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ORIGINAL ARTICLE

Safety and efficacy of [^{177}Lu]Lu-SibuDAB in patients with progressive metastatic castration-resistant prostate cancer

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Abstract

Purpose Prostate-specific membrane antigen (PSMA)-targeted radiopharmaceutical therapy (RPT) is a safe and well-tolerated treatment option for metastatic, castration-resistant prostate cancer (mCRPC). A new radioligand, comprising ibuprofen as an albumin-binding entity, [^{177}Lu]Lu-SibuDAB, demonstrated an increased tumour-absorbed dose and efficacy in preclinical studies while tumour-to-organ absorbed dose coefficient ratios were similar to conventional PSMA radiopharmaceuticals. We conducted a translational study to evaluate response rate, safety and efficacy, and quality of life of [^{177}Lu]Lu-Sibu-DAB in progressive mCRPC patients.

Methods From July 2021 to January 2023 a total of seventeen eligible patients, sixteen (median age 71 years, range 63–83) were selected to receive up to four cycles of [^{177}Lu]Lu-SibuDAB at an activity of 4.3 to 5.9 GBq (median 5.3 GBq). The response rate was assessed by serum prostate specific antigen (PSA) and by PET/CT using [^{18}F]PSMA-1007, at baseline and post-therapeutic up to eight weeks, using RECIP 1.0 criteria. Safety and adverse events were investigated clinically by analyzing serial blood biomarkers and the recording of adverse events according to CTCAE v5.0. Quality of life was assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life (EORTC) questionnaires QLQ-C30 and QLQ-PR25.

Results Seven participants received 4 cycles of [^{177}Lu]Lu-SibuDAB, 3 participants received 3 cycles and 6 participants received$\leq$2 cycles because of disease progression or advanced stage of the disease. A maximum PSA decline (median baseline PSA value: 49.1 ng/ml (min 0,84 ng/ml max 145,1 ng/ml) by at least$\geq$50%, was observed in four participants, while stable serum PSA was observed in five further participants. Longitudinal PET/CT was performed with 10 participants, showing partial remission in five, stable disease in two and progressive disease in three patients. We observed an association between the changes in PSA levels and PET/CT-image-based assessment of the response. Two participants experienced grade three anaemia, one of them also a grade four thrombocytopenia. Two patients, heavily pre-treated with chemotherapy, experienced grade 3 thrombocytopenia. Impairment of renal or liver function was not observed. Importantly, no xerostomia was recorded for any of the participants. No significant changes in the quality of life were reported. Median overall survival was 13.9 months in this cohort.

Conclusion Overall survival and response rates of patients are consistent with previous reports on PSMA-targeted RPT while the absence of xerostomia can be considered an improvement. Up to four cycles of [^{177}Lu]Lu-SibuDAB were well tolerated and [^{177}Lu]Lu-SibuDAB appears to be a valid option for effective treatment of patients with progressive mCRPC. Randomized clinical trials to assess efficacy compared to established RPT are warranted.

Keywords Prostate cancer · MCRPC · Radiopharmaceutical therapy · [^{177}Lu]Lu-SibuDAB · Efficacy · Safety

Extended author information available on the last page of the article

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignant entity in men, with an estimated global mortality of 375.000 premature deaths annually [1]. Patients with advanced PCa require androgen deprivation therapy, and it is estimated that 10–20% of them will progress to castration-resistant prostate cancer (CRPC), with or without metastases, within five years [2]. The overall survival of these patients has improved since the introduction of chemotherapy in 2004 [3] and the use of androgen receptor pathway inhibitors (ARPIs), such as abiraterone and enzalutamide, as second-line therapy after chemotherapy [4]. However, the use of ARPIs is subject to limitations imposed by certain patients' comorbidities, impairment of quality of life, homologous recombination repair gene alterations, such as BRCA2/BRCA1 mutations, or by progressive disease [5, 6]. Therefore, it becomes crucial to consider third-line treatments for patients with advanced disease who have become unresponsive to the actual therapeutic interventions.

The prostate-specific membrane antigen (PSMA) has emerged as a target for radiopharmaceutical therapy (RPT) in disseminated metastatic castration-resistant prostate cancer (mCRPC). The development of RPT targeting PSMA has led to the clinical approval of lutetium-177 vipivotide tetraxetan (the compound formerly known as [^{177}Lu]Lu-PSMA-617), due to the positive results in the clinical trials, TheraP (NCT03392428) and VISION (NCT03511664) [7, 8]. However, there is still a significant number of mCRPC patients who do not respond to ^{177}Lu-based RPT [9].

Recent efforts have been directed at developing radioligands with enhanced blood plasma half-lives to increase tumour uptake and, hence, the absorbed tumour dose, while simultaneously reducing kidney retention to avoid potential nephrotoxicity [10]. Pun et al. recently described a strategy in which an albumin-binding radiopharmaceutical, was used for targeting a protein highly expressed in aggressive melanomas. In preclinical models, this approach successfully improved the pharmacokinetic profile [11]. Likewise, our group published preliminary results of the clinical translation of [^{177}Lu]Lu-PSMA-ALB-56, a PSMA ligand modified with a para-tolylbutanoate entity for increased affinity to human serum albumin [12], indicating substantially higher tumour doses per injected activity. However, the study noted reduced tumour-to-kidney and tumour-to-red marrow ratios. Nonetheless, single doses of up to 4.25 GBq [^{177}Lu]Lu-PSMA-ALB-56 were well tolerated, with no severe adverse events reported [13]. In general, albumin-binding radiopharmaceuticals achieve greater incorporation into tumours, albeit at the cost of an increased risk of toxicity to normal tissue [14, 15].

Subsequent preclinical efforts led to the development of [^{177}Lu]Lu-SibuDAB, a PSMA ligand conjugated with *(S)*-ibuprofen with moderate affinity to human serum albumin (Fig. 1) [16]. Recently, we reported dosimetry estimates for this radioligand, revealing a substantial improvement in tumour-to-salivary gland ratios while maintaining tumour-to-kidney and tumour-to-red marrow ratios comparable to [^{177}Lu]Lu-PSMA-617 [17]. Here, we present preliminary data on the safety and efficacy of [^{177}Lu]Lu-SibuDAB observed in patients.

Materials and methods

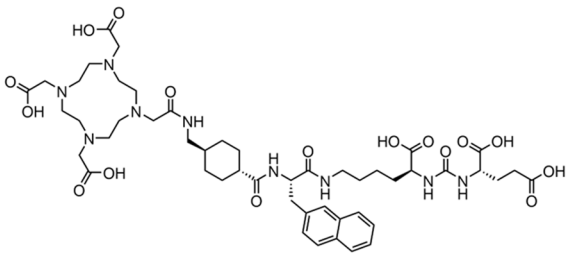
Study design and ethical approval

SibuDAB ((*S*)-Ibu-DAB-PSMA), was previously developed at the Paul Scherrer Institute (Switzerland) [16, 19] and used to prepare [^{177}Lu]Lu-SibuDAB [17]. Preliminary safety and efficacy data were gathered as secondary endpoints in a previously published dosimetry trial of [^{177}Lu]Lu-SibuDAB. Quality of life and pain scores were derived from the same study as additional endpoints. Briefly, 17 eligible patients (subjects Lu-001 to Lu-017) with progressive mCRPC and limited treatment options, were enrolled and sixteen patients (subjects Lu-001 to Lu-016, median age 71 years, range 63–83 years) were selected to receive up to four injections of 4.3 to 5.9 GBq (median 5.3 GBq) of [^{177}Lu]Lu-SibuDAB, for dosimetry and safety, efficacy, and quality of life assessments. The study was approved by the regional ethics committee of Santiago de Chile (Chile) (CEC SSM Oriente, permit 20210521). All patients gave written informed consent, and all reported investigations were conducted in accordance with the Declaration of Helsinki and local regulations. Formal inclusion and exclusion criteria are listed in the Supplementary material. Detailed information on the recruitment and study design was previously reported by Ritt et al. [17].

Efficacy

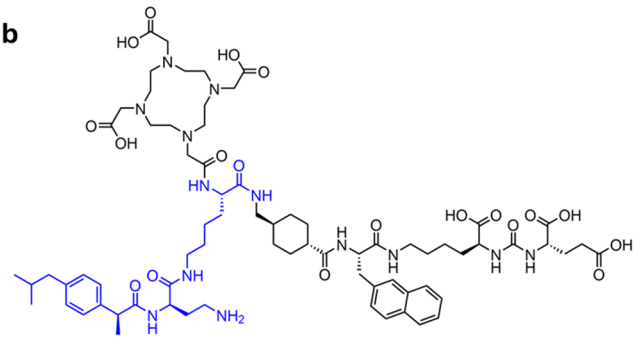
Efficacy was assessed by serum prostate-specific antigen (PSA) measurements at one, four to five, and eight to ten weeks after the injection of each dose. Pre-therapeutic PET/CT using [^{18}F]PSMA-1007 was performed before inclusion, while post-therapeutic PET/CT using [^{18}F]PSMA-1007 was performed eight to ten weeks after final dosing when possible. Lesions on pre-and post-therapeutic scans were segmented with a fixed standardized uptake value threshold of four, and total tumour volume (TTV) and total lesion PSMA

a



PSMA-617

b



SibuDAB

c

	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-SibuDAB
Human plasma protein-bound fraction [%]	60%	88%
ADC Tumour [Gy/GBq]	Bone: 3.57; Soft tissue: 4.19	9.9
Tumour-to-kidneys ADC ratio	6.2-7.2[a]	6.6
Tumour-to-red marrow ADC ratio	119-139[a]	102
Tumour-to-salivary gland ADC ratio	4.3-5.7[a]	33.1

a) not directly available in reference, range calculated based on values in the reference
ADC absorbed dose coefficient

Fig. 1 **a** Chemical structure of PSMA-617; **b** Chemical structure of SibuDAB; **c** Tumour absorbed dose coefficients (ADC) for [^{177}Lu]Lu-PSMA-617 [18] and [^{177}Lu]Lu-SibuDAB [17]; human plasma-bound fraction [16, 19], and tumour-to-organ ADC ratios for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-SibuDAB, respectively

uptake (TLP) were calculated with a threshold of SUV max >4 in Affinity Viewer 3.0.5 (Hermes Medical Solutions AB, Stockholm, Sweden). Manual adjustments were performed in an ad-hoc manner to include undetected lesion sites when considered applicable. The efficacy results were interpreted as described in RECIP 1.0, which includes PSA and TTV [20].

Safety

Complete blood counts and a standard blood panel including testosterone, erythrocyte sedimentation rate, prothrombin time, international normalized ratio, alkaline phosphatase activity, alanine aminotransferase activity, aspartate aminotransferase activity, lactate dehydrogenase activity, serum glucose, serum creatinine, plasma calcium, plasma phosphate, plasma urea nitrogen and plasma bilirubin (total), were obtained at one, four to five, and eight to ten weeks post-injection. After each cycle, adverse events, such as fatigue, pain, digestive and urological symptoms, xerostomia, and anxiety, were evaluated by a nurse, nuclear medicine physician, and urologist. Adverse events were recorded by the principal investigator according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 guidelines (published by National Institutes of Health, National Cancer Institute, Cancer Therapy Evaluation Program).

Quality of life

Quality of life was assessed before inclusion, and four to five and eight to ten weeks after each cycle using rating scales QLQ-30 and QLQ-PR25, (EORTC). The numeric pain rating scale, from 0 (no pain) to 10 (worst possible pain) was obtained on the injection days.

Statistical analysis

Descriptive statistics are provided in the format (arithmetic mean) ± (standard deviation) or as median value and interquartile range, where indicated. Bonferroni correction was used for multiple testing. The Kaplan-Meier method was used to estimate survival. Cox regression model, adjusted by lactate dehydrogenase (LDH), alkaline phosphate (ALP), total initial tumour volume (ml) and previous treatment burden, was used to assess multiple survival predictors. To evaluate the variable previous treatment burden, an index defined as the sum of the highest grades of each adverse event divided by the number of events recorded for a patient (toxicity index/total toxicity burden) was normalised on a scale from 0 to 5 based on side effects shown in other studies [21–27]. The proportional hazard assumption was tested with the Schoenfeld residual method. In general, two-sided p-values of less than a significance level of $\alpha = 0.05$ were considered statistically significant. Statistical analyses were carried out in GraphPad

Prism (GraphPad Software LLC, version 10.1.2) and R software version 4.2.0 (22 April 2022) [28].

Results

Participants and treatment regimen

Seventeen patients diagnosed with mCRPC were included in the study. One participant withdrew from the study before the first scheduled appointment and sixteen patients (median serum PSA: 51.2 ± 48.5 ng/mL, SUVmax: 41.9 ± 33.1, TTV: 533.6 ± 695.1 mL) received up to 4 cycles of [^{177}Lu]Lu-SibuDAB between June 2021 and January 2023 at the Center for Nuclear Medicine Positronmed in Santiago de Chile (Chile). All patients received previous androgen deprivation therapy, 13/16 patients received chemotherapy and detailed clinical parameters, including PSA values, SUVmax and total lesion volumes were assessed (Table 1, supplemental Table S1). Laboratory follow-up was available for sixteen participants. Post-therapeutic PET/CT using [^{18}F]PSMA-1007 was completed for ten out of sixteen patients.

[a] precursor mass had no significant impact on absorbed tumour and organ doses [17].

[b] Information on previous treatments for one participant was considered not consistent.

[c]ARPIs = Androgen receptor pathway inhibitors; ADT = Androgen deprivation therapy; IQR = Interquartile range; RPT = Radiopharmaceutical therapy; SUV = Standardized uptake value (standardized to body weight); SUV*ml = Standardized uptake value multiplied by tumour volume.

[d] Apalutamide, enzalutamide - pembrolizumab.

Clinical course of participants

Four patients were withdrawn from the trial following the first treatment cycle. Among those, two patients were withdrawn due to the severity of their underlying condition; one patient withdrew of his own volition, and one patient received care outside of the study protocol. After the second cycle, two additional patients were withdrawn. One patient was withdrawn due to adverse events, and one patient withdrew for personal reasons. Three patients were dismissed after the third cycle. Among those, two dismissed the treatment due to disease progression, and one due to adverse events. Seven patients received all four planned cycles of [^{177}Lu]Lu-SibuDAB therapy.

Table 1 Baseline information of patients treated with [^{177}Lu]Lu-SibuDAB

Patient characteristics	$n = 16$
Median age (IQR) – years	71 (63–83)
Median pre-treatment PSA value (IQR) – ng/ml	49.2 (4.8–87.4)
Median Total Tumour Uptake (IQR) -SUV*ml	2,084.00 (590.50–10,957.75)
Disease sites	
Bone	15/16
Lymph	10/16
Visceral	6/16
Prostate	10/16
Median injected activity (IQR) – GBq	5.4 (5.1–5.6)
Median Cycles of treatment (IQR), $n = 16$	3 (1–4)
Precursor mass[a]	80–400 µg
Previous lines of therapy[b]	$n = 16$
Number of previous lines of therapy per patient	No. of participants
0	1/16
1	2/16
2	7/16
3	2/16
4	4/16
Types of previous lines of therapy	No. of participants
Chemotherapy	
Docetaxel	12/16
Cabacitaxel	5/16
Docetaxel and Cabacitaxel	4/16
ARPIs/ADT agents[c]	
Enzalutamide	4/16
Abiraterone	9/16
Bicalutamide	3/16
Other[d]	2/16
RPT ([^{177}Lu]Lu-PSMA-617, 4x)	1/16
Other previous treatments	No. of participants
Surgery	Yes: 5; No: 11
Radiotherapy (RT) (all)	Yes: 13; No: 3
Curative RT (alone)	*Yes: 1; No: 15*
Brachytherapy	*Yes: 2; No: 14*
Adjuvant RT	*Yes: 4; No: 12*
Palliative RT	*Yes: 8; No: 8*
Hormone Blockade therapy	Yes: 16; No: 0
First line ARPIs	*Yes: 8; No: 8*

Response rate based on PSA levels and PET/CT imaging

The waterfall plot of the trial cohort's best change in PSA levels is shown in Fig. 2. Of the 16 evaluable participants, five (31%) showed PSA response (defined as a ≥ 50% PSA

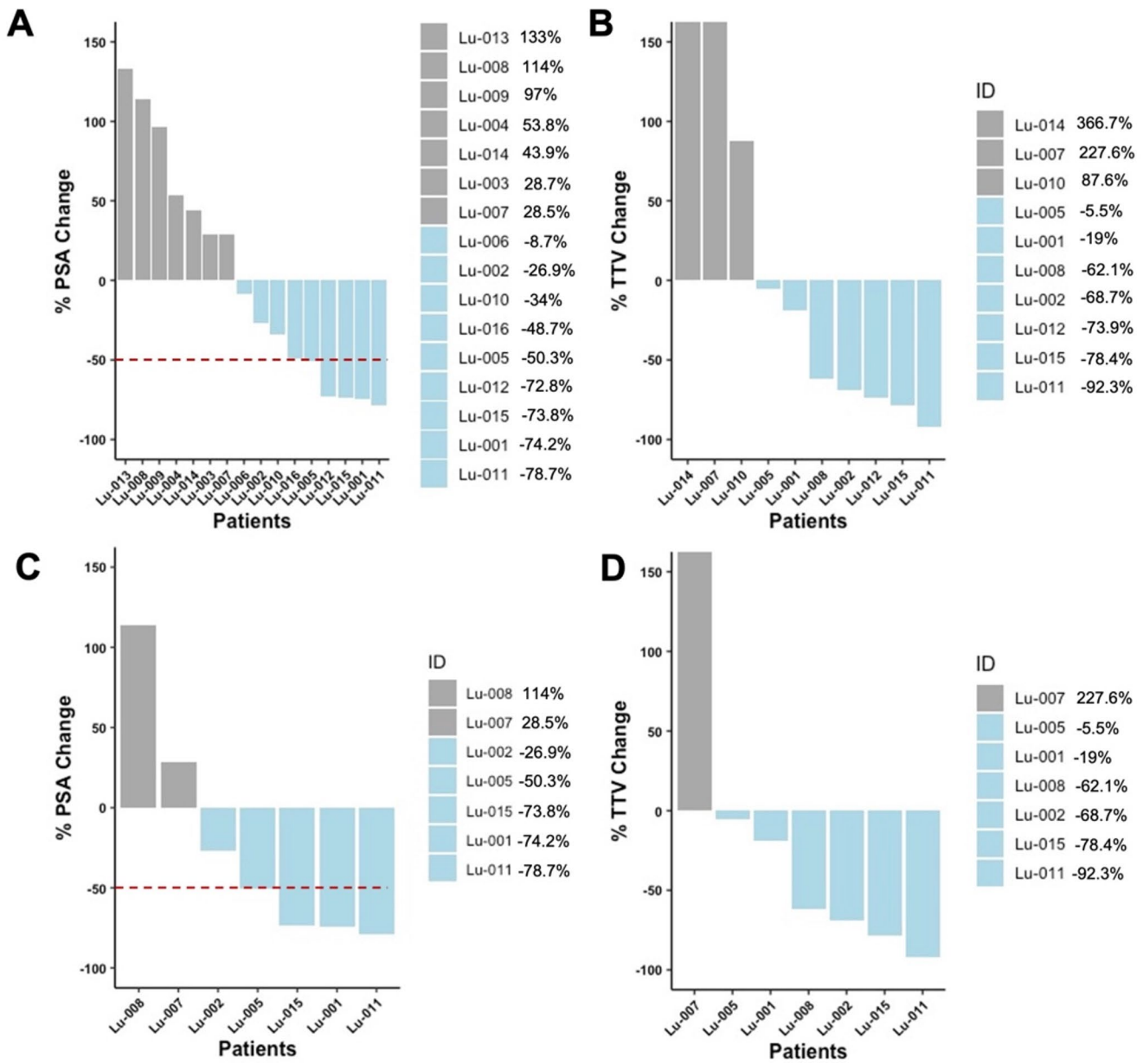


Fig. 2 Waterfall plots illustrate the responses rates based on PSA levels and TTV, expressed as percentage changes from baseline throughout [^{177}Lu]Lu-SibuDAB therapy. Light blue bars represent patients who experienced a decline in PSA levels or TTV (%). Light grey bars represent patients who experienced an increase in PSA levels or TTV (%) due to disease progression. (**A**) The best PSA responses (maximum percentage of PSA decline or minimum percentage PSA increase from baseline of each participant), expressed as percentage change from baseline throughout [^{177}Lu]Lu-SibuDAB therapy for all the subjects. (**B**) TTV responses, expressed as percentage change from baseline during [^{177}Lu]Lu-SibuDAB therapy. (**C**) The best PSA responses, expressed as percentage change from baseline throughout [^{177}Lu]Lu-SibuDAB therapy for subjects who completed four cycles. (**D**) TTV responses, expressed as percentage change from baseline during [^{177}Lu]Lu-SibuDAB therapy for subjects who completed four cycles

decline from baseline). Among the seven participants who completed all four cycles, four participants (57%) showed a PSA response. However, no statistically significant correlation was observed between treatment cycle and PSA response (r squared = 0.1, $p = 0.1$). Disease progression, defined as any PSA increase from baseline, was noted in seven participants.

Follow-up PET scans post-treatment were performed in ten participants at 82 days (median) after the last treatment cycle. On PSMA imaging, using RECIP criteria [20], five of ten evaluable participants showed partial remission, while two were assessed to show stable disease by the investigator team. The remaining three patients exhibited progressive disease. The median percentage change of

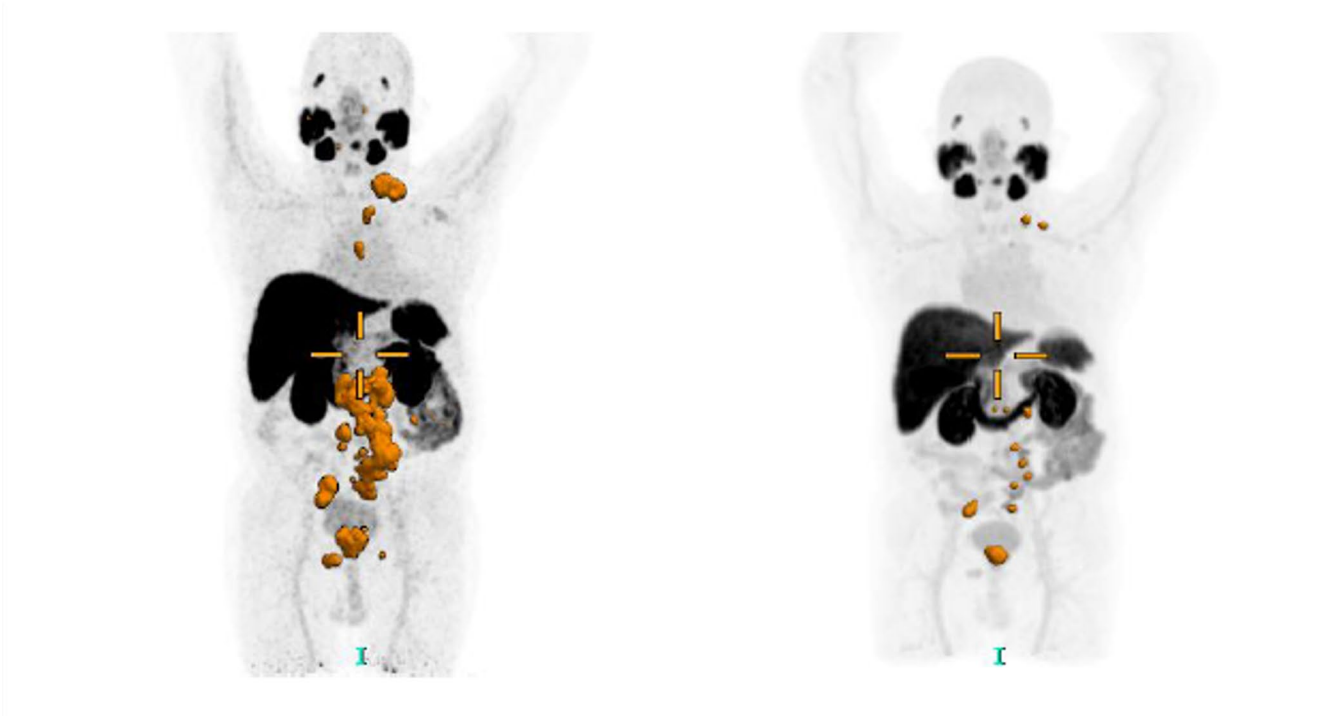


Fig. 3 PSMA-PET segmented Maximum-Intensity Projection (MIP) images of participant Lu-011, highlighting tumour volumes in orange. Left image shows the PSMA-PET/CT image before ther first cycle of [^{177}Lu]Lu-SibuDAB treatment, and the right image shows the PSMA-PET/CT after the 4th cycle. The image exhibits segmented MIP images of participant Lu-011 demonstrating a decline in tumoral lesions after the 4th cycle of [^{177}Lu]Lu-SibuDAB treatment. PSA showed a 79% decline from baseline; TTV and TLP showed a 92.3% and 97.8% decrease, respectively

TTV was − 40.6 ± 154.0% and the median change of TLP was − 59.9 ± 96.6%. Among five participants with partial response, three participants (subjects Lu-002, Lu-011 and Lu-015) showed a corresponding decline in PSA levels one month after the last therapy cycle compared to baseline. As an example, participant Lu-011 is shown in Fig. 3.

Participant Lu-012 showed a decrease in both TTV and TLP, with declines of 74% and 86%, respectively, in the post-therapy PET. Remarkably, this reduction occurred despite an increase in PSA levels by 9% one month after the last cycle compared to baseline levels. On follow-up PET imaging, the baseline lesions appeared diminished in size with a corresponding less intense uptake. However, a new faint and diffuse skeletal uptake appeared. This new uptake suggests a bone marrow infiltration, a hypothesis further sustained by laboratory results indicating a decline in haemoglobin (from 11.3 to 8.0 g/dL) and platelets (from 520,000 to 84,000/μL), over the course of the treatment. This faint uptake fell below the detection threshold of the automated segmentation algorithm, which had been set at SUVmax 4 eluding computational detection (Fig. 4).

Quality of life evaluation

To evaluate the quality of life of the participants throughout the treatment, EORTC scores of QLQ-30 and QLQ-PR25 were calculated at baseline and during the scheduled follow-up visits. Both scales range in score from 0 to 100, with higher scores representing greater subjective quality of life on functional scales, but greater impairment on symptomatic scales [29]. The participants exhibited slight fluctuations in scores, suggesting no systematic changes in symptoms or functions relevant to quality of life during the treatment period. The average scores at each scheduled visit failed to show any trend of worsening or improving the symptomatic, functional or quality of life items with the treatment. All scores for symptomatic items were no higher than 36 (0 to 100 scale). All scores for functional and quality of life items were no less than 66 except for Participant Lu-012, who reported a score of 33 for sexual function at 1 month after the third dose. Scores varied widely among individual participants.

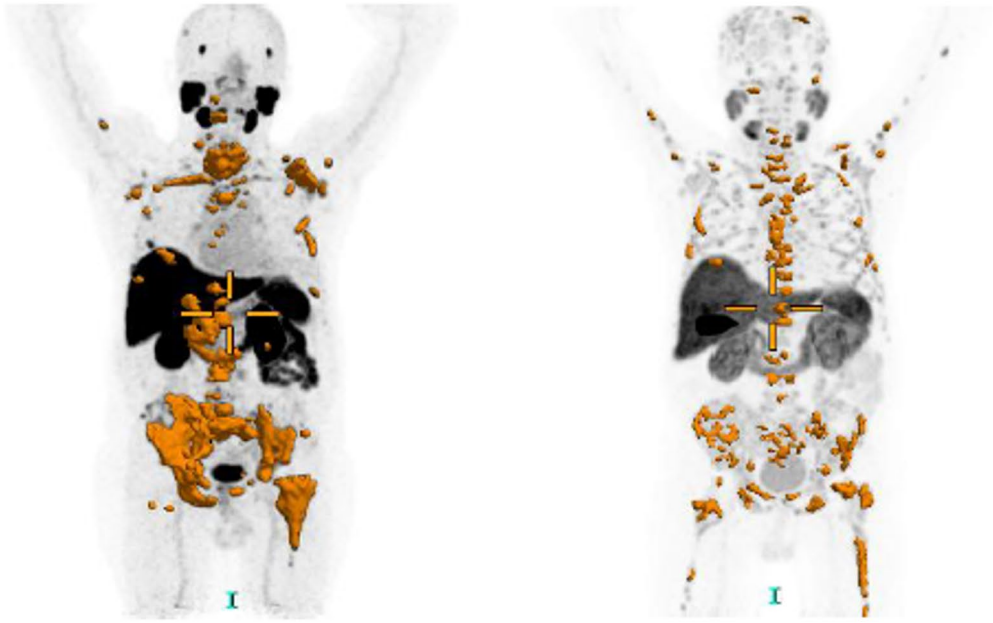


Fig. 4 PSMA-PET segmented MIP images of participant Lu-012, highlighting tumour volumes in orange. The left image is pre-therapy PSMA-PET, and the right image is PSMA-PET after 3 cycles of [^{177}Lu]Lu-SibuDAB

Table 2 Adverse events of patients treated with [^{177}Lu]Lu-SibuDAB in total numbers and (%)

		Worst Grade Event Post-Baseline			
Event	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	16 (100)	10 (62.5)	4 (25)	2 (12.5)	0
Pain	14 (87.5)	9 (56.3)	5 (31.3)	0	0
Thrombocytopenia	10 (62.5)	7 (43.8)	0	2 (12.5)	1 (6.3)
Nausea	9 (56.2)	8 (50)	1 (6.3)	0	0
Fatigue	8 (50)	8 (50)	0	0	0
Leukopenia	5 (31.2)	3 (18.8)	2 (12.5)	0	0
Diarrea	3 (18.8)	3 (18.8)	0	0	0
Dizziness	3 (18.8)	3 (18.8)	0	0	0
Depression	2 (12.5)	2 (12.5)	0	0	0
Inappetent	2 (12.5)	2 (12.5)	0	0	0
Pollakiuria	2 (12.5)	2 (12.5)	0	0	0
Vomiting	1 (6.3)	1 (6.3)	0	0	0
Anxiety	1 (6.3)	1 (6.3)	0	0	0
Gastric haemorrhage	1 (6.3)	0	0	1 (6.3)	0
Digestive problems	1 (6.3)	1 (6.3)	0	0	0
External bleeding	1 (6.3)	1 (6.3)	0	0	0
Gastritis	2 (12.5)	1 (6.3)	0	1 (6.3)	0
Heartburn	1 (6.3)	1 (6.3)	0	0	0
Low Weight	1 (6.3)	1 (6.3)	0	0	0
Muscular pain	1 (6.3)	1 (6.3)	0	0	0

Adverse events

In all patients at least one adverse event was observed throughout the study. Pain and haematological events were the most frequent adverse events. Throughout the study, six grade 3 adverse events were identified alongside a single grade 4 severe thrombocytopenia (Table 2).

During follow-up, one patient experienced grade 3 anaemia and grade 3 thrombocytopenia after suffering epistaxis, requiring coagulation of Kiesselbach's plexus. This event was considered unrelated to the study drug due to the patient 's past clinical history. None of the subjects presented any degree of xerostomia during the course of the study.

Survival associated with [^{177}Lu]Lu-SibuDAB therapy

From the first cycle of [^{177}Lu]Lu-SibuDAB therapy until the end of the study (September 2024), the median overall survival for all patients was 13.9 months (95% CI, 0.306–0.816 months) (Fig. 5A). Three patients were still alive in September of 2024. Within our cohort, patients who received more than two treatment cycles of [^{177}Lu]Lu-SibuDAB presented a prolonged median overall survival of 15.3 months (Fig. 5B). However, this difference was not statistically significant. To understand the impact of the [^{177}Lu]Lu-SibuDAB treatment cycles, we studied

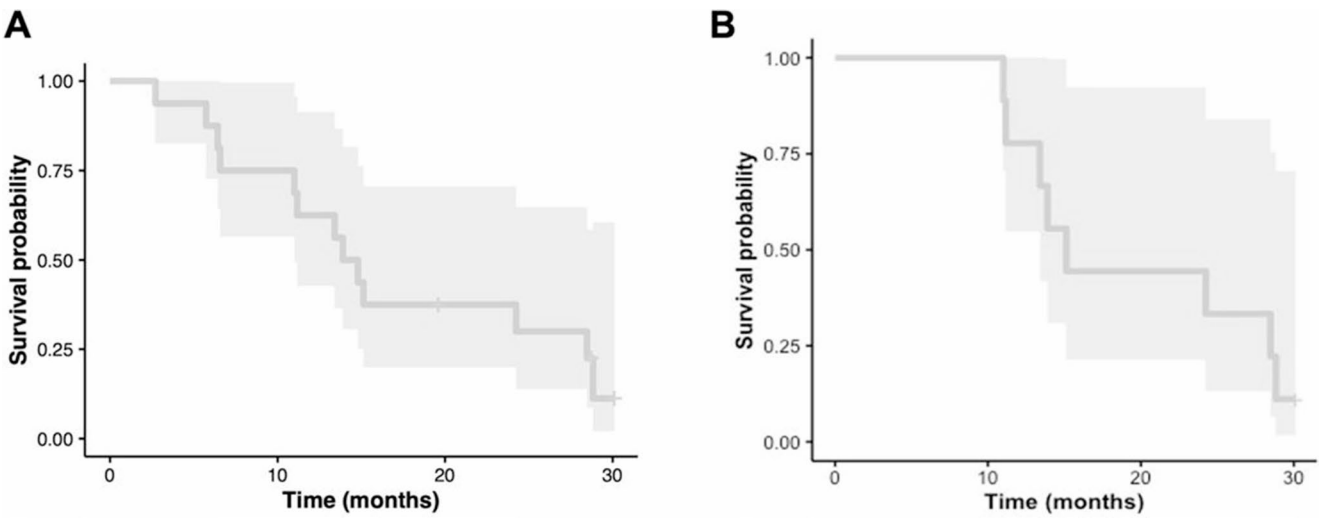


Fig. 5 Kaplan-Meier survival probability for patients after [^{177}Lu]Lu-SibuDAB treatment. (**A**) Patients showed a median overall survival of 13.9 months. (**B**) Patients who received more than two cycles of [^{177}Lu]Lu-SibuDAB had a median overall survival of 15.3 months. The shaded grey region represents the 95% confidence interval

variables before therapy, including levels of PSA, lactate dehydrogenase (LDH), alkaline phosphate (ALP), total initial tumour volume (ml) and previous treatments. The variable "previous treatments" was normalised on a scale from 0 to 5 based on the severity of adverse events published in other clinical trials. The Cox proportional-hazard model, adjusted for [^{177}Lu]Lu-SibuDAB cycles, showed that previous treatment burden significantly increased the hazard of experiencing the event. Specifically, patients who received heavy treatment burden before [^{177}Lu]Lu-SibuDAB therapy had a 31% higher risk compared to those who received fewer treatment lines (HR, 1.31; 95% CI, 1.09–1.59; $p=0.004$). Model discrimination had a concordance of 0.774.

Discussion

The use of radiopharmaceutical therapy targeting PSMA has emerged as a useful alternative for mCRPC patients. The results of the VISION trial (NCT03511664) demonstrated that the median overall survival of patients treated with [^{177}Lu]Lu-PSMA-617 was significantly longer (15.3 months) than the median overall survical of patients receiving standard-of-care (11.3 months) (HR of 0.62; 95% CI, 0.52–0.74; $p<0.001$). This treatment also conferred an improvement in radiographic progression-free survival [8]. These findings led to the approval of [^{177}Lu]Lu-PSMA-617 (Pluvicto™, Novartis) by the Food and Drug Administration and the European Medicines Agency. Nevertheless, due to the aggressive nature of the mCRPC lesions, a subset of patients continues to experience progression or death. RPT with actinium-225, an α-particle emitter, has shown similar antitumour efficacy. However, the high energy and short tissue range of this radionuclide were associated with grade 3/4 haematological toxicity and irreversible xerostomia. The structural incorporation of *p*-iodophenyl moiety, which binds to serum albumin with high affinity, resulted in prolonged blood circulation and consequently increased tumour uptake in the preclinical setting [12]. However, the approach of an albumin-binding PSMA radioligand result in elevated activity in the bloodstream and prolonged renal retention. To overcome these limitations, the radiopharmaceutical [^{177}Lu]Lu-PSMA-ALB-56 was developed, incorporating a *para*-tolylbutanoate entity as the albumin-binding entity. This modification reduced albumin-binding affinity in more than 10-fold compared with the *p*-iodophenyl-based albumin binder. Although clinical translation of [^{177}Lu]Lu-PSMA-ALB-56 was successful, demonstrating the absence of severe adverse events and an enhanced tumour dose [13], the activity level in the bloodstream and kidney remained higher than those observed with [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T. As an optimised alternative, [^{177}Lu]Lu-SibuDAB incorporated (*S*)-ibuprofen as an albumin-binding entity [16]. This optimisation conferred a significant therapeutic advantage over [^{177}Lu]Lu-PSMA-617 and a similar safety profile compared with [^{177}Lu]Lu-PSMA-ALB-56 in preclinical models. Moreover, biodistribution and pharmacokinetic analysis in our patients revealed that [^{177}Lu]Lu-SibuDAB displayed improved pharmacokinetics and increased absorbed tumour doses compared to [^{177}Lu]Lu-PSMA-ALB-56. The tumour-to-organ absorbed dose coefficients ratios observed for kidneys and red bone marrow remained within a comparable range to those reported for conventional PSMA radioligands [17].

In the present study, we assessed the response to [^{177}Lu]Lu-SibuDAB treatment by assessment of the serum PSA and PET imaging using [^{18}F]PSMA-1007. Our study cohort corresponded to patients with limited therapeutic options. Despite the wide range of systemic treatments available for mCRPC, the Chilean public insurance, FONASA, covers only ADT, docetaxel, and ARPIs (abiraterone or enzalutamide). ARPIs are covered only for mCRPC patients who either progress after chemotherapy or present with a contraindication to it. This limited coverage explains the treatment lines received by the majority of patients in the study.

After [^{177}Lu]Lu-SibuDAB therapy, of sixteen evaluable participants, five demonstrated a decline in PSA level greater than 50% and four demonstrated stable PSA, defined as declines of 0 to 50%. These results were in good accordance with radiographic response rates found on PET/CT images, showing partial remission in five and stable disease in two of ten evaluable participants. These results indicate robust biological activity of [^{177}Lu]Lu-SibuDAB in mCRPC patients. Response rates were consistent with those in a current meta-analysis of RPT using conventional ^{177}Lu-based PSMA radioligands, which reported that approximately half of the treated patients showed any PSA decline, with PSA reductions greater than 50% observed in approximately one third of cases [30]. It is also noteworthy that these results were obtained despite the fact that, in our study, the average activity administered per cycle was considerably lower than that used in most comparable studies employing other radioligands, thereby representing an advantage for our radioligand.

The case histories of four patients offer an opportunity to discuss the limitations of these results in some detail. For example, participant Lu-012 exhibited a PSA decline of 73% following two treatment cycles. However, this trend was reversed, with the final serum PSA rising by 9% above baseline one month after the third cycle. The patient was hereafter withdrawn from the study by the clinical investigator due to severe osseous disease, despite PSMA-targeted imaging demonstrating a declining tumour burden. This case exemplifies the heterogenic nature of progressive mCRPC, where resistance to previously effective therapies can emerge within weeks and unfold in eruptive clinical progression in the presence of generally favourable imaging and laboratory results. Participant Lu-010 exhibited overall disease progression despite frequent declines of serum PSA, which were subsequently countered with rises not associated with the study drug administration. This result suggested an evolution towards an undifferentiated disease. Participant Lu-011 demonstrated improvement (Fig. 3) despite initial rises in serum PSA (a tenfold increase) after the administration of the first cycle. This is an interesting result, considering that this event frequently occurs in other cases with PSMA-targeted RPT. Although other authors have reported that an increase in PSA levels of at least 25% after four weeks is predictive of shorter overall survival, it is important to consider the flare phenomenon [31]. Suspending therapy after an initial PSA rise may prematurely exclude patients who could potentially respond, as illustrated in this case, where, despite the initial rise in PSA a favourable response was eventually achieved. Further research is needed to identify additional elements or factors that can help us elucidate the decision-making process in patients who present with an early PSA increase after the initiation of the therapy. Similarly, participant Lu-008 showed steadily rising PSA levels after the first two cycles. However, during cycles three and four, a gradual decline in serum PSA became evident, culminating in a fourfold reduction from the peak value by the end of the study. Interestingly, the Cox regression analysis failed to show a significant correlation between PSA levels before the [^{177}Lu]Lu-SibuDAB therapy and the median overall survival of the patients. These findings encourage the continuation of treatment whenever clinically feasible, even when a transient increase in PSA is observed.

In evaluating the safety profile of [^{177}Lu]Lu-SibuDAB, we observed a slight decline in leukocyte and thrombocyte counts relative to baseline in 31.2% and 62.5% of patients, respectively. However, haemoglobin concentration remained largely stable. This aligns with dosimetry of [^{177}Lu]Lu-SibuDAB, where red marrow doses in some patients approached the conventionally accepted 2 Gy limit [17]. Remarkably, similar hematologic toxicities were reported in the VISION trial, where [^{177}Lu]Lu-PSMA-617 therapy was associated with anaemia grade 3 or greater in 12.9% of participants compared to 4.9% in the control group. Leukopenia grade 3 or greater in 2.5% of the treated participants compared to 0.5% in the control arm. Likewise, thrombocytopenia grade 3 or greater was documented in 7.9% of treated participants, in contrast to the 1.0% observed in the control cohort. These estimates are compatible with our findings for [^{177}Lu]Lu-SibuDAB despite the lower red marrow doses of [^{177}Lu]Lu-PSMA-617 [18]. Nevertheless, in two cases (subjects Lu-004 and Lu-008) our results suggested that the adverse effects could be associated to the previous cytotoxic treatments. Considering baseline blood counts and the context of progressive disease and previous treatments, [^{177}Lu]Lu-SibuDAB present an adequate safety profile.

Notably, we observed no cases of xerostomia or xerophthalmia of any grade in our study, which are side effects often associated with PSMA-targeted RPT. Dosimetry estimated salivary gland doses derived from external beam radiotherapy and RPT [17] were far below harmful thresholds. Despite the low number of participants in our trial, this significantly deviates from a report, in which grade 1 or 2 of xerostomia was documented in 38.8% of patients

treated with [^{177}Lu]Lu-PSMA-617 [8]. This favourable data obtained with [^{177}Lu]Lu-SibuDAB may be of particular value in view of using SibuDAB also with other radionuclides such as actinium-225 or terbium-161 [32, 33] and suggests a clinically meaningful benefit for quality of life.

Lastly, the median overall survival in our cohort was 13.9 months, similar to the median overall survival of 15.3 months reported for patients participating in the VISION trial [8] and other retrospective data in the all-comer mCRPC population treated with PSMA-targeted RPT [34]. Our cohort of patients exhibited advanced disease, with six of sixteen patients showing evidence of visceral metastasis, a constellation thought to reduce the efficacy of PSMA-targeted RPT [35], so the survival estimate may be subject to a downward bias in our trial. Levels of ALP less than 220 U/l have been associated with response to [^{177}Lu]Lu-PSMA therapy [36, 37], suggesting this biomarker as a predictor for a longer overall survival [38–40]. However, in our cohort, we failed to find this association, likely reflecting the specific characteristics of our patient population. In contrast, our results showed that heavily pre-treated schemes, particularly taxane chemotherapy, were significantly correlated with reduced median overall survival. The Cox regression results showed that patients with more lines of treatment, especially chemotherapy, had 31% higher risk of death (HR, 1.31; 95% CI, 1.09–1.59; $p < 0.01$). The effect of chemotherapy on [^{177}Lu]Lu-PSMA treatment outcomes has been reported previously, suggesting that taxane-based chemotherapy reduces PSMA uptake [41, 42]. These findings highlight the role of the correct patient selection who would benefit from [^{177}Lu]Lu-SibuDAB therapy.

This study is subject to several limitations. As common to all single-arm trials, some uncertainty persists as to whether adverse events were due to the study drug or a result of disease progression, particularly in participants with compromised haematopoiesis at baseline. The utility of the response rate in assessing the antineoplastic activity of investigational agents has been questioned on the grounds of substantial disagreement of this parameter with progression-free and overall survival in later phase trials [43]. We note the PSA response criteria have evolved [44], regrettably, without substantial accumulation of evidence in favour of their ability to predict the success of investigational agents in Phase III trials. Lastly, considering the clinical context of PSMA-targeted RPT, patients experiencing progressive disease may profit from delaying the disease progression, thereby deriving clinical benefit *without* achieving partial remission.

Randomized controlled trials comparing [^{177}Lu]Lu-SibuDAB to available radiopharmaceutical therapies such as [^{177}Lu]Lu-PSMA-617 or [^{177}Lu]Lu-PSMA-I&T, would be necessary for defining its comparative efficacy and safety. At this stage, SibuDAB labelled with terbium-161 ([^{161}Tb]Tb-SibuDAB [33]) is investigated in a clinical Phase I study with mCRPC patients at the University Hospital Basel in Switzerland (NCT06343038). The outcome of this on-going study will give further insight in the utility of this novel radioligand [45].

Conclusions

[^{177}Lu]Lu-SibuDAB was well tolerated, with a favourable safety profile, supporting administration of up to four cycles at therapeutic doses of up to 5.9 GBq. However, our findings revealed that patients with extensive prior chemotherapy burden (≥2 lines) experience heightened bone marrow toxicity. Therefore, pursuing treatment in earlier lines may yield a more favourable safety profile. Objective responses assessed via serum PSA levels and PSMA-PET/CT confirmed the robust antineoplastic activity of this novel agent in a heavily pretreated patient cohort with unfavourable late-stage disease. Consistent with prior dosimetry data establishing the red marrow as the dose-limiting organ at risk, mild myelotoxicity was observed in a minority of patients with baseline hematopoietic impairment, while salivary gland toxicity was not observed. These findings show that [^{177}Lu]Lu-SibuDAB is a promising agent for further clinical development of PSMA-targeted RPT.

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Data availability The datasets generated and analysed during this study are covered by data protection regulation and cannot be distributed.

Declarations

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the regional ethics committee board (CEC SSM Oriente, permit 20210521).

Consent to participate and publish Written informed consent for participation and publication was obtained from all individual participants included in the study.

Competing interests The authors declare the following competing financial interest(s): Patent applications on PSMA ligands with albumin-binding entities have been filed by ITM Medical Isotopes GmbH, Germany and the Paul Scherrer Institute, Switzerland. KZ and CM are listed as co-inventors. The authors further declare non-financial interest(s): non-carrier-added lutetium-177 was provided by ITM Medical Isotopes GmbH, Germany.

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