Influence of short-term dexamethasone on the efficacy of $^{177}$Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer

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Abstract

Background and Aim: Corticosteroids alone or in combination therapy are associated with favorable biochemical responses in metastatic castration-resistant prostate cancer (mCRPC). We speculated that the intermittent addition of dexamethasone may also enhance the antitumor effect of radioligand therapy (RLT) with $^{177}$Lu-prostate-specific membrane antigen (PSMA)-617.

Patients and Methods: Seventy-one patients with mCRPC were treated with 1 to 5 cycles of $^{177}$Lu-PSMA-617 (6.0-7.4 GBq per cycle) at 6 to 8 weeks intervals. Based on the clinical decision (eg, in the case of vertebral metastases), 56% of patients received 4 mg of dexamethasone for the first 5 days of each cycle. Biochemical response rates, PSA decline and progression-free survival (PFS) were analyzed after one, three, and five cycles of RLT.

Results: PSA response rates were not significantly different between patients receiving $^{177}$Lu-PSMA-617 plus dexamethasone and those receiving $^{177}$Lu-PSMA-617 alone after one, three, and five cycles (33% vs 39%, $P = .62$; 45% vs 45%, $P = 1.0$; and 38% vs 42%, $P = .81$). However, there was a nonsignificant trend for a more pronounced PSA decline in patients with bone metastases receiving adjunct dexamethasone ($-21\% \pm 50\%$ vs $+11\% \pm 90\%$, $P = .08$; $-21\% \pm 69\%$ vs $+22\% \pm 116\%$, $P = .07$; $-13\% \pm 76\%$ vs $+32\% \pm 119\%$, $P = .07$). Median PFS tended to be longer in patients with bone metastases receiving $^{177}$Lu-PSMA-617 plus dexamethasone (146 vs 81 days; hazard ratio: 0.87 [95% confidence interval: 0.47-1.61]; $P = .20$). Multiple regression analysis showed that age ($P = .0110$), alkaline phosphatase levels ($P = .0285$) and adjunct dexamethasone ($P = .0285$) were independent predictors of changes in PSA in patients with bone metastases.
Conclusions: We observed high response rates to $^{177}$Lu-PSMA-617 RLT in men with mCRPC. The short-term addition of dexamethasone to $^{177}$Lu-PSMA-617 had no striking antitumor effect but might enhance biochemical responses in patients with bone metastases. Future trials are warranted to test this hypothesis in a prospective setting.

**KEYWORDS**
glucocorticoids, prostate-specific membrane antigen (PSMA), PSMA-617, steroids, therapy

1 | INTRODUCTION

Prostate cancer is the most common cancer among males in developed countries, and one of the most common causes of cancer-related death. A substantial number of patients eventually develop metastatic castration-resistant prostate cancer (mCRPC). Although there is an increasing number of treatment options for men with mCRPC, patients subsequently progress, underlining the clinical need for effective therapies for patients who progress after standard treatments.

Small molecule inhibitors targeting the prostate-specific membrane antigen, such as prostate-specific membrane antigen (PSMA)-617 or PSMA I&T, have recently gained increased interest for both imaging and therapy of prostate cancer. Both retrospective and prospective studies have reported favorable biochemical and imaging responses to $^{177}$Lu-labelled PSMA ligands. In a recent phase 2 study, Hofman et al. demonstrated that $^{177}$Lu-PSMA-617 can induce a PSA decline of ≥50% in 57% of mCRPC patients, with limited toxic effects. However, a substantial number of patients will not respond to $^{177}$Lu-PSMA-617, or eventually progress, underlining an unmet clinical need for enhancing the antitumor effect of this therapy.

Historically, glucocorticoids have been extensively used alone or in combination chemotherapy of advanced prostate cancer, and are currently administered routinely with both docetaxel and abiraterone to prevent side effects. Importantly, low doses of oral dexamethasone have also been shown to be effective in the treatment of hormone-refractory prostate carcinoma, being able to induce significant biochemical responses, including declines in the serum PSA level of ≥50% in selected patients. Induction of the glucocorticoid receptor (GR) in prostate cancer cells decreases expression and inhibits the activity of the MAP-kinases and numerous transcription factors including nuclear factor-kappa B, p53, and STAT1, suggesting that GR functions as a tumor suppressor in prostate.

Pretreatment with corticosteroids has been empirically used to prevent tumor swelling that may cause compressive symptoms and pain in patients undergoing radionuclide treatment. When beginning with $^{177}$Lu-PSMA-617 radioligand therapy (RLT; and in the absence of experience with the potency of this specific RLT), we routinely administered corticosteroids in selected patients. To our knowledge, there are no data evaluating if the addition of dexamethasone to $^{177}$Lu-PSMA-617 can enhance PSA declines and increase biochemical response rates. We, therefore, retrospectively analyzed all patients who had undergone $^{177}$Lu-PSMA-617 therapy at our institution, where two subgroups of patients were readily available, that is, one subgroup which had received adjunct dexamethasone for the first days of each cycle based on clinical decision to prevent potential side effects, and another subgroup who had received $^{177}$Lu-PSMA-617 alone.

2 | PATIENTS AND METHODS

2.1 | Study population

A total of 71 patients (72.4 ± 7.1 years; range: 58-87 years) who were referred for a $^{177}$Lu-PSMA-617 RLT between October 2016 and February 2019 were included in this retrospective analysis. All patients suffered from mCRPC and had demonstrated progression following standard systemic therapies including androgen-deprivation therapy and second-line novel hormonal agents (abiraterone/enzalutamide), and had progressed following taxane-based chemotherapy, were unfit for chemotherapy or declined chemotherapy. Patients did not receive $^{177}$Lu-PSMA-617 RLT if they had poor bone marrow reserve (leucocyte count < $3 \times 10^{9}$/L, platelet count <75.000 3 × 10^{9}/L, hemoglobin <8 g/dL), severe renal insufficiency (eGFR <45 mL/minute/1.73m²), severely reduced liver function, Karnofsky performance status scale ≤50%, upper urinary tract obstruction as determined by renal scan, or absent PSMA expression as determined by $^{68}$Ga-PSMA ligand PET. Details on patient characteristics are summarized in Table 1. All interventions were performed in the course of the clinical diagnostic and therapeutic workup of patients. $^{177}$Lu-PSMA-617 was administered in compliance with the Declaration of Helsinki, §37 and the German Medicinal Products Act, AMG 513.2b. The institutional review board approved this retrospective study (No. 8148_BO_K_2018). All patients provided written informed consent for the retrospective data analysis.

2.2 | GMP-compliant preparation of the PSMA-targeting ligand $^{177}$Lu-PSMA-617

Lutetium-177 was purchased from Isotope Technologies Garching GmbH (Germany) as GMP-certified $^{177}$Lu-LuCl₃ in 0.04M HCl-solution (EndolucinBeta, 40 GBq/mL) in no carrier added (n.c.a.) quality.
The precursor PSMA-617 was obtained from Endocyte/ABX (USA/Germany) in GMP quality. The radiosynthesis was performed on a Gaia/Luna GMP automated radiosynthesizer (Elysia-raytest GmbH, Germany) using a sterile, single-use cassette, and reagent kit (ABX, Germany). Per patient dose, 100 to 125 µg PSMA-617 precursor was dissolved in 800 µL buffer solution (gentisic acid/sodium ascorbate/HCl). Between 7.0 and 9.0 GBq $^{177}$Lu-$^{177}$LuCl$_3$ per patient was provided in the sterile, rubber-sealed delivery vial (10 mL), which served as a reaction vessel in the automated process. The $^{177}$Lu-labelling step was conducted at 95°C for 30 minutes. The product solution was transferred into a product vial via a sterile filter and diluted by 10 to 15 mL 0.9% NaCl. Patient doses were calculated and dispensed into 50 mL syringes with the addition of 0.9% NaCl by a self-designed automated dispensing system. The radiosynthesizer and the dispensing system were both housed in a laminar airflow class-A glovebox under controlled conditions.

RadioHPLC as primary quality control was performed on a Merck HPLC system equipped with two L-7100 pumps, an L-7200 autosampler, an L-7400 UV/Vis detector, a D-7000 interface d-line and a GABI radiodetector (Elysia-raytest, Germany), and a Gemini C18, 5 µm, 100 Å column (250 x 4.6 mm) (Phenomenex, Germany). As eluent phosphate buffer (pH 2) and methanol were used in a gradient system at a flow of 0.6 mL/minute. Production batches were further tested for pH, sterility, endotoxins, and radionuclide purity (gamma spectroscopy). $^{177}$Lu-PSMA-617 was always of flawless quality with radiochemical purity of $\geq95\%$ and a peptide content of 14.3 to 15.6 µg/GBq.

### TABLE 1 Characteristics of the study population (n = 71)

| Parameter                        | $^{177}$Lu-PSMA-617 plus dexamethasone | $^{177}$Lu-PSMA-617 | P       | Total study population |
|----------------------------------|----------------------------------------|---------------------|---------|------------------------|
| Number (n)                       | 40 (56%)                               | 31 (44%)            | ...     | 71 (100%)              |
| Age, y                           | 72.3 ± 7.3 (58-87)                     | 72.5 ± 7.0 (60-86)  | .92     | 72.4 ± 7.1 (58-87)     |
| Gleason grade                    |                                        |                     |         |                        |
| Mean ± SD (range)                | 8 (6-10)                               | 8 (6-10)            | .69     | 8 (6-10)               |
| PSA at C1D1, ng/mL               |                                        |                     |         |                        |
| Mean ± SD (range)                | 473 ± 658 (2-3187)                     | 240 ± 580 (3-3205)  | .02     | 372 ± 632 (2-3205)     |
| Hemoglobin, g/dL                 |                                        |                     |         |                        |
| Mean ± SD (range)                | 11.3 ± 1.7 (7.3-14.5)                  | 12.4 ± 1.7 (8.2-15.8)| .005    | 11.7 ± 1.8 (7.3-15.8)  |
| Leukocyte count, $10^3$/µL       |                                        |                     |         |                        |
| Mean ± SD (range)                | 7.4 ± 2.3 (3.2-13.7)                   | 6.9 ± 2.2 (3.7-13.4)| .32     | 7.1 ± 2.3 (3.2-13.7)   |
| Platelet count, $10^3$/µL        |                                        |                     |         |                        |
| Mean ± SD (range)                | 224 ± 70 (107-410)                     | 255 ± 77 (153-442)  | .07     | 237 ± 75 (107-442)     |
| Alkaline phosphatase, U/L        |                                        |                     |         |                        |
| Mean ± SD (range)                | 236 ± 290 (58-1596)                    | 142 ± 136 (40-621)  | .01     | 196 ± 240 (40-1596)    |
| Serum creatinine, µmol/L         |                                        |                     |         |                        |
| Mean ± SD (range)                | 85 ± 22 (43-135)                       | 89 ± 26 (49-197)    | .32     | 87 ± 24 (43-197)       |
| Site of metastases (no. of patients) |                                  |                     |         |                        |
| Bone                             | 39 (98%)                               | 22 (71%)            | .0018   | 61 (86%)               |
| Lymph nodes                      | 32 (80%)                               | 26 (84%)            | .76     | 58 (82%)               |
| Liver                            | 9 (23%)                                | 4 (13%)             | .37     | 13 (18%)               |
| Lung                             | 3 (8%)                                 | 3 (10%)             | 1.0     | 6 (8%)                 |
| Other                            | 6 (15%)                                | 7 (23%)             | .54     | 13 (18%)               |
| Previous therapy (no. of patients) |                                  |                     |         |                        |
| Androgen-deprivation therapy     | 40 (100%)                              | 31 (100%)           | 1.0     | 71 (100%)              |
| Abiraterone acetate              | 21 (53%)                               | 14 (45%)            | .63     | 35 (49%)               |
| Enzalutamide                     | 26 (65%)                               | 15 (48%)            | .23     | 41 (58%)               |
| Chemotherapy                     | 32 (80%)                               | 22 (71%)            | .41     | 54 (76%)               |
| Docetaxel (1st line)             | 32 (80%)                               | 22 (71%)            | .41     | 54 (76%)               |
| Cabazitaxel (2nd line)           | 8 (20%)                                | 1 (3%)              | .07     | 9 (13%)                |
| Carboplatin (2nd/3rd line)       | 3 (8%)                                 | 4 (13%)             | .69     | 7 (10%)                |
| External radiation therapy       | 26 (65%)                               | 19 (61%)            | .81     | 45 (63%)               |

Note: Bold values indicate statistical significance (P < .05).
Abbreviations: C1D1, cycle 1 day 1; SD, standard deviation.
2.3 | \textbf{\textsuperscript{177}Lu-PSMA-617 RLT}

Patients received 6.0 to 7.4 GBq of \textsuperscript{177}Lu-PSMA-617 every 6 to 8 weeks by slow intravenous injection over 5 minutes. Before \textsuperscript{177}Lu-PSMA-617 administration, patients were intravenously hydrated (0.5 L of NaCl 0.9%). Afterward, intravenous hydration was continued (1 L of NaCl 0.9%), and they were encouraged to consume at least 1.5 L of oral fluids each day after \textsuperscript{177}Lu-PSMA-617 administration. Ice packs were used for 4 hours to minimize uptake in salivary glands after \textsuperscript{177}Lu-PSMA-617 administration. Based on the clinical decision (eg, in case of vertebral metastases involving the posterior vertebral body, or neuroforaminal infiltration), a total of 40 (56%) of 71 patients received adjunct dexamethasone at a dose of 4 mg for the first 5 days of each cycle to prevent treatment-related edema and potential spinal cord compression. \textsuperscript{177}Lu-PSMA-617 treatment was repeated every 6 to 8 weeks until progression. PSA levels and additional laboratory parameters (including full blood count, liver function parameters, serum creatinine levels, and alkaline phosphatase) were re-evaluated every 2 weeks. In addition, a \textsuperscript{68}Ga-PSMA ligand PET/CT scan was performed before cycles 3 and 5 for evaluation of treatment response.

2.4 | Assessment of treatment response and toxicity

Treatment response was defined as a PSA response rate according to Prostate Cancer Clinical Trials Working Group 2 criteria defined as a 50% or more PSA decline from baseline with confirmation 3 to 4 weeks apart.\textsuperscript{25} PSA response rate and the percentage PSA decline after 1 cycle (ie, at cycle 2 day 1), 3 (ie, at cycle 4 day 1) and 5 (ie, at cycle 6 day 1) cycles were compared between patients receiving either \textsuperscript{177}Lu-PSMA-617 plus dexamethasone or \textsuperscript{177}Lu-PSMA-617 alone. A cycle was completed, if patients proceeded to the next cycle (ie, completion of cycle 3 at cycle 4 day 1). Data were analyzed on an intention-to-treat basis. In patients who discontinued RLT, the PSA level at the termination of therapy was used for further analyses.

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (version 4.03).

2.5 | Assessment of progression-free survival

Progression-free survival (PFS) was compared between patients receiving either \textsuperscript{177}Lu-PSMA-617 plus dexamethasone or \textsuperscript{177}Lu-PSMA-617 alone. Progression was defined as the fulfillment of at least one of the following criteria: (a) PSA progression of more than 25% and more than 2 ng/mL\textsuperscript{26} (b) appearance of at least two new lesions on \textsuperscript{68}Ga-PSMA-ligand PET/CT performed for re-evaluation before cycles 3 and 5 (modified according to Scher et al\textsuperscript{27}), (c) death, or (d) rapid deterioration of performance status leading to termination of RLT. Time-to-progression after commencing RLT was recorded for all patients. Patients without progression were censored at day 336 of follow-up (five full cycles plus 8-week follow-up) to standardize the follow-up interval. Overall survival could not be reasonably compared between groups because of the low number of recorded events during follow-up.

2.6 | Statistical analysis

Categorical variables are presented with absolute and relative frequencies. Continuous variables are expressed as mean ± standard deviation and 95% confidence intervals (CI). PSA-stratified response rates were calculated, and corresponding CIs were calculated using the modified Wald method. The student t test was used to compare differences in PSA levels between treatment groups. Fisher’s exact test was used to evaluate the relationship between adjunct dexamethasone and treatment response. Waterfall plots were used to visualize the relationship between PSA response and the prevalence of adjunct dexamethasone. Scatter graphs were used to visualize differences in PSA decline between groups. Survival curves were created using the Kaplan-Meier method, and data were compared using the log-rank test. Simple linear regression and multiple linear regression analyses were performed to identify clinical, blood-based and imaging-based predictors of change in PSA. Statistical significance was established for P values of <.05. Statistical analysis was performed using GraphPad QuickCalcs and GraphPad Prism (version 6.0 and 8.30 for Windows; Graphpad Software).

3 | RESULTS

Relevant baseline characteristics of the study cohort are shown in Table 1 (total study population) and Table 2 (patients with bone metastases). All 71 patients received at least one cycle of \textsuperscript{177}Lu-PSMA-617, and 46 (65%) and 25 (35%) completed cycles 3 and 5, respectively. The reasons for not completing all cycles are shown in Figure 1.

3.1 | Addition of dexamethasone does not significantly improve the overall response to \textsuperscript{177}Lu-PSMA-617 RLT but might enhance responses in selected patients with bone metastases

3.1.1 | Evaluation at cycle 2 day 1

A total of 13 of 40 (33%) patients receiving adjunct dexamethasone and 12 (39%) of the 31 remaining patients achieved a PSA decline of 50% or more after one cycle (P = .62) (Figure 2). Mean PSA decline was −20% ± 49% (95% CI: −36% to −4%) in patients receiving \textsuperscript{177}Lu-PSMA-617 plus dexamethasone, whereas PSA decreased by −8% ± 83% (95% CI: −39% to +23%) in patients receiving \textsuperscript{177}Lu-PSMA-617 alone (P = .45). There was a trend toward improved responses in patients with bone metastases receiving \textsuperscript{177}Lu-PSMA-617 plus dexamethasone (−21% ± 50% [95% CI: −37% to −4%] vs +11% ± 90% [95% CI: −28% to +51%], P = .08).
3.1.2 | Evaluation at cycle 4 day 1

A total of 18 of 40 (45%) patients receiving adjunct dexamethasone and 14 (45%) of the 31 remaining patients achieved a PSA decline of 50% or more after three cycles \((P = 1.0)\) (Figure 3). Mean PSA decline was \(-20\% \pm 68\%\) (95% CI: \(-42\%\) to +1%) in patients receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone, whereas PSA decreased by \(+4\% \pm 108\%\) (95% CI: \(-43\%\) to +36%) in patients receiving \(^{177}\text{Lu-PSMA-617}\) alone \((P = .03)\). There was a trend toward improved response in patients with bone metastases receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone \((-21\% \pm 69\%\) [95% CI: \(-43\%\) to +1%] vs +22\% \pm 116\% [95% CI: +30% to +73%], \(P = .07\)).

3.1.3 | Evaluation at cycle 6 day 1

A total of 15 of 40 (38%) patients receiving adjunct dexamethasone and 13 (42%) of the 31 remaining patients achieved a PSA decline of 50% or more after five cycles \((P = .81)\) (Figure 3). Mean PSA decline was \(-13\% \pm 75\%\) (95% CI: \(-37\%\) to +11%) in patients receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone, whereas PSA increased by +5\% \pm 111\% (95% CI: \(-36\%\) to +46%) in patients receiving \(^{177}\text{Lu-PSMA-617}\) alone \((P = .42)\). There was a trend toward improved responses in patients with bone metastases receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone (-13\% \pm 76\% [95% CI: -38% to +11%] vs +32\% \pm 119\% [95% CI: -21% to +85%], \(P = .07\)).

### TABLE 2 Characteristics of patients with bone metastases \((n = 61)\)

| Parameter                                | \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone | \(^{177}\text{Lu-PSMA-617}\) | All patients with bone metastases |
|------------------------------------------|-----------------------------------------------|-----------------------------|----------------------------------|
| Number (n)                               | 39 (64%)                                      | 22 (36%)                    | 61 (100%)                        |
| Age, y                                   | Mean ± SD (range) 72.5 ± 7.2 (58-87)          | 71.9 ± 6.5 (61-86)          | 72.3 ± 6.9 (58-87)               |
| Gleason grade                            | 8 (6-10)                                      | 8 (7-10)                    | 8 (6-10)                         |
| PSA at C1D1, ng/mL                       | Mean ± SD (range) 457 ± 659 (2-3187)          | 259 ± 672 (3-3205)          | 385 ± 665 (2-3205)               |
| Hemoglobin, g/dL                         | Mean ± SD (range) 11.3 ± 1.6 (7.3-14.5)       | 12.3 ± 1.8 (8.2-15.8)       | 11.7 ± 1.8 (7.3-15.8)            |
| Leukocyte count, 10^3/μL                 | Mean ± SD (range) 7.2 ± 2.4 (3.2-13.7)        | 6.8 ± 2.2 (4.2-13.4)        | 7.1 ± 2.3 (3.2-13.7)             |
| Platelets, 10^3/μL                       | Mean ± SD (range) 221 ± 69 (107-410)          | 251 ± 84 (153-442)          | 232 ± 76 (107-442)               |
| Alkaline phosphatase, U/L                | Mean ± SD (range) 236 ± 290 (58-1596)         | 169 ± 152 (43-621)          | 213 ± 251 (43-1596)              |
| Site of metastases (no. of patients)     |                                               |                             |                                 |
| Bone                                     | 39 (100%)                                     | 22 (100%)                   | 61 (100%)                        |
| Lymph nodes                              | 31 (79%)                                      | 18 (82%)                    | 49 (80%)                         |
| Liver                                    | 9 (23%)                                       | 4 (18%)                     | 13 (21%)                         |
| Lung                                     | 3 (8%)                                        | 3 (14%)                     | 6 (10%)                          |
| Other                                    | 6 (15%)                                       | 4 (18%)                     | 10 (16%)                         |
| Previous therapy (no. of patients)       |                                               |                             |                                 |
| Androgen-deprivation therapy             | 39 (100%)                                     | 22 (100%)                   | 61 (100%)                        |
| Abiraterone acetate                      | 21 (54%)                                      | 9 (41%)                     | 30 (49%)                         |
| Enzalutamide                             | 26 (67%)                                      | 10 (45%)                    | 36 (59%)                         |
| Chemotherapy                             | 31 (79%)                                      | 15 (68%)                    | 46 (75%)                         |
| Docetaxel (1st line)                     | 31 (79%)                                      | 15 (68%)                    | 46 (75%)                         |
| Cabazitaxel (2nd line)                   | 8 (21%)                                       | 1 (5%)                      | 9 (15%)                          |
| Carboplatin (2nd/3rd line)               | 2 (5%)                                        | 3 (14%)                     | 5 (8%)                           |
| External radiation therapy               | 25 (64%)                                      | 12 (55%)                    | 37 (61%)                         |

Note: Bold values indicate statistical significance \((P < .05)\).
Abbreviations: C1D1, cycle 1 day 1; SD, standard deviation.
The addition of dexamethasone does not improve overall or early response to $^{177}$Lu-PSMA-617 RLT. Waterfall plots (left panel) and scatter graphs (right panel) showing the best PSA response (A and B) in patients receiving either $^{177}$Lu-PSMA-617 (grey bars) or $^{177}$Lu-PSMA-617 plus dexamethasone (green bars) and early PSA response at cycle 2 day 1 (C and D). Change in PSA from baseline is not significantly different between treatment groups ($P = .48$ and $P = .45$, respectively). RLT, radioligand therapy [Color figure can be viewed at wileyonlinelibrary.com]
3.1.4 | Best PSA response

A total of 19 of 40 (48%) patients receiving adjunct dexamethasone and 15 (48%) of the 31 remaining patients achieved a PSA decline of 50% or more \((P = 1.0)\) (Figure 2). Mean PSA decline was \(-34\% \pm 55\%\) (95% CI: \(-51\%\) to \(-16\%\)) in patients receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone, whereas PSA decreased by \(-21\% \pm 91\%\) (95% CI: \(-55\%\) to \(+12\%\)) in patients receiving \(^{177}\text{Lu-PSMA-617}\) alone \((P = .48)\). There was a trend toward improved responses in patients with bone metastases receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone \((-35\% \pm 56\%\) [95% CI: \(-53\%\) to \(-17\%\)] vs \(-1\% \pm 98\%\) [95% CI: \(-44\%\) to \(+43\%\)]\), \(P = .09\).

Patients with lymph node metastases \((P \geq .59\) in all cases) or visceral metastases \((P \geq .41\) in all cases) did not demonstrate improved responses when receiving adjunct dexamethasone. Detailed data on overall response rates and magnitude of PSA decline after one, three, and five cycles of \(^{177}\text{Lu-PSMA-617}\) are shown in Table 3. Examples of patients receiving \(^{177}\text{Lu-PSMA-617}\) with or without dexamethasone are shown in Figure 4.

The observed toxicity of \(^{177}\text{Lu-PSMA-617}\) was predominantly mild, and the addition of dexamethasone did not increase the incidence of adverse events. Of note, the \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone group had more severely reduced bone marrow reserve and more severe pre-existing liver damage (Table 4).

3.2 | Adjunct dexamethasone is an independent predictor of PSA change in patients with bone metastases

Simple linear regression analysis (Table 5) demonstrated that age \((P = .0035)\) and serum levels of alkaline phosphatase \((P = .0391)\) predicted PSA change at cycle 6 day 1 in patients with bone metastases receiving RLT. Adjunct dexamethasone demonstrated a borderline significant association with change in PSA \((P = .0740)\). Multiple regression analyses (Table 5) revealed that age \((P = .0110)\), levels of alkaline phosphatase \((P = .0380)\) and adjunct dexamethasone \((P = .0285)\) were independent predictors of change in PSA.

3.3 | PFS in patients receiving \(^{177}\text{Lu-PSMA-617}\) RLT with or without dexamethasone

Median PFS (Figure 5) was 138 days in patients receiving \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone, and 159 days in those receiving \(^{177}\text{Lu-PSMA-617}\) alone (hazard ratio [HR]: 1.23 [95% CI: 0.71-2.12]; \(P = 1.0\)). However, there was a nonsignificant trend for longer PFS in patients with bone metastases treated with \(^{177}\text{Lu-PSMA-617}\) plus dexamethasone \((146 \text{ vs } 81\) days; HR: 0.87 [95% CI: 0.47-1.61]; \(P = .20\)).
### Table 3
Overall response rates and magnitude of PSA decline after one, three, and five cycles of $^{177}$Lu-PSMA-617

| Treatment group                  | Cycle     | PSA decline (% of patients) | % | 95% CI (%) | % | 95% CI (%) | % | 95% CI (%) | % | 95% CI (%) | % | 95% CI (%) | % | 95% CI (%) |
|----------------------------------|-----------|-----------------------------|---|------------|---|------------|---|------------|---|------------|---|------------|---|------------|
|                                  |           | ≥90% |                        |   |      | ≥80% |                        |   |      | ≥70% |                        |   |      | ≥60% |                        |   |      | ≥50% |                        |   |      | Any PSA decline |   |      |
| $^{177}$Lu-PSMA-617 plus dexamethasone | Cycle 2 day 1 | 8   | 2.21 | 13  | 5.27 | 18  | 8.32 | 12  | 12.38 | 33  | 20.48 | 68  | 52.80 |
|                                  | Cycle 4 day 1 | 15  | 7.29 | 23  | 12.38 | 30  | 18.46 | 35  | 22.51 | 45  | 31.60 | 68  | 52.80 |
|                                  | Cycle 6 day 1 | 18  | 8.32 | 28  | 16.43 | 30  | 18.46 | 35  | 22.51 | 38  | 24.53 | 63  | 47.76 |
|                                  | Best response | 20  | 10.35 | 30  | 18.46 | 33  | 20.48 | 38  | 24.53 | 48  | 33.63 | 73  | 57.84 |
| $^{177}$Lu-PSMA-617               | Cycle 2 day 1 | 16  | 7.33 | 19  | 9.37 | 23  | 11.40 | 29  | 16.47 | 39  | 24.56 | 61  | 44.76 |
|                                  | Cycle 4 day 1 | 39  | 24.56 | 39  | 24.56 | 39  | 24.56 | 45  | 29.62 | 45  | 29.62 | 58  | 41.74 |
|                                  | Cycle 6 day 1 | 35  | 21.53 | 35  | 21.53 | 35  | 21.53 | 42  | 26.59 | 42  | 26.59 | 55  | 38.71 |
|                                  | Best response | 39  | 24.56 | 42  | 26.59 | 42  | 26.59 | 45  | 29.62 | 48  | 32.65 | 65  | 47.79 |
| Total study cohort               | Cycle 2 day 1 | 11  | 6.21 | 15  | 9.26 | 20  | 12.31 | 25  | 17.37 | 35  | 25.47 | 65  | 53.75 |
|                                  | Cycle 4 day 1 | 25  | 17.37 | 30  | 20.41 | 34  | 24.45 | 39  | 29.51 | 45  | 34.57 | 63  | 52.74 |
|                                  | Cycle 6 day 1 | 25  | 17.37 | 31  | 21.43 | 32  | 23.44 | 38  | 28.50 | 39  | 29.51 | 59  | 48.70 |
|                                  | Best response | 28  | 19.40 | 35  | 25.47 | 37  | 26.48 | 41  | 30.52 | 48  | 37.59 | 69  | 57.79 |

Abbreviations: CI, confidence interval; $^{177}$Lu, $^{177}$Lutetium; n, number; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

### Figure 4
Examples of patients receiving $^{177}$Lu-PSMA-617 RLT with or without dexamethasone. Post-therapeutic whole-body scan after one, three, and five cycles of RLT (A) and change in PSA levels over time (B) in a 77-year-old man receiving $^{177}$Lu-PSMA-617 and a 64-year-old man receiving $^{177}$Lu-PSMA-617 plus dexamethasone (C and D). RLT, radioligand therapy.
| Parameter                  | Pre-existing toxicity before therapy | AE occurring during therapy |
|---------------------------|--------------------------------------|-----------------------------|
|                           | 177Lu-PSMA-617 | 177Lu-PSMA-617 plus dexamethasone | 177Lu-PSMA-617 | 177Lu-PSMA-617 plus dexamethasone |
|                           | Grade 1-2 | Grade 3 | Grade 4 | Grade 1-2 | Grade 3 | Grade 4 | Grade 1-2 | Grade 3 | Grade 4 |
| Hematotoxicity            |            |        |        |            |        |        |            |        |        |
| Anaemia                   | 12 (39%)  | 0      | 0      | 31 (78%)  | 0      | 0      | 9 (29%)   | 0      | 0      |
| Leucopenia                | 0         | 0      | 0      | 1 (3%)    | 0      | 0      | 5 (16%)   | 0      | 0      |
| Lymphocytopenia           | 7 (23%)   | 2 (6%) | 0      | 13 (33%)  | 5 (13%)| 0      | 9 (29%)   | 0      | 0      |
| Thrombocytopenia          | 1 (3%)    | 0      | 0      | 8 (20%)   | 0      | 0      | 3 (10%)   | 0      | 0      |
| Hepatotoxicity            |            |        |        |            |        |        |            |        |        |
| Alanine aminotransferase increased | 3 (10%) | 0 | 0 | 3 (8%) | 0 | 0 | 3 (10%) | 0 | 0 |
| Aspartate aminotransferase increased | 8 (26%) | 0 | 0 | 14 (35%) | 0 | 0 | 5 (16%) | 0 | 0 |
| Gamma-glutamyltransferase increased | 5 (16%) | 0 | 0 | 15 (38%) | 1 (3%) | 0 | 0 | 0 | 0 |
| Renal toxicity            |            |        |        |            |        |        |            |        |        |
| Serum creatinine increased | 5 (16%) | 0 | 0 | 7 (18%) | 0 | 0 | 3 (10%) | 0 | 0 |
| Hyperkalemia              | 3 (10%)   | 0      | 0      | 5 (13%)   | 0      | 0      | 2 (6%)    | 0      | 0      |
| Xerostomia, xerophthalmia | 9 (29%)   | 0      | 0      | 6 (15%)   | 0      | 0      | 4 (13%)   | 0      | 0      |

Note: Data are n (%). Grade 1 to 2 adverse events occurring in ≥10% of the cohort and all grade ≥3 adverse events are presented. Abbreviations: AE, adverse event; 177Lu, 177Lutetium; PSMA, prostate-specific membrane antigen.
The administration of exogenous dexamethasone has been shown to improve treatment response in men with mCRPC, with notable PSA response rates ranging from 12% to 34% at a daily dose of 10 to 20 mg in case of prostate cancer, docetaxel, is frequently given in combination with prednisone based on the results of the TAX327 study in which patients in the docetaxel arm also received 5 mg of prednisone twice daily.24 Considerably higher PSA response rates have been observed using dexamethasone which appears more active than other corticosteroids in the treatment of CRPC, at least for the PSA endpoints. In 102 patients with progressive CRPC receiving oral dexamethasone (0.5 mg daily), a PSA response rate of 49% was observed,71.26 to 28.89 0.4007 and the median duration of the PSA response of 11.6 months. In another study, 62% of patients with hormone-refractory prostate carcinoma treated with oral dexamethasone (0.5-2.0 mg daily) demonstrated a PSA decline of ≥50%, which was confirmed by a second PSA value obtained ≥4 weeks later.6 It is important to note that dexamethasone has antitumor efficacy in prostate cancer beyond the suppression of adrenal androgen production. The cellular response to glucocorticoids is mediated through a specific GR that has a glucocorticoid-mediated signaling promotes differentiated state in PC cells where potential oncogenes are downregulated and the expression of tumor suppressor maspin is increased.18 Another study

| TABLE 5 | Results of regression analyses to identify predictors of treatment response in patients with bone metastases at C6D1 |
| Parameter | Simple regression analysis | | Multiple regression analysis | |
| | Estimate | SE | 95% CI | P | Estimate | SE | 95% CI | P |
| Age | -5.093 | 1.677 | -8.448 to -1.738 | .0035 | -4.490 | 1.705 | -7.906 to -1.073 | .0110 |
| Gleason grade | 18.28 | 12.56 | -6.910 to 43.46 | .1515 | ... | ... | ... | ... |
| Blood-based parameters | | | | | | | | |
| PSA at C1D1 | 0.002054 | 0.01865 | -0.03526 to 0.03937 | .9127 | ... | ... | ... | ... |
| Hemoglobin | -0.8372 | 5.345 | -11.53 to 9.857 | .8761 | ... | ... | ... | ... |
| Leukocyte count | -6.032 | 7.017 | -20.07 to 8.010 | .3935 | ... | ... | ... | ... |
| Platelet count | 0.004476 | 0.1637 | -0.3231 to 0.3321 | .9783 | ... | ... | ... | ... |
| Alkaline phosphatase | 0.1024 | 0.04847 | 0.005311 to 0.1994 | .0391 | 0.09696 | 0.04561 | 0.005548 to 0.1884 | .0380 |
| Lactate dehydrogenase | 0.005823 | 0.08036 | -0.1556 to 0.1672 | .9425 | ... | ... | ... | ... |
| Aspartate transaminase | 0.7970 | 0.5658 | -0.3355 to 1.930 | .1643 | ... | ... | ... | ... |
| Alanine transaminase | 0.7695 | 0.6305 | -0.4926 to 2.032 | .2273 | ... | ... | ... | ... |
| Serum creatinine | -0.8804 | 0.6133 | -2.108 to 0.3474 | .1566 | ... | ... | ... | ... |
| Site of metastases | | | | | | | | |
| Lymph nodes | -2.068 | 30.94 | -63.98 to 59.84 | .9469 | ... | ... | ... | ... |
| Liver | -9.740 | 30.031 | -69.79 to 50.31 | .7467 | ... | ... | ... | ... |
| Previous therapy | | | | | | | | |
| Androgen-deprivation therapy | ... | ... | ... | ... | ... | ... | ... | ... |
| Abiraterone acetate | 0.4580 | 24.60 | -48.77 to 49.69 | .9852 | ... | ... | ... | ... |
| Enzalutamide | 1.938 | 25.01 | -48.10 to 51.98 | .9385 | ... | ... | ... | ... |
| Chemotherapy | 18.08 | 28.47 | -38.88 to 75.03 | .5279 | ... | ... | ... | ... |
| External radiation therapy | -21.18 | 25.03 | -71.26 to 28.89 | .4007 | ... | ... | ... | ... |
| Current therapy | | | | | | | | |
| Dexamethasone | -45.34 | 24.92 | -95.21 to 4.537 | .0740 | -53.01 | 23.56 | -100.2 to -5.796 | .0285 |

Note: Bold values indicate statistical significance (P < .05). Abbreviations: C1D1, cycle 1 day 1; CI, confidence interval; SE, standard error.

4 | DISCUSSION

In the present study, we analyzed if the addition of dexamethasone to 177Lu-PSMA-617 RLT in men with mCRPC can improve treatment response in terms of PSA response rates. Adjunct dexamethasone 4 mg daily for 5 days at the beginning of each cycle did not significantly improve response rates after one, three, and five cycles in the total study population, and did not significantly improve PFS. However, our data support the hypothesis that the short-term addition of dexamethasone to 177Lu-PSMA-617 may enhance response in patients with bone metastases. These data provide a rationale for larger prospective studies to evaluate the effect of intermittent or continuous dexamethasone on clinically meaningful endpoints.

Corticosteroids have long been recognized as active agents in the treatment of mCRPC. The administration of exogenous corticosteroids suppresses the adrenal production of androgens, being a potential mechanism of action accounting for the efficacy seen in the treatment of patients with mCRPC. Notable PSA response rates (≥50% PSA decline) in CRPC have been observed using different corticosteroids in numerous prospective studies, ranging from 12% to 34% at a daily dose of 10 to 20 mg in case of prednisone. The standard chemotherapeutic agent in prostate cancer, docetaxel, is frequently given in combination with prednisone based on the results of the TAX327 study in which patients in the docetaxel arm also received 5 mg of prednisone twice daily. Considerably higher PSA response rates have been observed using dexamethasone which appears more active than other corticosteroids in the treatment of CRPC, at least for the PSA endpoints. In 102 patients with progressive CRPC receiving oral dexamethasone (0.5 mg daily), a PSA response rate of 49% was observed, and the median duration of the PSA response of 11.6 months. In another study, 62% of patients with hormone-refractory prostate carcinoma treated with oral dexamethasone (0.5-2.0 mg daily) demonstrated a PSA decline of ≥50%, which was confirmed by a second PSA value obtained ≥4 weeks later. It is important to note that dexamethasone has antitumor efficacy in prostate cancer beyond the suppression of adrenal androgen production. The cellular response to glucocorticoids is mediated through a highly specific GR that has a glucocorticoid-mediated signaling promotes differentiated state in PC cells where potential oncogenes are downregulated and the expression of tumor suppressor maspin is increased. Another study
Future trials should, therefore, also evaluate the efficacy of corticosteroids in prostate cancer. Indeed, 76% of patients in a study of patients with bone metastases treated with \(^{177}\)Lu-PSMA-617 plus dexamethasone (22, HR: 0.87 [95% CI: 0.47-1.61]; P = .20). CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RLT, radioligand therapy. [Color figure can be viewed at wileyonlinelibrary.com]

Dexamethasone demonstrated a PSA response after the first cycle, underlining the high efficacy of \(^{177}\)Lu-PSMA-617 RLT, and this trend, although observed over all three cycles, did not reach statistical significance, likely due to the fact that the number of patients within this study cohort was limited, affecting statistical power. Consistent with enhanced biochemical responses, we observed a trend for longer PFS in patients with bone metastases treated with \(^{177}\)Lu-PSMA-617 plus dexamethasone (146 vs 81 days; HR: 0.87 [95% CI: 0.47-1.61]; P = .20). Of note, multiple regression analysis demonstrated that adjunct dexamethasone was an independent predictor of change in PSA (P = .0285), further supporting the hypothesis that dexamethasone may enhance biochemical responses in patients with bone metastases.

The limited overall effect of dexamethasone in the setting of \(^{177}\)Lu-PSMA-617 therapy may be explained by the development of a glucocorticoid-resistant phenotype through progression on prior prednisone (coadministered with docetaxel). Weitzman et al have demonstrated that administration of 20 mg dexamethasone given every 6 hours for 1 day every 3 weeks does not increase the incidence of adverse events, although the number of patients within this study cohort was limited, affecting statistical power. Consistent with enhanced biochemical responses, we observed a trend for longer PFS in patients with bone metastases treated with \(^{177}\)Lu-PSMA-617 plus dexamethasone (146 vs 81 days; HR: 0.87 [95% CI: 0.47-1.61]; P = .20). Of note, multiple regression analysis demonstrated that adjunct dexamethasone was an independent predictor of change in PSA (P = .0285), further supporting the hypothesis that dexamethasone may enhance biochemical responses in patients with bone metastases.

The limited overall effect of dexamethasone in the setting of \(^{177}\)Lu-PSMA-617 therapy may be explained by the development of a glucocorticoid-resistant phenotype through progression on prior prednisone (coadministered with docetaxel). Indeed, 76% of patients in this study had previously progressed under docetaxel chemotherapy. Other studies have reported minimal efficacy postchemotherapy. In the control arm of the postchemotherapy COU-AA-301 study of abiraterone/prednisone vs prednisone-alone, patients receiving 10 mg prednisone daily had a PSA response rate of only 6% and a PFS of only 3.6 months, underlining that the single-agent activity of prednisone appears reduced when used postdocetaxel. Another potential explanation is the applied regimen of dexamethasone administration. Although the administered dose was relatively high compared to dexamethasone-alone studies, we only prescribed dexamethasone for the first 5 days of each cycle. The aforementioned studies on the antitumor efficacy of steroids applied a continuous regimen of drug administration. It is conceivable that short-term coadministration is not sufficient to augment \(^{177}\)Lu-PSMA-617 RLT in a clinically meaningful way. Indeed, Weitzman et al have demonstrated that administration of 20 mg dexamethasone given every 6 hours for 1 day every 3 weeks does not significantly contribute to the PSA response rate of estramustine and docetaxel, suggesting a schedule-dependent activity of dexamethasone. Future trials should, therefore, also evaluate the efficacy of a continuous dexamethasone regimen in mCRPC patients treated with \(^{177}\)Lu-PSMA-617. Of note, the addition of dexamethasone did not increase the incidence of adverse events, although the \(^{177}\)Lu-PSMA-617 plus dexamethasone group had a more severely reduced bone marrow reserve and more severe pre-existing liver damage.

Regarding the overall efficacy of \(^{177}\)Lu-PSMA-617 RLT in this study, the results are largely in line with previous studies. Rahbar et al reported a PSA decline of ≥50% in 45% of patients in their retrospective multicenter study, and a PSA response in 40% of patients after one cycle. Using a different PSMA ligand, Heck et al observed a PSA decline of ≥50% in 38% of patients receiving \(^{177}\)Lu-PSMA I&T. Hofman et al reported higher overall response PSA rates of 57% of patients, however, their study cohort was considerably smaller. In this study, a PSA decline of 50% or more was achieved in 48% of patients, and 35% of patients already demonstrated a PSA response after the first cycle, underlining the high efficacy of \(^{177}\)Lu-PSMA-617 in advanced mCRPC.

Some limitations should be acknowledged. First, the retrospective study nature may be associated with inherent limitations such as...
selection bias. Second, the included patients did not have a uniform pretreatment history. However, this reflects the clinical practice and can be explained by the fact that 177Lu-PSMA-617 RLT is typically indicated in advanced, heavily pretreated patients. Other studies have included similarly pretreated patient cohorts. Third, a prospective evaluation of symptomatic response, pain relief, and toxicity was not performed in this study. It cannot be excluded that the impact of dexamethasone on PSA endpoints will not translate into a clear effect on clinically meaningful endpoints. Fourth, medication with steroids may be associated with relevant side effects (e.g., osteoporosis), particularly in case of long-term administration, and a careful balance needs to be struck between potential beneficial effects and side effects of steroid use. Importantly, steroid use has been associated with short survival in certain combination therapies, for example, when given with enzalutamide. Finally, it would be desirable to evaluate GR expression in specimens of mCRPC patients in future studies and to integrate these data with biochemical response rates.

5 | CONCLUSION

We demonstrated high response rates to 177Lu-PSMA-617 RLT in men with mCRPC who had progressed after standard treatments. The short-term addition of dexamethasone to 177Lu-PSMA-617 may enhance responses in selected patients with bone metastases. Future larger trials are warranted to test this hypothesis in a prospective setting and to evaluate the potential effect of continuous corticosteroid therapy in mCRPC patients receiving 177Lu-PSMA-617.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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How to cite this article: Derlin T, Sommerlath Sohns JM, Schmuck S, et al. Influence of short-term dexamethasone on the efficacy of $^{177}$Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. *The Prostate*. 2020;80:619-631. [https://doi.org/10.1002/pros.23974](https://doi.org/10.1002/pros.23974)