Lutetium-177-PSMA-617 in Low-Volume Hormone-Sensitive Metastatic Prostate Cancer: A Prospective Pilot Study

Bastiaan M. Privé1, Steffie M.B. Peters1, Constantijn H.J. Muselaers2, Inge M. van Oort2, Marcel J.R. Janssen1, J.P. Michiel Sedelaar2, Mark W. Konijnenberg1,3, Patrik Zámecník1, Maïke J.M. Uijen1, Melline G.M. Schilham1, Annemarie Eek1, Tom W.J. Scheenen1, J. Fred Verzijlbergen1, Winald R. Gerritsen4, Niven Mehra4, Linda G.W. Kerkmeijer4, Robert J. Smeenk5, Diederik M. Somford6, Jean-Paul A. van Basten6, Sandra Heskamp1, Jelle O. Barentsz1, Martin Gotthardt1, J. Alfred Witjes2, and James Nagarajah1,7

ABSTRACT

Background: [177Lu]Lu-PSMA-617 radioligand therapy ([177Lu-PSMA] is a novel treatment for metastatic castration-resistant prostate cancer (mCRPC), which could also be applied to patients with metastatic hormone-sensitive prostate cancer (mHSPC) with PSMA expression. In this prospective study (NCT03828838), we analyzed toxicity, radiation doses, and treatment effect of [177Lu-PSMA in patients with low-volume mHSPC.

Patients and Methods: Ten progressive patients with mHSPC following local treatment, with a maximum of ten metastatic lesions on [18F]Ga-PET/diagnostic-CT imaging (PSMA-PET) and serum PSA doubling time <6 months received two cycles of [177Lu-PSMA]. Whole-body single-photon emission CT/CT (SPECT/CT) and blood dosimetry was performed to calculate doses to the tumors and organs at risk (OAR). Adverse events (AE), laboratory values (monitoring response and toxicity), and quality of life were monitored until week 24 after cycle 2, the end of study (EOS). All patients underwent PSMA-PET at screening, 8 weeks after cycle 1, 12 weeks after cycle 2, and at EOS.

Results: All patients received two cycles of [177Lu-PSMA without complications. No treatment-related grade III-IV adverse events were observed. According to dosimetry, none of the OAR reached threshold doses for radiation-related toxicity. Moreover, all target lesions received a higher radiation dose than the OAR. All 10 patients showed altered PSA kinetics, postponed androgen deprivation therapy, and maintained good quality of life. Half of the patients showed a PSA response of more than 50%. One patient had a complete response on PSMA-PET imaging until EOS and two others had only minimal residual disease.

Conclusions: [177Lu-PSMA appeared to be a feasible and safe treatment modality in patients with low-volume mHSPC.

Introduction

Prostate cancer is the most common non-skin cancer in the world with over 1.3 million patients diagnosed every year, of which the majority receive surgery or external beam radiotherapy (EBRT) as a curative treatment option (1, 2). However, 20% to 40% of these patients will develop disease recurrence, which is generally revealed by rising serum PSA levels (3). If salvage surgery or EBRT is insufficient to control disease progression, androgen deprivation therapy (ADT) is generally offered, with early initiation in patients with high PSA velocity (e.g., PSA doubling time <6 months; ref. 3).

Despite favorable responses to ADT and novel drug combinations, there is an increasing interest in metastasis-directed therapies (MDT) for low-volume metastatic (i.e., oligometastatic) disease, primarily to postpone relevant ADT-related side-effects (e.g., cardiovascular disease, osteoporosis, fatigue, loss of libido, depression, hot flashes, and weight gain) and thus preserve quality of life for as long as possible (4–9). The STOMP trial offering stereotactic EBRT to very low-volume metastatic hormone-sensitive prostate cancer (mHSPC) observed minimal treatment-related toxicity. Moreover, Ost and colleagues recently reported a five-year ADT-free survival of 34% in the EBRT group compared with 8% in the surveillance group (HR, 0.57; 80% confidence interval (CI): 0.38–0.84; log-rank P = 0.06; refs. 4, 10). However, MDT with surgery or EBRT is limited by previous interventions and to particular anatomic regions. Thus, there is an unmet need for treatment options in early-stage patients to control recurrent tumor progression while preserving quality of life.

In recent years, [177Lu-PSMA-617 radioligand treatment ([177Lu-PSMA] is increasingly applied to patients with end-stage metastatic castrate-resistant prostate cancer (mCRPC) with encouraging responses and tolerable side effects (11–13). This has resulted in an international registration study for use of [177Lu-PSMA in patients with mCRPC (NCT03511664). However, to date, there are

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Clinical Trial registration: NCT03828838.

Prior presentations: This work was previously presented at European Association of Nuclear Medicine 2019, European Association of Nuclear Medicine 2020, and Nuklearmedizin 2019, European Association of Nuclear Medicine 2020, American Society of Clinical Oncology 2020, and Nuklearmedizin 2020.

Corresponding Author: James Nagarajah, Radboud UMC, Geert Grooteplein Zuid10, Nijmegen, Netherlands. Phone: 3102-4309-0031; E-mail: james.nagarajah@radboudumc.nl

Clin Cancer Res 2021;XX:XX-XX
doi: 10.1158/1078-0432.CCR-20-4298
©2021 American Association for Cancer Research.

Published OnlineFirst April 21, 2021; DOI: 10.1158/1078-0432.CCR-20-4298
Translational Relevance

[177Lu]Lu-PSMA-617 radioligand therapy ([177Lu]-PSMA) is a novel treatment for end-stage metastatic castration-resistant prostate cancer. To date, [177Lu]-PSMA is not investigated in either the hormone-sensitive or the low-volume metastatic stage, mainly because of toxicity concerns. This prospective pilot study evaluated the toxicity, dosimetry, and treatment effect of [177Lu]-PSMA in 10 fast-progressing patients with low-volume metastatic hormone-sensitive prostate cancer (mHSPC). Therewith, this trial opened the door for (salvage) radiogand therapy as metastasis-directed therapy next to surgery and external beam radiotherapy. During follow-up, no treatment-related grade III–IV adverse events were observed. None of the organs at risk reached threshold doses for radiation-related toxicity while doses to tumors were consistently higher. Moreover, all 10 patients showed altered PSA kinetics, postponed androgen deprivation therapy, and maintained good quality of life. These results suggest that [177Lu]-PSMA is feasible and safe in patients with low-volume mHSPC. Therefore, we initiated a randomized controlled multicenter phase II study in the same patient cohort (NCT04443062).

Materials and Methods

Males (age >50 years) with histologic proven prostate cancer and progressive disease after local therapy (PSA >0.2 μg/L), with a PSA doubling time of <6 months and no curable treatment options (e.g., surgery or EBRT) left were eligible for this trial. In addition, only low-volume disease (≥1 but ≤10 positive lesions) on [18F]Ga-PSMA-11 PET/diagnostic-CT imaging (PSMA-PET) with tumor PSMA uptake higher than liver PSMA uptake were included. Temporarily ADT adjuvant to EBRT in the curative setting was allowed; however, this must have been discontinued ≥3 months prior to inclusion. Normal renal and bone marrow functions were required (MDRD- GFR ≥60 mL/minute, white blood cell count ≥3.5 × 10^9/L, platelet count >150 × 10^9/L, and hemoglobin ≥6 mmol/L). Patients with visceral metastases were excluded. All inclusion and exclusion criteria are added in the Supplementary Data.

The study was approved by the Medical Review Ethics Committee Region Arnhem-Nijmegen (NL62774.091.17) and was registered on clinicaltrials.gov (NCT03828838). All subjects provided written informed consent before study entry. The trial was done in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki.

Study procedures

During clinical workup, patients underwent PSMA-PET imaging to evaluate PSMA-positive tumor lesions. The PSMA-PET was repeated 1 week prior to the second cycle of [177Lu]-PSMA and 3 and 6 months after the second administration. PSMA-PET was executed under the protocol as described previously (17). All images were reviewed by board-certified nuclear medicine physicians with over 5 years of experience. The radiolabeling of [177Lu]-PSMA-617 is described in the Supplementary Material.

The first cycle of [177Lu]-PSMA consisted of 3 GBq, followed by a second cycle with 3–6 GBq after 7–9 weeks. Thus, the second cycle could be adjusted in case of unfavorable dosimetry results or toxicity. [177Lu]-PSMA was administered by slow intravenous injection over 2–5 minutes. Patients were advised to have adequate oral fluid intake next to a NaCl 0.9% infusion of 2 L per 24 hours. No specific actions were taken to prevent xerostomia. After each cycle, single-photon emission CT/CT (SPECT/CT) was acquired approximately 1, 24, 48, 72, and 168 hours postinjection to perform 3D dosimetry, according to the MIRD scheme (18). For SPECT/CT imaging a Siemens Symbia T16 and Intevo Bold gamma camera was used with a 128 × 128 matrix over 3 bed positions at each time point (including head/neck, abdomen, and pelvis region). The energy window was set at 20% around 208 keV with a lower scatter window of 20% around 170 keV. The SPECTs were reconstructed with a 3D-OSEM algorithm (6 iterations and 16 subsets) with CT-based attenuation and scatter correction (Siemens Flash 3D software). Blood was drawn at 5, 30, 60, 120, and 180 minutes and 24, 48, 72, and 168 hours postinjection to perform blood dosimetry (19). During these same time points vital signs were recorded (blood pressure, heart rate, and temperature).

After administration of [177Lu]-PSMA, patients were monitored weekly at the outpatient clinic until 12 weeks after cycle two and at the end of the study (EOS; 24 weeks after cycle two), to evaluate tolerability, vital signs, and adverse events. Blood for hematology, chemistry, and PSA was drawn weekly to monitor toxicity and response. Quality-of-life questionnaires (EORTC-QLQ-C30) were filled in before and monthly after the first [177Lu]-PSMA injection, until three months after cycle 2. An end-of-study quality-of-life questionnaire was filled in 24 weeks after cycle two. The Supplementary Material includes a study flowchart.

Outcomes

The primary aim of this study was to evaluate the toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) and radiation doses to the target lesions and organs at risk. Secondary outcomes were patient-reported quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30; ref. 20), ADT-free survival, best PSA response from baseline according to Prostate Cancer Working Group 3 (PCWG3) criteria, and imaging response following RECIST 1.1 and the consensus statements on PSMA-PET/CT response assessment criteria in prostate cancer (21, 22).

Statistical analysis

Because of the explorative nature of this study, no sample size calculations were performed. All data was managed according to GCP requirements using EPIC Software and CastorEDC (https://www.castedc.com/). Dose calculations to tumor and organs at risk were performed by Hermes Medical Solutions dosimetry software (v2.0), using organ-based dosimetry and cubic or spherical tumor volumes. Data was analyzed by Graphpad Prism version 5.03 and R studio version 1.1.463.

Data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request.
Ethics approval and consent to participate
The study protocol was approved by the Medical Review Ethics Committee Arnhem-Nijmegen, the Netherlands (NL62774.091.17). All study participants provided informed consent before study entry.

Results
Patients
Between September 1, 2018 and September 23, 2019, 12 patients were screened; 10 of these patients were found eligible. Two patients were found ineligible as they exceeded the maximum allowed tumor volume (>10 metastases). All 10 patients received two cycles of $^{177}$Lu-PSMA. Baseline patient characteristics and administered dose of $^{177}$Lu-PSMA are summarized in Fig. 1. All patients underwent prior local treatment for their prostate cancer with either surgery and/or EBRT. None of the patients received ADT within one year before study inclusion.

Toxicity
All injections of $^{177}$Lu-PSMA were well tolerated (see Table 1). No significant changes were observed in temperature, blood pressure, or heart rate following injection. Seven of the 10 patients developed grade I–II fatigue (with only 1 patient grade II fatigue) after injection which resolved within 2–4 weeks. Two of 10 patients (patient #8 and #9) reported a brief grade 1 xerostomia after treatment injection. Twelve weeks after cycle two and at EOS, none of the patients reported xerostomia or lacrimal gland toxicity. Patient #2 had a minor rash at the injection site which disappeared without interventions within three days, which was deemed to be most likely related to the adhesive band-aid and not to $^{177}$Lu-PSMA. Patient #4, who had pain at baseline originating from bone metastases, reported brief pain increment following both cycles, with all pain finally disappearing four weeks after cycle two. At 21 weeks following cycle 2, he started ADT due to recurrence of pain progression.

No treatment-related laboratory (hematology, kidney, or liver function) adverse events were observed in any of the 10 patients during the weekly blood evaluation. No major changes were observed in the quality of life of the patients pre- and posttreatment (Fig. 2). The Supplementary Data provides a detailed table of the completed EORTC-QLQ-C30 questionnaires.

Dosimetry
$^{177}$Lu-PSMA was rapidly eliminated from the blood with >90% and >99% excreted within approximately 24 and 48 hours, respectively. According to the dose calculations, the salivary glands, kidneys, liver, and bone marrow were not at risk with a median total organ dose of 3.4 Gy (range 1.2–5.9 Gy), 4.3 Gy (range 3.1–6.1 Gy), 0.8 Gy (range 0.6–1.1 Gy), and 0.15 Gy (range 0.1–0.2 Gy), respectively. All target lesions had a higher $^{177}$Lu-PSMA uptake compared with the healthy organs with a median dose of 12.7 Gy (range 4.6–48.7 Gy). All doses in Gy/GBq to the organs at risk and target lesions are specified in the Supplementary Material.

Table 1. Adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade I–II attributed to $^{177}$Lu-PSMA</th>
<th>Grade ≥III attributed to $^{177}$Lu-PSMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7 (70%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>2 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Data are n (%).
aPossibly, probably, or definitely according to the CTCAE v4.03. A table with all adverse events, including those unrelated to $^{177}$Lu-PSMA, are given in the Supplementary Data.

Figure 1.
Patient characteristics and applied treatments of all 10 patients. Columns from left to right: Age, in years; GS, Gleason score; PSA, prostate-specific antigen at study inclusion in µg/L; DT, PSA doubling time in months; PET, number of metastases on baseline 68Ga-PSMA-PET/CT scan; Inj. dose, injected activity of $^{177}$Lu-PSMA in gigabecquerel. In the swimmers plot, progressive disease (PD) is defined as initiation of any androgen deprivation therapy (ADT). Those still without ADT are considered having an ongoing response (OR). The black dot indicates study inclusion.
Response

All 10 patients showed altered PSA kinetics as shown in Fig. 3. At EOS, 5 patients had response of serum PSA >50% (patients #1, #3, #5, #8, and #9), of which 1 patient had an undetectable PSA (patient #8). Two patients remained stable in PSA (patients #6 and #10) and 3 patients had PSA progression compared with the baseline measurement (patients #2, #4, and #7). In 3 patients, the PSA was still decreasing at EOS (patients #5, #8, and #9), whereas in 6 patients (patients #1, #2, #3, #4, #7, and #10) the PSA had started rising again. After the first treatment injection, 8 patients (patients #1–3, #6, #7, #9, and #10) had a brief surge in PSA, which declined after a maximum of 5 weeks.

At the end of the study, 6 patients still showed a radiologic response on PSMA-PET imaging and had a stable, partial, or complete response on PSMA-PET, whereas 4 patients had progressive disease (Table 2). The PSMA-PET images of the best responding patients in PSA (patients #1, #8, and #9) are presented in Fig. 4. Lymph node metastases appeared to have a better response on $^{177}$Lu-PSMA compared with bone metastases. Hence, patients (#1, #3, #5, #6, #8, and #9) with solely lymph node metastases had a better response compared with patients (#2, #4, #7, and #10) who also had bone metastases. The Supplementary Data provides a detailed description of all observed metastases, including the size of soft-tissue metastases and SUV$_{\text{max}}$ of all tumors as well as the SUV$_{\text{mean}}$ of the salivary glands and liver.

Discussion

Asymptomatic patients with low-volume mHSPC are increasingly seeking alternative therapies to defer from ADT-related side effects with negative impact on quality of life (4, 6–9). Hence, a growing number of studies are addressing treatment-related side effects as important trial outcomes (4, 6, 23, 24). Since the development of novel radioligands for PET imaging, salvage surgery or EBRT became an optional therapeutic approach in selected patients with low-volume mHSPC (3, 25, 26). However, not all patients are eligible for these treatments because of tumor location(s) and/or prior therapies. This raises the question whether these early-stage patients can benefit from therapeutic radioligands such as $^{177}$Lu-PSMA.

This study prospectively evaluated $^{177}$Lu-PSMA for the first time in low-volume mHSPCs and observed safety and tolerability in 10 patients. During the study, there were no grade III–IV treatment-related toxicities. Even the observed grade I–II toxicities (e.g., fatigue) subsided within a few weeks. Importantly, only 2 patients reported (very) mild xerostomia, which resolved spontaneously within 1 month after treatment. At the end of the study, none of the patients reported xerostomia or lacrimal gland toxicity. No liver, kidney, or bone marrow toxicity was seen during the weekly blood evaluations.

The outcomes regarding toxicity and quality of life are in concordance with the results from recent prospective trials as well as retrospective data from global compassionate-use programs, considering the poor health of the heavily pretreated patients with mCRPC in those studies (11–13, 27). We administered two cycles containing 3 and approximately 6 GBq $^{177}$Lu-PSMA with 8 weeks in between. This is a relatively low total amount of activity compared with the current standard protocol in end-stage patients with 4–6 cycles and 7.4 GBq per administration (11). The minimal observed toxicity may also be related to the low administered total activity. However, according to the dosimetry results of this study, a higher amount of activity should be safe and is therefore feasible.

After each treatment cycle, a comprehensive 3-D dosimetry protocol was carried out to calculate the delivered doses to the tumor(s) and the organs at risk, including blood collections to evaluate bone marrow dose. This state-of-the-art dosimetry protocol precluded the...
Table 2. Radiographic response.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>C1W8</th>
<th>C2W12</th>
<th>C2W24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>4</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>8</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>9</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>10</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
</tr>
</tbody>
</table>

Note: This table shows the PSMA-PET imaging response after two cycles of 177Lu-PSMA. The Supplementary Data provide a detailed description of all observed metastases, including SUV<sub>max</sub> and the size of soft tissue metastases. Imaging response was evaluated following RECIST 1.1 and the consensus statements on PSMA-PET response assessment criteria in prostate cancer (21, 22). A disappearance of all lesions was considered a complete response (CR). A 20% increase of size (or SUV<sub>max</sub> for bone) over baseline or the appearance of a new lesion was found to be progressive disease (PD). Thirty percent decrease in size (or SUV<sub>max</sub> for bone) was considered partial response (PR). Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD was treated as stable disease (SD).

Abbreviations: C1W8: cycle one, week 8; C2W12: cycle two, week 12; C2W24: cycle two, week 24; SUV<sub>max</sub>: maximum standardized uptake value.

*Patient #4 was taken off the study after 21 weeks because of clinical progression.

need for a dose-escalation study. We observed that the tumor target lesions (median 12.7 Gy; range 4.6–48.7 Gy) received a 4–6 times higher radiation dose compared with the kidneys and salivary glands, being the critical dose-limiting organs. The salivary glands received a median cumulative dose of 3.4 Gy (range 1.2–5.9 Gy), which was well below the reported organ threshold dose of 35 Gy (28). This threshold, however, relates to EBRT because the organ limitations for 177Lu-PSMA are yet unresolved. This also applies to the kidneys (radiation dose in this study: median 4.3 Gy; range 3.1–6.1 Gy), which has an organ limitation dose of 40 Gy according to the recent 177Lu-PSMA guideline (28). The dosimetry outcomes in this study are comparable with the results in patients with high-volume mCRPC implying that the sink-effect with unfavorable radioligand distribution to the organs at risk in low-volume disease is of less concern than anticipated (29–31). Nonetheless, long-term toxicities, which could develop over time, need evaluation in following studies.

In accordance to the inclusion criteria, all patients had a PSA doubling time < 6 months prior to the study and showed stabilization of the PSA velocity after two cycles as seen in Fig. 3. Five of the 10 patients showed a PSA decline >50%. At the end of the study, PSA was still decreasing in 3 patients, of which 1 patient had a biochemical complete response. The PSA responses observed in this study are similar to those reported by Ost and colleagues after salvage EBRT (4). Eight of 10 patients had a brief surge in PSA after the first therapeutic injection of 177Lu-PSMA, which may implicate a flare phenomenon after 177Lu-PSMA. This has also been described after EBRT, 223RaCl₂, chemotherapy, and novel ADTs (32–37).

There were two imaging findings that were remarkable. One patient (patient #1) showed a complete response on PSMA-PET. The treated lymph node in this patient was not detectable on the follow-up PSMA-PET scans (Fig. 4). The other interesting observation was that several tumors (patients #5, #6, #8, and #9) were in regression on the PSMA-PET at the end of the study. This may suggest that 177Lu-PSMA could

Figure 4. PSMA-PET before and 6 months after 177Lu-PSMA of the three best responding patients. A and C, Axial image and MIP, respectively, from the baseline PSMA-PET of patient #1 showing a 10 mm para-rectal lymph node positive in PSMA uptake. B and D, Axial image and MIP, respectively, of the PSMA-PET 24 weeks after cycle two, showing a complete response in patient #1. E and G, Axial image and MIP, respectively, from the baseline PSMA-PET of patient #8 showing two lymph node metastases (para-aortal (10.9 mm) and at the carina of the trachea (11.6 mm)) with high PSMA uptake. F and H, Axial image and MIP, respectively, of the PSMA-PET at EOS of patient #8, showing a complete response in the lymph node next to the aorta and a partial response of the lymph node in proximity of the carina of the trachea (4 mm). I and K, Axial image and MIP, respectively, from the baseline PSMA-PET of patient #9 showing four pelvic lymph node metastases. J and L, Results at EOS; patient #9 had a partial response of the biggest lymph node, while all others were not visible anymore on PSMA-PET. Note the urinary 68Ga-PSMA uptake in the left ureter. A red arrow indicates a metastasis. An orange arrow presents a partial response, whereas a green arrow demonstrates a complete response. A yellow arrow points out urinal uptake of 68Ga-PSMA-11 in the ureter. EOS, end of study; MIP, maximum intensity projection.
have a prolonged genotoxic effect to the tumors with tracer uptake, or that 177Lu-PSMA could induce an immunogenic cell death.

After two cycles of 177Lu-PSMA therapy, the median ADT-free survival of all 10 patients was 9.5 months (range 6.5–21 months) with 6 patients still deferring from hormonal treatments. Thus far, the ADT-free survival is less than reported after salvage EBRT or surgery (e.g., STOMP trial: median 21 months; 80% CI, 14–29 months) but can be related to the shorter follow-up time of our study [10.6 months (range, 8.3–21 months); refs. 4, 9, 38]. Moreover, this study included a patient cohort with higher tumor volume, higher Gleason score, and higher PSA velocity compared with those reports. Besides, most patients were already pretreated with salvage EBRT or surgery. Therefore, the observation and comparison with literature has its limitations.

Even though our findings regarding both toxicity and efficacy are performed in a small cohort of selected patients, the results indicate a potential favorable role for 177Lu-PSMA in patients with hormone-sensitive prostate cancer with low-volume metastatic disease and good PSA uptake on PET imaging. At least 6 patients had long-lasting PSA responses, especially considering their initial short PSA doubling time. All patients showed only minimal low-grade toxicity after two cycles of 177Lu-PSMA, with promising tumor to organ radiation dose. Therefore, we assume that higher treatment activity dosages or more treatment cycles are now feasible, with potentially better results. These findings encourage larger prospective studies to provide stronger evidence for the effect of 177Lu-PSMA in patients with low-volume mHSPC. To investigate this, we recently initiated a randomized controlled multicenter phase II study in the same patient cohort, administering two cycles of 7.4 GBq 177Lu-PSMA in a 6-week interval (NCT04443062; ref. 39).

Conclusion

177Lu-PSMA appeared to be a feasible and safe treatment modality in ten patients with low-volume mHSPC. Although the patients were treated with a relatively low dose of 177Lu-PSMA, the majority of patients showed a promising response to this therapy. This supports the need for following trials to further evaluate the efficacy of 177Lu-PSMA in low-volume metastatic disease as well as in HSPC.

Authors’ Disclosures

B.M. Privé reports grants from Dutch Prostate Cancer Foundation and grants from Radboud Oncology Foundation during the conduct of the study. S.M.B. Peters reports grants from Radboud Oncology Fonds and grants from Prostaatkankerstichting during the conduct of the study; I.M. van Oort also reports grants from Astellas, Janssen, Bayer, and Bristol-Myers Squibb, IMS Health/QiVua, and Janssen-Cilag, as well as personal fees from Novartis. No disclosures were reported by the other authors.

Authors’ Contributions

B.M. Privé: Conceptualization, resources, data curation, software, formal analysis, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. S.M.B. Peters: Data curation, software, formal analysis, validation, methodology, writing–original draft, project administration, writing–review and editing. C.H.J. Muselaers: Conceptualization, resources, validation, methodology, writing–original draft, project administration, writing–review and editing. I.M. van Oort: Resources, methodology, writing–original draft, writing–review and editing. M.J.R. Janssen: Resources, validation, methodology, writing–original draft, writing–review and editing. J.P.M. Sedelaar: Resources, writing–original draft, writing–review and editing. M.W. Konijnenberg: Software, writing–original draft, writing–review and editing. P. Žaměncik: Resources, methodology, writing–review and editing. M.J.M. Uijen: Resources, writing–original draft, writing–review and editing. M.G.M. Schilham: Resources, writing–original draft, writing–review and editing. A. Eek: Resources, funding acquisition, writing–review and editing. T.W.J. Scheenen: Resources, funding acquisition, methodology, writing–review and editing. J.F. Verziijlbergen: Resources, supervision, funding acquisition, methodology, writing–original draft, writing–review and editing. W.R. Gerritsen: Resources, supervision, methodology, writing–original draft, writing–review and editing. N. Mehra: Resources, methodology, writing–original draft, writing–review and editing. J. Nagarajah: Resources, data curation, software, methodology, writing–review and editing. S. Heskamp: Data curation, software, methodology, writing–review and editing. J.A. Witjes: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, visualization, methodology, writing–original draft, writing–review and editing. J. Nagarajah: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, visualization, methodology, writing–original draft, writing–review and editing.

Acknowledgments

We thank all the investigators of the study, the patients, and their families. This work was supported by Radboud Oncology Foundation and the Dutch Prostate Cancer Foundation (Prostaatkankerstichting).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 2, 2020; revised March 25, 2021; accepted April 16, 2021; published first April 21, 2021.

References

Clinical Cancer Research

Lutetium-177-PSMA-617 in Low-Volume Hormone-Sensitive Metastatic Prostate Cancer: A Prospective Pilot Study


Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-20-4298

Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2021/04/21/1078-0432.CCR-20-4298.DC1

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/early/2021/05/14/1078-0432.CCR-20-4298. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.