo; 95%CI 8.6–15.1; $p=0.007$) and PSA progression (median: 6.5 mo; 95%CI 5.2–7.8; $p<0.001$) (Fig. 2A). Patients with $\geq 30\%$ decline in PSA at 6 wk also had a reduced risk of death compared with patients with stable PSA (hazard ratio (HR): 0.54; 95%CI 0.33–0.86; $p=0.01$), whereas patients with PSA progression had a higher risk of death compared with those who had stable PSA (HR: 1.77; 95%CI 1.11–2.85; $p=0.01$). In the multivariable Cox model including the $\geq 30\%$ PSA decline, PSA changes at 6 wk (response, HR: 0.45; 95%CI 0.25–0.78 and progression, HR: 1.98; 95%CI 1.11–3.52), presence of visceral metastases (HR: 1.97; 95%CI 1.17–3.32), ECOG performance status (0 vs. 2, HR: 3.54; 95%CI 1.36–9.20), time since prostate cancer diagnosis (HR: 0.34; 95%CI 0.14–0.78), and baseline PSA levels (HR: 1.63; 95%CI 1.14–2.33) were significantly associated with overall survival (Table 3).

In brief, $\geq 50\%$ decline in PSA at 6 wk (median 19.4 mo; 95%CI 13.9–24.9) was not significantly associated with longer overall survival compared to stable PSA (median 12.6 mo; 95%CI 10.7–14.6; $p=0.052$), but to PSA progression (median 6.5 mo; 95%CI 5.2–7.8; $p<0.001$) (Figure 2B).

Early PSA Changes and Progression-Free Survival

A $\geq 30\%$ decline in PSA at 6 wk was associated with longer imaging-based progression-free survival (median: 7.1 mo; 95%CI 4.7–9.5) compared to stable PSA (median: 2.0 mo; 95%CI 0.1–4.1; $p=0.01$) and PSA progression (median: 1.2 mo; 95%CI 1.1–1.3; $p<0.001$) (Figure 3A). Patients with $\geq 30\%$ decline in PSA at 6 wk also had a

reduced risk of imaging-based progression compared with patients with stable PSA (HR: 0.60; 95%CI 0.38–0.94; $p=0.02$), while patients with PSA progression had a higher risk of imaging-based progression compared with those who had stable PSA (HR: 3.18; 95%CI 1.95–5.21; $p<0.001$). In the multivariable Cox model including the $\geq 30\%$ PSA decline, PSA changes at 6 wk (response, HR: 0.47; 95%CI 0.28–0.80 and progression, HR: 3.70; 95%CI 2.09–6.89), chemotherapy status (HR: 1.75; 95%CI 1.02–3.00), and metastasis status at diagnosis (HR: 1.78; 95%CI 1.05–3.02) were significantly associated with imaging-based progression-free survival (Table 4).

In brief, $\geq 50\%$ decline in PSA at 6 wk was not significantly associated with longer imaging-based progression-free survival (median: 7.1 mo; 95%CI 4.6–9.6) compared to stable PSA (median: 3.6 mo; 95%CI 1.1–6.1; $p=0.30$), but to PSA progression (median: 1.2 mo; 95%CI 1.1–1.3; $p<0.001$) (Fig. 3B).

DISCUSSION

In the present retrospective analysis, we found that PSA measurements as early as 6 wk after LuPSMA initiation are associated with clinical outcome in patients with mCRPC. Most important, a 30% PSA decline at 6 wk was associated with longer overall survival compared with patients with stable PSA and PSA progression. Moreover, PSA flare-up was very uncommon, involving less than 1% of the entire patient population. As the treatment of mCRPC becomes more complex with definitions of disease progression to evolve, improved biomarkers for rapid recognition of resistance are warranted. It is discussed that rapid treatment discontinuation in patients showing inherent resistance to

a drug may have decisive implications for the clinical outcome to the following therapies (19). A recent study inquiring specialists' experience in treating mCRPC outside clinical trials, reported that 41.4% of the interviewed physicians disregarded changes in PSA before 12 wk of treatment, taking decision for treatment discontinuation based only on clinical progression (20). Evaluation of PSA changes earlier than 12 wk of treatment has been traditionally discouraged (12), since flare reactions have been described in $\geq 20\%$ patients treated with taxanes (13,21). Unlike chemotherapy, our data indicate that an early PSA flare-up, defined as an increase of 25% in the first 6 wk followed by a decline below baseline levels at 12 wk, is very uncommon following LuPSMA. Only 1 of 36 (3%) patients showing an initial PSA progress achieved a PSA decline below baseline levels at 12 wk, involving less than 1% of the entire cohort. Similar results have been reported for the new-generation hormonal agents (15,16).

Early switch strategy between taxanes based on PSA performances at 12 wk has been associated with an improved PSA response rate (TAXYNERGY) versus historical control (TAX327) (11). In our study, 30% or greater decline in PSA at 12 wk has been associated with a longer overall survival compared to stable PSA or PSA progression (16.6 vs. 10.7 vs. 5.8 mo; $p < 0.001$). Therefore, a switching strategy at 12 wk based on 30% PSA decrease might identify patients who may or may not further benefit from the therapy and should be further investigated. Nevertheless, therapies can increase differentiation (and slow progression) of prostate cancer leading to increasing PSA levels despite reducing tumor volume (22). With this in mind, the current guidelines (12,23) highlight the importance of avoiding sole reliance on PSA measurements during therapeutic assessment and recommend a sufficient window of drug exposure, enabling treatment

until there is clear sign of imaging-based or clinical progression. However, we found that 94% of patients showing a PSA progression at 6 wk after LuPSMA initiation developed a imaging-based progression within 12 wk resulting in treatment discontinuation. In addition, patients who had a 25% PSA rise at 6 wk had a shorter survival and were 8.7 more likely to achieve biochemical progression at 12 wk. These results may be of clinical relevance especially in the scenario when LuPSMA is administered in earlier stage of mCRPC with other therapeutic options still being available. In addition to the ongoing Phase III clinical trial investigating the efficacy of LuPSMA versus best standard of care (VISION: NCT03511664), LuPSMA is also investigated versus second-line chemotherapy cabazitaxel in a Phase II randomized trial (TheraP: NCT03392428). These clinical trials might enable drug approval and the possibility to be offered as the third or even second line for mCRPC. Positive results on the long-term outcome from a Phase II clinical trial in patients treated with LuPSMA have been recently reported (24).

One previous study found a PSA decline of at least 20.9% after 1 cycle of LuPSMA to be independently associated with longer overall survival (25). However, the clinical utility of this definition is limited since this cutoff has been derived by fitting a retrospective receiver-operator curve analysis. In other retrospective analyses, the lack of a 30% PSA decline after first therapy cycle was associated with a shorter survival following LuPSMA (9,26). However, in corresponding multivariate analyses only the presence of visceral metastases and elevated lactate dehydrogenase levels remained an independent predictor for overall survival. In the present multivariable Cox model, PSA changes at 6 wk were independently associated with overall survival along with other variables (presence of visceral metastases, ECOG performance status, time since diagnosis of

prostate cancer, and baseline PSA levels). For patients with insufficient response to LuPSMA two modified treatment regimens have been proposed for an improved therapeutic outcome: an accelerated administration at 4-weeks interval (currently 6-8 weeks) and a dose-escalation strategy (27). However, these two regimens may not improve treatment efficacy in patients showing inherent drug resistance, with possibly high toxicity levels. Thus, patients showing an initial high sensitivity to LuPSMA (>30% PSA decrease at 6 wk) are most likely to have a clinical benefit from any of the above proposed regimens.

Imaging-based progression-free survival (often termed as “radiographic” progression-free survival) has been commonly used as a primary/coprimary endpoint in Phase III clinical trials for mCRPC, being significantly associated with overall survival (28). In our analysis, PSA response at 6 wk was significantly associated with a longer imaging-based progression-free survival compared with patients showing stable PSA or progression (median imaging-based progression-free survival: 8.4 vs. 3.3 vs. 2.5 mo). Similar to overall survival, PSA changes at 6 wk were significantly associated with imaging-based progression-free survival along with other variables (chemotherapy status and presence of distant metastases at diagnosis).

We found that 50% decline in PSA at 6 wk showed a clear trend towards improved survival, however, in contrast to 30% decline in PSA, it failed to be associated with a longer survival. At first glance, this finding appears paradoxical; intuitively, greater PSA declines should be associated with a stronger antitumor effect. However, the inability to establish the association of early PSA measurements with clinical outcome at higher rates of PSA decline may reflect the fact that fewer patients achieved higher-percentage PSA

declines, leading to a reduction in statistical power. In our study, 24% of patients had PSA decline greater than 50%, whereas 40% of patients had PSA decline greater than 30% at 6 wk following LuPSMA. However, other studies testing PSA changes at 12 wk for surrogacy found similar results, with a 50% decline in PSA failing to meet the surrogacy criteria, while 30% decline did (7).

Our study has several limitations. First, due to its retrospective nature and single center experience this study remains limited and thus, our findings need to be further evaluated in a prospective multicenter setting. Second, the current guidelines recommend the use of bone scan and CT for the imaging-based assessment (12), while in the present analysis patients were evaluated using hybrid PSMA-targeted PET/CT. As PSMA-targeted PET showed a higher sensitivity compared to conventional imaging techniques, this might enable a bias towards a shorter imaging-based progression-free survival (29).

Compared with taxanes, the new generation hormonal agents as well as LuPSMA seem to have a different impact on the PSA kinetics, with flare reactions being rare. Following prospective validation, these findings should be considered by the upcoming guidelines for mCRPC.

CONCLUSIONS

PSA changes at 6 wk after LuPSMA initiation are an early indicator of long-term clinical benefit for both overall survival and imaging-based progression-free survival. Patients progressing by PSA after 6 wk of treatment could benefit from a very early

treatment switch decision and decrease overtreatment. PSA flare-up during LuPSMA treatment is very uncommon. Prospective studies are now warranted to validate our findings and potentially inform clinicians earlier on the effectiveness of LuPSMA.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article exist.

KEY POINTS

QUESTION: Are the PSA changes after 6 weeks of treatment with LuPSMA associated with the clinical outcome in patients with metastatic castration-resistant prostate cancer?

PERTINENT FINDINGS: In a retrospective study including 124 patients, PSA progression after 6 weeks of LuPSMA was associated with shorter overall survival and progression-free survival compared with patients showing PSA response and stable PSA. Overall, only 3% of patients with PSA progression at 6 weeks achieved any PSA decline at 12 wk (1% of the entire cohort).

IMPLICATIONS FOR PATIENT CARE: Patients progressing by PSA after 6 weeks of LuPSMA could benefit from a very early treatment switch decision and decrease overtreatment. PSA flare-up during LuPSMA treatment is very uncommon.

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Figure 1. Study protocol. mCRPC = metastatic castration-resistant prostate cancer.
LuPSMA = ¹⁷⁷Lutetium-Prostate-specific membrane antigen-I&T.

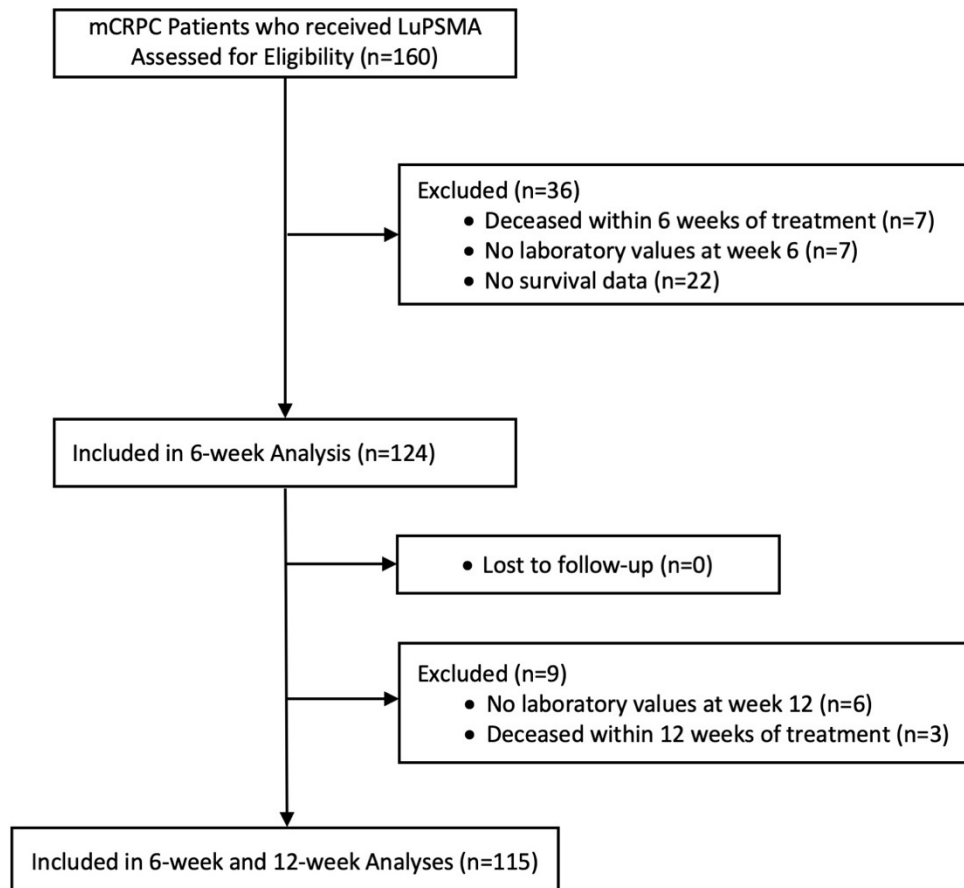


Figure 2. Kaplan-Meier curves of landmark analyses of overall survival by changes in PSA at 6 wk considering response **(A)** a ≥ 30 PSA decline and **(B)** a $\geq 50\%$ PSA decline. HR = hazard ratio; 95%CI = 95% confidence interval.

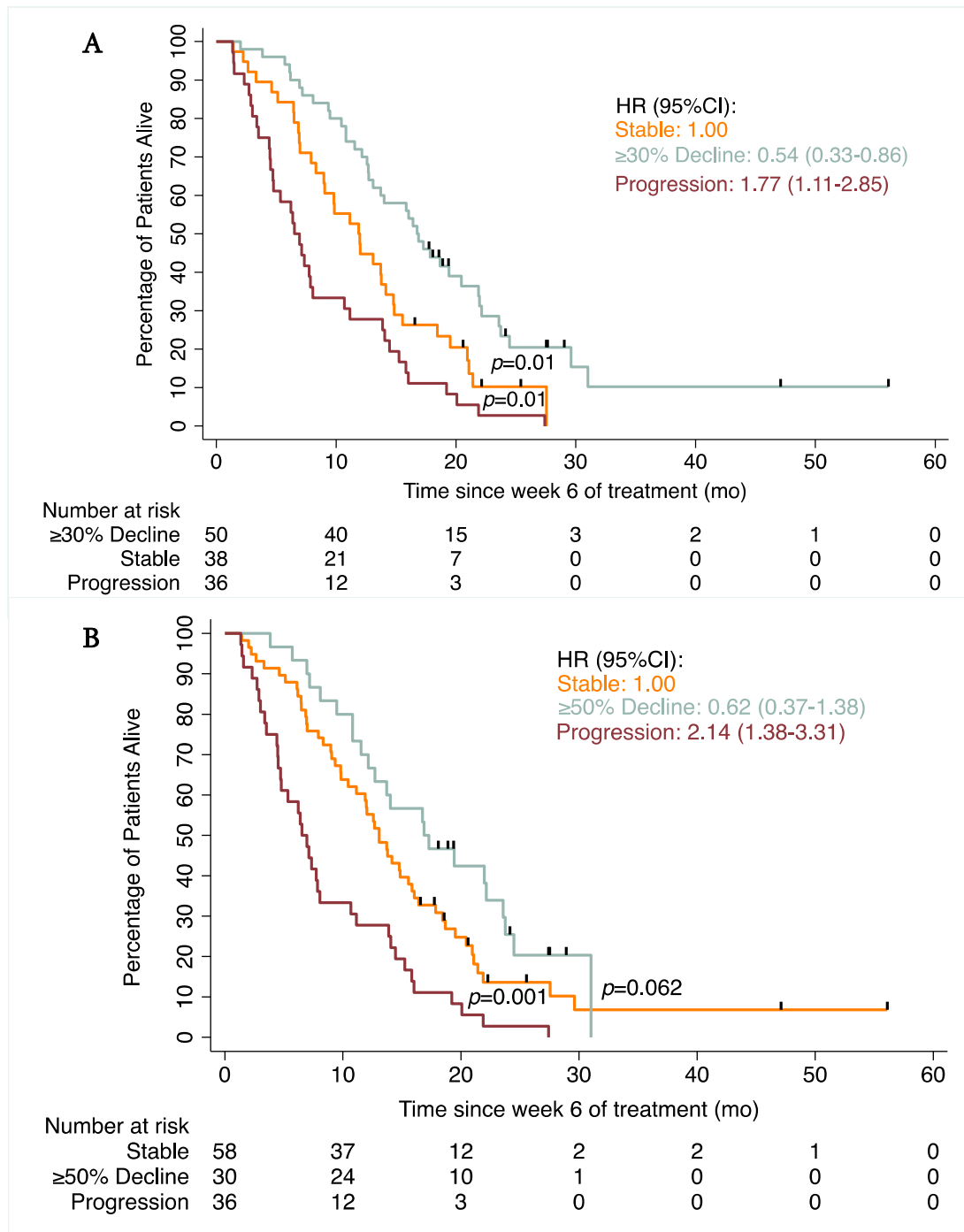
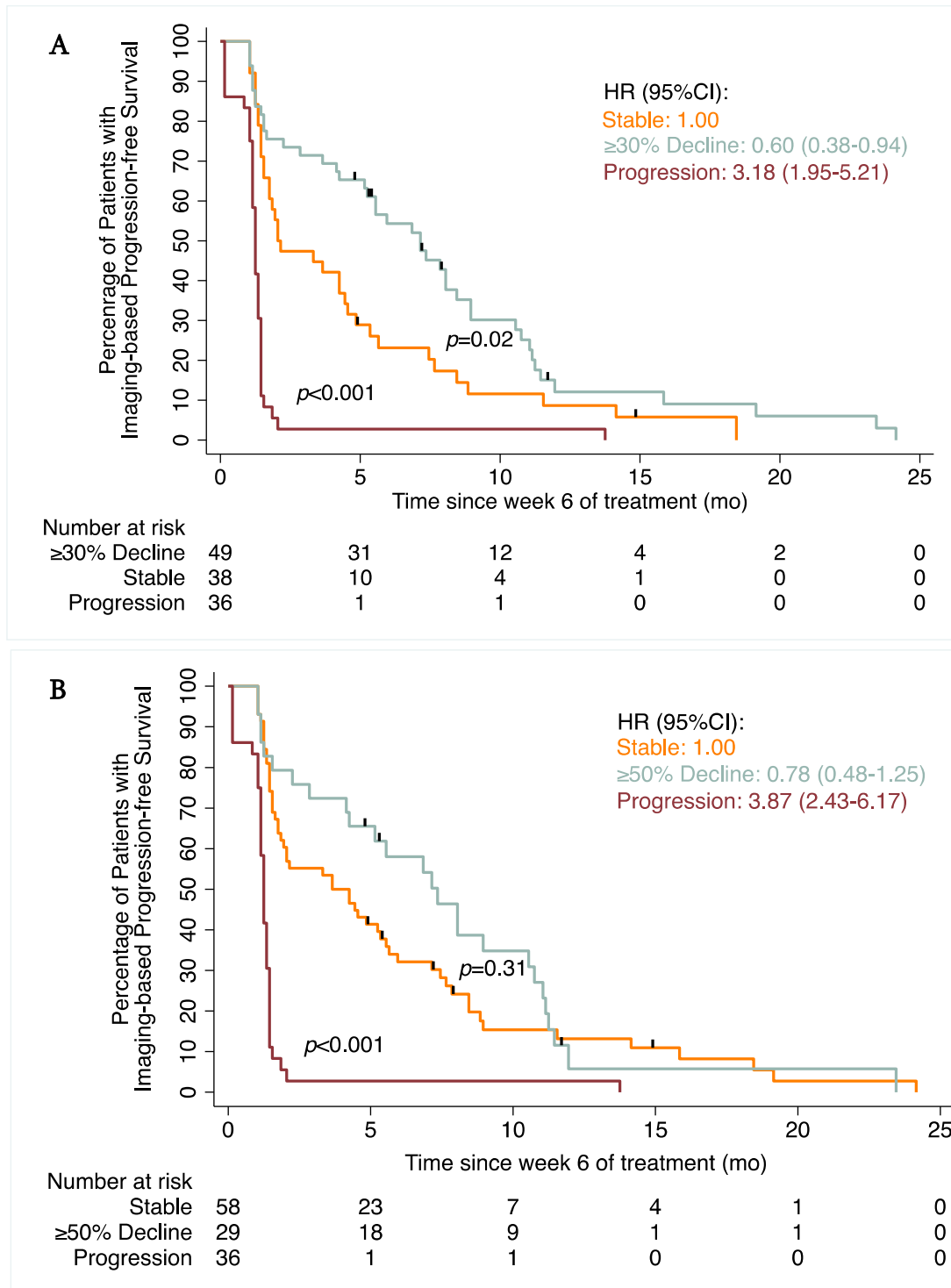


Figure 3. Kaplan-Meier curves of imaging-based progression-free survival in a landmark analysis based on PSA changes at 6 wk considering response **(A)** a ≥ 30 PSA decline and **(B)** a $\geq 50\%$ PSA decline. HR = hazard ratio; 95%CI = 95% confidence interval.



	All patients (n=124)
Age (years)	73 (66-77)
Time since diagnosis of prostate cancer (years)	7 (4-11)
Gleason score at diagnosis*	
<8	41 (36%)
≥8	74 (64%)
M status at diagnosis	
M0	79 (64%)
M1	45 (36%)
Primary treatments	
Prostatectomy ± lymphadenectomy	72 (58%)
Local radiotherapy	15 (12%)
Systemic treatment	37 (30%)
PSA (ng/ml)	137 (35-347)
Lactate dehydrogenase (U/l)	264 (217-349)
Total alkaline phosphatase (U/l)	121 (72-247)
Haemoglobin (g/dl)	11.2 (9.9-12.3)
ECOG performance status	
0	28 (23%)
1	87 (70%)
2	9 (7%)
Pain status at baseline †	
Symptomatic disease	77 (62%)
Asymptomatic disease	47 (38%)
Previous systemic treatments	
Androgen deprivation therapy	124 (100%)
Docetaxel	94 (76%)
Cabazitaxel	20 (16%)
Previous chemotherapy	96 (77%)
Abiraterone or enzalutamide or both	124 (100%)
Radium-223	24 (19%)
Prior lines of systemic treatments	
1	8 (7%)
≥2	116 (94%)
≥3	70 (56%)
≥4	27 (22%)
≥5	6 (5%)
Sites of disease on PSMA-PET	
Bone	116 (94%)
Lymph nodes	101 (82%)
Visceral ‡	38 (31%)
Bone + lymph nodes	92 (74%)
Bone + lymph nodes + visceral	28 (23%)

Table 1. Baseline characteristics. Data are median (IQR) or n (%); ECOG=Eastern Cooperative Oncology Group; PSMA=prostate-specific membrane antigen; *Data missing for nine patients; †Symptomatic disease was defined as having pain, and/or using opioids for cancer related pain at treatment initiation. Asymptomatic disease was defined as no pain and no opioid use at baseline; ‡ Visceral includes lung, liver and adrenal;

Table 2. Relationship in PSA changes between 6-week and 12-week time points, including $\geq 30\%$ PSA decline as an early PSA response **(A)** and $\geq 50\%$ PSA decline as an early PSA response **(B)**. (%) are given as percentage of total across rows.

A	PSA changes at 6 wk	PSA changes after 12 wk		
		Stable	$\geq 30\%$ decline	Progression
	Stable	19 (53%)	8 (22%)	9 (25%)
	$\geq 30\%$ decline	7 (15%)	41 (85%)	0 (0%)
	Progression	1 (3%)	1 (3%)	29 (94%)

B	PSA changes at 6 wk	PSA changes after 12 wk		
		Stable	$\geq 50\%$ decline	Progression
	Stable	33 (53%)	14 (25%)	9 (%)
	$\geq 50\%$ decline	3 (11%)	25 (89%)	0 (0%)
	Progression	2 (7%)	0 (0%)	29 (94%)

<i>Categorical variables</i>	<i>N</i>	<i>%</i>	<i>HR</i>	<i>95% CI</i>	<i>p value</i>
PSA changes after 6 wk					
Stable	38	31	1.00	-	-
Response	50	40	0.45	0.25-0.78	0.005
Progression	36	29	1.98	1.11-3.52	0.01
Gleason score at diagnosis					
<8	41	36	1.00	-	-
≥8	74	64	0.83	0.51-1.36	0.47
M status at diagnosis					
M0	76	66	1.00	-	-
M1	39	34	1.16	0.70-1.94	0.54
Chemotherapy status					
Prechemotherapy	26	23	1.00	-	-
Postchemotherapy	89	77	1.08	0.65-1.81	0.75
Site of metastases					
Non-visceral	79	69	1.00	-	-
Visceral	36	31	1.97	1.17-3.32	0.01
ECOG performance status					
0	27	23	1.00	-	-
1	79	69	1.40	0.85-2.30	0.17
2	9	8	3.54	1.36-9.20	0.009
Pain status at baseline					
Asymptomatic disease	42	36	1.00	-	-
Symptomatic disease	73	64	0.68	0.42-1.09	0.11
<i>Continuous variables</i>	<i>Med</i>	<i>IQR</i>	<i>HR</i>	<i>95% CI</i>	<i>p value</i>
Time since diagnosis (lg₁₀ years)	0.81	0.57-1.05	0.34	0.14-0.78	0.01
PSA (lg₁₀ ng/ml)	2.13	1.54-2.54	1.63	1.14-2.33	0.007
LDH (lg₁₀ U/l)	2.42	2.33-2.54	1.03	0.29-3.56	0.96
tALP (lg₁₀ U/l)	2.08	1.85-2.39	0.87	0.43-1.76	0.68

Table 3. Landmark (week 6) multivariable Cox model for association with overall survival. PSA = prostate-specific antigen; Stable = PSA decline <30% and <25% increase; Response = PSA decline ≥30%; Progression = PSA increase ≥25%; LDH = lactate dehydrogenase; tALP = total alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; Symptomatic disease = having pain, or using opioids for cancer related pain at treatment initiation, while Asymptomatic disease = no pain and no opioid use at baseline; HR = hazard ratio; CI = confidence interval; IQR=interquartile range;

<i>Categorical variables</i>	<i>N</i>	<i>%</i>	<i>HR</i>	<i>95% CI</i>	<i>p value</i>
PSA changes after 6 wk					
Stable	35	30	1.00	-	-
Response	45	40	0.47	0.28-0.80	0.006
Progression	34	30	3.79	2.09-6.89	<0.001
Gleason score at diagnosis					
<8	40	35	1.00	-	-
≥8	74	65	0.67	0.40-1.11	0.12
M status at diagnosis					
M0	75	64	1.00	-	-
M1	39	36	1.78	1.05-3.02	0.03
Chemotherapy status					
Prechemotherapy	26	23	1.00	-	-
Postchemotherapy	88	77	1.75	1.02-3.00	0.04
Site of metastases					
Non-visceral	78	68	1.00	-	-
Visceral	36	32	1.28	0.79-2.07	0.31
ECOG performance status					
0	27	24	1.00	-	-
1	79	69	1.03	0.63-1.66	0.90
2	8	7	1.27	0.53-3.08	0.58
Pain status at baseline					
Asymptomatic disease	42	37	1.00	-	-
Symptomatic disease	73	63	0.87	0.55-1.37	0.55
<i>Continuous variables</i>	<i>Med</i>	<i>IQR</i>	<i>HR</i>	<i>95% CI</i>	<i>p value</i>
Time since diagnosis (lg₁₀ years)	0.81	0.57-1.05	0.61	0.27-1.37	0.23
PSA (lg₁₀ ng/ml)	2.13	1.54-2.54	1.05	0.76-1.44	0.76
LDH (lg₁₀ U/l)	2.42	2.33-2.54	0.35	0.08-1.38	0.13
tALP (lg₁₀ U/l)	2.08	1.85-2.39	0.64	0.30-1.34	0.24

Table 4. Landmark (week 6) multivariate Cox model for association with imaging-based progression-free survival. PSA = prostate-specific antigen; Stable = PSA decline <30% and <25% increase; Response = PSA decline ≥30%; Progression = PSA increase ≥25%; LDH = lactate dehydrogenase; tALP = total alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; Symptomatic disease = having pain, or using opioids for cancer related pain at treatment initiation, while Asymptomatic disease = no pain and no opioid use at baseline; HR = hazard ratio; CI = confidence interval; IQR=interquartile range;

Supplementary Table 1. Eligibility criteria to receive LuPSMA radionuclide treatment

Inclusion criteria to receive LuPSMA

- Histopathological confirmed adenocarcinoma of the prostate
- Confirmed metastatic castration-resistant prostate cancer (testosterone levels below 50 ng/dL)
- Failure of standard treatments, including taxane-based chemotherapy (docetaxel, cabazitaxel) and androgen-signaling-targeted inhibitor (abiraterone, enzalutamide, or both), unless patients were unsuitable or refused these standard treatment regimens
- Progressive disease by prostate-specific antigen according to PCWG2 criteria or radiographic progression according to RECIST 1.1 criteria
- ECOG performance status score of 2 or lower
- Life expectancy greater than 3 months
- Hemoglobin concentration greater than 90 g/L
- Platelet count greater than $110 \times 10^9/L$
- Neutrophil count greater than $1.5 \times 10^9/L$
- PSMA-avid lesions on the screening PSMA-targeted PET

Exclusion criteria:

- Presence of active infection or symptomatic viral hepatitis
 - Myocardial infarction or thromboemboly within the last 6 months
 - Heart insufficiency grade II-IV according to the New York Heart Association (NYHA).
 - Brain metastases
 - Active secondary malignoma
 - Acute or chronic glomerulonephritis
 - Untreated hydronephrosis
 - Nephrotoxic comedication
 - Previous radiation of the spine column or the pelvis including >25% of the bone marrow
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