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ORIGINAL ARTICLE

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Any decline in prostate-specific antigen levels identifies survivors scheduled for prostate-specific membrane antigen-directed radioligand therapy

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Abstract

Background: Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) is increasingly incorporated in the therapeutic algorithm of patients with metastatic castration-resistant prostate cancer (mCRPC). We aimed to elucidate the predictive performance of early biochemical response for overall survival (OS).

Materials and Methods: In this bicentric analysis, we included 184 mCRPC patients treated with ^{177}Lu-PSMA RLT. Response to treatment was defined as decrease in prostate-specific antigen (PSA) levels 8 weeks after the first cycle of RLT (any decline or >50% according to Prostate Cancer Working Group 3). OS of responders and nonresponders was then compared using Kaplan–Meier curves and log-rank comparison.

Results: A total of 114/184 patients (62.0%) showed any PSA decline (PSA response >50%, 55/184 [29.9%]). For individuals exhibiting a PSA decline >50%, OS of 19 months was significantly longer relative to nonresponders (13 months; hazard ratio of death [HR] = 0.64, 95% confidence interval [95% CI] = 0.44–0.93; $p = 0.02$). However, the difference was even more pronounced for any PSA decline, with an OS of 19 months in responders, but only 8 months in nonresponders (HR = 0.39, 95% CI = 0.25–0.60; $p < 0.001$).

Conclusions: In mCRPC patients scheduled for RLT, early biochemical response was tightly linked to prolonged survival, irrespective of the magnitude of PSA decline. As such, even in patients with PSA decrease of less than 50%, RLT should be continued.

KEYWORDS

prostate cancer, PSA response, PSMA I&T, PSMA-617, theranostics

Rudolf A. Werner and Ralph A. Bundschuh equally contributed.

1 | INTRODUCTION

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) has demonstrated convincing outcome benefits in metastatic castration-resistant prostate cancer (mCRPC), rendering ^{177}Lu-PSMA as an attractive treatment option in patients with advanced disease.[1,2] As a non-negligible portion of those patients do not adequately respond to therapy, early indicators of treatment failure, preferably after the first cycle, are intensively sought, thereby allowing to switch to another, more effective therapy early in the treatment course. In this regard, recent clinical trials defined response as >50% decline of prostate-specific antigen (PSA) levels,[1–4] thereby following recommendations of the Prostate Cancer Working Group (PCWG) 3.[5] Other investigations, however, interpreted any PSA decline after one cycle as successful treatment.[3,6,7] Given those varying definitions of early biochemical response in the context of RLT, we aimed to evaluate the predictive performance of those criteria (including any response and PSA response >50%) for overall survival (OS) in mCRPC patients scheduled for ^{177}Lu-labeled RLT.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

A total of 184 mCRPC patients treated with at least two cycles of PSMA-directed RLT at the University Hospitals of Würzburg ([^{177}Lu]Lu-PSMA I&T, n = 86) and Bonn ([^{177}Lu]Lu-PSMA-617, n = 98) were included in this bicentric, retrospective study (Table 1). Parts of these cohorts were previously reported in,[8] without investigating different definitions of PSA response as a surrogate parameter for survival. The cohort was further stratified according to the classification of the International Society of Urological Pathology (ISUP) into subgroups of ISUP 1–3 and ISUP 4–5.[9,10] The need for approval was waived by the local ethical committee due to the retrospective nature of this analysis (20210422 04).

2.2 | Treatment protocol

Standard institutional protocols were used to perform RLT. Labeling of PSMA ligands with [^{177}Lu] was performed in-house and has been

TABLE 1 Baseline patient characteristics

	Entire cohort (n = 184)	[^{177}Lu]Lu-PSMA-617 (n = 98)	[^{177}Lu]Lu-PSMA I&T (n = 86)
Clinical variables			
Age at first cycle of PSMA RLT (years)	71.0 (43.0–89.0)	71.0 (43.0–86.0)	71.0 (46.0–89.0)
Treatment cycles per patient	3 (2–10)	3 (2–10)	3 (2–9)
Cumulative activity (GBq)	19.0 (7.9–60.1)	19.3 (7.9–60.1)	18.5 (10.4–54.6)
Activity per cycle (GBq)	6.1 (3.8–12.4)	6.1 (3.8–12.4)	6.1 (3.9–6.8)
Gleason score	8 (6–10)	8 (6–10)	8 (6–10)
Tumor volume (according to CHAARTED)	High: 161 Low: 23	High: 91 Low: 7	High: 70 Low: 16
Baseline laboratory values			
PSA (ng/ml)	163.0 (0.1–3130)	178.5 (0.4–2600)	157.5 (0.1–3130)
Previous treatments (%)			
Radical prostatectomy	44.0	43.9	44.2
Primary radiation therapy to the prostate	16.3	16.3	16.3
Adjuvant radiation therapy	17.4	14.3	20.9
Salvage radiation therapy	12.0	9.2	15.1
Antihormonal treatment	100	100	100
Enzalutamide	70.7	70.4	70.9
Abiraterone	67.9	65.3	70.9
Chemotherapy	70.1	74.5	65.1

Abbreviations: GBq, Gigabecquerel, PSA, prostate-specific antigen.

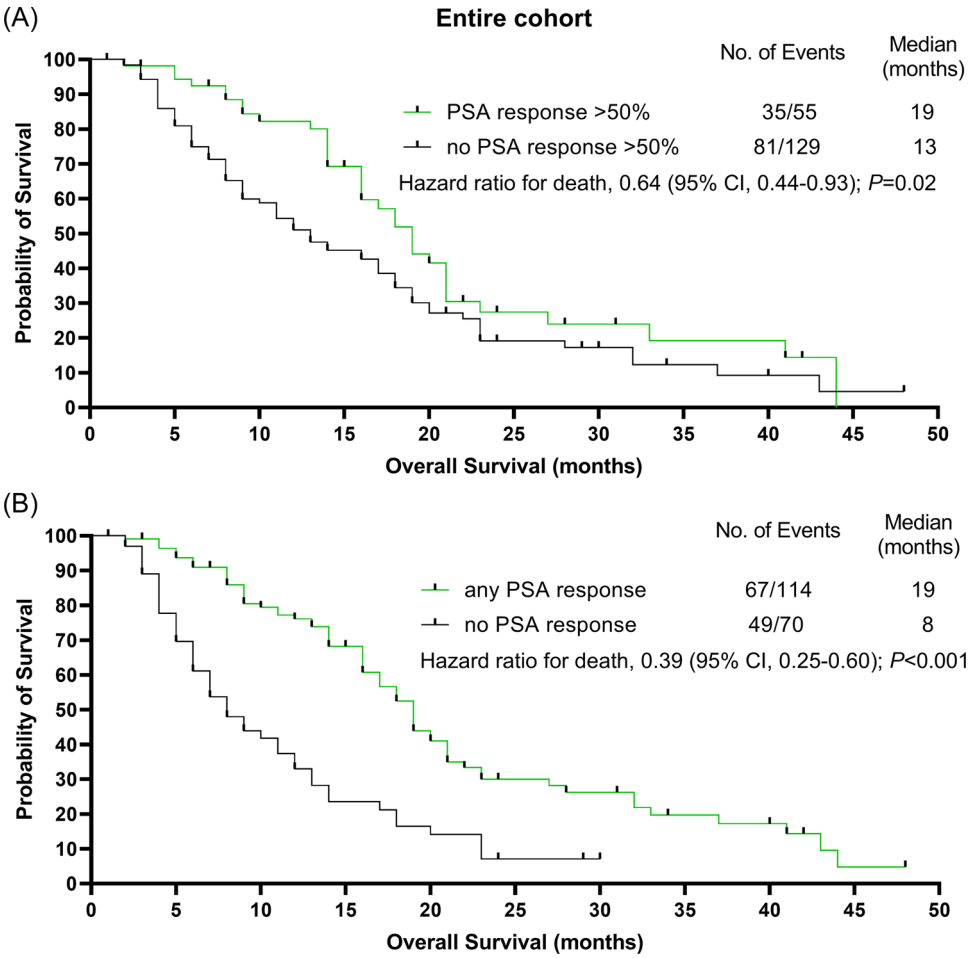

FIGURE 1 Kaplan–Meier curves and log rank comparisons of all patients with and without PSA response >50% (A) and with and without any PSA response (B), with the latter definition reaching a more pronounced discrimination between survivors and nonsurvivors. PSA, prostate-specific antigen [Color figure can be viewed at wileyonlinelibrary.com]

described elsewhere.[8,11] Treatment protocols at both study sites have also been described elsewhere[8,11] and included administration of approximately 6.0 GBq of PSMA ligands every 8 weeks with up to a maximum of 10 cycles, depending on treatment response.

2.3 | Definitions of early biochemical response

Blood samples including PSA levels were collected before the first RLT (cycle 1, day 0) and after 8 weeks on the admission day for the second cycle (cycle 2, day 0). Relative changes in PSA levels were calculated, and response to treatment was defined either as any decline in PSA levels or decrease >50%. We then compared survival between responders and nonresponders (with OS including the time span between initiation of RLT and date of death).

2.4 | Statistical analysis

GraphPad Prism version 9.3.0 (GraphPad Software) was applied. We herein report on descriptive data as median and range in parentheses and we used Kaplan–Meier curves and log-rank comparison to compare OS of responders and nonresponders. Median survival is presented in months with hazard ratio of death (HR) and 95% confidence interval (95% CI). We considered a p value of less than 0.05 to be statistically significant.

3 | RESULTS

3.1 | Early biochemical response for the entire cohort

During a median follow-up of 10 (2–48) months, 116 patients died. The median OS after initiation of RLT was 16 (2–48) months. The median baseline PSA-value was 163 (0.1–3130) and the median PSA-value after the first cycle was 117 (0.07–2490). 55/184 (29.9%) patients showed a PSA response >50%. OS between patients with PSA response >50% (19 months) was significantly longer when compared to patients without PSA response >50% (13 months; HR = 0.64, 95% CI = 0.44–0.93; $p = 0.02$). Applying the criterion of any PSA decline (range: 0.6–98.5%), 114/184 (62.0%) of patients were considered as treatment responders. Survival

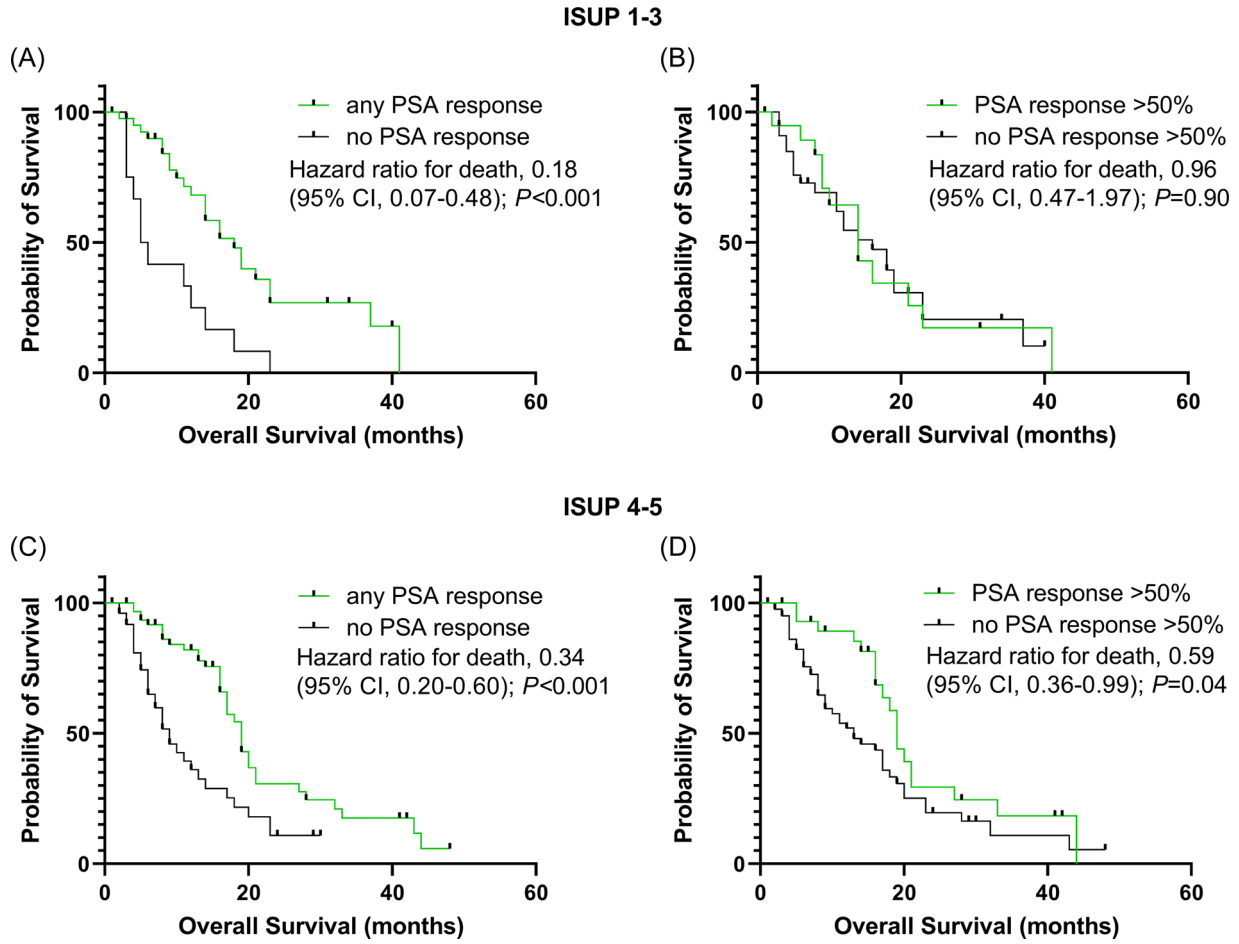

FIGURE 2 Kaplan–Meier curves and log rank comparisons of all patients divided in to subgroups of ISUP 1–3 (A, B) and ISUP 4–5 (C, D) with and without any PSA response and with and without PSA response >50%, with the latter definition reaching only a significant discrimination for ISUP 4–5. PSA, prostate-specific antigen [Color figure can be viewed at wileyonlinelibrary.com]

differences, however, were then more pronounced, with 19 months for responders and only 8 months for nonresponders (HR = 0.39, 95% CI = 0.25–0.60; $p < 0.001$) (Figure 1). For 167 patients, Gleason score was available and these patients were stratified according to ISUP. Difference in OS between patients with PSA response >50% compared to patients without PSA response >50% was not significant in the ISUP 1–3 group (14 vs. 16 months; HR = 0.96, 95% CI = 0.47–1.97; $p = 0.90$) and reached significance in the ISUP 4–5 group (19 vs. 13 months; HR = 0.59, 95% CI = 0.36–0.99; $p = 0.04$). Applying the criterion of any PSA decline, survival differences, were significant for the ISUP 1–3 cohort (18 vs. 5.5 months; HR = 0.18, 95% CI = 0.07–0.48; $p < 0.001$) and the ISUP 4–5 cohort (19 vs. 9 months; HR = 0.34, 95% CI = 0.20–0.60; $p < 0.001$; Figure 2).

3.2 | Early biochemical response for patients treated with [^{177}Lu]Lu-PSMA-617

Of 98 patients treated with [^{177}Lu]Lu-PSMA-617, 34 patients (34.7%) showed a PSA decrease >50%. OS in patients with PSA response >50% was 19 months, which was significantly longer than for patients without PSA response >50% (11 months; HR = 0.60, 95% CI = 0.37–0.98; $p = 0.03$). 64/98 (65.3%) patients showed any PSA decline (range: 0.6–98.5%) and survival differences were then again more pronounced for patients with any PSA decline (19 months) when compared to patients without any PSA decline (7 months; HR = 0.45, 95% CI = 0.24–0.82; $p < 0.001$; Figure 3).

3.3 | Early biochemical response for patients treated with [^{177}Lu]Lu-PSMA I&T

Of 86 patients treated with [^{177}Lu]Lu-PSMA I&T, 21 patients (24.4%) had a PSA response >50%. OS in patients with PSA response >50% (18 months) was not significantly different to those without PSA response >50% (14 months; HR = 0.63, 95% CI = 0.35–1.14; $p = 0.15$). 50/86 (58.1%) patients had any PSA decline (range: 0.7–93.8%) and significance for OS was achieved for patients with any PSA decline (20 months) when compared to patients without any PSA decline (9 months; HR = 0.32, 95% CI = 0.17–0.61; $p < 0.001$; Figure 4).

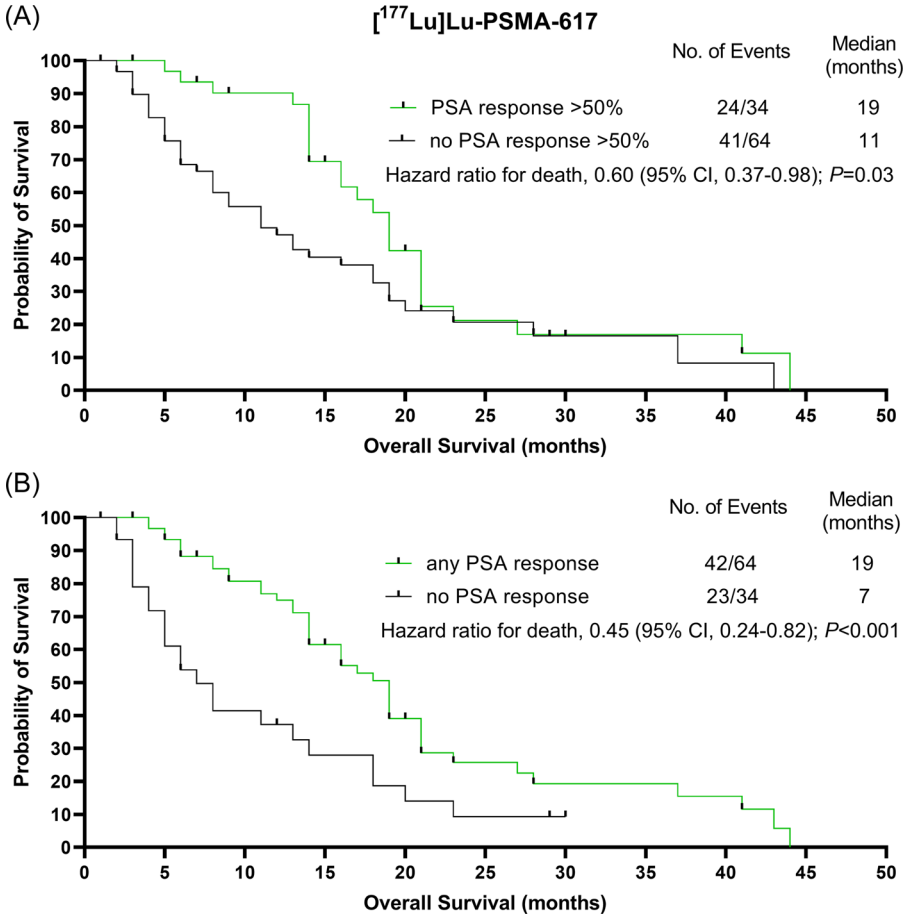

FIGURE 3 Kaplan–Meier curves and log rank comparisons of patients under [^{177}Lu]Lu-PSMA-617 with and without PSA response >50% (A) and with and without any PSA response (B). Again, the latter definition better separated between survivors and nonsurvivors during long-term follow-up. PSA, prostate-specific antigen [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

To date, definitions of early biochemical response in the context of RLT is not consistently clarified and varies from PSA decline of >50%[1–4] to any decrease in PSA levels.[3,6,7] Comparing both definitions, the latter criterion better separated between survivors and non-survivors, thereby indicating that any PSA decline may serve as a more reliable surrogate parameter for long-term outcome. As such, irrespective of the magnitude of PSA decline, RLT should be continued if early serologic assessments indicate a PSA drop. Of note, this also applied to patients stratified according to ISUP.

As a substantial portion of mCRPC patients do not respond to RLT, assessment of early biochemical response using PSA levels is commonly applied during follow-up.[1–4] Established criteria, such as the PCWG3, recommend analysis of PSA changes 12 weeks after initiating treatment.[5] Earlier assessments, however, have also been tested in the context of PSMA-RLT,[6,7,12] with significant correlations between OS and PSA decline as early as 4 weeks after therapy.[12] We, therefore, analyzed changes in PSA levels as early as 8 weeks after the first cycle of RLT, thereby investigating a time frame that would still allow to alter treatment if necessary and if other treatment options are still available as PSMA-RLT is often used as last line treatment. In this regard, the herein observed response rates of 62.0% for any response and 29.9% for PSA response >50% are comparable to previous studies,[6,7,13] rendering our results applicable to a real-world scenario. Differences in OS between survivors and nonsurvivors, however, were more pronounced in patients with any PSA decline when compared to PSA response >50% for the entire cohort. In addition, any PSA response, but not PCWG3 definition, reached significance in a subanalysis investigating patients only treated with [^{177}Lu]Lu-PSMA I&T or [^{177}Lu]Lu-PSMA-617. Those findings are consistent with a previous study reporting on 27 mCRPC patients receiving the latter agent. In this study, the PCWG3 recommended threshold of 50% PSA decline did not correlate with survival, while lower PSA deltas 4 weeks after treatment on-set were linked to late biochemical response at week 17 and longer OS.[12] Including a substantially larger number of patients treated with the most commonly administered RLT agents, our study provides further evidence that early biochemical response is tightly linked to prolonged survival, irrespective of the magnitude of PSA decline and thus, even in patients not meeting the strict criteria of the PCWG3, RLT should be continued. It is also of interest, that the OS in patients treated with [^{177}Lu]Lu-PSMA I&T and not responding according to PSA criteria, still show a tendency for a longer OS than patients treated with [^{177}Lu]Lu-PSMA-617. In detail, this means 9 compared to 7 months in case of PSA increase and 14 compared to 11 months for patients with PSA decrease less than 50% or a PSA increase.

The limitations of the present analysis include its retrospective nature. Further studies in a prospective setting are needed to

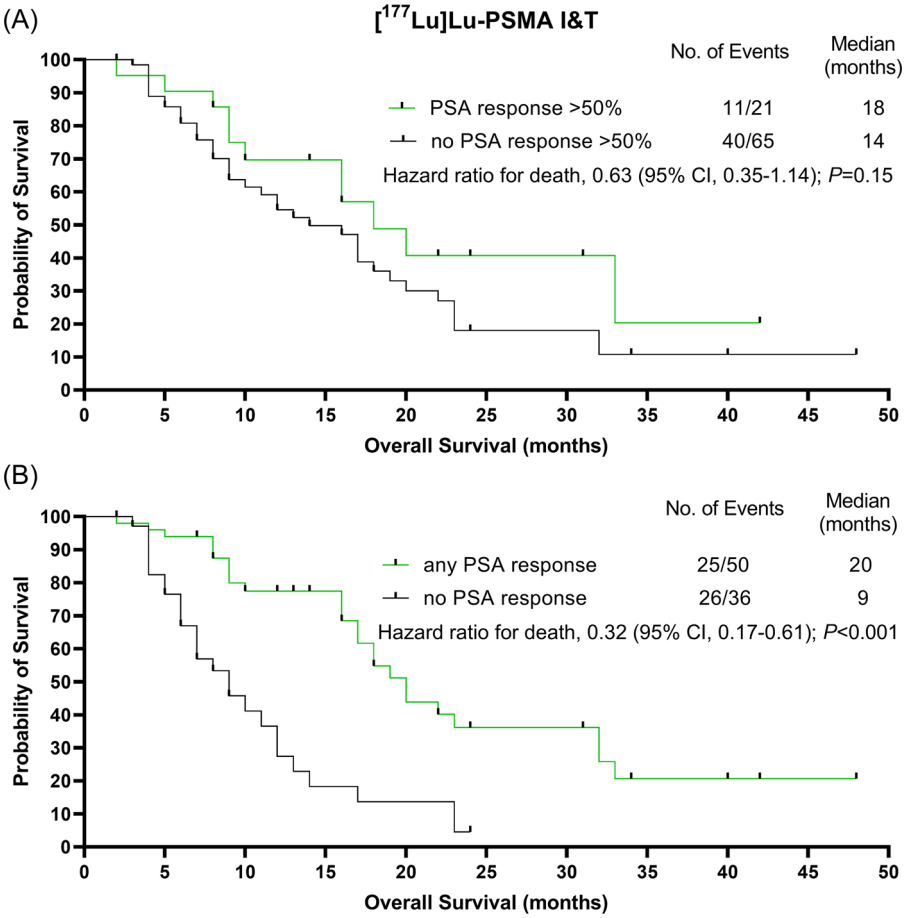

FIGURE 4 Kaplan–Meier curves and log rank comparisons of patients under [^{177}Lu]Lu-PSMA I&T with and without PSA response >50% (A) and with and without any PSA response (B). For (a), no significant difference was reached, while for (B), a significant difference between surviving and nonsurviving patients was observed. PSA, prostate-specific antigen [Color figure can be viewed at wileyonlinelibrary.com]

corroborate our findings, e.g., to assess the predictive capability of any PSA decline at a later time-point (cycle 3 day 0). Nonetheless, we focused on early biochemical response at cycle 2 day 0, thereby providing decision-support for the practitioner to switch therapy already at a very early stage in the treatment course.

AUTHOR CONTRIBUTIONS

Conceptualization: Philipp E. Hartrampf, Rudolf A. Werner, Andreas K. Buck, Andreas K. Buck; *Methodology*: Franz-Xaver Weinzierl; *Software*: Franz-Xaver Weinzierl; *Validation*: Philipp E. Hartrampf, Rudolf A. Werner, Andreas K. Buck; *Formal analysis*: Philipp E. Hartrampf, Franz-Xaver Weinzierl, Andreas K. Buck; *Investigation*: Philipp E. Hartrampf, Andreas K. Buck, Franz-Xaver Weinzierl; *Resources*: Andreas K. Buck, Markus Essler; data curation, Philipp E. Hartrampf, Franz-Xaver Weinzierl; *Writing—original draft preparation*: Philipp E. Hartrampf, Rudolf A. Werner, Andreas K. Buck; *Writing—review and editing*: Rudolf A. Werner, Andreas K. Buck, Andreas K. Buck, Anna Katharina Seitz, Markus Essler, Hubert Kübler; *Visualization*: Franz-Xaver Weinzierl, Philipp E. Hartrampf; *Supervision*: Rudolf A. Werner, Andreas K. Buck; *Project administration*: Philipp E. Hartrampf, Rudolf A. Werner, Andreas K. Buck, Andreas K. Buck; *Funding acquisition*: Philipp E. Hartrampf. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

Ralph A. Bundschuh is Consultant for Bayer Healthcare (Leverkusen, Germany) and Eisai GmbH (Frankfurt, Germany). Ralph A. Bundschuh has a noncommercial research agreement and is on the speakers list of Mediso Medical Imaging (Budapest, Hungary). Markus Essler is Consultant for Bayer Healthcare (Leverkusen, Germany), Eisai GmbH (Frankfurt, Germany), IPSEN and Novartis.

DATA AVAILABILITY STATEMENT

Detailed information on the results presented in this study are available on reasonable request from the corresponding author.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study by the local Ethics Committee due to the retrospective character of the study (#20210422 04). All procedures have been conducted as part of clinical routine care. Informed consent has been obtained from all subjects.

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