available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Declan G. Murphy, Arun A. Azad, Shahneen Sandhu, John Violet and Michael S. Hofman on pp. 927–928 of this issue

Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with ^{177}Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer

Matthias M. Heck[a,†,*], *Robert Tauber*[a,†], *Sebastian Schwaiger*[a,b], *Margitta Retz*[a], *Calogero D'Alessandria*[b], *Tobias Maurer*[a,‡], *Andrei Gafita*[b], *Hans-Jürgen Wester*[c], *Jürgen E. Gschwend*[a], *Wolfgang A. Weber*[b], *Markus Schwaiger*[b], *Karina Knorr*[b,§], *Matthias Eiber*[b,§]

[a] *Department of Urology, Medical Center rechts der Isar, Technical University of Munich, Munich, Germany;* [b] *Department of Nuclear Medicine, Medical Center rechts der Isar, Technical University of Munich, Munich, Germany;* [c] *Pharmaceutical Radiochemistry, Technical University of Munich, Garching, Germany*

Article info

Article history:
Accepted November 8, 2018

Associate Editor:
Giacomo Novara

Statistical Editor:
Andrew Vickers

Keywords:
Metastatic castration-resistant prostate cancer
Radioligand therapy
Prostate-specific membrane antigen
Lutetium

Abstract

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) is increasingly being used in metastatic castration-resistant prostate cancer (mCRPC). The objective of this study is to report our clinical experience with RLT using 177-lutetium–labeled PSMA-I&T. A total of 100 patients were treated under a compassionate use protocol with a total number of 319 cycles (median two cycles, range 1–6). Eligibility criteria included previous treatment with abiraterone or enzalutamide, previous taxane-based chemotherapy or chemoineligibility, and positive PSMA-ligand uptake at positron-emission tomography scan. The ^{177}Lu-PSMA-I&T was given 6–8 weekly with an activity of 7.4 GBq up to six cycles. The median number of previous mCRPC regimens was 3 (range 1–6), and 35 patients had visceral metastases. Prostate-specific antigen decline of $\geq$50% was achieved in 38 patients, median clinical progression-free survival (cPFS) was 4.1 mo, and median overall survival (OS) was 12.9 mo. Subgroup analyses identified an association of visceral metastases with a poor prostate-specific antigen (PSA) response and shorter cPFS and OS, and an association of rising lactate dehydrogenase (LDH) with shorter cPFS and OS. Patients achieving PSA decline of $\geq$50% within 12 wk of treatment showed longer cPFS and OS. Treatment-emergent hematologic grade 3/4 toxicities were anemia (9%), thrombocytopenia (4%), and neutropenia (6%). Grade 3/4 nonhematologic toxicities were not observed. RLT with ^{177}Lu-PSMA-I&T showed good activity in more than one-third of patients with late-stage mCRPC at low toxicity. Presence of visceral metastases and rising LDH were associated with worse treatment outcome.
Patient summary: We analyzed the treatment outcome and toxicity of prostate-specific membrane antigen–targeted radioligand therapy in patients with metastatic castration-resistant prostate cancer. We found that a good treatment response could be achieved in a subgroup of patients with few side effects. We also observed that treatment outcome was worse in patients with organ metastases and elevated lactate dehydrogenase in blood tests.

† Both authors contributed equally.
‡ Current affiliation: Martini-Clinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
§ Joint senior authorship.
* Corresponding author. Department of Urology, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, München 81675, Germany. Tel. +49 89 4140 2520; Fax. +49 89 4140 4843.
E-mail address: matthias.heck@tum.de (M.M. Heck).

https://doi.org/10.1016/j.eururo.2018.11.016
0302-2838/

Radioligand therapy (RLT) targeting prostate-specific membrane antigen (PSMA) with the ligands PSMA-617 and PSMA-I&T labeled to the β-emitter ^{177}Lu has been applied in compassionate use programs with patients who exhausted the approved treatment regimens for metastatic castration-resistant prostate cancer (mCRPC). Several retrospective case series for ^{177}Lu-PSMA-617 RLT have been reported, with the largest series consisting of pooled data of 145 patients from 12 German centers [1]. In addition, recently, the first prospective phase II trial with 30 mCRPC patients treated with ^{177}Lu-PSMA-617 has been reported [2].

In contrast, the literature on treatment outcome with ^{177}Lu-PSMA-I&T is scarce [3,4]. The aim of the present analysis is to report treatment outcome, corresponding subgroup analysis, and toxicity of 100 consecutive mCRPC patients who completed RLT with ^{177}Lu-PSMA-I&T (Supplementary material, Material and methods).

Between December 2014 and August 2017, 100 consecutive mCRPC patients fulfilled our institutional eligibility criteria [4] and were treated under a compassionate use protocol. Of 100 patients, 57 had received three or more prior treatment regimens for mCRPC. Consistent with the advanced state of the mCRPC population, bone, lymph node, and visceral metastases were present in 96, 87, and 35 patients, respectively (Supplementary Table 1).

Overall, 319 cycles were applied with a median of two cycles per patient (range 1–6); two, four, and six cycles were applied in 85, 44, and 20 patients, respectively (Supplementary Fig. 1). The median time on treatment was 3.8 mo. RLT was completed without evidence of clinical or imaging progression in 19 patients. None of the patients stopped treatment due to side effects.

The treatment with ^{177}Lu-PSMA-I&T was well tolerated (Supplementary Table 2). Treatment-emergent grade 3–4 nonhematologic adverse events were not observed. The most common nonhematologic grade 1–2 adverse events were transient xerostomia in 24 patients within the first 2 wk after treatment, fatigue in 20 patients, loss of appetite in 10 patients, and diarrhea in seven patients. Treatment-emergent grade 3–4 hematologic adverse events were anemia in nine, neutropenia in six, and thrombocytopenia in four patients.

The number of patients achieving maximum prostate-specific antigen (PSA) declines of ≥30%, ≥50%, and ≥90% were 47, 38, and 11, respectively (Fig. 1). At the time of analysis, 90 patients had developed clinical progression and 60 were dead. Median follow-up of patients being alive was 9.5 mo (interquartile range 7.0–16.3). Median clinical progression-free survival (cPFS) was 4.1 mo (95% confidence interval [CI] 2.4–5.7) and median overall survival (OS) was 12.9 mo (95% CI 9.9–15.9; Supplementary Fig. 2).

Figure 2 displays a swimmer plot for the individual treatment outcome. In 19 patients who completed ^{177}Lu-PSMA-I&T RLT without progression, sustained tumor control was achieved. The median time to clinical progression after completion of RLT in these patients was 6.0 mo (95% CI 3.9–8.1 mo). PSA response under RLT was strongly associated with survival. In a landmark analysis after 12 wk of treatment, we analyzed treatment outcome from that time point depending on PSA response within 12 wk of RLT. Herein, a maximum PSA decline of ≥50% was associated with longer cPFS (median 8.1 [n = 32] vs 0.4 [n = 53] mo, p = 0.001; difference 7.4 mo [95% CI 5.8–9.0]) and longer OS (median 16.7 [n = 32] vs 6.2 [n = 60] mo, p = 0.007; difference 10.5 mo [95% CI 1.4–19.6]; Fig. 3).

Next, we performed subgroup analyses for baseline variables and their association with treatment outcome. Presence of visceral metastasis was the only variable associated with a poor PSA response (p = 0.049; Supplementary Table 3). Only nine of 35 (26%) patients with visceral metastasis but 29 of 65 (45%) patients without visceral metastasis achieved a maximum PSA decline of ≥50%.

The presence of visceral metastasis, younger age, and rising lactate dehydrogenase (LDH) were significantly

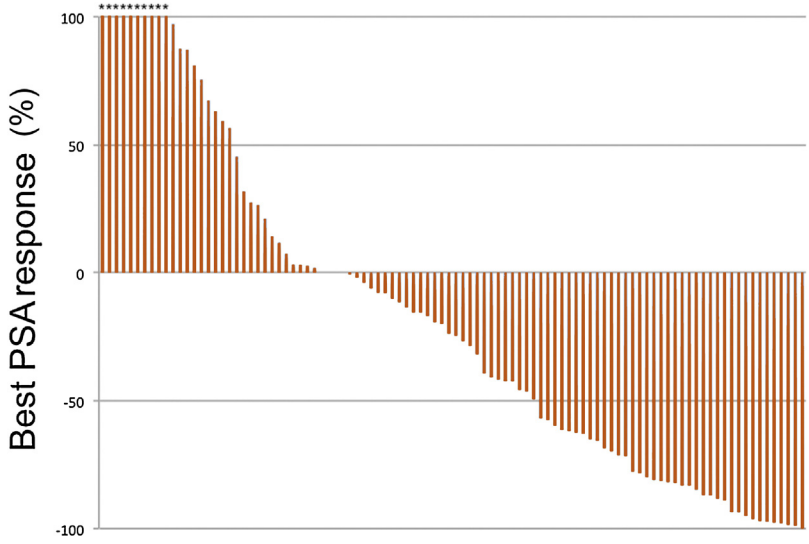

Fig. 1 – Waterfall plot depicting the best PSA response under radioligand therapy with ^{177}Lu-PSMA-I&T. Asterisks indicate an increase of >100% in the best PSA response. PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

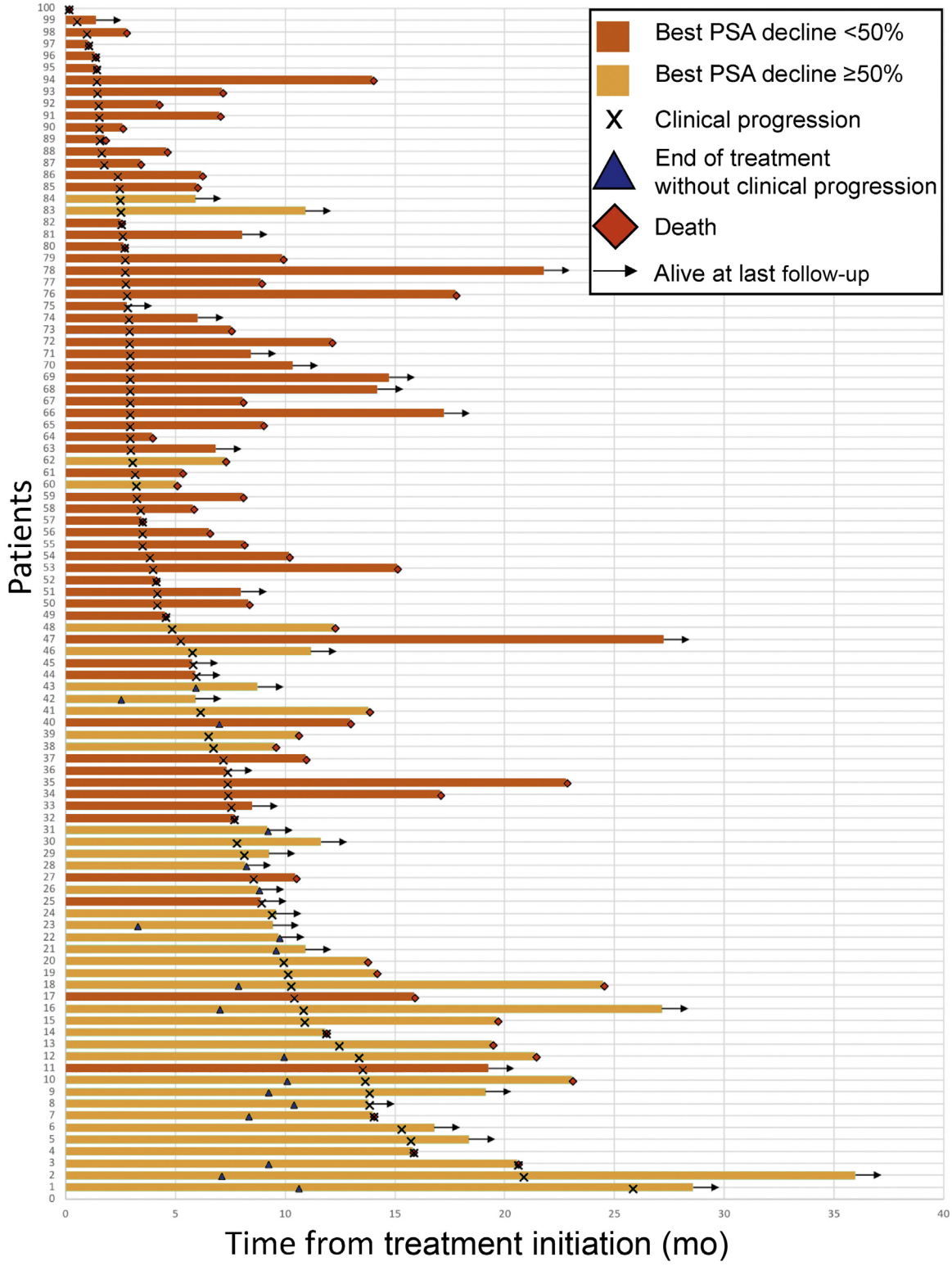

Fig. 2 – Swimmer plot depicting individual treatment outcomes after initiation of radioligand therapy with ^{177}Lu-PSMA-I&T. PSA = prostate-specific antigen.

associated with worse cPFS on univariable analysis (Supplementary Table 4) and confirmed as independent predictors of shorter cPFS on multivariable analysis ($p = 0.02$, $p = 0.01$, and $p < 0.001$, respectively; Table 1). Median cPFS was 3.1 mo in patients with visceral metastasis versus 5.9 mo in those without visceral metastasis (difference 2.8 mo [95% CI–0.8 to 6.4]; Fig. 4A).

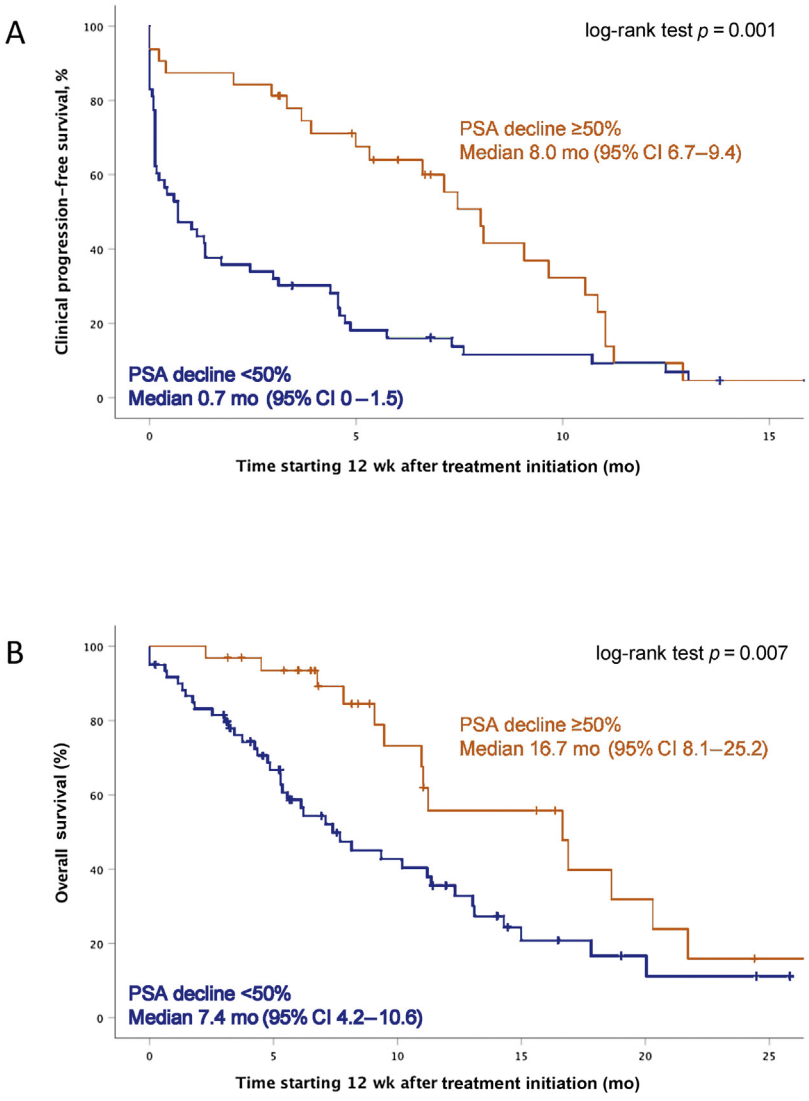

Fig. 3 – Maximum PSA decline of ≥50% was associated with (A) longer clinical progression-free survival and (B) longer overall survival. CI = confidence interval; PSA = prostate-specific antigen.

Table 1 – Multivariable Cox regression model for the association of baseline risk factors with clinical progression-free survival and overall survival

	Hazard ratio	95% CI	*p* value[a]
Clinical progression-free survival			
Visceral metastasis	1.7	1.1–2.6	**0.02**
Age, risk change with 10 yr increase	0.7	0.5–0.9	**0.01**
LDH, risk change with 50 U/l increase	1.1	1.0–1.1	**<0.001**
Overall survival			
Primary metastatic prostate cancer	1.5	0.8–2.7	0.16
Visceral metastasis	2.1	1.2–3.5	**0.006**
Age, risk change with 10 yr increase	0.7	0.5–1.0	0.07
PSA, risk change with 50 ng/ml increase	1.0	1.0–1.0	0.11
AP, risk change with 50 U/l increase	1.0	1.0–1.1	0.5
LDH, risk change with 50 U/l increase	1.1	1.0–1.1	**<0.001**

AP = alkaline phosphatase; CI = confidence interval; LDH = lactate dehydrogenase; PSA = prostate-specific antigen.
[a] Significant *p* values are given in bold.

For OS, primary metastatic disease, presence of visceral metastasis, younger age, rising PSA, rising alkaline phosphatase, and rising LDH were associated with worse outcome on univariable analysis (Supplementary Table 5). However, in a multivariable Cox regression model, only the presence of visceral metastasis ($p = 0.006$) and rising LDH ($p < 0.001$) remained independent predictors of poor OS (Table 1). Median OS was 7.6 mo in patients with visceral metastasis versus 14.0 mo in those without visceral metastasis (difference 6.6 mo [95% CI 3.0–10.2]; Fig. 4B).

In summary, the present retrospective series reports treatment outcome with corresponding subgroup analysis and toxicity under RLT with ^{177}Lu-PSMA-I&T in 100 consecutive mCRPC patients.

According to our institutional eligibility criteria, we included late-stage patients who exhausted approved treatment regimens, which resulted in a high tumor load (visceral metastases in 35 patients). In these patients, a

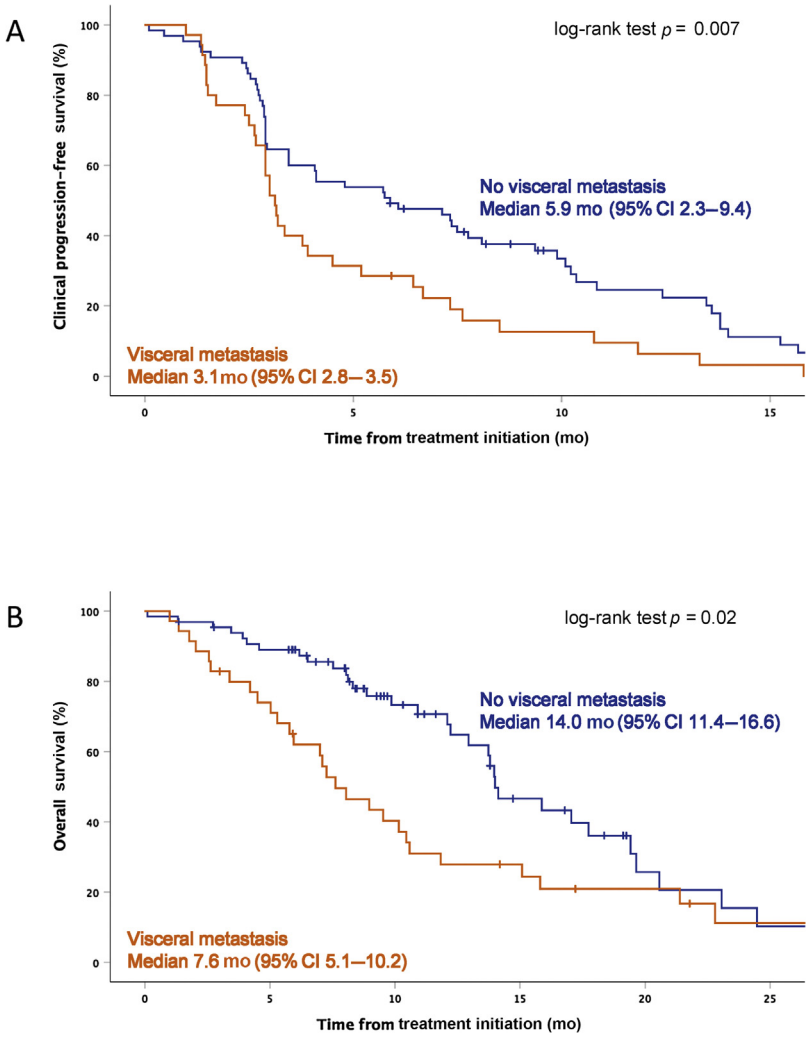

Fig. 4 – Presence of visceral metastasis was associated with (A) shorter clinical progression-free survival and (B) shorter overall survival. CI = confidence interval.

maximum PSA decline of ≥50% was achieved in 38 patients, median cPFS was 4.1 mo, and median OS was 12.9 mo. This is comparable with the recent data from Rahbar et al. [5] who reported treatment outcome for ^{177}Lu-PSMA-617 in 104 late-stage mCRPC patients who were pretreated with docetaxel and abiraterone or enzalutamide; 32% of patients presented with visceral metastasis at baseline. In these patients, PSA decline of ≥50% was achieved in 33% and median OS was 56 wk.

In our subgroup analysis, we identified the presence of visceral metastases besides elevated LDH as a predictor of worse treatment outcome. This could explain the differences from other groups, which treated patients with less advanced disease. Baum et al. [3] reported a maximum PSA decline of ≥50% in 33 of 56 (59%) patients using ^{177}Lu-PSMA-I&T, while liver and lung metastases were present in five (9%) and seven (13%) patients, respectively. The largest retrospective series for ^{177}Lu-PSMA-617 showed a maximum PSA decline of ≥50% in 45 of 99 (45%) patients, while liver and lung metastases were present in 20% and 14%, respectively [1]. In the only prospective trial using ^{177}Lu-PSMA-617, a maximum PSA decline of ≥50% was achieved in 17 of 30 (57%) patients, while visceral metastases were present only in four (13%) patients [2].

The median cPFS in our cohort was relatively short (4.1 mo). This is also partly related to the advanced state of the patients. Notably, patients in our cohort without visceral metastases achieved significantly longer survival with median cPFS of 5.9 mo and median OS of 14.0 mo. In a landmark analysis after 12 wk of RLT, treatment outcome was even more favorable in patients who had achieved a maximum PSA decline of ≥50%. Starting from this time point, these patients reached median cPFS of 8.1 mo and median OS of 16.7 mo.

Partly, the short cPFS for the total cohort may also be explained by the fact that we used ^{68}Ga-PSMA-11 positron-emission tomography (PET) imaging at baseline and restaging to identify tumor progression. The ^{68}Ga-PSMA-11 PET has a higher sensitivity in detecting metastases in soft tissue and bones compared with computed tomography and bone scan, respectively [6,7]. This may have resulted in earlier detection of tumor progression and shorter cPFS.

Treatment-emergent adverse events under RLT with ^{177}Lu-PSMA-I&T were mild, and no treatment was stopped due to side effects, which is comparable with ^{177}Lu-PSMA-617 [2,5]. Thus, PSMA-targeted RLT using a β-emitter such as ^{177}Lu seems to be less toxic than using a high-energetic alpha-emitter such as 225-actinium. In a retrospective series of 31 mCRPC patients who were treated with ^{225}Ac-PSMA-617 per protocol, 15 (48%) patients reported severe xerostomia and four (13%) discontinued treatment due to intolerable xerostomia or loss of taste [8].

Based on the low toxicity profile of ^{177}Lu-PSMA RLT, both earlier application of the treatment before chemotherapy and dose escalation to increase efficacy are under discussion. However, in patients with longer life-expectancy potential, late toxicity to the kidneys as a critical organ for PSMA-targeted RLT has not yet been investigated [9–11]. Currently, no data are available regarding whether ^{177}Lu-PSMA RLT poses a risk of renal insufficiency after several years.

As a dose escalation has not been performed so far, we used a fixed activity of ^{177}Lu-PSMA-I&T. The low toxicity of the current regimen suggests that higher activities per cycle are probably feasible and may increase the response rates and/or duration of response. A further increase in the activity of ^{177}Lu-PSMA-I&T RLT may be achieved by individualized dosing based on pretherapeutic PET and/or dosimetry studies [12]. Patient-specific dosimetry may allow a significant increase in the administered activity in patients with a high tumor burden, because a large percentage of activity accumulated in the tumor tissue reduces tracer uptake and radiation dose for normal tissues (so-called sink effect) [13].

Notably, the range of PSA responses and survival in our cohort is strikingly wide even in the subgroups of patients with or without visceral metastases. Future studies are necessary to investigate the underlying molecular mechanisms of resistance.

Main limitations of the present analysis are its single-center and retrospective design. Currently, several further prospective trials are in progress to investigate PSMA-targeted RLT at phases 1 (NCT03403595), 2 (NCT03454750, NCT03042312, NCT03392428), and 3 (NCT03511664), all of which use PSMA-617 as a ligand. The VISION study will be the first randomized phase 3 trial and will compare ^{177}Lu-PSMA-617 with best standard of care investigating OS as the primary endpoint. This study will further elucidate the potential survival benefit of lutetium-labeled PSMA-targeted RLT.

In conclusion, RLT with ^{177}Lu-PSMA-I&T showed mild toxicity and good antitumor activity in a subgroup of late-stage mCRPC patients. A PSA decline of ≥50% under RLT within 12 wk was associated with longer cPFS and OS. A subgroup analysis identified an association of visceral metastasis at baseline and rising LDH with worse treatment outcome. In these patients, alternative treatment options need to be considered. Several prospective trials are currently enrolling and will further elucidate the clinical benefit of PSMA-targeted RLT.

Author contributions: Matthias M. Heck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Heck, Tauber, Knorr, Eiber.
Acquisition of data: Tauber, Retz, Heck, S. Schwaiger, Gafita, Knorr, Eiber.
Analysis and interpretation of data: Heck, S. Schwaiger, Eiber.
Drafting of the manuscript: Heck, Tauber, Eiber.
Critical revision of the manuscript for important intellectual content: M. Schwaiger, Weber, Maurer, Wester, D'Alessandria.
Statistical analysis: Heck, S. Schwaiger.
Obtaining funding: Eiber.
Administrative, technical, or material support: Retz, Gschwend, M. Schwaiger, Weber, Wester.
Supervision: Heck, Eiber.
Other: None.

Financial disclosures: Matthias M. Heck certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: Matthias Eiber received funding from the SFB 824 (DFG Sonderforschungsbereich 824, Project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany. Siemens Healthineers (Erlangen, Germany) provided the continuous bed motion option for the Biograph mCT as part of an academic collaboration.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.016.

References

[1] Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med 2017;58:85–90.
[2] Hofman MS, Violet J, Hicks RJ, et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825–33.
[3] Baum RP, Kulkarni HR, Schuchardt C, et al. Lutetium-177 PSMA radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med 2016;57:1006–13.
[4] Heck MM, Retz M, D'Alessandria C, et al. Systemic radioligand therapy with (177)Lu-PSMA-I&T in patients with metastatic castration-resistant prostate cancer. J Urol 2016;196:382–91.
[5] Rahbar K, Boegemann M, Yordanova A, et al. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging 2017;5:114–8.
[6] Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of (68) gallium-PSMA-PET compared to conventional imaging in lymph node staging of 130 consecutive patients with intermediate to high-risk prostate cancer. J Urol 2016;195:1436–43.
[7] Pyka T, Okamoto S, Dahlbender M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:2114–21.

[8] Kratochwil C, Bruchertseifer F, Giesel FL, et al. 225Ac-PSMA-617 for PSMA targeting alpha-radiation therapy of patients with metastatic castration-resistant prostate cancer. J Nucl Med 2016;57:1941–4.
[9] Zechmann CM, Afshar-Oromieh A, Armor T, et al. Radiation dosimetry and first therapy results with a (124)I/(131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. Eur J Nucl Med Mol Imaging 2014;41:1280–92.
[10] Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:42–51.
[11] Herrmann K, Bluemel C, Weineisen M, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med 2015;56:855–61.
[12] Begum NJ, Thieme A, Eberhardt N, et al. The effect of total tumor volume on the biologically effective dose to tumor and kidneys for 177Lu-labeled PSMA peptides. J Nucl Med 2018;59:929–33.
[13] Gaertner FC, Halabi K, Ahmadzadehfar H, et al. Uptake of PSMA-ligands in normal tissues is dependent on tumor load in patients with prostate cancer. Oncotarget 2017;8:55094–103.