First Safety and Efficacy Data with the Radiohybrid ^{177}Lu-rhPSMA-10.1 for the Treatment of Metastatic Prostate Cancer

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We recently published the first dosimetry data, to our knowledge, for the radioligand therapy agent ^{177}Lu-rhPSMA-10.1, providing an intrapatient comparison with ^{177}Lu-PSMA-I&T in patients with metastatic prostate cancer. Here, we report efficacy and safety findings from these patients. **Methods:** Four consecutive patients with prostate-specific membrane antigen (PSMA)–positive metastatic prostate cancer received up to 6 cycles of ^{177}Lu-rhPSMA-10.1 (7.4–7.7 GBq per cycle). Efficacy (prostate-specific antigen response according to Prostate Cancer Working Group 3 criteria and the Response Evaluation Criteria in PSMA PET/CT), progression-free survival, and overall survival were evaluated. Adverse events were recorded from the first dose until 16–24 mo after treatment. **Results:** The patients received a total activity of 29.6–59.4 GBq (4–6 cycles). Prostate-specific antigen was reduced by 100%, 99%, 88%, and 35%. Progression-free survival was not reached for 2 patients at 24 and 18 mo of follow-up and was 15 and 12 mo for the other 2 patients. One patient had a sustained complete response with 2 y of follow up. All patients were alive at the last time point of data collection. No serious adverse events were reported. **Conclusion:** ^{177}Lu-rhPSMA-10.1 demonstrated encouraging preliminary efficacy and was well tolerated. Formal clinical trials are now under way to evaluate its potential prospectively (NCT05413850).

Key Words: prostate cancer; radioligand therapy; prostate-specific membrane antigen; therapeutic response

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A recently developed radiohybrid technology platform has enabled engineering of prostate-specific membrane antigen (PSMA)–targeted ligands (rhPSMA) that can be labeled with ^{18}F for diagnostic imaging or with α- or β-emitting radiometals for systemic radiation therapy (*1*). The lead diagnostic rhPSMA, ^{18}F-flotufolastat (^{18}F-rhPSMA-7.3), was recently approved by the U.S. Food and Drug Administration for diagnostic imaging in patients with newly diagnosed and recurrent prostate cancer (*2,3*). A pharmacokinetically tuned ^{177}Lu-labeled rhPSMA therapeutic candidate for patients with metastatic prostate cancer, ^{177}Lu-rhPSMA-10.1, has shown encouraging results in a series of preclinical assessments (*4,5*).

We recently reported the first clinical data, to our knowledge, comparing pretherapeutic dosimetry of ^{177}Lu-rhPSMA-10.1 with ^{177}Lu-PSMA-I&T (*6*). In an intrapatient comparison in patients with metastatic prostate cancer, we were able to show that ^{177}Lu-rhPSMA-10.1 delivers an increased radiation dose to the tumor compared with ^{177}Lu-PSMA-I&T, reaching an up to 8-fold improvement in tumor dose in one of the patients (*6*). Data on the recently approved ^{177}Lu-labeled vipivotide tetraxetan (^{177}Lu-PSMA-617) suggest that the greater the radiation dose delivered to the tumor, the better the response observed (*7,8*). Additionally, data from the use of external-beam radiation therapy in over 30,000 patients with prostate cancer are highly supportive of longer survival in patients receiving higher radiation doses to their tumor (*9*). Furthermore, we were able to demonstrate a more favorable tumor-to-kidney therapeutic index (TI), defined as the mean absorbed radiation dose to tumors divided by the absorbed dose to kidneys, for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T. This is of clinical importance because the kidneys are a significant organ at risk in patients undergoing radioligand therapy (RLT) (*10*) and because as the use of such compounds moves earlier in the disease timeline, possibly even into the curative setting, the risk of a delayed radiation nephropathy may increase.

As a result of the favorable TI of ^{177}Lu-rhPSMA-10.1, and in the absence of an approved RLT in Germany at that time, all 4 patients in our analysis ultimately proceeded to receive RLT with ^{177}Lu-PSMA-10.1. Here, we report the efficacy and safety findings among these 4 patients who, to the best of our knowledge, were the first globally to receive RLT with ^{177}Lu-rhPSMA-10.1.

MATERIALS AND METHODS

Radiopharmaceutical Preparation and Approval

As previously reported (*6*), all investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The local institutional review board (review board of the Ludwig-Maximilians-Universität München) approved this analysis (permit 22-1011). ^{177}Lu-rhPSMA-10.1 was prepared in compliance with the German Medicinal Products Act, Arzneimittelgesetz §13 2b,

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and after informing the responsible regulatory body. All patients gave written informed consent to the imaging and therapeutic procedures.

Patients and Lesions

Four consecutive patients with metastatic prostate cancer were included in this retrospective analysis. All subjects were previously treated with a spectrum of prostate cancer therapies including surgery, radiation therapy, androgen deprivation, novel androgen-axis drugs, and chemotherapy. To be eligible, the patients were required to have PSMA-positive metastatic prostate cancer, defined by the presence of at least 1 PSMA-positive metastatic lesion and no PSMA-negative lesions. The presence of PSMA-positive lesions was determined with ^{68}Ga-PSMA-I&T PET/CT and defined in accordance with the criteria used in the VISION trial (*11*). PSMA expression was also assessed using the PSMA PET tumor–to–salivary gland ratio (*12*).

The SUV_{max} of the most avid metastasis was measured with ^{68}Ga-PSMA-I&T PET/CT. Additionally, each PET scan was analyzed with a semiautomatic tumor segmentation algorithm (LIFEx software (*13*)). The total PSMA-positive tumor volume was estimated as previously described using an absolute SUV threshold of at least 3 for segmentation (*14*). Physiologic uptake sites, such as salivary glands, liver, spleen, kidneys, intestine, ureters, and urinary bladder, were manually excluded.

After sufficient PSMA expression was confirmed, the patients underwent dosimetry with both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T to determine the TI (*6*). All 4 patients went on to receive treatment with ^{177}Lu-rhPSMA-10.1 because it was determined to provide the more favorable TI (*6*).

Therapeutic Dosimetry of First Treatment Cycle

Therapeutic dosimetry in 3 of 4 patients (patient 4 was excluded because of claustrophobia) was conducted after the first treatment cycle as previously described (*6*).

^{177}Lu-rhPSMA-10.1 Therapy and Response Assessment

The patients received up to 6 cycles of ^{177}Lu-rhPSMA-10.1 (7.4–7.7 GBq), with an interval of 6 wk between cycles.

Efficacy, or serum prostate-specific antigen (PSA) response, was evaluated using Prostate Cancer Working Group 3 criteria (*15*) and the Response Evaluation Criteria in PSMA PET/CT (*16*). In addition, estimations of progression-free survival and overall survival were calculated until the last evaluated time point (July 2023).

Safety

All patients were monitored for the frequency of adverse events and treatment-related adverse events graded according to version 5.0 of

TABLE 1
Clinical Characteristics

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
ECOG performance score	1	1	1	1
Site of disease				
Lung	No	No	No	No
Liver	No	No	No	No
Lymph node	No	No	Yes	Yes
Bone	Yes	Yes	No	Yes
PSA level (ng/mL)	0.9	9.9	15	20
Alkaline phosphate level (U/L)*	85	66	95	82
LDH (U/L)†	208	190	183	180
Median time since diagnosis (y)	10	3	12	8
Gleason score at diagnosis	8	9	7	9
Prior treatment				
Prostatectomy	Yes	No	Yes	Yes
Androgen receptor pathway	None	1	3	2
Inhibitor		Abiraterone	Abiraterone, enzalutamide, apalutamide	Enzalutamide, abiraterone
Taxane therapy	None	Docetaxel	Docetaxel	Docetaxel
PSMA expression				
PROMISE V2 score	2	2	3	3
PSMA status (VISION criteria)	Positive	Positive	Positive	Positive
SUV_{max} (most avid lesion)	17.4	10.1	97.1	68.0
Metastases: PSMA-positive TV (cm^3)	19.1	7.9	47.7	118.3

*Reference range, 40–130 U/L.
†Reference range, 0–250 U/L.
ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PROMISE V2 = Prostate Cancer Molecular Imaging Standardized Evaluation, version 2; TV = tumor volume.

the Common Terminology Criteria for Adverse Events (*17*) from the first dose of treatment to 24 mo after treatment.

Blood samples for monitoring of hemoglobin, white blood cells, platelets, creatinine, glomerular filtration rate, alkaline phosphatase, and liver parameters were obtained directly before RLT and every 2–4 wk thereafter.

Statistics

Most of the reported data are descriptive. All continuous data are reported as mean, SD, and range.

RESULTS

Patients

Four patients aged between 65 and 80 y were included in the analysis. Three of 4 patients presented with bone metastases, and 2 presented with lymph node involvement. Their clinical characteristics are shown in Table 1.

PSMA Expression

All patients were positive for PSMA according to the VISION criteria (*11*), with the SUV_{max} of the most avid metastasis ranging between 10.1 and 97.1. Two patients were rated 2, and 2 patients were rated 3, using the PSMA PET tumor–to–salivary gland ratio (*12*). The PSMA-positive tumor volume varied greatly across patients (range, 7.9–118.3 cm^3). Pretherapeutic ^{68}Ga-PSMA-I&T scans of patients 1 and 4 can be found in Figure 1.

Therapy

Three of the 4 patients had previously undergone prostatectomy. The patients' treatment before and during ^{177}Lu-rhPSMA-10.1 is presented in Figure 2. The patients received 4–6 cycles of ^{177}Lu-rhPSMA-10.1 (Table 2). In posttherapeutic dosimetry for the first treatment cycle, tumor-absorbed doses for reference lesions varied between 0.23 and 0.87 mGy/MBq injected dose of ^{177}Lu-rhPSMA-10.1 in patient 1, 0.93–1.24 mGy/MBq in patient 2, and 5.5–8.9 mGy/MBq in patient 3, whereas in patient 4, no dosimetry could be performed because of claustrophobia (*6*).

All 4 patients showed a PSA response while receiving ^{177}Lu-rhPSMA-10.1 as presented in Figure 3. Progression-free survival was not reached for 2 patients at 24 and 18 mo of follow up and was 12 and 15 mo in the other 2 patients.

As of July 2023, all patients were alive, with 1 patient showing an ongoing complete response more than 2 y after starting RLT. Two patients had a partial response, with one having residual lesions in the pelvic lymph nodes and the other having residual disease in the local tumor, thoracic lymph node, and bone. The remaining patient showed disease progression according to the Response Evaluation Criteria in PSMA PET/CT (*16*).

Safety

No serious or treatment-related adverse events were reported. All reported events are listed in Table 3 and Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

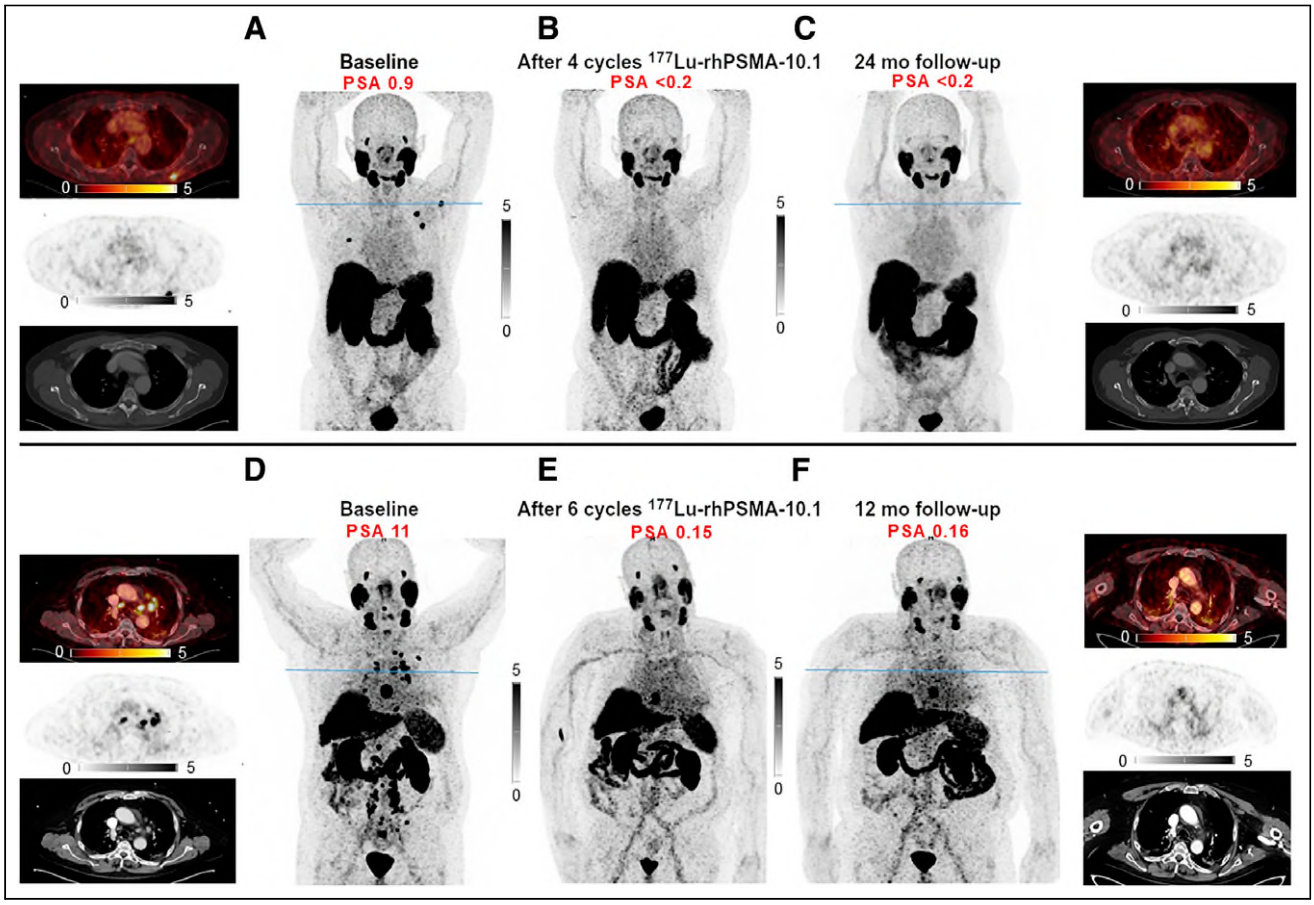

FIGURE 1. Example of tumor response to RLT with ^{177}Lu-rhPSMA-10.1: ^{68}Ga-PSMA-I&T PET/CT at baseline (A and D), at end of treatment with ^{177}Lu-rhPSMA-10.1 (B and E), and during follow-up (C and F) of patients 1 (top) and 4 (bottom).

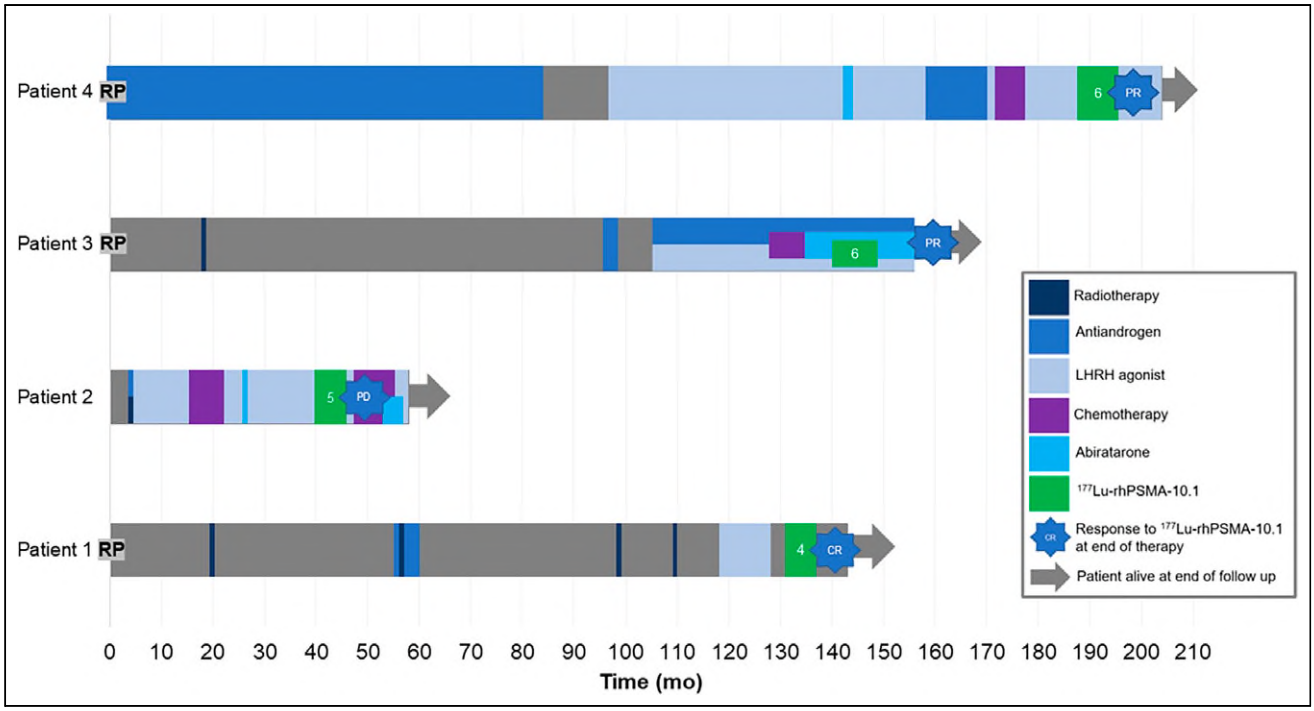

FIGURE 2. Patients' treatment before and during ^{177}Lu-rhPSMA-10.1. All 4 patients were followed up until July 2023. Number of ^{177}Lu-rhPSMA-10.1 cycles is indicated by number in green bar. CR = complete response; PD = progressive disease; PR = partial response; RP = radical prostatectomy.

All events were mild and graded 1 or 2 according to version 5.0 of the Common Terminology Criteria for Adverse Events (*17*).

DISCUSSION

Here, we present efficacy and safety data from the clinical use of ^{177}Lu-rhPSMA-10.1 RLT in 4 patients with metastatic prostate cancer. Our data show that ^{177}Lu-rhPSMA-10.1 was well tolerated and induced a profound PSA response in 3 of 4 patients, with a smaller PSA response in the fourth patient.

We previously showed that, in the same 4 patients, ^{177}Lu-rhPSMA-10.1 provided a high TI, indicating a high dose to tumors relative to the absorbed dose to the kidneys. The present data extend these findings to demonstrate that this was able to bring about a remarkable complete response in 1 patient that was still ongoing after more than 2 y of follow-up, with 2 further patients showing partial responses that comprised a 99% and 88% decrease in PSA. The patients received therapeutic ^{177}Lu-rhPSMA-10.1 activities of between 7.4 and 7.7 GBq per cycle. The favorable TI with ^{177}Lu-rhPSMA-10.1 raises the possibility that the administered therapeutic activities of ^{177}Lu-rhPSMA-10.1 could be optimized according to patient need—maximizing tumor-absorbed doses in patients with significantly shortened life expectancy while tolerating higher kidney-absorbed radiation doses. For patients who are earlier in the disease timeline and have a longer life expectancy, the radiation exposure to the kidneys could be reduced while still achieving an effective dose to the tumor (*6*).

TABLE 2
^{177}Lu-rhPSMA-10.1 Treatment and Response

^{177}Lu-rhPSMA-10.1	Patient 1	Patient 2	Patient 3	Patient 4
Number of cycles	4	5	6	6
Cumulative dose (GBq)	29.6	37.6	44.4	44.7
Greatest PSA decrease in response to ^{177}Lu-rhPSMA-10.1 (%)	100	35	88	99
Best response to ^{177}Lu-rhPSMA-10.1 (RECIP)	Complete response	Stable disease	Partial response	Partial response
Response to ^{177}Lu-rhPSMA-10.1 at end of therapy (RECIP)	Complete response	Progressive disease	Partial response	Partial response
Progression-free survival (mo)	24 (not reached)	12	15	18 (not reached)
Overall survival	Alive	Alive	Alive	Alive

RECIP = Response Evaluation Criteria in PSMA PET/CT.

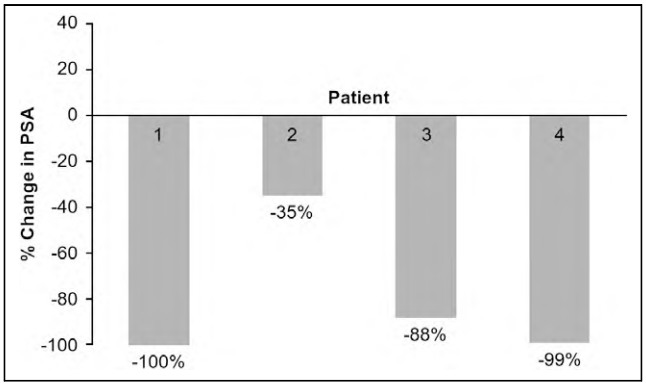

FIGURE 3. Waterfall plot to show each patient's response to ^{177}Lu-rhPSMA-10.1

Our previous data from these patients show that the dose to the tumor varied by patient and by lesion. Data derived with ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer suggest that efficacy increases when a higher radiation dose is delivered to the tumor (*7,18*). In the present study, we used the criteria applied in the VISION study to determine the PSMA positivity of lesions before initiating RLT (i.e., SUV greater than liver) (*11*). Notably, the patient showing the lowest SUV (SUV_{max}, 10.1; patient 2) and a highly variable tumor-absorbed dose was the only patient who showed any disease progression. Despite a 35% reduction in PSA during his 5 cycles of ^{177}Lu-rhPSMA-10.1, this patient was determined to have progressive disease at the end of treatment. This perhaps highlights the importance of identifying predictive factors that may help select patients with the best chance of success before initiation of ^{177}Lu-PSMA–based RLT. Recent studies have proposed nomograms that include pretherapeutic imaging with ^{68}Ga- or ^{18}F-labeled PSMA ligands to help predict outcomes from ^{177}Lu-PSMA–based RLT (*19,20*). In addition, the use of radiomics features and artificial intelligence applied on pretherapeutic PET has been suggested (*21*). On the other hand, it has to be acknowledged that in subjects with lower tracer uptake but no other therapeutic options, PSMA therapy may still be preferable to no treatment at all.

TABLE 3
Frequency and Severity of Adverse Events

Adverse event category	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	4	0	0	0
Leukopenia	1	0	0	0
Thrombocytopenia	1	0	0	0
Salivary gland toxicity	4	0	0	0
Decline in kidney function	2	2*	0	0
Hepatotoxicity	0	0	0	0

*One patient had grade 2 chronic kidney disease at baseline and did not deteriorate.

Data are number of patients (total $n = 4$). All events were graded according to Common Terminology Criteria for Adverse Events version 5.0 (*17*).

Although ^{177}Lu-labeled radiopharmaceuticals are generally well tolerated, the kidneys remain one of the most important normal organs to consider when planning RLT because of the risk of delayed radiation nephropathy (*22,23*). Although this is less concerning in patients with heavily pretreated disease and a short life expectancy, several years from now it is entirely plausible that this class of agents could be used as neoadjuvant or adjuvant therapies in men with high-risk newly diagnosed prostate cancer undergoing radical primary therapy. Therefore, understanding the exposure to normal organs and the long-term safety is critical. Our data show that there were only minimal adverse events in these patients receiving ^{177}Lu-rhPSMA-10.1, including grade 1 (mild) chronic kidney disease (*17*). However, our data are limited by a maximum follow-up period of 24 mo, and data extending many years might be necessary to detect a safety signal.

There are some limitations to the present work. Whereas the follow-up period of up to 24 mo after treatment is longer than for most other studies, even longer-term safety data are needed to accurately quantify the risk to normal-organ function. We report data from only a small number of patients who were the first to receive ^{177}Lu-rhPSMA-10.1 RLT at our clinic. The encouraging findings, however, show ^{177}Lu-labeled rhPSMA compounds to be suitable candidates for clinical translation, and the results of the ongoing phase 1/2 clinical trial of ^{177}Lu-rhPSMA-10.1 in patients with metastatic castration-resistant prostate cancer (NCT05413850) are eagerly anticipated.

CONCLUSION

These clinical data from patients with metastatic castration-resistant prostate cancer undergoing ^{177}Lu-rhPSMA-10.1 RLT show ^{177}Lu-rhPSMA-10.1 to be well tolerated and, in all 4 patients evaluated, to bring about PSA responses accompanied by durable radiologic responses to therapy.

DISCLOSURE

Constantin Lapa reports prior consulting activities for Blue Earth Diagnostics Ltd. and Novartis. Ralph Bundschuh is a consultant for and has received speaker honoraria from Bayer Healthcare, Novartis, and Eisai GmbH and has received travel expenses from Blue Earth Diagnostics Ltd. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: Does ^{177}Lu-rhPSMA-10.1 provide a therapeutic response in patients with metastatic prostate cancer?

PERTINENT FINDINGS: In these 4 patients who received RLT with ^{177}Lu-rhPSMA-10.1, no serious adverse events were noted. All 4 patients showed a PSA response, with 1 patient showing a complete biochemical and radiologic response that was maintained for the 2 y until last follow-up.

IMPLICATIONS FOR PATIENT CARE: ^{177}Lu-rhPSMA-10.1 is well tolerated and brought about decreases in PSA levels ranging from 33% to 100% in all patients evaluated. Prospective clinical studies are under way to confirm these findings (NCT05413850).

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