Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study

Prof Mike M Sathekge MD [a c d], Ismaheel O Lawal MD [a e], Prof Chandrasekhar Bal MD [f], Frank Bruchertseifer PhD [g], Sajana Ballal PhD [f], Giuseppe Cardaci MD [h], Cindy Davis BSc [c], Prof Mathias Eiber MD [i], Türkay Hekimsoy MD [i], Otto Knoesen PhD [j], Clemens Kratochwil MD [k], Prof Nat P Lenzo MD [h], Johncy Mahapane MSc [b], Letjie C Maserumule MD [a c d], Amanda H Mdlophane PhD [a d], Kgomotso M G Mokoala MD [a c d], Honest Ndlovu MD [a c d], Vineet Pant MD [l], Hendrik Rathke MD [k m], Janet Reed MD [a], Ishita B Sen MD [n], Aviral Singh MD [h], Prof Ashwani Sood MD [o], Robert Tauber MD [p], Parul Thakral PhD [n], Madhav Prasad Yadav PhD [f], Alfred Morgenstern PhD [a g]

[a]Department of Nuclear Medicine, University of Pretoria, Pretoria, South Africa
[b]Department of Radiography, University of Pretoria, Pretoria, South Africa
[c]Department of Nuclear Medicine, Steve Biko Academic Hospital, Pretoria, South Africa
[d]Nuclear Medicine Research Infrastructure, Pretoria, South Africa
[e]Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA, USA
[f]Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India
[g]European Commission, Joint Research Centre, Karlsruhe, Germany
[h]GenesisCare, Murdoch, WA, Australia
[i]Department of Nuclear Medicine, Klinikum Rechts Der Isar, Technical University of Munich and Bavarian Cancer Research Center (BZKF), Munich, Germany
[j]Nuclear Technology Products (NTP), Division of the South African Nuclear Energy Cooperation (NECSA), Pelindaba, South Africa
[k]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany
[l]Royal Liverpool University Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
[m]Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[n]Department of Nuclear Medicine, Fortis Memorial Research Institute, Gurugram, India
[o]Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[p]Department of Urology, School of Medicine, and Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany

*Correspondence to: Prof Mike M Sathekge, Department of Nuclear Medicine, University of Pretoria, Pretoria 0001, South Africa. Email: mike.sathekge@up.ac.za

Summary

Background: Actinium-225 (^{225}Ac) prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) is a novel therapy for metastatic castration-resistant prostate cancer (mCRPC). We aimed to report the safety and antitumour activity of ^{225}Ac-PSMA RLT of mCRPC in a large cohort of patients treated at multiple centres across the world.

Methods: This retrospective study included patients treated at seven centres in Australia, India, Germany, and South Africa. We pooled data of consecutive patients of any age and Eastern Cooperative Oncology Group performance status with histopathologically confirmed adenocarcinoma of the prostate who were treated with one or more cycles of 8 MBq ^{225}Ac-PSMA RLT administered intravenously for mCRPC. Previous lines of mCRPC treatment included taxane-based chemotherapy, androgen-receptor-axis inhibitors, lutetium-177 (^{177}Lu) PSMA RLT, and radium-223 dichloride. The primary outcomes were overall survival and progression-free survival.

Findings: Between Jan 1, 2016, and May 31, 2023, 488 men with mCRPC received 1174 cycles of ^{225}Ac-PSMA RLT (median two cycles, IQR 2–4). The mean age of the patients was 68·1 years (SD 8·8), and the median baseline prostate-specific antigen was 169·5 ng/mL (IQR 34·6–519·8). Previous lines of treatment were docetaxel in 324 (66%) patients, cabazitaxel in 103 (21%) patients, abiraterone in 191 (39%) patients, enzalutamide in 188 (39%) patients, ^{177}Lu-PSMA RLT in 154 (32%) patients, and radium-223 dichloride in 18 (4%) patients. The median follow-up duration was 9·0 months (IQR 5·0–17·5). The median overall survival was 15·5 months (95% CI 13·4–18·3) and median progression-free survival was 7·9 months (6·8–8·9). In 347 (71%) of 488 patients, information regarding treatment-induced xerostomia was available, and 236 (68%) of the 347 patients reported xerostomia after the first cycle of ^{225}Ac-PSMA RLT. All patients who received more than seven cycles of ^{225}Ac-PSMA RLT reported xerostomia. Grade 3 or higher anaemia occurred in 64 (13%) of 488 patients, leukopenia in 19 (4%), thrombocytopenia in 32 (7%), and renal toxicity in 22 (5%). No serious adverse events or treatment-related deaths were recorded.

Interpretation: ^{225}Ac-PSMA RLT shows a substantial antitumour effect in mCRPC and represents a viable therapy option in patients treated with previous lines of approved agents. Xerostomia is a common side-effect. Severe bone marrow and renal toxicity are less common adverse events.

Funding: None.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is the lethal form of prostate cancer progression. Treatment options for mCRPC that improve survival include chemotherapy with docetaxel and cabazitaxel,[1,2] androgen-axis-pathway inhibition with abiraterone and enzalutamide,[3,4] and radionuclide therapy of mCRPC skeletal metastasis with radium dichloride.[5] Prostate-specific membrane antigen (PSMA) is overexpressed by mCRPC, making it a suitable target for imaging and therapy of mCRPC. In the phase 2 TheraP trial, radioligand therapy (RLT) with a Lutetium-177 (^{177}Lu)-labelled PSMA-targeted ligand induced a stronger prostate-specific antigen (PSA) response and fewer adverse events than cabazitaxel.[6] The VISION trial, which led to the approval of ^{177}Lu-PSMA RLT as a treatment option for mCRPC, reported improved overall survival in patients randomly assigned to ^{177}Lu-PSMA RLT plus standard of care compared with standard of care alone.[7] However, PSA response is induced in only 46% of patients who receive at least one cycle of treatment.[8] The median duration of disease control in patients who responded ranged between 8 months and 14 months.[9] ^{177}Lu-PSMA RLT is often administered to patients after failure of previous mCRPC treatments.

Actinium-225 (^{225}Ac)-PSMA RLT uses the alpha emitter ^{225}Ac to potentially improve the treatment effect of PSMA-targeted RLT. ^{225}Ac emits several alpha particles in its decay scheme that are much more energetic than the beta particles emitted by ^{177}Lu. Their ability to induce double-stranded DNA damage makes them effective for tumour cellular killing with much fewer DNA hits.[10] In a proof-of-concept study, a complete response of mCRPC to ^{225}Ac-PSMA-targeted RLT was demonstrated in two patients whose disease was refractory to ^{177}Lu-PSMA RLT.[11] ^{225}Ac-PSMA RLT, when applied as a last-line therapy option, induces a longer duration of tumour control than agents applied earlier in the treatment course.[12] The effectiveness of ^{225}Ac-PSMA RLT has been shown in other settings, including in patients with

extensive skeletal metastases of mCRPC,[13] in combination with ^{177}Lu-PSMA RLT,[14] and in the post-^{177}Lu-PSMA RLT setting.[15] A major limitation of these studies is their single-centre nature and the low number of patients included. A need, therefore, exists for a large multicentre study to support the safety and antitumour activity of ^{225}Ac-PSMA RLT of mCRPC.

Research in context

Evidence before this study

We searched PubMed for relevant articles published in any language from database inception to the search date on Oct 13, 2023 using the search terms "Prostate cancer" AND ("225Ac-PSMA-617" OR "225Ac-PSMA-I&T" OR "225Ac-PSMA"). A few studies have reported the antitumour activity of Actinium-225 (^{225}Ac) prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) in different categories of patients with metastatic castration-resistant prostate cancer (mCRPC). In one retrospective study, ^{225}Ac-PSMA RLT induced a longer duration of tumour control in heavily pretreated patients than other agents used earlier in the disease course. [^{177}Lu]Lu-PSMA-617 is a novel radiopharmaceutical approved for mCRPC treatment. ^{225}Ac-PSMA RLT has also been shown to have tumour control activity in patients with mCRPC that is refractory to or progressive after ^{177}Lu-PSMA RLT. Xerostomia is the most commonly reported side-effect of ^{225}Ac-PSMA RLT, severe enough to cause treatment discontinuation in some patients. Bone marrow and renal toxicities are also common types of treatment-induced toxicity, with a small proportion of patients developing severe bone marrow or renal toxicity due to ^{225}Ac-PSMA RLT.

Added value of this study

To our knowledge, this is the largest investigation of the antitumour effect and toxicity of ^{225}Ac-PSMA RLT in mCRPC treatment. We found that ^{225}Ac-PSMA RLT induces a decline in prostate-specific antigen (PSA) of 50% or greater in more than half of patients. The overall survival and progression-free survival of patients with mCRPC treated with ^{225}Ac-PSMA RLT are associated with level of PSA decline (ie, ≥50%), number of previous lines of mCRPC treatment, pattern of metastasis, and the presence of anaemia. Xerostomia is a common treatment-induced side-effect, and its prevalence increases with the number of administered treatment cycles. Patients with mCRPC treated with ^{225}Ac-PSMA RLT have limited bone marrow and renal functional reserve at treatment initiation, with an increase in the prevalence of bone marrow and renal toxicity after ^{225}Ac-PSMA RLT. Incidence of new-onset severe (grade ≥3) bone marrow or renal toxicity is low.

Implications of all the available evidence

The results of this international multicentre study provide the strongest evidence to date supporting the antitumour activity and safety of ^{225}Ac-PSMA RLT for mCRPC treatment. The antitumour effect of ^{225}Ac-PSMA RLT in mCRPC is influenced by several factors, including previous treatment with taxane-based chemotherapies and the pattern of mCRPC metastases. These factors should be considered in selecting patients for ^{225}Ac-PSMA RLT, especially considering the current limitation in ^{225}Ac supply and the prevalence of xerostomia induced by this therapy.

The World Association of Radiopharmaceutical and Molecular Therapy (WARMTH) is a multi-professional organisation that promotes the advancement of the science and education of therapeutic nuclear medicine and radiopharmaceutical therapy through educating nuclear medicine professionals, increasing worldwide access to radionuclide therapy, and harmonising good practice. One of the ways WARMTH achieves its goal is through the conduct of multicentre international studies to strengthen the science of radionuclide therapy.[16,17] This study, performed under the auspices of WARMTH, aimed to report the safety and antitumour

activity of ^{225}Ac-PSMA RLT in patients with mCRPC who were treated in different centres across the world.

Methods

Study design and participants

This is a WARMTH-initiated multicentre retrospective study of patients with histologically diagnosed adenocarcinoma of the prostate gland who were treated with ^{225}Ac-PSMA RLT for mCRPC at seven centres in Australia, India, Germany, and South Africa. Inclusion criteria were a diagnosis of mCRPC, PSMA-avidity in mCRPC lesions demonstrated on PET or single-photon emission computed tomography (SPECT) imaging, treatment with at least one cycle of ^{225}Ac-PSMA RLT, and the availability of post-treatment follow-up data including PSA for PSA response assessment. There were no restrictions on age or Eastern Cooperative Oncology Group (ECOG) performance status. [^{18}F]fluorodeoxyglucose PET imaging was not used for selecting patients for ^{225}Ac-PSMA RLT. Previous lines of mCRPC treatment included taxane-based chemotherapy, androgen-receptor-axis inhibitors, ^{177}Lu-PSMA RLT, and radium-223 dichloride. Patient selection for treatment and the administration of ^{225}Ac-PSMA RLT are as previously published.[18] In the planning of this study, we designed an Excel spreadsheet indicating the required data (appendix 1). The spreadsheet was sent to all major centres applying ^{225}Ac-PSMA RLT for mCRPC (appendix 2 p 1). All centres completed the spreadsheet with the anonymised data of all qualifying patients (per inclusion and exclusion criteria) who had been treated with ^{225}Ac-PSMA RLT for mCRPC up to that time. The completed spreadsheet was sent to the Department of Nuclear Medicine at the University of Pretoria, South Africa, for analysis. The Human Research Ethics Committee of the University of Pretoria gave approval for this retrospective study. ^{225}Ac-PSMA RLT was administered for the treatment of mCRPC in each participating centre in accordance with local prevailing laws and in accordance with the updated version of the Declaration of Helsinki. ^{225}Ac-PSMA RLT is not an approved treatment for mCRPC and was administered on a compassionate use basis in patients with advanced progressive mCRPC based on local and national laws of the respective contributing centres.

Procedures

Patients included received 8 MBq of ^{225}Ac-PSMA RLT administered intravenously every 8 weeks until disease remission, disease progression, death, or patient withdrawal from treatment. Data regarding patients who received a lower dose of ^{225}Ac-PSMA RLT (4–6 MBq) for salivary gland protection following favourable response to treatment were collected. Laboratory data, including serum PSA, full blood count, and renal function tests done at baseline, after each subsequent treatment cycle, and during follow-up were collected. Laboratory values from the full blood count and renal function tests obtained at baseline and after each cycle of ^{225}Ac-PSMA RLT were reported by each participating centre. We used these safety data to centrally grade the severity of haematological (anaemia, leukopenia, and thrombocytopenia) and renal (estimated glomerular filtration rate) toxicities using the Common Terminology Criteria for Adverse Events (version 5) grading system. We also used the baseline laboratory values for full blood count and renal function tests to determine the proportion of patients in whom baseline bone marrow and renal functional indices were below lower limits of normal before ^{225}Ac-PSMA RLT initiation. Each patient treated with ^{225}Ac-PSMA RLT was asked about treatment-induced xerostomia and these details were documented, but the grading of the severity of ^{225}Ac-PSMA RLT-induced xerostomia was not uniformly practiced by all

participating centres. Therefore, we reported xerostomia as a binary, xerostomia present or absent, and the proportion of patients with xerostomia after each treatment cycle was determined. We collected data on any grade 3 or greater toxicity other than haematological, renal, or salivary gland toxicities. No data regarding the race or ethnicity of the patients were collected.

Outcomes

The primary outcomes were overall survival and progression-free survival. We defined overall survival as the time from treatment initiation until death or last follow-up, whichever occurs first. We defined progression-free survival as the time from treatment initiation to disease progression, death, or last follow-up, whichever occurs first. Disease progression was defined using a composite of PSA progression, imaging-based progression, or clinical progression. PSA progression was defined as an increase in PSA concentration by at least 25% above the nadir reached, confirmed on a second measurement. Imaging-based progression was defined as the appearance of one or more new lesions on PSMA-targeted PET or conventional imaging. Clinical progression was defined as the worsening or appearance of new mCRPC-related clinical symptoms. The computation of overall and progression-free survival for each patient was done centrally based on information provided by the treating centre (ie, the date each patient received their first cycle of ^{225}Ac-PSMA RLT and the date of last follow-up, death, or disease progression).

The secondary outcomes measured were the proportion of patients who achieved PSA response or any decline in PSA concentration and the proportion of patients who developed salivary gland, haematological, and renal toxicities after ^{225}Ac-PSMA RLT. We defined PSA response as a decline of at least 50% in serum PSA, confirmed on a second reading as recommended by the Prostate Cancer Clinical Trials Working Group.[19]

Statistical analysis

Descriptive statistics were used to describe the baseline clinical and demographic characteristics of the patients. We used the Kaplan-Meier method to estimate survival functions, and used Cox proportion hazards regression to calculate hazard ratios (HRs) and 95% CIs. A waterfall plot was created to illustrate the best PSA response for each patient that was included in the study. We stratified patients based on previous lines of treatment they received for mCRPC, the pattern of mCRPC metastases, and clinical and laboratory parameters, and used the unstratified log-rank test to compare survival distributions between subgroups dichotomised based on PSA decline of at least 50% (yes or no), previous docetaxel or enzalutamide (yes or no), previous abiraterone (yes or no), previous treatment with ^{177}Lu-PSMA RLT (yes or no), presence of liver metastases (yes or no), presence of peritoneal metastases (yes or no), presence of visceral metastases (yes or no), presence of anaemia at baseline (yes or no), baseline platelet count greater than 300 000/mm^3 (yes or no), and baseline ECOG performance status of 2 or higher (yes or no), as well as the number of cycles of ^{225}Ac-PSMA RLT and time since diagnosis as continuous variables. For increasing ^{225}Ac-PSMA RLT treatment cycles, the HR represents the odds of an event occurring per unit increase in treatment cycles while the HR for time since diagnosis represents the odds of event occurring for every additional year since prostate cancer diagnosis. For the categorical variables, the HR represents the odds of the event occurring. We set statistical significance at a p value of less than 0·05 and used IBM SPSS Statistics version 27 for statistical analysis.

Role of the funding source

There was no funding source for this study.

Results

A total of 488 men who were treated with ^{225}Ac-PSMA RLT for mCRPC between Jan 1, 2016 and May 31, 2023 were included. The patients were treated at GenesisCare, Murdoch, WA, Australia (n=57); Postgraduate Institute of Medical Education and Research, Chandigarh, India (n=15); Fortis Memorial Research Institute, Gurgaon, India (n=40); All India Institute of Medical Sciences, New Delhi, India (n=56); University Hospital Heidelberg, Heidelberg, Germany (n=22); Technical University Munich, Munich, Germany (n=50); and University of Pretoria, Pretoria, South Africa (n=248). At the commencement of ^{225}Ac-PSMA RLT, the mean age of patients was 68·1 years (SD 8·8) and the median serum PSA concentration was 169·5 ng/mL (IQR 34·6–519·8). Table 1 shows the details of the mCRPC characteristics and previous lines of treatment of the patients. A total of 118 (24%), 114 (23%), 71 (15%), and 185 (38%) patients had received one, two, three, and four or more lines of treatment for mCRPC before treatment with ^{225}Ac-PSMA RLT, respectively. PSMA-avidity in mCRPC lesions was determined by PET in 464 (95%) patients and SPECT imaging in 24 (5%) patients. A total of 1174 cycles of ^{225}Ac-PSMA RLT were administered to the patients, with a median of two cycles (IQR 2–4). 162 (33%) of 488 patients responded to treatment based on gallium-68 PSMA PET-CT findings of minimal residual disease, and the administered activity of ^{225}Ac-PSMA RLT was reduced for salivary gland protection. At the time of data collection, 34 (7%) of 488 patients were still receiving ^{225}Ac-PSMA RLT. Of the remaining 454 (93%) patients who were not on treatment at the time of data collection, 174 (36%) had interruption (temporarily or permanently) to their ^{225}Ac-PSMA RLT treatment schedule, while 280 (57%) completed their schedule of ^{225}Ac-PSMA RLT as planned. The reasons for treatment interruption included favourable response to treatment (n=84), disease progression (n=24), logistical issues such as disruption in ^{225}Ac supply (n=34), xerostomia (n=11), unstable clinical condition (n=8), and other not-specified reasons (n=13). 446 (91%) of 488 patients treated in this study received ^{225}Ac-PSMA RLT as a last line therapy option because they had exhausted or were ineligible for other treatment options. Of these 446 patients, 276 (62%) died while on this treatment or received repeated cycles of ^{225}Ac-PSMA RLT for disease stabilisation. Treatment with other active anticancer agents after disease progression on ^{225}Ac-PSMA RLT was rare (out of 306 patients who died, 30 [10%] received another form of treatment after disease progression).

Table 1. Baseline clinical variables of patients treated with ^{225}Ac-PSMA RLT

	All patients (n=488)
Age, years	
Mean (SD)	68·1 (8·8)
Range	37–90
PSA at baseline, ng/mL	
Median (IQR)	169·5 (34·6–519·8)
ISUP grade group*	
Grade 1	21/363 (6%)
Grade 2	37/363 (10%)
Grade 3	46/363 (13%)
Grade 4	89/363 (25%)
Grade 5	170/363 (47%)
Not available	125/488 (26%)
ECOG performance status	
0	124 (25%)
1	194 (40%)
2	78 (16%)
3	42 (9%)
4	13 (3%)
Not available	37 (8%)
Previous treatment for mCRPC	
Docetaxel	324 (66%)
Cabazitaxel	103 (21%)
Abiraterone	191 (39%)
Enzalutamide	188 (39%)
^{177}Lu-PSMA RLT	154 (32%)
Radium-223 dichloride	18 (4%)
Pattern of disease	
Bone metastases	435 (89%)
Lymph node metastases	352 (72%)
Visceral metastases	99 (20%)
Peritoneal metastases	8 (2%)

Data are n (%) or n/N (%) unless otherwise indicated. ^{177}Lu=Lutetium-177. ^{225}Ac=Actinium-225. ECOG=Eastern Cooperative Oncology Group. ISUP=International Society of Urological Pathology. mCRPC=metastatic castration-resistant prostate cancer. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. RLT=radioligand therapy.
*Data on ISUP grade were available for 363 patients.

The median follow-up duration was 9·0 months (IQR 5·0–17·5). A total of 306 (63%) of 488 patients had died at the time of data collection, with a median overall survival of 15·5 months (95% CI 13·4–18·3). All deaths occurred due to mCRPC and its complications. No treatment-related death was recorded. Median overall survival was significantly longer in patients who had a decline of at least 50% in PSA; those without previous exposure to taxane-based chemotherapy, androgen-axis-receptor inhibitors, or ^{177}Lu-PSMA RLT; those without liver, peritoneal, or visceral metastases of mCRPC; and those without anaemia at the time of ^{225}Ac-PSMA RLT commencement (table 2 and appendix 2 pp 2–9). Median overall survival was not significantly different according to the patients' ECOG performance status or baseline platelet count (table 2, appendix 2 p 10).

Table 2. Median overall survival and progression-free survival for patient subgroups

	Overall survival			Progression-free survival		
	Median (95% CI)	**Log-rank test**	**p value**	**Median (95% CI)**	**Log-rank test**	**p value**
PSA decline of ≥50%						
Yes	24·214 (18·300–30·094)	59·772	<0·0001	11·598 (9·626–13·799)	79·120	<0·0001
No	9·331 (7·294–10·612)	..	..	4·008 (3·318–4·534)	..	..
Previous docetaxel or cabazitaxel						
Yes	13·700 (12·057–16·000)	5·7916	0·016	6·834 (5·487–7·589)	21·366	<0·0001
No	24·214 (14·982–28·715)	..	..	13·930 (9·626–15·671)	..	..
Previous abiraterone or enzalutamide						
Yes	12·682 (11·466–15·244)	10·110	0·0015	5·914 (4·632–7·392)	35·040	<0·0001
No	19·943 (15·573–25·659)	..	..	10·612 (8·312–14·259)	..	..
Previous ^{177}Lu-PSMA RLT						
Yes	10·546 (9·199–12·419)	13·471	0·0002	5·487 (4·041–6·834)	21·957	<0·0001
No	18·793 (15·573–22·538)	..	..	9·331 (8·049–11·598)	..	..
Liver metastasis						
Yes	7·688 (5·421–12·255)	20·134	<0·0001	3·975 (3·187–4·797)	27·704	<0·0001
No	17·577 (14·522–20·632)	..	..	8·312 (7·491–9·626)	..	..
Peritoneal metastasis						
Yes	4·797 (2·858–5·520)	30·815	<0·0001	1·544 (1·380–4·435)	21·915	<0·0001
No	15·671 (13·700–18·793)	..	..	7·984 (7·195–9·166)	..	..
Anaemia at baseline						
Yes	10·612 (7·819–13·634)	21·737	<0·0001	5·749 (4·567–7·819)	10·567	0·0012
No	19·351 (15·934–25·561)	..	..	8·838 (7·589–10·743)	..	..
Platelet count at baseline >300 000/mm^3						
Yes	15·474 (13·339–22·078)	0·105	0·75	8·444 (6·341–13·700)	1·317	0·25
No	15·573 (12·616–19·318)	..	..	7·589 (6·472–8·805)	..	..
Baseline ECOG performance status ≥2						
Yes	14·653 (11·466–21·125)	1·716	0·19	6·637 (4·567–8·608)	9·661	0·0019
No	16·000 (13·667–20·632)	..	..	8·608 (7·786–10·349)	..	..

These analyses were unstratified. Median survival values are in months. ^{177}Lu=Lutetium-177. ^{225}Ac=Actinium-225. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. RLT=radioligand therapy.

In univariable analysis (table 3), a PSA decline of at least 50% and increasing ^{225}Ac-PSMA RLT treatment cycles were significantly associated with a lower risk of death. On the contrary, previous treatment with taxane-based chemotherapy, androgen-receptor-axis inhibitors, or ^{177}Lu-PSMA RLT; the presence of liver metastases or peritoneal metastases; and anaemia at the commencement of ^{225}Ac-PSMA RLT were significantly associated with a higher risk of death. Platelet count at baseline, baseline ECOG performance status, and time since diagnosis

were not associated with overall survival in univariable analysis. On multivariable analysis, PSA decline of at least 50%, presence of liver or peritoneal metastases, and anaemia at baseline maintained their significant association with risk of death.

Table 3. Univariable and multivariable analyses of factors associated with progression-free survival and overall survival

	Overall survival				**Progression-free survival**			
	Univariable HR (95% CI)	**p value**	**Multivariable HR (95% CI)**	**p value**	**Univariable HR (95% CI)**	**p value**	**Multivariable HR (95% CI)**	**p value**
PSA decline of ≥50%	0·348 (0·263–0·460)	<0·0001	0·415 (0·307–0·561)	<0·0001	0·367 (0·291–0·461)	<0·0001	0·431 (0·330–0·565)	<0·0001
Previous docetaxel or cabazitaxel	1·398 (1·062–1·841)	0·017	1·114 (0·772–1·608)	0·56	1·714 (1·360–2·160)	<0·0001	1·370 (1·012–1·853)	0·041
Previous abiraterone or enzalutamide	1·512 (1·170–1·955)	0·0016	1·175 (0·822–1·681)	0·38	1·882 (1·521–2·329)	<0·0001	1·282 (0·966–1·702)	0·085
Treatment with ^{177}Lu-PSMA RLT	1·663 (1·264–2·188)	0·0003	1·213 (0·876–1·680)	0·25	1·693 (1·355–2·116)	<0·0001	1·100 (0·838–1·443)	0·49
Liver metastasis	2·344 (1·597–3·440)	<0·0001	1·895 (1·253–2·867)	0·0025	2·395 (1·712–3·352)	<0·0001	1·878 (1·308–2·696)	0·0006
Peritoneal metastasis	6·728 (3·084–14·676)	<0·0001	5·025 (2·177–11·601)	0·0002	5·115 (2·386–10·966)	<0·0001	4·080 (1·675–9·937)	0·0020
Number of cycles of ^{225}Ac-PSMA RLT	0·861 (0·801–0·927)	0·0001	0·924 (0·850–1·006)	0·067	0·887 (0·834–0·943)	0·0001	0·970 (0·905–1·039)	0·38
Anaemia at baseline	1·886 (1·438–2·473)	<0·0001	1·615 (1·198–2·176)	0·0016	1·450 (1·157–1·817)	0·0012	1·249 (0·965–1·615)	0·091
Platelet count at baseline >300 000/mm^3	0·952 (0·709–1·279)	0·75	NA	NA	0·865 (0·674–1·109)	0·25	NA	NA
Baseline ECOG performance status ≥2	1·223 (0·904–1·653)	0·19	NA	NA	1·452 (1·146–1·839)	0·0020	1·031 (0·7930–1·340)	0·82
Time since diagnosis	1·021 (0·994–1·049)	0·13	NA	NA	1·019 (0·996–1·042)	0·099	NA	NA

^{177}Lu=Lutetium-177. ^{225}Ac=Actinium-225. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NA=not applicable (only variables whose association demonstrated statistical significance with the outcome on univariable analysis are included in the multivariable analysis). PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. RLT=radioligand therapy.

Disease progression occurred in 397 (81%) of 488 patients at the time of data collection, with an overall median progression-free survival of 7·9 months (95% CI 6·8–8·9). Median progression-free survival was significantly longer in patients who had a PSA decline of at least

50%; those without previous exposure to taxane-based chemotherapy, androgen-axis-receptor inhibitors, or ^{177}Lu-PSMA RLT; those without liver, peritoneal, or visceral metastases; those without anaemia at the commencement of ^{225}Ac-PSMA RLT; and those whose ECOG performance status was less than 2 (table 2 and appendix 2 pp 11–19).

In univariable analysis (table 3), a PSA decline of at least 50% and an increasing number of ^{225}Ac-PSMA RLT treatment cycles were significantly associated with a lower risk of disease progression. Previous treatment with taxane-based chemotherapy, androgen-receptor-axis inhibitors, or ^{177}Lu-PSMA RLT; the presence of liver or peritoneal metastases; anaemia at ^{225}Ac-PSMA RLT initiation; and ECOG performance status of 2 or higher were significantly associated with a higher risk of disease progression on ^{225}Ac-PSMA RLT. Platelet count at baseline and time since diagnosis were not associated with progression-free survival in univariable analysis. On multivariable analysis, PSA decline of at least 50%, previous treatment with taxane-based chemotherapy, liver metastases, and peritoneal metastases maintained their significant association with the risk of disease progression. Eight (2%) of 488 patients with peritoneal metastases mostly had nodular peritoneal masses in addition to nodal and skeletal metastases of mCRPC.

A total of 358 (73%) of 488 patients had any PSA decline after receiving at least one cycle of ^{225}Ac-PSMA RLT (figure). In 278 (57%) of 488 patients, there was a PSA decline of 50% or more.

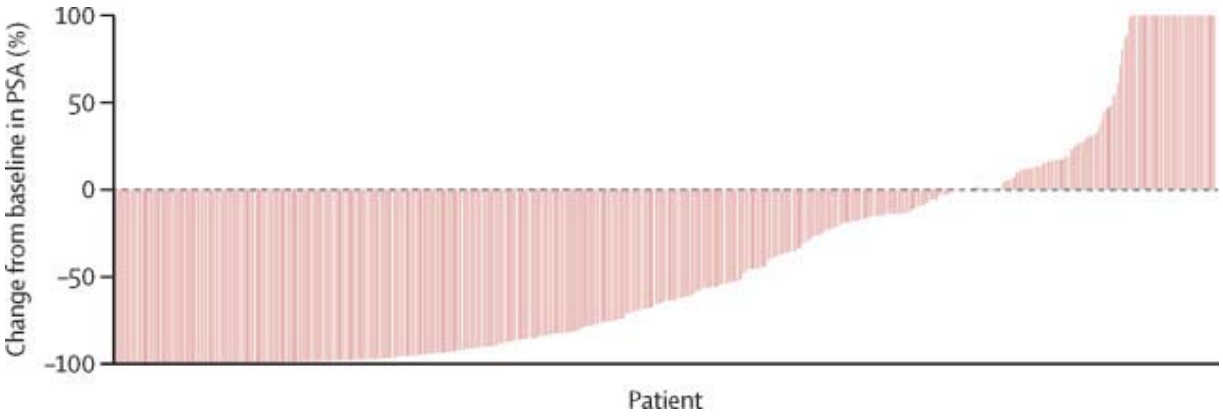

Figure. Waterfall plot showing the best PSA response in 488 patients treated with Actinium-225 prostate-specific membrane antigen radioligand therapy

278 patients (57%) had a ≥50% PSA decline. PSA=prostate-specific antigen.

Xerostomia emerged as a common adverse event. In 347 (71%) of 488 patients, information about xerostomia was available after the first cycle of ^{225}Ac-PSMA RLT. 236 (68%) of 347 patients reported xerostomia after the first cycle of treatment, 206 (86%) of 239 patients after the second cycle, 129 (91%) of 142 patients after the third cycle, 72 (88%) of 82 patients after the fourth cycle, 42 (95%) of 44 patients after the fifth cycle, 17 (94%) of 18 patients after the sixth cycle, and 15 (94%) of 16 patients after the seventh cycle. 15 patients received eighth, ninth, and tenth cycles of ^{225}Ac-PSMA RLT, and they all developed xerostomia. 11 (2%) of 488 patients discontinued treatment because of xerostomia.

Bone marrow toxicities were present in a substantial number of patients before ^{225}Ac-PSMA RLT. Grade 1 anaemia was present in 181 (37%) of 488 patients, grade 2 in 120 (25%), and grade 3 in 23 (5%). Baseline white blood cell count corresponding to grade 1 toxicity was observed in 68 (14%) of 488 patients, grade 2 in 17 (3%), and grade 3 in four (<1%). For baseline platelet count, levels corresponding to grade 1 toxicity were found in 127 (26%) of 488 patients, grade 2 in eight (2%), grade 3 in five (1%), and grade 4 in ten (2%). After ^{225}Ac-PSMA RLT, any grade of anaemia was found in 393 (81%) of 488 patients, leukopenia in 217 (44%), and thrombocytopenia in 262 (54%). Grade 3 or higher anaemia occurred in 64 (13%) of 488 patients, leukopenia in 19 (4%), and thrombocytopenia in 32 (7%; table 4).

Table 4. Bone marrow toxicity and renal functional impairment before and after ^{225}Ac-PSMA RLT

	Before ^{225}Ac-PSMA RLT (n=488)				**After ^{225}Ac-PSMA RLT (n=488)**			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Anaemia	301 (62%)	23 (5%)	0	0	329 (67%)	64 (13%)	0	0
Leukopenia	85 (17%)	4 (<1%)	0	0	198 (41%)	18 (4%)	1 (<1%)	0
Thrombocytopenia	135 (28%)	5 (1%)	10 (2%)	0	230 (47%)	17 (3%)	15 (3%)	0
Renal function impairment (eGFR)	229 (47%)	11 (2%)	3 (<1%)	0	250 (51%)	17 (3%)	5 (1%)	0

^{225}Ac=Actinium-225. PSMA=prostate-specific membrane antigen. RLT=radioligand therapy. eGFR=estimated glomerular filtration rate.

At baseline, 243 (50%) of 488 patients had renal functional impairment (grade 1 in 158 [32%], grade 2 in 71 [15%], grade 3 in 11 [2%], and grade 4 in three [<1%]). After ^{225}Ac-PSMA RLT, any grade of renal functional impairment was seen in 272 patients (56%), including 22 patients (5%) with grade 3 or higher renal functional impairment.

There was no other incidence of grade 3 or higher adverse events reported, nor any serious adverse events. No treatment-induced adverse events or death were recorded.

Discussion

In our multicentre retrospective analysis, we report the results of 488 patients with mCRPC treated with ^{225}Ac-PSMA RLT. The median overall survival was 15·5 months (95% CI 13·4–18·3) and the median progression-free survival was 7·9 months (6·8–8·9). Any PSA decline was seen in 73% of patients while a PSA decline of 50% or more was recorded in 57% of patients. Several factors were associated with overall survival, including PSA response, previous treatments received before ^{225}Ac-PSMA RLT, the pattern of mCRPC metastases, and the presence of anaemia at baseline.

Multiple lines of therapeutic agents with life-prolonging activity are available for the treatment of mCRPC.[1, 2, 3, 4, 5, 6, 7] Agents used earlier in the evolution of mCRPC induce a longer duration of treatment control compared with those used later in the advanced phase of the disease. The safety and efficacy of ^{225}Ac-PSMA RLT for mCRPC have been reported in different settings, including in patients with de novo hormone-sensitive prostate cancer, patients with chemotherapy-naive mCRPC, patients previously treated with androgen-deprivation therapy for mCRPC, and patients previously treated with ^{177}Lu-PSMA RLT for mCRPC.[15, 20, 21, 22] Notably, ^{225}Ac-PSMA RLT given as a last-line therapy intervention induces a similar or longer

duration of disease control compared with agents given earlier in the disease evolution.[12] These reports are mostly single-centre studies, and their conclusions are limited by the low patient numbers.

The comparatively larger patient population included in this study made robust comparisons between subsets of patient cohorts feasible. We confirmed the impact of previous treatments with any taxane-based chemotherapy, androgen-receptor-axis inhibitors, or ^{177}Lu-PSMA RLT on overall survival and progression-free survival. Patients pretreated with any of these lines of agents had significantly shorter overall survival and progression-free survival compared with patients who were not pretreated. Given the natural history of disease progression, mCRPC tends to evolve more aggressively despite currently available treatment options. In several retrospective analyses for ^{177}Lu-PSMA RLT studies, previous treatment with taxane chemotherapy has been shown to be associated with a shorter time to death or disease progression in mCRPC.[17, 23, 24] ^{225}Ac-PSMA RLT is a viable treatment option inducing disease control in patients who have not responded to or have progressed after initial response to ^{177}Lu-PSMA RLT.[11, 15] However, ^{225}Ac-PSMA RLT applied after previous ^{177}Lu-PSMA RLT is associated with a lower PSA response rate and shorter time to death or disease progression.[25] In a 2023 systematic review of studies reporting outcomes of patients treated with ^{225}Ac-PSMA RLT, pooled median overall survival of patients with mCRPC with previous exposure to ^{177}Lu-PSMA RLT was 11·1 months versus 9·2 months in ^{177}Lu-PSMA RLT-naive patients.[26] The median pooled progression-free survival was 4·3 months for ^{177}Lu-PSMA RLT-exposed patients versus 13 months for ^{177}Lu-PSMA RLT-naive patients. While the relationship between progression-free survival and previous ^{177}Lu-PSMA RLT exposure agrees with our findings, a longer median overall survival in ^{177}Lu-PSMA RLT-exposed patients is counterintuitive. This longer overall survival in ^{177}Lu-PSMA RLT-exposed patients was driven by one study included in the meta-analysis, which reported a median overall survival of 17 months. By contrast, the shortest median overall survival reported by a study in the meta-analysis was 1·3 months.

Other factors such as the pattern of metastases and the presence of anaemia showed significant association with both overall and progression-free survival in patients with mCRPC treated with ^{225}Ac-PSMA RLT. The presence of visceral metastases has been widely reported to be associated with worse PSMA-targeted radioligand treatment outcomes.[24] In our study, we found significantly shorter overall survival and progression-free survival in patients with peritoneal metastases. The eight patients with peritoneal metastases mostly had nodular peritoneal masses in addition to nodal and skeletal metastases of mCRPC. The short range of alpha particles emitted by ^{225}Ac might make ^{225}Ac-PSMA RLT ineffective for the eradication of these bulky lesions, explaining the association between peritoneal metastases and poor treatment outcomes. Anaemia in mCRPC results from many factors, including the bone marrow toxicities induced by previous lines of treatment, the burden of bone marrow metastases of mCRPC,[13] the impact of age, and the effect of comorbidities. The presence of anaemia might contribute to a poorer performance status of patients with mCRPC. The significant association between the trio of peritoneal metastases, liver metastases, and baseline anaemia on overall and progression-free survival with mCRPC suggests that patients with comparatively lower burden of disease might benefit more from ^{225}Ac-PSMA RLT. Importantly, to our knowledge, this is the first study demonstrating the significant association between the presence of peritoneal metastases of mCRPC and anaemia at ^{225}Ac-PSMA RLT commencement with therapy outcome.

Two variables, ECOG performance status and number of cycles of ^{225}Ac-PSMA RLT administered, showed interesting associations with progression-free survival. ECOG

performance status of 2 or higher showed significant association with higher risk of disease progression at univariable analysis but not at multivariable analysis, demonstrating that considered alone, performance status of 0 or 1 is associated with a longer time to disease progression but not when other factors such as previous lines of treatment, pattern of metastases, and the presence of anaemia were considered together. ECOG performance status showed no significant association with overall survival. As for the number of cycles of ^{225}Ac-PSMA RLT administered for treatment, more treatment cycles did not translate into better progression-free survival or overall survival on multivariable analysis in our study cohort. This finding might be explained by patients with favourable response after one or two cycles of ^{225}Ac-PSMA RLT not requiring further treatment and showing durable remission and long-term survival.

Treatment-induced xerostomia was prevalent in our cohort, occurring in 68% of patients after one cycle of ^{225}Ac-PSMA RLT and in all patients who were treated with eight cycles or more. This finding shows the dose-dependent nature of salivary gland damage due to ^{225}Ac-PSMA RLT. A contributing factor to the high prevalence of xerostomia in our study cohort might relate to almost a third of patients included in this study having been previously treated with xerostomia-inducing ^{177}Lu-PSMA RLT. Overall, only 11 patients discontinued treatment due to xerostomia, which suggests that the degree of xerostomia experienced by the patients was largely tolerable. In the dose-finding study of Kratochwil and colleagues, 100 kBq/kg was the optimum activity of [^{225}Ac]Ac-PSMA-617 that induced an antitumour effect with tolerable side-effects.[27] Administered at this activity, treatment-induced xerostomia is still highly prevalent in patients with mCRPC treated with ^{225}Ac-PSMA RLT. The optimum dosing of [^{225}Ac]Ac-PSMA-617 is being investigated further in the ongoing phase 1 dose-escalation AcTION trial (NCT04597411).

Bone marrow toxicity is a known adverse effect of ^{225}Ac-PSMA RLT. In our study, there was a high prevalence of bone marrow toxicity in the included patients, with any grade of anaemia seen in 81%, leukopenia in 44%, and thrombocytopenia in 54% of patients. Of these patients, grade 3 or higher anaemia was seen in 13%, leukopenia in 4%, and thrombocytopenia in 7%. This high level of haematological toxicity is attributable to the high prevalence of impaired bone marrow reserve at baseline. The level of bone marrow toxicity reported after ^{225}Ac-PSMA RLT in this study represents a moderate increase compared with baseline. ^{225}Ac-PSMA RLT is mostly administered as a last-line compassionate treatment in patients who have not responded to or are unfit for other lines of therapy. At the time of ^{225}Ac-PSMA RLT initiation, bone marrow functional reserve is typically limited by the impact of previous haematotoxic therapies or the advanced mCRPC disease. The renal tubular epithelium expresses PSMA, and the urinary system serves as the excretory route for PSMA-targeted ligands, making the kidneys susceptible to potential PSMA RLT-induced nephrotoxicity. In our cohort, renal toxicity was prevalent at baseline, with a minimal rise in the number of patients with renal functional impairment after ^{225}Ac-PSMA RLT. Overall, our data show a modest level of haematological and renal toxicity of ^{225}Ac-PSMA RLT, even in this cohort of patients with limited bone marrow and renal functional reserve at the time of therapy initiation.

The strength of this study is in the large number of patients included, representing, to our knowledge, the largest series of patients with mCRPC treated with ^{225}Ac-PSMA RLT published to date. This study included the data of consecutive patients treated with ^{225}Ac-PSMA RLT in most of the major centres offering this service across the world. The large number of patients included allowed for robust subgroup comparisons based on a number of variables. The subgroup comparison is important in selecting patients for ^{225}Ac-PSMA RLT to address the

limitation in the availability of ^{225}Ac and to offer the treatment to the patients with the highest odds of response.

This study also has some important limitations, including its retrospective design. Laboratory data obtained at baseline and after each treatment cycle were used to compute the toxicities of ^{225}Ac-PSMA RLT. This only provides data for the acute and subacute toxicity due to the treatment. Laboratory data from long-term follow-up of patients are still necessary to determine the long-term effects of this treatment. In addition, the prevalence and severity of xerostomia were not captured by validated questionnaires, or their severity graded, but were based on clinical assessment. The investigation of the safety of ^{225}Ac-PSMA RLT was limited to the assessment of salivary gland, bone marrow, and renal toxicities as they are the most commonly known side-effects of this treatment modality. We sought but found no incidence of grade 3 or higher treatment-induced adverse events other than haematological or renal toxicities, which indicates that no severe adverse effects of treatment were missed. Despite this, the risk of under-reporting of the full extent of treatment-induced toxicities remains a potential limitation of this study as less severe adverse events (grades 1 and 2) might have been missed and not reported. In multicentre studies such as this one, there might be important differences in the source of radionuclide or peptide used for synthesising the therapy agent and the protocol for therapy administration, with potential impact on treatment outcome.

In conclusion, ^{225}Ac-PSMA RLT has substantial antitumour effects in mCRPC, including in patients with compromised bone marrow and renal functional reserve. Previous lines of mCRPC treatment and metastatic burden affect the time to death or disease progression. Xerostomia is a common treatment-induced toxicity of ^{225}Ac-PSMA RLT. Prospective trials are needed to validate the safety and survival benefits of ^{225}Ac-PSMA RLT in patients with mCRPC. Specifically, future prospective studies investigating the safety and efficacy of ^{225}Ac-PSMA RLT in patients who have not responded to ^{177}Lu-PSMA RLT are needed to validate its use for this indication.

Contributors
MMS and IOL conceived and designed the study. IOL designed the Excel spreadsheet for data collection. CB, SB, GC, CD, TH, CK, NPL, JM, LCM, KMGM, HN, VP, HR, JR, IBS, ASo, ASi, RT, PT, and MPY did the data collection. MMS, CB, SB, CD, ME, CK, NPZ, HR, ABS, ASo, ASi, RT, PT, and MPY were responsible for patients' accrual and treatment. MMS and IOL had full access to, and verified, the data. MMS and IOL wrote the first draft of the manuscript. FB, OK, JM, AHM, and AM provided technical and material supports. MMS supervised the study. All authors approved the draft and final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

The de-identified individual-level patient data, data dictionary, and protocol for this study can be provided to researchers upon written request 24–36 months after publication of the Article. Please send enquiries to the corresponding author. A detailed proposal for how the data will be used is required and we will assess applications on a case-by-case basis, and only for the purpose of individual participant data meta-analysis. A data access agreement must be signed for these data to be released.

Declaration of interests

MMS reports grants or contracts from Novartis; payment or honoraria from Bayer, Johnson & Johnson, NTP, and Sanofi; support for attending meetings from the International Atomic Energy Agency; and receipt of equipment or materials from POINT Biopharma. ME reports grants or contracts from Blue Earth Diagnostics; royalties from patent on radiohybrid PSMA; consulting fees from Novartis, Point Biopharma, payment from Novartis; payment for expert testimony from Novartis, Bayer, Telix, and Blue Earth Diagnostics; support for attending meetings from Blue Earth Diagnostics; and patent ownership on radiohybrid PSMA. TH reports grants or contracts from Siemens. CK reports patent ownership. NPL reports contracts from Telix, Ipsen/Ariceum, and Clarity; receipt of educational material from Telix; support for attending meetings from Telix; participation on the advisory board of Telix; and family stock ownership at Clarity. ASi reports support for attending meetings from Telix International, Australia and participation on Data Safety Monitoring Borad for Telix International. RT reports payment or honoraria from Astella, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Merck, MSD, Novartis, Orion, Pfizer, Roche, and Sanofi; support for attending meetings from Bayer, Janssen, Orion, Pfizer, and Roche; participation on Data Safety Monitoring Board or Advisory Board of Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Eisei, EUSA, IPSEN, Janssen, Merck, MSD, Novartis, Orion, Pfizer, Philogen, Roche, and Sanofi; stock ownership at Bayer; and financial or non-financial interests at Thieme compliance and Elsevier. AM reports patents owning a patent for treatment of PSMA-expressing cancers. All other authors declare no competing interests.

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