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# Safety Profile and Therapeutic Efficacy of One Cycle of Lu177-PSMA in End-Stage Metastatic Castration-Resistant Prostate Cancer Patients with Low Performance Status

Manoj Gupta[1] · Partha Sarathi Choudhury[1] · Sudhir Rawal[2] · G. Karthikeyan[3] · Vineet Talwar[4] · Kumar Deep Dutta[4] · Amitabh Singh[2]

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## Abstract

**Purpose** The aim of this study was to evaluate safety and therapeutic efficacy of lutetium 177 prostate-specific membrane antigen (Lu-177-PSMA) in metastatic castration-resistant prostate cancer (mCRPC) patients with low performance status.

**Methods** Twenty-two patients already treated with anti-androgens and docetaxel were enrolled for one cycle of Lu-177-PSMA therapy. Haemoglobin, total leukocyte counts, platelets and serum creatinine for toxicity profile while prostate specific antigen (PSA), Eastern Cooperative Oncology Group (ECOG) performance status, visual analogue scale (VAS) and analgesic quantification scale (AQS) for therapeutic efficacy were recorded pre and 8 weeks post therapy. Wilcoxon signed-rank and ANOVA tests were used for statistical analysis.

**Results** Partial response (PR), stable disease (SD) and progressive disease (PD) for PSA were seen in 5 (22.7%), 13 (59.1%) and 4 (18.2%) patients respectively treated with mean 6.88 GBq dose of Lu-177-PSMA. 8/22 (36.4%) patients showed ≥ 30% drop in PSA. Grade 3 haemoglobin toxicity was seen in 5/22 (22.7%) patients. No patient developed grade 4 haemoglobin toxicity. No patients had grade 3 or 4 leukocytopenia or thrombocytopenia. Wilcoxon signed-rank test showed statistical significant ($P < 0.05$) difference in pre and post treatment ECOG, VAS, and AQS scores. The ANOVA test showed statistically significant difference in mean doses of Lu-177-PSMA used in three PSA response groups while difference was non-significant for other variables.

**Conclusion** We concluded that Lu-177-PSMA therapy has adequate pain palliation in end-stage mCRPC patients with low performance status and it has a potential to become effective therapeutic option in properly selected patients.

**Keywords** Lu-177-PSMA · Safety and efficacy · Metastatic castration resistant prostate cancer · Low performance status

## Introduction

Prostate cancer (PCa) is the 2nd most common cancer in men and 3rd most frequent cause of cancer-related deaths [1]. Incidence of prostate cancer in India is lower than western world; however, it is showing a rising trend and indeed it has become the 2nd commonest cancer in Delhi [2]. A patient with early-stage PCa has an excellent prognosis whereas all patients with distant metastasis ultimately develop resistance to standard drugs during various time intervals [3]. In last decade, different novel therapies have been developed for metastatic castration-resistant prostate cancer (mCRPC), e.g. abiraterone, enzalutamide, cabazitaxel and radium 223 [4–7]. However, these newer modalities are also remaining effective for a limited period and further treatment options become mandatory.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s13139-019-00624-8) contains supplementary material, which is available to authorized users.

✉ Manoj Gupta
docmanojgupta@yahoo.com

[1] Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

[2] Department of Uro - Gynae Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

[3] Amity Institute of Virology and Immunology, Amity University, Noida, Uttar Pradesh, India

[4] Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Lutetium 177 prostate-specific membrane antigen (Lu-177-PSMA) is a novel targeted peptide receptor radioligand therapy (PRLT), based on theranostic concept developed by the German Cancer Research Center (DKFZ) Heidelberg [8, 9]. PSMA is a transmembrane antigen which is 100–1000 times over expressed on prostate cancer cells, and its expression is directly proportional to the Gleason score, metastatic status and hormone resistance [10, 11]. In this study, we have reported safety and efficacy of our initial experience of one cycle of Lu-177-PSMA treatment in end-stage mCRPC patients with low performance status.

## Methods

Between September 2015 and June 2018, 25 histologically proven mCRPC patients with progression on standard treatment protocols were referred for Lu-177-PSMA therapy on compassionate grounds. All patients were previously treated with at least first-line anti-androgens and first-line chemotherapy with docetaxel. A gallium 68-prostate-specific membrane antigen 11 (Ga68-PSMA) PET-CT was performed on all patients to document adequate receptor expression for inclusion. Other inclusion criteria were haemoglobin (Hb) $\geq 8$ g/dl, total leukocytes counts (TLC) $> 3000$ per $mm^3$, platelets $> 75{,}000$ per $mm^3$, serum creatinine $\leq 1.8$ mg/dl. Finally, 22 patients who fulfilled the above criteria were treated with one cycle of Lu-177-PSMA therapy. This study was approved by the hospital scientific committee (res/scm/31/2018/105).

### Radiopharmaceutical Preparation and Administration of Lu-177-PSMA

PSMA-617 was obtained from advanced biochemical compounds (ABx) Gmbh, Germany. Non-carrier-added Lu-177 was procured from ITG, Germany. It was supplied in aqueous 0.04 M HCL solution with more than 3000 GBq/mg-specific activity and $> 99\%$ radiochemical purity. Radio-labelling of Lu-177 and PSMA-617 was done with vendor-specific protocol by qualified radio-pharmacist on-site. Sodium ascorbate and ascorbic acid buffer with pH between 4.5 and 5.0 was used for radio-labelling. Quality control of 0.22 μm millipore-filtered product was done with trisodium citrate buffer by Eckert & Ziegler thin layer chromatography scanner before administration.

Lu-177-PSMA was administered intravenously with 50 ml of normal saline infusion over 15 min. Patient was also hydrated with 1 l of normal saline infusion at 250 ml per hour started 30 min before radioactive injection for renal protection. No specific measures were taken to minimize salivary gland concentration.

### Safety Parameters

Baseline Hb, TLC, platelet counts, kidney function test (KFT), liver function test (LFT) and Technetium99m-diethylenetriaminepentaacetic acid (Tc99m-DTPA) glomerular filtration rate (GFR) were done with-in 2 weeks before therapy and 8 weeks after therapy in all patients to assess the safety profile of Lu-177-PSMA therapy. Toxicity profile was categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 on a scale of 1 to 5 [12].

### Therapeutic Efficacy Parameters

#### Biochemical Parameter

Prostate-specific antigen (PSA) is a biochemical marker for prostate cancer and recommended for evaluation of therapeutic efficacy by the prostate cancer working group 3 (PCWG 3) [13]. PSA was done within 2 weeks prior to Lu-177-PSMA therapy and 8 weeks post therapy. A drop of $\geq 50\%$ in PSA was considered as partial response (PR). A $\geq 25\%$ increase was considered as progressive disease (PD). Change in-between PR and PD ($< -50\%$ and $< +25\%$) was considered as stable disease (SD).

#### Clinical Parameters

Eastern Cooperative Oncology Group (ECOG) performance status was recorded pre and 8 weeks post therapy [14]. Visual analogue scale (VAS) for pain on a scale of 0 to10 was recorded within 24 h pre therapy and 8 weeks post therapy [15]. Positive pain response rate was defined as 2-point absolute improvement in our study. Analgesic Quantification scale (AQS) of 0 to 6 was recorded pre therapy and 8 weeks post therapy. AQS 0, 1, 2, 3, 4, 5 and 6 were considered as no analgesic, occasional non-opioids analgesic, regular non-opioids analgesic, occasional weak opioids analgesic, regular weak opioids analgesic, occasional strong opioids analgesic and regular strong opioids analgesic respectively. Daily use of analgesic was considered as regular. A decrease of one point AQS score was considered as positive for response in our study. The adverse events reported by the patients within 24 h and 8 weeks post therapy were recorded. Symptomatic skeleton events (SSEs), e.g. symptomatic fracture, spinal cord compression, radiation or surgery for bone lesion during treatment, were also recorded post therapy and on follow-up.

### Statistical Analysis

Mean, median, and range (minimum to maximum) were presented for quantitative data and absolute frequencies with percentage for categorical data. Pre and 8 weeks post treatment

changes in safety parameters and efficacy parameters were tabulated. Wilcoxon signed-rank test was used to compare pre and post treatment changes in safety parameters and efficacy parameters. One-way analysis of variance (ANOVA) or Welch's tests were used to compared three PSA response groups (PR, SD and PD) for mean age, haemoglobin, Gleason score, time interval between diagnosis of prostate cancer and referred for Lu-177-PSMA therapy, dose of Lu-177-PSMA, ECOG, VAS, and AQS variables. Fisher's exact test was used to compare metastasis stage (M1b or M1c) distribution among three PSA response groups. $P$ value $< 0.05$ was considered statistically significant. SPSS version 23 (IBM New York) was used for the statistical analysis.

## Results

Patient's characteristics were given in supplementary Table 1. Twenty-two patients with average age 67.7 years (range 45–81, median 69 years) with 8.3 mean Gleason score (range 7–10, median 8) were treated with 6.88 GBq mean dose of one cycle of Lu-177-PSMA (range 3.7–7.7, median 7.4 GBq). These patients were referred for Lu-177-PSMA therapy after an average of 48.7 months (range 19–113, median 35 months) following first diagnosis of prostate cancer. All these patients were treated with first-line hormone therapy and docetaxel chemotherapy. Abiraterone, enzalutamide and cabazitaxel were also used in 59.1%, 27.3% and 45.5% of our patients. All patients had multiple sites of PSMA avid metastatic disease. Bone and lymph nodes were the most common sites of metastatic disease. Visceral metastasis was found in 12/22 (54.6%) patients.

### Therapeutic Efficacy Results

Clinical and biochemical parameters for evaluation of therapeutic efficacy, pre and 8 weeks post Lu-177-PSMA therapy were presented in Table 1. Average ECOG score pre and post Lu-PSMA therapy was 3.3 (range 2–4, median 3) and 3.1 (range 2–4, median 3) respectively. Overall, 6/22 (27.3%) patients had improvement in ECOG score by 1 point. Average VAS for pain pre and post Lu-PSMA therapy was 5.2 (range 1–8, median 5) and 3.6 (range 0–6, median 4) respectively. 12/22 (54.6%) patients showed 2 points or more improvement in VAS while other 5/22 (22.7%) showed 1 point absolute improvement in VAS. Average AQS pre and post Lu-177-PSMA therapy was 3.6 (range 3–4, median 4) and 2.9 (range 1–4, median 3) respectively. 13/22 (59.1%) patients showed 1 point or more improvement in AQS while 3/22 (13.6%) showed 2 points absolute improvement in AQS following therapy. Average PSA pre and post Lu-PSMA therapy was 143.3 (range 14.1–456, median 81) and 134 (range 5.4–494, median 45.6) respectively. PR, SD and PD for PSA following one cycle of Lu-177-PSMA were seen in 5 (22.7%), 13 (59.1%) and 4 (18.2%) patients respectively (Figs. 1, 2 and 3). 8/22 (36.4%) of our patients showed ≥ 30% drop in PSA. Wilcoxon signed-rank test showed statistically significant difference in pre and post treatment changes in ECOG ($P = 0.014$), VAS ($P < 0.000$) and AQS ($P = 0.001$) safety parameters while it was statistical in-significant for PSA difference ($P = 0.115$). ANOVA and Welch's test showed statistically significant (< 0.05) difference in mean doses of Lu-177-PSMA in three PSA response group patients while there was no significant difference found in mean age, haemoglobin, time interval between diagnoses of prostate cancer and referred for Lu-177-PSMA therapy, ECOG, VAS and AQS score distribution among these three groups (Table 2). Fisher's exact test showed no significant difference in M stage (M1b or M1c) distribution among three PSA response groups ($P > 0.05$).

**Table 1** Comparison of clinical and biochemical parameters for therapeutic efficacy evaluation pre and 8 weeks post Lu177-PSMA therapy by Wilcoxon signed-rank test

| Parameters | Pre therapy Mean ± SD | Post therapy Mean ± SD | $P$ value |
|---|---|---|---|
| ECOG score (0–5) | 3.32 ± 0.57 | 3.05 ± 0.72 | 0.014 |
| VAS for pain (0–10) | 5.18 ± 2.15 | 3.63 ± 2.04 | < 0.000 |
| AQS (0–6) | 3.64 ± 0.49 | 2.91 ± 0.81 | 0.001 |
| PSA (ng/ml) | 143.32 ± 142.84 | 133.99 ± 159.21 | 0.115 |

*Lu177-PSMA* lutetium 177-prostate-specific membrane antigen, *EGOG* Eastern Cooperative Oncology Group, *VAS* visual analogue scale, *AQS* Analgesic Quantification scale, *PSA* prostate-specific antigen

### Safety Results

Safety parameters for toxicity evaluation pre and 8 weeks post Lu-177-PSMA therapy were presented in Table 3. Average Hb (g/dl) pre and post Lu-177-PSMA therapy was 10.4 (range 8.0–13.4, median 9.9) and 10.0 (range 6.9–13.1, median 9.6) respectively. As per CTCAE (version 4.03) criteria, number of patients belongs to grade 0, 1, and 2 for haemoglobin (our normal range 13–15 g/dl) pre therapy was 3, 8 and 11, while number of patient belongs to grade 0, 1, 2 and 3 for haemoglobin post therapy was 1, 9, 7 and 5. Fall in haemoglobin was seen in 8/22 (36.4%) of the patients which was maximum of 1 point. Grade 3 haemoglobin toxicity was seen in 5/22 (22.7%) of the patients who already had underlying grade 2 haemoglobin toxicity before Lu-177-PSMA therapy. No patient developed grade 4 haemoglobin toxicity. No patient with normal or grade 1 haemoglobin toxicity before Lu-177-PSMA therapy developed grade 3 haemoglobin toxicity. All patients had normal TLC before Lu-177-PSMA therapy (our normal range 4000–11,000 per $mm^3$). Average

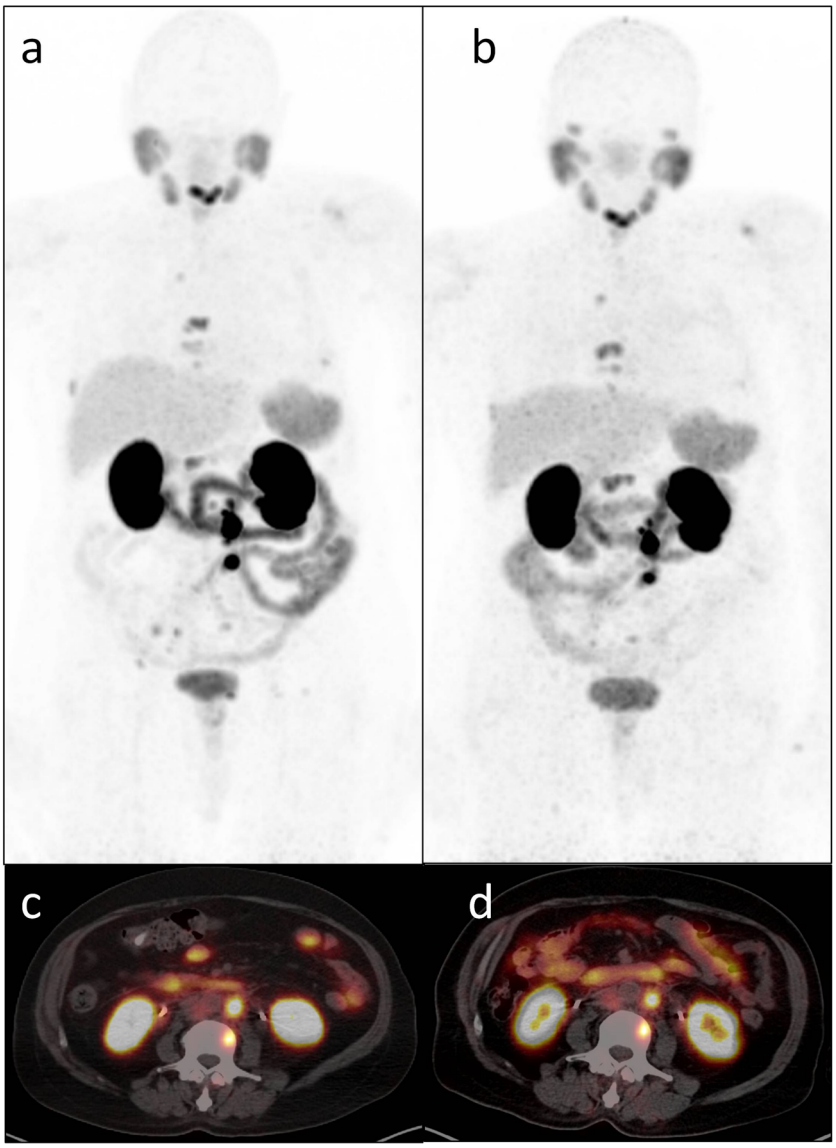


**Fig. 1** Ga68-PSMA PET-CT maximum intensity projection (**a**, **b**) and axial (**c**, **d**) images. Pre (**a**, **c**) and 8 weeks post (**b**, **d**) Lu-177-PSMA therapy, images showed partial molecular response (> 30% decrease in highest SUVmax). This 69 years old prostate cancer patient earlier treated with multiple lines of anti-androgens and two lines of chemotherapy docetaxel and cabazitaxel. Pre and 8 weeks post Lu-177-PSMA therapy, PSA showed partial response (21.3 ng/ml vs 5.4 ng/ml)

TLC (per $mm^3$) pre and post Lu-177-PSMA therapy was 8123 (range 4380–13,110, median 7700) and 6761 (range 3450–11,456, median 6400) respectively. One patient had developed grade 1 TLC toxicity following Lu-177-PSMA therapy. All patients had normal platelet counts before Lu-177-PSMA therapy (our normal range 1.5–4.5 lac per $mm^3$). Average platelet counts (lac per $mm^3$) pre and post Lu-177-PSMA therapy were 3.4 (range 1.7–6.6, median 3.3) and 2.5 (range 1.5–4.7, median 2.3) respectively. No significant change in grade of thrombocytopenia in any patient was seen following therapy in our study.

Average creatinine (mg/dl) pre and post Lu-177-PSMA therapy was 1.0 (range 0.5–1.8, median 1.0) and 1.0 (range 0.5–1.9, median 1.0) respectively. Grade 1 nephrotoxicity was present in 2/22 (9.1%) patient before Lu-177-PSMA therapy in our group (our normal range 0.2–1.2 mg/dl), and out of these two, one patient developed grade 2 nephrotoxicity following therapy. Grade 3 or 4 nephrotoxicity was not seen in any patient. Average total bilirubin (mg/dl) pre and post Lu-177-PSMA therapy was 0.9 (range 0.6–1.1, median 0.8) and 0.9 (range 0.6–1.2, median 0.9) respectively. No deterioration of hepatic function was seen in our study group following Lu-177-PSMA therapy. Average GFR (ml/min) pre and post Lu-177-PSMA therapy was 70.9 (range 48.8–94.8, median 68.7) and 70.5 (range 46.1–95.6, median 70.7) respectively. No deterioration of GFR was seen in our study group. Wilcoxon signed-rank test showed statistical significant difference in pre and post treatment change in CTCAE toxicity grade for Hb ($P = 0.005$), while no significant difference was seen in TLC, platelets, creatinine, total bilirubin and GFR ($P > 0.05$). However, the Wilcoxon signed-rank test showed no significant change in absolute value of Hb while it was statistically significant for TLC and platelet absolute value post Lu-177-PSMA therapy. This was likely due to most of

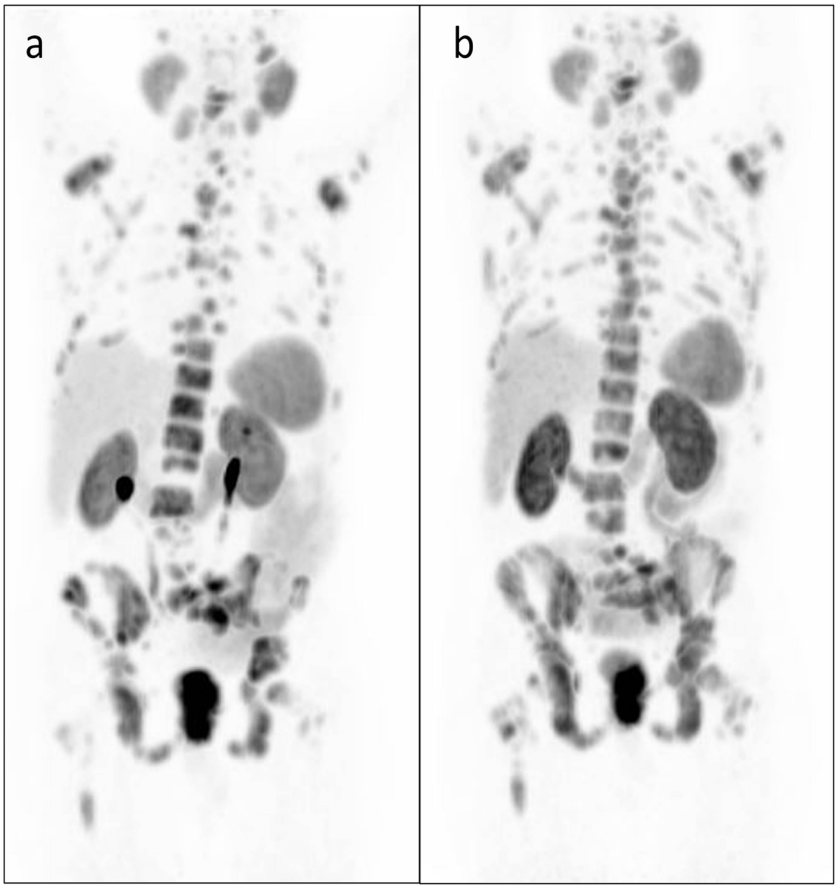


**Fig. 2** Ga68-PSMA PET-CT maximum intensity projection pre (**a**) and 8 weeks post (**b**) Lu-177-PSMA therapy images showed stable disease. This 68 years old prostate cancer patient earlier treated with bilateral orchidectomy, multiple lines of anti-androgens including abiraterone, enzalutamide and two lines of chemotherapy docetaxel and cabazitaxel. Pre and 8 weeks post Lu-177-PSMA therapy, PSA showed stable disease (396.6 ng/ml vs 344 ng/ml)

our patients had low Hb to begin with, hence a small change leads to change in CTCEA grade which leads to statistically significant change in the later parameter. While for TLC and platelet counts, our all patients had normal counts to begin with and a small change in an absolute value in a big normal range not leads to change in CTCEA toxicity grading.

No symptomatic skeletal events were reported following Lu-177-PSMA therapy. Two patients reported nausea and gastritis following therapy within 4 h of infusion which were managed conservatively. Pain 'flare' was seen in one patient which regressed in next 4 weeks with an overall improvement in VAS for pain from 4 to 2. No patient reported pain in salivary glands following Lu-177-PSMA therapy. Xerostomia was reported in one patient 8 weeks post Lu-177-PSMA therapy. No dryness of eyes was reported.

## Discussion

Molecular radionuclide therapy is an innovative way to specifically target only tumour cells and to spare normal tissue. With the growing knowledge of molecular targets, many cancer specific treatments have been introduced in recent past. There is development in both molecular diagnostic and therapeutic. We have seen development of specific monoclonal antibodies, peptides, small molecules and other agents with various successes rate [16]. The concept of 'Theranostic (We treat what we see)' has now become popular in cancer research [17]. In this concept, a specific antigen or receptor which is over-expressed on tumour cell is being looked for by an imaging radiopharmaceutical and if positive, the same antigen or receptor is being targeted by a therapeutic radiopharmaceutical. PRLT is one of the examples of this concept and is being investigated in docetaxel pre-treated mCRPC patients.

One of the successful theranostic targets in prostate cancer is PSMA. PSMA is a type II membrane glycoprotein consisting of 750 amino acids (100–120 kDa), with a 19 amino acid intracellular component, a 24 amino acid intramembrane segment, and a large 707 amino acid extracellular component [18]. PSMA exhibits folate hydrolase/glutamate carboxypeptidase II enzymatic activity [19]. However, its precise role in-vivo has not yet been fully elucidated. In-vitro, its folate hydrolase activity has been associated with prostate carcinogenesis [20]. It is a non-secreting antigen and internalization after ligand binding endocytosis (via clathrin-coated pits).

Lu-177-labelled anti PSMA antibody J591 was the first murine-based monoclonal antibody (mAb) bind to extracellular part of PSMA and was being utilized for treatment of

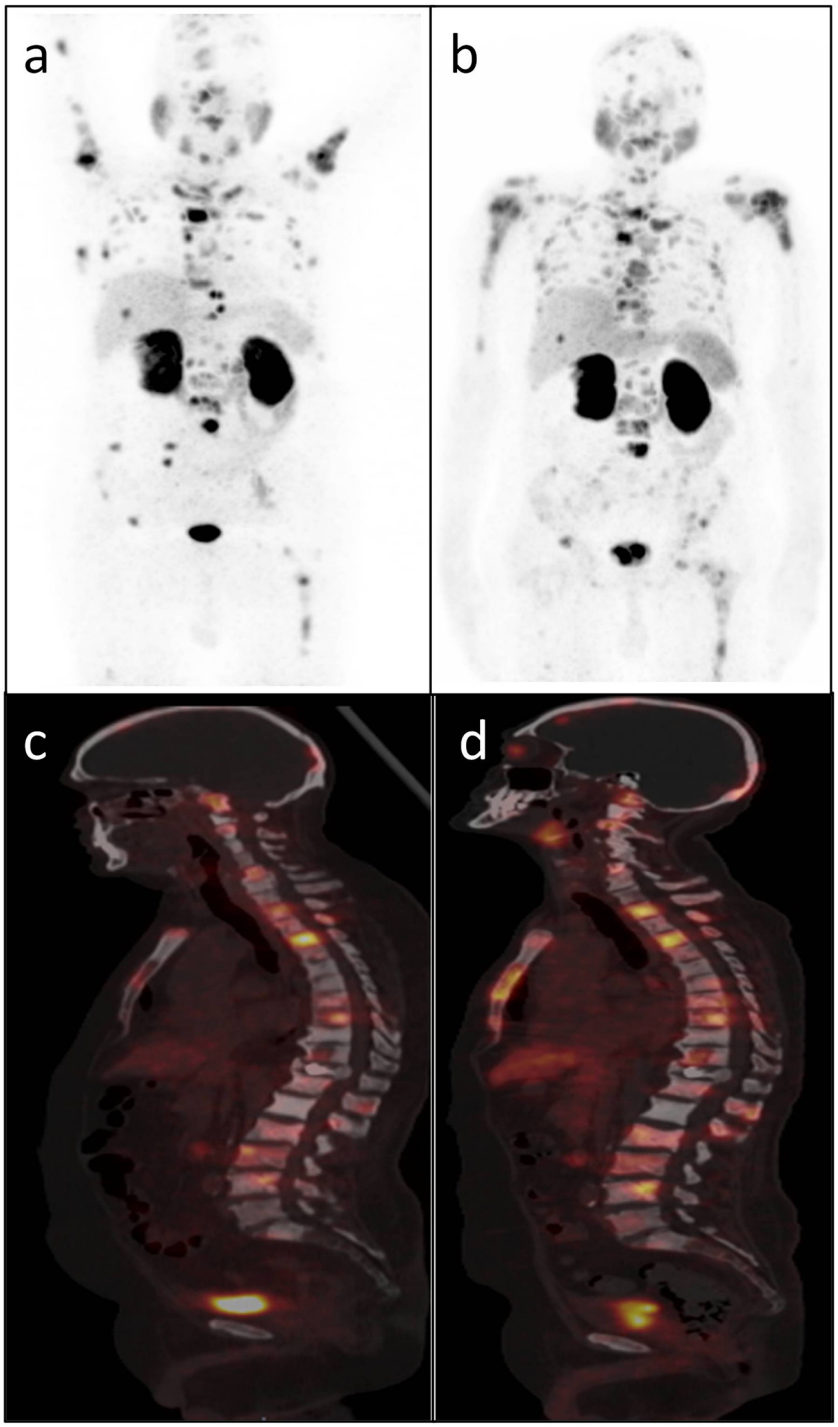


**Fig. 3** Ga68-PSMA PET-CT maximum intensity projection (**a**, **b**) and sagittal (**c**, **d**) images. Pre (**a**, **c**) and 8 weeks post (**b**, **d**) Lu-177-PSMA therapy, images showed molecular progressive disease (new PSMA avid lesions and increase extent of previous lesions). This 69 years old prostate cancer patient earlier treated with multiple lines of anti-androgens and docetaxel chemotherapy. Pre and 8 weeks post Lu-177-PSMA therapy, PSA showed progressive disease (277 ng/ml vs 400 ng/ml)

mCRPC. A phase II trial of Lu-177-labelled anti PSMA mAb J591 showed moderate results with > 50% decline of serum PSA in 10.6%, > 30% decline of PSA in 36.2% and stable PSA in 59.6% of patients [21]. In our study, we have seen similar moderate results for PR (22.7%), SD (59.1%) and for > 30% decline of PSA (36.4%) as well. The main limitations of antibody-based targeted treatment was slow localisation and low tumour to background ratio.

Due to above said limitations of antibodies based treatments, researchers have developed small molecules with high PSMA binding affinity. These molecules harbour anti PSMA enzymatic activity. One such novel urea based PSMA specific pharmacophore is Glu-NH-CO-NH-Lys-(Axe)-[Ga68(HBED-CC)] also known as Ga68-HDED-CC-PSMA-11 [22]. It has shown early detectability for prostate cancer recurrence and lymph node metastasis than conventional imaging [23].

**Table 2** Comparison of three PSA response groups (PR, SD, PD) for various characteristics by one-way ANOVA and Welch's test

| Characteristic | Overall Mean ± SD | PR Mean ± SD | SD Mean ± SD | PD Mean ± SD | *P* value |
|---|---|---|---|---|---|
| Age (years) | 67.7 ± 8.91 | 70.2 ± 8.98 | 65.4 ± 9.39 | 72.3 ± 5.85 | 0.3301 |
| Haemoglobin (g/dl) | 10.4 ± 1.55 | 10.9 ± 1.56 | 10.4 ± 1.68 | 9.78 ± 1.18 | 0.6030 |
| Gleason score | 8.27 ± 0.77 | 8.00 ± 1.22 | 8.38 ± 0.51 | 8.25 ± 0.96 | 0.6560 |
| Time interval between first diagnosis of prostate cancer & referred for Lu177-PSMA therapy (months) | 48.7 ± 27.6 | 67.2 ± 41.0 | 43.6 ± 22.6 | 42.3 ± 17.3 | 0.5128* |
| Lu177-PSMA dose (GBq) | 6.88 ± 1.22 | 7.43 ± 0.27 | 7.19 ± 0.92 | 5.16 ± 1.48 | 0.0026 |
| ECOG (0–5) | 3.32 ± 0.57 | 3.00 ± 0.00 | 3.46 ± 0.52 | 3.25 ± 0.96 | 0.3069 |
| VAS (0–10) | 5.18 ± 2.15 | 4.60 ± 2.30 | 5.38 ± 2.40 | 5.25 ± 1.26 | 0.8010 |
| AQS (0–6) | 3.64 ± 0.49 | 3.80 ± 0.44 | 3.54 ± 0.52 | 3.75 ± 0.50 | 0.5504 |

*PSA* prostate-specific antigen, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ANOVA* analysis of variance, *Mean ± SD* mean ± standard deviation, *Lu177-PSMA* lutetium 177 prostate-specific membrane antigen, *GBq* giga becquerel, *EGOG* Eastern Cooperative Oncology Group, *VAS* visual analogue scale, *AQS* Analgesic Quantification scale

*calculated by Welch's test

Another urea-based motif of 2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid, also known as DKFZ-PSMA-617 has also been synthesized and successfully labelled with Lu-177. Preclinical studies of Lu-177-DKFZ-PSMA-617 have shown faster blood clearance, lower uptake in liver, high binding affinity, high tumour to background ratio and efficient internalization into the prostate cancer cells. The early uptake and clearance from the kidney within 24 h post injection makes it excellent for effective targeted therapy.8.

Acceptable dosimetry of 177Lu-DKFZ-PSMA-617 with various renal protection protocols has been reported [24, 25]. Ahmadzadehfar et al. reported first results of Lu-177-PSMA ($n = 10$) and showed low early side effects and PSA PR in 50% of patients [26]. Rahbar et al. reported 31% PR for PSA and well tolerability of single dose of Lu-177-PSMA-617 in mCRPC patients ($n = 74$) [27]. A retrospective German multicenter study ($n = 145$) shown overall biochemical response rate (≥ 50% decline of PSA) 45% after all therapy cycles [28]. Grade 3–4 hematotoxicity occurred in 18 patients: 10%, 4% and 3% of the patients experienced anaemia, thrombocytopenia and leukocytopenia, respectively. Xerostomia occurred in 8%. No grade 3–4 nephrotoxicity was however noted. In our study group, 22.7% of the patients showed grade 3 anaemia and no grade 4 anaemia was reported. There was no grade 3 or 4 thrombocytopenia and leukocytopenia was seen in our study. Main reason for high incidence of grade 3 anaemia in our study was that a most of our patients (50%) were heavily pre-treated and already had compromised bone marrow reserve (grade 2 toxicity). No significant nephrotoxicity was however noted in our study. Only 1/22 (4.6%) of our patient reported mild xerostomia on follow-up.

A meta-analysis of 10 studies published by Calopedos et al. on Lu-177 labelled PSMA antibodies and ligands for

**Table 3** Comparison of safety parameters for toxicity evaluation pre and 8 weeks post Lu177-PSMA therapy by Wilcoxon signed-rank test

| Parameters | Pre therapy | | Post therapy | | *P* value | |
|---|---|---|---|---|---|---|
| | Absolute value (mean ± SD) | CTCEA grade (0–5) (Mean ± SD) | Absolute value (mean ± SD) | CTCEA grade (0–5) (Mean ± SD) | For absolute value | For CTCEA grade |
| Hb (g/dl) | 10.41 ± 1.55 | 1.36 ± 0.73 | 10.05 ± 1.89 | 1.73 ± 0.88 | 0.073 | <0.05 |
| TLC (per $mm^3$) | 8123.50 ± 2425.53 | 0 ± 0 | 6761.14 ± 2474.70 | 0.45 ± 0.21 | 0.001 | 1.000 |
| Platelets (lac/$mm^3$) | 3.36 ± 1.27 | 0 ± 0 | 2.50 ± 0.79 | 0 ± 0 | 0.001 | 1.000 |
| Creatinine (mg/dl) | 143.32 ± 142.84 | 0.09 ± 0.29 | 133.99 ± 159.21 | 0.13 ± 0.47 | 0.568 | 0.317 |
| Total bilirubin (mg/dl) | 0.89 ± 0.15 | 0 ± 0 | 0.85 ± 0.14 | 0 ± 0 | 0.496 | 1.000 |
| DTPA GFR (ml/min) | 71.82 ± 13.13 | 0.14 ± 0.35 | 71.41 ± 13.74 | 0.18 ± 0.39 | 0.307 | 0.307 |

*Lu177-PSMA* lutetium 177 prostate-specific membrane antigen, *Hb* haemoglobin, *TLC* total leukocyte count, *DTPA* diethylenetriaminepentaacetic acid, *GFR* glomerular filtration rate, *CTCAT* Common Terminology Criteria for Adverse Events version 4.03

treatment of mCRPC showed > 50% PSA decline in 51% of patients treated with Lu-177-PSMA DKZ/ I&T studies [29]. There was a significant heterogeneity across these studies. Further, many patients in these studies have been treated with multiple cycles of Lu-177-PSMA and had a good performance status in contrast to our study.

A recently published phase 2 study ($n = 30$) on Lu-177-PSMA radionuclide treatment in mCRPC patients reported grade 3–4 thrombocytopenia in 13%, grade 3 anaemia and neutropenia in 13% and 7% respectively [30]. In this study, patients with haemoglobin < 9 g/dl and ECOG score > 2 were excluded. In our study group, we had 21/22 (95.5%) patients with ECOG 3 or 4 and 3/22 (13.6%) patients with Hb < 9 g/dl. We found that these were the main factors of higher haemoglobin toxicity in our study. In a subgroup analysis, we found that no patients in our study with normal or grade 1 haemoglobin toxicity at inclusion developed grade 3 or 4 toxicity following Lu-177-PSMA therapy. Similarly, none of our patients had grade 3 or 4 leukocytopenia or thrombocytopenia. In the said study, authors have also reported > 50% decline in PSA in 57% and > 30% decline in 70% of patients. That might be attributed to better performance status of their study population at inclusion and that 93% of their patients received more than 1 cycle of Lu-177-PSMA and mean 7.5 GBq dose per cycle. In our study, patients have received only one cycle Lu-177-PSMA with mean dose of 6.88 GBq. In further analysis, we found that initial 4 patients in our study received mean 4.4 GBq Lu-177-PSMA dose and remaining 18 received mean 7.4 GBq Lu-177-PSMA dose. Out of those 4 patients with low doses, 3 had PD and one had SD on biochemical response criteria. In remaining 18 patients, 5 (27.8%) had PR, 12 (66.7%) had SD while 1 (5.6%) had PD. More than 30% decline in PSA was seen in 8 (44.4%) out of these 18 patients. Therefore, we realized that optimal dose of Lu-177-PSMA, good performance status and good bone marrow reserve were important to have adequate PSA response and low toxicity.

There were a few limitations of this study. The number of patients treated was only 22 and many were of low performance status. PRLT being an investigational treatment at this point of time, most patients were referred on compassionate ground after exhausting all standard of care treatments. These patients already had large burden of disease and compromised bone marrow reserve. Despite these limitations, we have found that 77.3% of these patients had improvement in pain. Another limitation was variability in doses of Lu-177-PSMA in our study patients. Although, we found that a patient with 7.4 GBq dose of Lu-177-PSMA had better chance of PSA response than 4.4 GBq and this difference was statistically significant in our study. Yet, we believe, proper randomisation trial is required to prove this hypothesis. Another limitation in our study was that we have used only one cycle of Lu-177-PSMA. For toxicity analysis, we do not have follow-up data to say that this drug will not increase the long term toxicity in these already compromised patients. Further, we found that there is significant change in absolute values of TLC and platelets counts while CTCAE grade remain unchanged. This issue of discrepancy will be important to research in future so that a parameter for acute toxicity can be validated. We have also not analysed markers of long term therapeutic outcomes e.g. progression free survival, and overall survival. Long interval time between diagnosis of prostate cancer and introduction of PRLT might be an important factor of future research. Further, we believe a combination of anti-androgens and Lu-177-PSMA might improve its efficacy due to known synergistic effect of anti-androgen on PSMA expression [31–33].

## Conclusion

Our initial results of efficacy and toxicity of one cycle of Lu-177-PSMA therapy have showed adequate palliation of pain and PSA response in heavily pre-treated mCRPC patients with low performance status. It has the potential to become effective therapeutic option for docetaxel pre-treated and properly selected mCRPC patients. Further prospective studies are warranted to determine the optimal dose, number of cycles, long term out comes and feasibility of combination treatments with anti-androgens.

### Compliance with Ethical Standards

**Conflict of Interest** Manoj Gupta, Partha Sarathi Choudhury, Sudhir Rawal, G. Karthikeyan, Vineet Talwar, Kumar Deep Dutta and Amitabh Singh declare that they have no conflict of interest.

**Ethical Statement** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent** The institutional review board waived the need to obtain informed consent for this retrospective study.

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