

First-in-human evaluation of ^{225}Ac -PSMA-Trillium™ (BAY 3563254; ^{225}Ac felivotide mopaxetan) in metastatic castration-resistant prostate cancer: the phase 1 PAnTHA study

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ABSTRACT (150/150)

Prolonged survival demonstrated with the alpha-emitting radionuclide radium-223 dichloride and the prostate-specific membrane antigen (PSMA)-targeting radioligand [¹⁷⁷Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC) provides a rationale for combining the potent alpha-emitter actinium-225 ([²²⁵Ac]Ac) with a PSMA-targeting moiety. We report the dose escalation part (n=50) of the phase 1 PAnTHA study (NCT06217822) evaluating safety and efficacy of [²²⁵Ac]Ac-PSMA-Trillium (BAY 3563254; ²²⁵Ac felivotide mopaxetan) in heavily pretreated patients with mCRPC. [²²⁵Ac]Ac-PSMA-Trillium was relatively well tolerated with no dose-limiting toxicities. Xerostomia occurred in 86% of patients (grade 1: 56%, grade 2: 30%) and did not cause treatment discontinuation. Overall, 44% had grade 3 treatment-emergent adverse events, most commonly lymphopenia (22%) and anemia (6%). Two patients had grade 4 lymphopenia. Finally, 62% achieved PSA50, with respective overall response and disease control rates of 50% and 83%. [²²⁵Ac]Ac-PSMA-Trillium has a manageable safety profile and strong preliminary efficacy in heavily pretreated patients with mCRPC.

INTRODUCTION

Available agents for treating metastatic castration-resistant prostate cancer (mCRPC) include androgen receptor pathway inhibitors (ARPIs), taxane-based chemotherapy, Poly(ADP-ribose) polymerase (PARP) inhibitors, immunotherapy and targeted radionuclide therapies (TRT).^{1,2} With ARPIs and taxanes now used earlier in the management of prostate cancer (PC), e.g., metastatic hormone-sensitive PC and non-metastatic CRPC,¹ limited options remain for patients progressing to mCRPC having already received these treatments. Furthermore, with median overall survival (OS) <18 months in patients previously treated with ARPIs and taxanes,^{3,4} new treatments are needed to improve outcomes in patients with mCRPC.

The first TRT approved to treat mCRPC was the alpha-emitter radium-223 dichloride (hereafter radium-223), which targets areas of bone remodeling, such as bone metastases.^{5,6} Compared with beta particles, such as those emitted by lutetium-177 (¹⁷⁷Lu)Lu, alpha particles have a much stronger linear energy transfer (LET; 100 KeV/mm vs 0.2 KeV/mm) which induce clusters of difficult to repair double-stranded DNA breaks, promoting cell cycle arrest and cell death.⁷⁻⁹ Alpha particles also have a shorter emission range than beta particles (40–90 µm vs 0.5–12 mm), which can minimize DNA damage to healthy tissues.¹⁰

The transmembrane glycoprotein, prostate-specific membrane antigen (PSMA) is expressed in 95% of patients with mCRPC.¹¹ Moreover, high PSMA-avidity on PSMA positron emission tomography (PET) imaging is a marker of tumor burden in PC.^{12,13} The therapeutic utility of targeting PSMA was demonstrated in the phase 3 VISION trial, where the PSMA-binding, beta-emitting [¹⁷⁷Lu]Lu-PSMA-617 (lutetium-177 vipivotide tetraxetan) elicited a survival benefit when added to standard care in patients with mCRPC previously treated with ≥1 ARPI and 1–2 taxane-based chemotherapy regimens.⁴ The subsequent phase 3 PSMAfore study demonstrated a radiographic progression-free survival (rPFS) advantage in taxane-naïve mCRPC, although no significant OS benefit.¹⁴

Given the proven tolerability and efficacy seen with the alpha-emitting radium-223 and the PSMA-targeting [¹⁷⁷Lu]Lu-PSMA-617 in mCRPC,^{4,15} there is a rationale for developing novel alpha-emitting PSMA-targeted therapies capable of emitting stronger radiation and targeting PSMA-expressing PC metastases in soft tissues as well as bone.

A few PSMA-targeting investigational agents utilizing the alpha-emitter actinium-225 (²²⁵Ac)Ac have been developed and assessed in preclinical and early clinical studies,¹⁶⁻²² including [²²⁵Ac]Ac-PSMA-Trillium (BAY 3563254; ²²⁵Ac felivotide mopaxetan),²³ as well as other agents under compassionate use.²⁴ [²²⁵Ac]Ac-PSMA-Trillium comprises a high-affinity PSMA-binding motif, a customized albumin-binding moiety designed to prolong plasma residence time and increase tumor uptake, and a Macropa[™] chelator complexed with [²²⁵Ac]Ac, which facilitates the targeted delivery of cytotoxic radiation to PSMA-expressing cells (**Supplementary Figure 1**).^{23,25-28} In preclinical models of PC, [²²⁵Ac]Ac-PSMA-Trillium strongly suppressed tumor growth.²³

The first-in-human phase 1 PAnTHA study is assessing the safety, tolerability and preliminary efficacy of [²²⁵Ac]Ac-PSMA-Trillium in patients with mCRPC (NCT06217822). The study consists of a dose escalation part followed by a dose expansion part (**Supplementary Figure 2**). Here, we report results for the former. The primary aims were to assess the safety and efficacy of [²²⁵Ac]Ac-PSMA-Trillium and establish the recommended dose for expansion (RDE). Exploratory analyses included correlative analyses with PSMA-PET and pharmacokinetics.

RESULTS

Preclinical proof-of-concept

In an initial, separate proof-of-concept experiment, the efficacy and safety of [²²⁵Ac]Ac-PSMA-Trillium was compared with [¹⁷⁷Lu]Lu-PSMA-617 in a LNCap cell line-derived xenograft model. Based on effective activities established in previous studies,^{29,30} the administered activity for [¹⁷⁷Lu]Lu was chosen to be ~1,000-fold higher than [²²⁵Ac]Ac. Tumor-bearing mice were treated with two doses of either 150 kBq/kg [²²⁵Ac]Ac-PSMA-Trillium, 150 MBq/kg [¹⁷⁷Lu]Lu-PSMA-617, 300 MBq/kg [¹⁷⁷Lu]Lu-PSMA-617, or vehicle given one week apart. Compared with vehicle, both agents significantly inhibited tumor growth, with [²²⁵Ac]Ac-PSMA-Trillium ($P<0.0001$ versus vehicle) eliciting a greater effect than [¹⁷⁷Lu]Lu-PSMA-617 ($P<0.001$ and $P<0.05$) (**Supplementary Figure 3a**). Of note, both agents were well tolerated, as demonstrated by stable body weights (**Supplementary Figure 3b**).

Patients

The study was initiated on 7 March 2024 with the first patient treated on 23 April 2024. As of 13 March 2026 (data cutoff), 50 patients had received ≥ 1 dose of [²²⁵Ac]Ac-PSMA-Trillium (**Figure 1**). Doses of 75, 100, 125, and 150 kBq/kg were investigated, administered intravenously in 6-weekly cycles for a maximum of 4 cycles. Patients received a median of 4 (range 2–4) doses; 80% received all 4 doses. Median time on study from start of treatment was 8.3 (range 2.5–21.7) months. Baseline characteristics are shown in **Table 1**.

Safety: Treatment emergent adverse events (TEAEs)

All patients experienced ≥ 1 TEAE, with most (98%) having ≥ 1 TEAE considered treatment related (**Table 2** and **Extended Data Table 1**). The most common any-grade TEAEs were xerostomia (86%), fatigue (54%), nausea (48%), decreased appetite (40%), anemia (38%), and lymphopenia (including decreased lymphocyte count; 30%) (**Figure 2a** and **Extended Data Table 2**).

Grade 3 TEAEs were experienced by 44% of patients, and those seen in ≥ 1 patient were predominantly hematological, namely lymphopenia (22%), anemia (6%) and neutropenia (including decreased neutrophil count; 4%) (**Extended Data Table 2**). Two patients (4%) had grade 4 events, both lymphopenia (at 125 and 150 kBq/kg). Importantly, no patients required granulocyte-colony stimulating factor injections for myelosuppression. Five patients required a total of seven red blood cell transfusions during the treatment period ($n=4$) and/or during follow-up ($n=3$).

Lymphopenia, including treatment-emergent cases and non-clinically significant cases, was seen in 46 (92%) patients in total, including 27 (54%) patients with grade ≥ 3 . The median time to first occurrence of worsening grade was 12.6 (range 0.6–48.0) weeks, and the median time to first occurrence of grade ≥ 3 lymphopenia was 9.1 (range 0.0–20.9) weeks (**Extended Data Figure 1a**). Of the 46 affected patients, lymphopenia improved in 44 (96%), with a median time to improved grade of 2.2 (range 0.7–56.7) weeks. Of the 27 patients with grade ≥ 3 lymphopenia, 25 (93%) had an improvement in their lymphopenia, including 13 (48%) who improved to grade 2, nine (33%) to grade 1 and three (11%) who resolved to grade 0.

During treatment, a decline in lymphocyte count was observed at all doses ($P<0.0001$). Of note, a low baseline lymphocyte count was significantly associated with increased risk of developing clinically meaningful lymphopenia, i.e., lymphopenia reported as a TEAE ($P=0.008$). After treatment, a consistent recovery trend across all dose levels was seen ($P<0.0001$) (**Extended Data Figure 1b**). No grade 3–4 infectious events related to lymphopenia were observed.

Serious TEAEs, as defined in the methods, occurred in 16% of patients and included xerostomia (grade 2; 6%), elevated creatinine (grade 1), diarrhea (grade 2), fecaloma (grade 2), hydronephrosis (grade 3), hypoxia (grade 3), pseudomonal bacteremia (grade 3), pyrexia (grade 1), and vomiting (grade 3) (all 2%) (**Extended Data Table 3**). Three patients (6%) discontinued [^{225}Ac]Ac-PSMA-Trillium due to TEAEs. These were grade 3 uncomplicated lymphopenia (125 kBq/kg; related to study drug), grade 3 decreased glomerular filtration rate (75 kBq/kg; unrelated to study drug) and grade 2 irreversible renal impairment (100 kBq/kg; related to study drug). No patient discontinued treatment due to xerostomia.

TEAEs led to dose modifications in 12% of patients, including dose interruptions in 8% (**Table 2**), of which two (4%) were related to treatment (renal impairment [100 kBq/kg] and lymphopenia [125 kBq/kg]). There were no dose-limiting toxicities (DLTs; defined in the online methods).

Safety: multifactorial assessment of xerostomia (dry mouth)

During the study, 43 patients developed treatment-emergent xerostomia. Four patients had pre-existing xerostomia at baseline (all grade 1). All treatment-emergent cases were grade 1 ($n=28$; 56%) or 2 ($n=15$; 30%), with no grade ≥ 3 events observed (**Extended Data Table 4**). Half (8/16) of all grade 2 cases occurred at the highest dose investigated (150 kBq/kg).

Median time from start of treatment to first occurrence of xerostomia for all affected patients was 1.1 (range 0.1–22.1) weeks. For grade 1 and grade 2 cases, the median time to first occurrence was 0.9 (range 0.1–32.1) and 17.6 (range 6.1–21.0) weeks, respectively. Full or partial recovery in xerostomia was seen in 13 patients (30%), including five patients with worst grade 1 and eight patients with worst grade 2 (seven improved to grade 1 and one recovered to grade 0). Of the patients with grade 2 xerostomia, full or partial recovery was seen in all patients treated at 75 kBq/kg (3/3 cases, including one grade 0 resolution) and 125 kBq/kg (3/3) and in half of patients (1/2) treated at 100 kBq/kg. At 150 kBq/kg, improvement in grade was seen in one of eight patients with grade 2 xerostomia, although the follow-up time was shorter in these patients (**Figure 2b**, **Extended Data Table 4**). For those with a reported improvement, the median time from first occurrence to improvement of grade 1 xerostomia was 3.3 (range 1.0–60.1) weeks. For grade 2 xerostomia, median time to improvement to grade 1 and grade 0 was 5.7 (range 0.4–30.6) and 27.1 weeks, respectively.

The Xerostomia Inventory Questionnaire³¹ was used to record xerostomia-related patient symptoms and showed that 17% of patients had high baseline scores (defined as ≥ 10 out of a maximum of 25). At the 24-week follow-up timepoint, the median scores were lower than at the end of treatment for all doses (**Extended Data Figure 2a** and **Extended Data Table 4**).

Interestingly, in post-hoc analyses assessing PSA50 by xerostomia grade, PSA50 was achieved in 2/7 (29%), 19/27 (70%), and 10/16 (63%) patients with grade 0, grade 1, and grade 2 xerostomia, respectively (**Extended Data Figure 2b**).

Analysis of salivary α -amylase (sAA) and pancreatic α -amylase (pAA) levels revealed a transient elevation in sAA but not pAA following treatment (**Extended Data Figures 3a–b**).

Overall, for sAA, the median baseline level was 32 (interquartile range [Q1, Q3] 23–45) U/L. The main peak was seen following the first dose, where median sAA at cycle (C) 1, day (D) 2 was 150 (62–246) U/L. This largely resolved by C1D8 (44 [33–63] U/L), with only minimal elevation seen at later cycles. Correlative analysis found no difference in mean sAA peak between xerostomia grades ($P=0.6791$) (**Extended Data Figure 3c**). Salivary gland dosimetry revealed a significant monotonic trend between administered activity and absorbed dose per cycle, across all available cycles ($P<0.0001$) (**Extended Data Figure 3d**).

Efficacy

Overall, 62% of patients achieved PSA50 and 42% achieved PSA90 (**Table 3**). Respective PSA 50 and PSA 90 rates were 5/12 (42%) and 3/12 (25%) at 75 kBq/kg, 8/13 (62%) and 5/13 (39%) at 100 kBq/kg, 10/12 (83%) and 8/12 (67%) at 125 kBq/kg, and 8/13 (62%) and 5/13 (39%) at 150 kBq/kg (**Figure 2c** and **Table 3**). Although time-to-event data are preliminary, with follow-up continuing across all cohorts, the median time to PSA50 response was 2.2 (range 0.7–4.2) months. PSA responses lasted for a median of 8.9 (range 1.9–14.5) months and the median time to PSA progression was 8.3 (range 1.4–21.7) months, with 68% of patients being PSA-progression-free at 6 months (rate: 0.68, 95% CI 0.53–0.80) (**Table 3**).

Of the 24 patients with measurable target lesions at baseline, the overall response rate (ORR) per Prostate Cancer Working Group 3 criteria was 50% (12/24), including 11 confirmed partial responses (PR) and 1 unconfirmed PR (**Figure 2d** and **Table 3**). At data cutoff, the ORRs for measurable patients at the 75, 100, 125, and 150 kBq/kg dose levels were 33% (1/3), 50% (4/8), 71% (5/7), and 33% (2/6), respectively. The overall disease control rate (DCR) was 83%. Time-dependent PSA and radiographic responses are shown in **Figure 2e**.

Based on the observed safety and efficacy data, the recommended dose for expansion (RDE) was initially established as 125 kBq/kg.

Pharmacokinetics

The injected amount of PSMA-Trillium was constant across cohorts (0.001 mg/kg). Following the first dose, the mean area under the concentration-time curve (AUC) for PSMA-Trillium and mean maximum concentration ($C_{\max}$) in whole blood was similar between cohorts (84–105 $\mu\text{g}\cdot\text{h/L}$ and 18.7–23.6 $\mu\text{g/L}$, respectively), as was the median time to reach $C_{\max}$ ($T_{\max}$) (~0.1 hours) (**Extended Data Table 5**). Both PSMA-Trillium and [^{225}Ac]Ac showed biexponential declines (**Extended Data Figure 4**), and the mean AUC for [^{225}Ac]Ac showed a dose-dependent increase from 10,800 kBq·h/L (75 kBq/kg) to 22,500 kBq·h/L (150 kBq/kg). [^{225}Ac]Ac $C_{\max}$ ranged from 977–2,080 kBq/L, but the $T_{\max}$ and terminal half-life for [^{225}Ac]Ac were similar between cohorts (~0.1 kBq·h/L and ~20 hours, respectively) (**Extended Data Table 5**).

Biomarker analyses

Baseline PSMA-PET/computed tomography [CT] was available for analysis in 46 patients. PSMA expression of the total tumor was assessed by measuring the mean standardized uptake value (SUVmean) and compared with the PSA response. PSA50 and PSA 90 response rates for patients with low (SUVmean ≤ 6), medium ($>6-\leq 10$), and high (>10) groups were 20% and 10%, 57% and 38%, and 93% and 73%, respectively, with deep responses observed in patients with SUVmean >10 ($P=0.0053$). Further analyses examining the relationship between PSA50 response and baseline SUVmean showed that the odds of

achieving a PSA50 response were significantly greater in the high SUVmean group versus the low ($P=0.002$) and medium ($P=0.037$) SUVmean groups (**Figure 3a** and **Extended Data Table 6**).

Case studies

Patient 1 vignette

This patient was aged 73 years at screening, with one Response Evaluation Criteria in Solid Tumors (RECIST) target lesion (16 mm lymph node), two non-target lesions (both lymph nodes), and over 25 bone metastatic lesions. He had previously received three lines of treatment, including 10 cycles of docetaxel, and abiraterone/prednisone. He received [^{225}Ac]Ac-PSMA-Trillium at the RDE (125 kBq/kg) and completed 3 of 4 planned doses before discontinuing. With a confirmed PR, a reduction in PSMA total tumor volume (TTV) of 83.2% was observed from 2799.5 mL at screening to 471.3 mL at the end of cycle 2 (**Figure 3b**). His PSA declined from 39.0 ng/mL at screening to 0.1 ng/mL by the end of treatment, with an almost complete response on the follow-up PSMA-PET/CT at week 30, remaining at this level over seven months after receiving his third and final dose (**Figure 3c**). The patient experienced TEAEs that included grade 1 nausea and thrombocytopenia, grade 2 anemia and grade 2 xerostomia (subsequently improving to grade 1), and a worsening in lymphopenia (grade 2, present at start of treatment, to grade 4). Although the lymphopenia improved to grade 3, the decision was made to discontinue treatment.

Patient 2 vignette

This patient was aged 79 years at screening, with two RECIST target lesions (both lymph nodes), two non-target lesions (lymph nodes), and over 20 bone metastatic lesions. He had previously been treated with docetaxel plus an investigational agent, and enzalutamide. He received [^{225}Ac]Ac-PSMA-Trillium at the RDE (125 kBq/kg) and completed all 4 planned doses. The best overall response for target lesions was stable disease, with a 86.4% reduction in TTV from screening (1207.8 mL) to the end of cycle 4 (164.4 mL) and a corresponding reduction in SUVmean from 11.6 to 5.0 (**Figure 3d**). PSA levels initially increased from 70.0 ng/mL at screening to 105.6 ng/mL at C1D1 but then declined to 4.8 ng/mL at C4D1 (**Figure 3e**). The patient experienced several grade 1 TEAEs, including xerostomia, fatigue, nausea, and neutropenia, none of which led to treatment discontinuation.

DISCUSSION

In the dose escalation part of the first-in-human phase 1 PAnTHA study, [^{225}Ac]Ac-PSMA-Trillium was well tolerated in patients with previously treated mCRPC, with 80% receiving all 4 planned doses. No DLTs were observed, all cases of xerostomia were grade 1–2 and none led to treatment discontinuation (**Supplementary Figure 4**). Similar to prior studies with [^{177}Lu]Lu-PSMA-617 and [^{225}Ac]Ac-PSMA-617, hematological TEAEs (lymphopenia and anemia) were the only grade ≥ 3 TEAEs seen in $>5\%$ of patients.^{4,33} Preliminary efficacy was seen across all doses tested, with PSA50 and PSA90 rates of 62% and 42%, and, in those with measurable disease at baseline, an ORR and DCR of 50% and 83%, respectively. Based on the totality of the preliminary efficacy data, along with the manageable toxicity profile, 125 kBq/kg was selected as the initial RDE. At this dose, the PSA50 and PSA90 rates were 83% and 67%, respectively, and the ORR and DCR were both 71%.

Trillium-PSMA comprises a PSMA-binding motif linked to a Macropa chelator, and an albumin-binding domain. The Macropa chelator complexes with [^{225}Ac]Ac, allowing delivery of a cytotoxic dose of radiation to PSMA-expressing cells while minimizing nonspecific radiotoxicity in non-target tissues.^{26,27,34} Compared with 4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-based chelators, as used in PSMA-617 and PSMA-I&T, chelation with Macropa occurs at lower temperatures and provides greater stability when complexed with [^{225}Ac]Ac.^{27,35,36} Macropa chelators have also been shown to re-complex daughter radionuclides resulting from alpha recoil.^{27,37} Inclusion of an albumin-binding domain extends the systemic half-life of small molecules, circumventing rapid renal elimination and increasing tumor uptake.²⁸

As an alpha-emitter, [^{225}Ac]Ac has the advantage of a much higher LET and shorter range than beta-emitting radionuclides such as [^{177}Lu]Lu. This can result in double-stranded DNA breaks, causing death of PSMA-expressing cancer cells while potentially decreasing the impact on non-target tissues.^{9,10} Indeed, [^{225}Ac]Ac-labelled PSMA investigational agents have shown promising efficacy and a tolerable safety profile in previous early-phase studies in mCRPC.^{38,39} However, while PSMA is a validated therapeutic target in PC, the uptake of [^{225}Ac]Ac-labelled PSMA in PSMA-expressing normal tissues, notably the salivary glands,⁴⁰ may lead to toxicity such as xerostomia.⁴¹ As such, the higher LET of alpha particles may be associated with a higher incidence of xerostomia, as seen with [^{225}Ac]Ac-labeled PSMA agents (72–100%)^{20,21,42} versus [^{177}Lu]Lu-labeled PSMA agents (37–39%).^{4,43}

Xerostomia was a dose-limiting adverse event for [^{225}Ac]Ac-PSMA-617 and [^{225}Ac]Ac-PSMA-I&T, leading to treatment discontinuation in 10–23% of patients.^{20,21,42} Moreover, in a dose-finding study of [^{225}Ac]Ac-PSMA-617, ≥ 150 kBq/kg was considered intolerable due to xerostomia.⁴⁴ In the present study, prophylaxis for xerostomia was not permitted and, although xerostomia was the most frequent TEAE (in 86% of patients), it was not dose-limiting or a cause for discontinuation at any dose assessed, including 150 kBq/kg. The improved tolerability of [^{225}Ac]Ac-PSMA-Trillium versus [^{225}Ac]Ac-PSMA-617 at this dose could simply be due to the effect of their different structures on salivary gland uptake. Another possible explanation is the capacity for Macropa chelators to re-complex daughter radionuclides, which may limit nonspecific radiotoxic effects. Here, all treatment-emergent cases of xerostomia were grade 1–2, and most (8/15) grade 2 events occurred at 150 kBq/kg, which is above the RDE. Persistent xerostomia has been reported for other studies with [^{225}Ac]Ac-labeled PSMA agents.²⁰ However, here, xerostomia improved across all doses, with an improvement of grade seen in >50% of all patients with grade 2 xerostomia, including 7/8 events (88%) at the RDE and below, and complete recovery in one patient. Patient-reported xerostomia-related symptoms improved across all doses during follow-up, suggesting some recovery of the salivary glands, although further investigation is warranted. Elevated salivary amylase is common following radiation therapy and is thought to be a sign of inflammation of the salivary glands.³² However, xerostomia incidence and grade did not correlate with peak sAA levels, which were transient and occurred mainly during cycle 1. Peak sAA levels were similar across all dose levels investigated, despite a significant monotonic trend between absorbed dose by salivary glands and administered activity.

Hematologic TEAEs are common in patients treated with both alpha- and beta-emitting PSMA-targeting agents. In the VISION trial investigating [^{177}Lu]Lu-PSMA-617 in mCRPC in the post-taxane setting, grade ≥ 3 anemia (13%), thrombocytopenia (17%), lymphopenia (8%), and leukopenia (3%) were reported.⁴ In a systematic review and meta-analysis of [^{225}Ac]Ac-labelled PSMA-targeting agents in patients with mCRPC, anemia, leukopenia and thrombocytopenia were the most common grade ≥ 3 adverse events.⁴⁵ Similarly, in a phase 2 study assessing [^{225}Ac]Ac-J591 (an [^{225}Ac]Ac-labeled anti-PSMA monoclonal antibody) in

mCRPC, the majority of grade ≥ 3 TEAEs were hematologic and thrombocytopenia was dose-limiting.⁴⁶ In our study, the only grade ≥ 3 TEAEs seen in $>5\%$ of patients were lymphopenia and anemia, and both grade 4 TEAEs observed were lymphopenia (at 125 kBq/kg and 150 kBq/kg doses). Although a reason for treatment discontinuation in one patient, lymphopenia clinically improved in 96% of affected patients, including 25/27 with grade ≥ 3 lymphopenia, and this trended with an increase in lymphocyte count seen across all doses following the end of treatment.

The other TEAEs leading to discontinuation of [²²⁵Ac]Ac-PSMA-Trillium in two patients were grade 3 decreased glomerular filtration rate and grade 2 renal impairment, with only the latter deemed treatment related. Nephrotoxicity is a potential concern with small molecule PSMA-TRTs due to primarily urinary excretion, and PSMA being expressed on the epithelium of renal tubules.^{47,48} Although notable kidney accumulation is observed with some PSMA-TRTs,⁴⁰ reports of renal toxicities were relatively uncommon in a systematic review and meta-analysis of six retrospective [²²⁵Ac]Ac-PSMA-617 studies (n=201); reports of any-grade nephrotoxicity ranged from 0–32%, and 3% overall had grade 3 nephrotoxicity.³³ This is consistent with the current study, where the only treatment-related TEAE affecting the renal and urinary system was grade 2 renal impairment in one patient. However, longer follow-up is needed to fully characterize the risk of late onset renal toxicity.

In a preclinical PC model, we showed that [²²⁵Ac]Ac-PSMA-Trillium elicited stronger efficacy than [¹⁷⁷Lu]Lu-PSMA-617, providing a rationale for further development of this molecule. Our findings, while preliminary, seem consistent with clinical data reported in other trials with beta- and alpha-emitting PSMA-TRTs, although care should be taken when comparing across trials due to differences in molecules investigated, and patient populations and numbers enrolled. In our study, almost two-thirds of patients had a PSA50 response and almost half achieved a PSA90 response. In the VISION trial, investigating [¹⁷⁷Lu]Lu-PSMA-617, PSA50 was 46%.⁴ PSA50 rates for the alpha-emitters [²²⁵Ac]Ac-PSMA-I&T, [²²⁵Ac]Ac-PSMA-617 and [²²⁵Ac]Ac-J591 were 50%, 69% and 34%, respectively.¹⁹⁻²¹ For the latter two, the respective ORRs were 50% and 18%, and the DCRs were 67% and 82%.^{19,20} In our study, the ORR was 50% and DCR was 83%. In the retrospective WARMTH Act study, in which 488 patients with mCRPC received at least one cycle of a [²²⁵Ac]Ac-PSMA agent, the PSA50 rate was 57%, and PSA50 response was significantly associated with longer OS and PFS.¹⁷ Of note, all of these trials included patients previously treated with [¹⁷⁷Lu]Lu-PSMA agents, whereas the current study did not. The phase 1 AcTION study assessing [²²⁵Ac]Ac-PSMA-617 in patients with mCRPC included cohorts of both [¹⁷⁷Lu]Lu-PSMA-naïve and [¹⁷⁷Lu]Lu-PSMA pre-treated patients.²² PSA50 and PSA90 were 59% and 44%, respectively, in the [¹⁷⁷Lu]Lu-PSMA-naïve patients, similar to the overall results in the present study, but lower than at the RDE. For patients with prior [¹⁷⁷Lu]Lu-PSMA in the AcTION study, PSA50 was 53% and PSA90 was 18%. The effect of prior [¹⁷⁷Lu]Lu-PSMA on outcomes following [²²⁵Ac]Ac-PSMA-Trillium treatment is being investigated in the ongoing dose expansion part of the current study.⁴⁹

Here, we found a greater depth of PSA response in patients with high baseline SUVmean, based on PSMA-PET imaging, compared with patients with medium or low baseline SUVmean. More patients with high baseline SUVmean achieved a PSA50 response, including all four patients with high baseline SUVmean treated at 125 kBq/kg, compared with patients with medium or low baseline SUVmean. This is consistent with findings from the phase 3 PSMAfore study, in which higher baseline SUVmean (≥ 8.7) was associated with improved rPFS, ORR, PSA response and OS with [¹⁷⁷Lu]Lu-PSMA-617 treatment,⁵⁰ and the phase 3 VISION study in which a 1-unit increase in baseline SUVmean was associated with a 12% and 10% decrease in the risk of radiological progression and death, respectively.⁵¹

Compared with cabazitaxel, patients were more likely to achieve a PSA response with [¹⁷⁷Lu]Lu-PSMA-617 if they had a high (≥ 10) SUVmean.⁵¹ Similarly, SUVmean, along with tumor volume and total number of lesions, were identified as PSMA-PET parameters that significantly predicted PSA response, PFS, and OS.⁵²

The dose expansion part of the present study is ongoing and is further evaluating safety and efficacy at the RDE (125 kBq/kg) in three different patient cohorts based on treatment sequence. These include post-taxane chemotherapy (1 or 2 lines), prior to chemotherapy, and post [¹⁷⁷Lu]Lu-PSMA. The expansion cohorts will assess how prior chemotherapy or [¹⁷⁷Lu]Lu-PSMA impact safety and efficacy of [²²⁵Ac]Ac-PSMA-Trillium.

In conclusion, [²²⁵Ac]Ac-PSMA-Trillium had a manageable safety profile with no DLTs or discontinuations due to xerostomia and showed strong preliminary efficacy in patients with heavily pretreated mCRPC. These data support the further clinical investigation of [²²⁵Ac]Ac-PSMA-Trillium, including in the ongoing dose-expansion part of this study where outcomes at the RDE are being further assessed.

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CONFLICTS OF INTEREST

Sebastien J. Hotte declares honoraria from Advanced Accelerator Applications/Novartis, Astellas Scientific and Medical Affairs Inc, and Bayer; consulting/advisory roles for Astellas Pharma, Bayer, Janssen, Merck, Novartis Canada Pharmaceuticals Inc, and Pfizer; institutional research funding from Astellas Pharma, AstraZeneca, Ayala Pharmaceuticals, Bristol-Myers Squibb, ESSA, Janssen Oncology, Merck, Pfizer, Seagen, and Signal Chem. **Fred Saad** declares honoraria from Astellas Pharma, Janssen Oncology, Sanofi, Bayer, AstraZeneca, AbbVie, Myovant Sciences, Pfizer, BMS, Novartis, Advanced Accelerator Applications, Merck, Knight Therapeutics, Tolmar; consulting/advisory role from Abbvie, Astellas Pharma, Janssen Oncology, Sanofi, AstraZeneca/MedImmune, Bayer, Pfizer, Myovant Sciences, AbbVie, Novartis, Advanced Accelerator Applications, Knight Therapeutics, Tolmar; research funding from Abbvie, Astellas Pharma (Inst), Bayer (Inst), Janssen Oncology (Inst), Sanofi (Inst), AstraZeneca (Inst), Pfizer (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Advanced Accelerator Applications (Inst), Merck (Inst). **Anuradha Jayaram** declares honoraria from Bayer, Merck and Novartis, and speaker fees from Bayer. **Carlos Artigas** declares a consulting/advisory Role: Advanced Accelerator Applications, ARTbio, Bayer, and Telix Pharmaceuticals. **Corinne Maurice-Dror** declares honoraria from AstraZeneca, Janssen, Merck, and Pfizer; consulting/advisory role from Biomica, Eisai, Janssen Oncology, Merck, Novartis, and Pfizer; travel/accommodation/expenses from GlaxoSmithKline, Janssen and Pfizer. **Siska Van Bruwaene** declares speakers honoraria from Astellas, Bayer, Janssen; consulting/advisory role for Bayer, Novartis, Janssen. **Zineb Hamilou** declares speaker/advisory role honoraria from AstraZeneca, Merck, Pfizer, Amgen, Astellas Pharma, Novartis. **Daniel Juneau** declares honoraria from Bayer, Ipsen, Novartis and Spectrum Dynamics; consulting/advisory role from Bayer, Ipsen, Novartis and Spectrum Dynamics. **Johann De Bono** declares honoraria from Amgen, Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, Genentech/Roche, GlaxoSmithKline, ImCheck Therapeutics, Janssen Oncology, Merck Serono, Merck Sharp & Dohme, Pfizer, and Sanofi; consulting/advisor role from Abbvie, Acai Therapeutics, Amgen, Amunix, Astellas Pharma, AstraZeneca, Bayer, BioXCel Therapeutics, Boehringer Ingelheim, CellCentric, Crescendo Biologics, Daiichi Sankyo, Dark Blue Therapeutics, Eisai, Genentech/Roche, Genmab, GlaxoSmithKline, Harpoon Therapeutics, ImCheck Therapeutics, Immunic Therapeutics, Janssen Oncology, Merck Serono, Merck Sharp & Dohme, MetaCurUm, Myricx, Novartis, Nurix, Oncternal Therapeutics, Orion, Pfizer, Qiagen, Sanofi Aventis GmbH, Sierra Oncology, Taiho Oncology, Takeda, and Tango Therapeutics; speaker's bureau from AstraZeneca; travel/accommodation/expenses from Amgen, Astellas Pharma, AstraZeneca, Bayer, CellCentric, Daiichi Sankyo, Genentech/Roche, GlaxoSmithKline, Halda Therapeutics, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, and Sanofi; institutional patents/royalties/other intellectual property are abiraterone rewards for inventors, PARP

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Non-financial competing interests

Sebastien J. Hotte is Chair of the Genito-Urinary Disease Site Team (GU DST) of the Canadian Cancer Trials Group (CCTG) Cooperative group; he is also a member of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Genitourinary Steering Committee (GUSC). Both are unpaid roles.

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DATA SHARING

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the US and EU regulatory agencies on or after January 01, 2014.

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Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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ONLINE METHODS

Xenograft tumor models

Xenograft experiments were approved by the local animal welfare committee (LaGeSo, Berlin, Germany; study number B3300a0017/E0149-22).

PSMA-Trillium was radiolabeled with [²²⁵Ac]Ac (Terrapower LLC, Bellevue, WA, USA) in 0.1 M acetate buffer (pH 5.5) at room temperature for 60 minutes resulting in [²²⁵Ac]Ac-PSMA-Trillium. PSMA-DOTA was radiolabeled with [¹⁷⁷Lu]Lu (Eckert & Ziegler, Berlin, Germany) in 0.1 M acetate buffer (pH 5.5) at 95°C for 30 minutes. Radiochemical purity of [²²⁵Ac]Ac-PSMA-Trillium and [¹⁷⁷Lu]Lu-PSMA-617, defined as the amount of [²²⁵Ac]Ac bound to PSMA-Trillium or the amount of [¹⁷⁷Lu]Lu bound to PSMA-617, was determined by instant thin layer chromatography as described previously.⁵³

Immunoreactive fraction (IRF) assays were used to assess radiolabeling whereby radiolabeled molecules were incubated with unblocked (UBL) or blocked (BL; prior incubation with excess unlabeled PSMA-Trillium or PSMA-DOTA) PSMA-coated M-270-carboxy Dynabeads resuspended in IRF buffer (1% bovine serum albumin [Gibco, #A10008-01] and 0.1% Tween-20 [Fisher Scientific, BP337-100] in Dulbecco's phosphate-buffered saline [Gibco, #14190-094]) in Protein LoBind® tubes (Eppendorf #0030 108 132) (50 Bq/tube) for 60 minutes at room temperature while shaking at 750 rpm. Magnetic beads were washed and isolated using a DynaMag-2 magnet (Fisher Scientific, #12321D) and half the supernatant (SN) transferred to a scintillation vial. The remaining supernatant was used to resuspend the beads and transferred to a second scintillation vial (Bi). Samples in scintillation vials were measured using a DSPEC 50 digital gamma-ray spectrometer. Gamma counting analysis of radioactivity was performed at secular equilibrium (>6 hours after sample collection). The sum of Bi + SN is the total activity per IRF sample and to calculate the total binding of the radiolabeled antibody-chelator conjugate to the coated beads; SN was subtracted from Bi and divided by the total activity [(Bi) + (SN)] in unblocked (UBL) samples:

$$Total\ binding\ (\%) = \left(\frac{(Bi)_{UBL} - (SN)_{UBL}}{(Bi)_{UBL} + (SN)_{UBL}} \right) \times 100$$

The unspecific binding was calculated using the same formula, but with the respective values for the blocked (BL) samples:

$$Unspecific\ binding\ (\%) = \left(\frac{(Bi)_{BL} - (SN)_{BL}}{(Bi)_{BL} + (SN)_{BL}} \right) \times 100$$

Subsequently, IRF for each sample was calculated using the formula:

$$IRF\ (\%) = Total\ binding - Unspecific\ binding$$

Two days prior to cell inoculation, each mouse was implanted subcutaneously (s.c.) with a 90-day release testosterone pellet (12.5 mg, 4 mm, release rate >15 µg/day for 90 days, prepared in-house). 8-week-old male SCID mice were subsequently inoculated s.c. with 5×10⁶ LNCaP cells suspended in 100 mL of 100% Matrigel into the right flank. After 18 days, the mice were randomized and assigned to experimental groups (n=10/group) and treated with two intravenous injections of vehicle (0.1 M acetate, pH 5.5 + 50 mM methionine), [²²⁵Ac]Ac-PSMA-Trillium (2 × 150kBq/kg) or [¹⁷⁷Lu]Lu-PSMA-617 (2 × 150 or 2 × 300 MBq/kg), given seven days apart. Tumor volumes (measured using a caliper) and body

weights were monitored at least twice weekly. Individual mice were sacrificed when tumor volume reached $>1,500 \text{ mm}^3$, they had lost $>20\%$ body weight loss or other morbidity was observed. Tumor size was assessed by determination of the tumor area using a caliper. Tumor volume was calculated using the equation: $V = 0.5 \times L \times W^2$, where L and W refer to tumor length and width, respectively.

Patients

For the dose escalation, eligible patients were aged ≥ 18 years with confirmed mCRPC with ≥ 1 PSMA-positive distant metastatic lesion with uptake higher than liver physiologic activity. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1, and to have either undergone an orchiectomy and/or be receiving ongoing androgen deprivation therapy, with a baseline testosterone level of $<50 \text{ ng/dL}$. All patients had to have received ≥ 1 prior line of ARPI therapy and, unless they refused or were deemed ineligible, 1–2 taxanes. Prior radiotherapy was permitted if completed >6 weeks before study start, although palliative radiotherapy was allowed within 6 weeks of study start if $\leq 10\%$ of the bone marrow was irradiated and it did not encompass all potential target lesions in dose expansion. Prior radiopharmaceuticals were not permitted. Patients were excluded if they had diffuse bone or bone marrow involvement, known brain metastases or spinal cord compression, or osteonecrosis of the jaw (known or suspected). Patients were also excluded if they had >3 or any diffuse liver metastases, or if they presented with PSMA-negative measurable lesions.

Study design and treatment

The global, multicenter phase 1 PAnTHA study consists of a dose-escalation and dose-expansion part. Dose-escalation decisions were based on clinical safety data and supported by the evaluation of available pharmacokinetic (PK) activity and efficacy. A joint Time-to-Event-continual reassessment model (TITE-CRM) method was employed to assist dose-escalation decisions by incorporating information on early and late-onset toxicity and activity into the model. Based on preliminary efficacy (overall response rate [ORR] per Prostate Cancer Working Group 3 [PCWG3] criteria and $\geq 50\%$ decline in prostate-specific antigen from baseline [PSA50 response]) and safety data, dose-escalation cohorts were back filled (up to a total of 18 patients) to allow for the determination of the recommended dose for expansion (RDE).

$[^{225}\text{Ac}]\text{Ac-PSMA-Trillium}$ was administered intravenously in 6-weekly cycles with a constant concentration of PSMA-Trillium (0.001 mg/kg per dose) and escalating doses of activity (75, 100, 125, and 150 kBq/kg). A maximum of 4 cycles were given. The PSMA-Trillium dose was selected based on factors including nonclinical biodistribution and toxicology data, as well as clinical results from a phase 0 imaging and dosimetry study. The starting $[^{225}\text{Ac}]\text{Ac}$ dose of 75 kBq/kg was selected based on a number of considerations, such as organ tolerance limits, the patient population to be treated, and previous clinical experience with other ^{225}Ac -PSMA-targeting investigational agents.

The trial was conducted in compliance with Good Clinical Practice guidelines, the Council for International Organization of Medical Sciences International Ethical Guidelines and the Declaration of Helsinki. The study protocol was approved in accordance with national legislation and by independent ethics committees and the institutional review board at each participating study site. Each participant provided written informed consent. Data were collected and analyzed by the sponsor and reviewed by all investigators.

Study endpoints and assessments

Primary objectives were to determine the safety and tolerability and preliminary efficacy of $[^{225}\text{Ac}]\text{Ac-PSMA-Trillium}$. A further primary objective for the dose-escalation part was to determine the RDE, based on the incidence of dose-limiting toxicities (DLTs) and preliminary efficacy (ORR per PCWG3 criteria and the PSA50 response rate).

Secondary objectives included duration of PSA50 responses and PK characterization. PSA was centrally assessed at predefined timepoints and changes from baseline were documented, with PSA progression defined as a $\geq 25\%$ increase from baseline and an absolute increase of ≥ 2 ng/mL from the nadir confirmed after ≥ 3 weeks (if there was a decline from baseline) or after 12 weeks of treatment (if no decline from baseline). Exploratory objectives included pharmacodynamic and biomarker analysis.

Assessment of adverse events and dose-limiting toxicity

Treatment-emergent adverse events (TEAEs) were defined as an adverse event that first appeared any time following the first administration of [^{225}Ac]Ac-PSMA-Trillium, until 42 days after the last administration. TEAEs and serious TEAEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class using preferred terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0) using the safety analysis set (i.e., all patients who received ≥ 1 dose of [^{225}Ac]Ac-PSMA-Trillium). Serious TEAEs were defined as those resulting in death, or that were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, congenital anomalies, or were deemed medically important. All cases of dry mouth are reported as xerostomia here. DLTs were assessed over the first three treatment cycles and included:

- Grade 4 neutropenia (lasting >7 days), anemia, or thrombocytopenia
- Grade 3 thrombocytopenia with a bleeding event
- Febrile neutropenia (any Grade)
- Alanine transaminase (ALT) or aspartate transaminase (AST) $>3\times$ upper limit of normal (ULN) and concomitant total bilirubin $>2\times$ ULN, and alkaline phosphatase $<2\times$ ULN (except for participants with liver metastases or hepatic comorbidities)
- Any AST or ALT elevation $>8\times$ ULN regardless of duration, or AST or ALT elevation $5-8\times$ ULN that persists for >2 weeks (regardless of liver metastases or hepatic comorbidities)
- Any grade ≥ 3 non-hematologic toxicity, except:
 - Transient (improving within 72 hours), asymptomatic elevations of laboratory values
 - Nausea, vomiting or diarrhea (controlled by antiemetic/antidiarrheal agents within 72 hours)
 - Transient (improving within 72 hours) fatigue
 - Amylase or lipase increase (not associated with symptoms or clinical manifestations of pancreatitis)
 - Transient xerostomia (dry mouth) that improves within 72 hours
- Any death not clearly due to the underlying disease or extraneous causes

Adverse events of special interest included myelodysplastic syndrome, aplastic anemia, any secondary primary malignancies, and any abnormality associated with radiation-induced toxicity, including delayed or cumulative effects in any organ or body system, including grade ≥ 2 xerostomia.

Patient-reported outcomes: Xerostomia Inventory questionnaire

The short form Xerostomia Inventory questionnaire was used to assess the effects of ^{225}Ac -PSMA-Trillium on dry mouth symptom-related quality of life.³¹ Patients completed the questionnaire at baseline, the start of all treatment cycles, the end of treatment and during active follow-up visits (6-weekly).

Biomarker sample collection, assessments, and data analyses

Serum samples were collected from all patients to measure salivary α -amylase and pancreatic α -amylase at baseline, day 1, day 2, and day 8 of each cycle and at end of treatment. Concentrations of Salivary amylase and pancreatic amylase in serum samples were assessed using the Roche Cobas AMYL2 (α -amylase EPS ver.2) enzymatic colorimetric assay, based on an IFCC-aligned ethylidene-protected substrate method.

Whole body PSMA-PET/CT scans were performed using commercially available approved PSMA diagnostic radiotracers. Patients were scanned at screening for patient selection, after 2 cycles and after 4 cycles. fluorodeoxyglucose PET/CT for mismatch assessment was optional at screening. All images were centrally reviewed and analyzed following PROMISE V2⁵⁴ and RECIP 1.0⁵⁵ recommendations for TTV quantification and SUVmean measurements. Delta TTV and the presence of new lesions were measured for example patients response assessment in the two case studies. For SUVmean, patients were categorized in three groups for high, medium and low PSMA expression based on previously reported correlative analyses of PSMA TRT.^{51,56}

For pharmacokinetic and dosimetry analysis, participants underwent gamma imaging using Single-Photon Emission Computed Tomography-Computed Tomography (SPECT/CT) scans at 3 time points in Cycle 1 and Cycle 4. SPECT/CT images were centrally reviewed and analyzed for dosimetry time-activity-curve calculations for organs at risk. Initial results are presented for salivary glands.

Statistical analysis

For preclinical experiments, GraphPad Prism was used to analyze data. One-way ANOVA was used to compare treatment versus vehicle in xenograft experiments.

Clinical data were analyzed using R (version 4.2.1) and statistical analyses performed using SAS (version 9.4).

Descriptive statistics were used for demographic, safety, efficacy, PK, and biomarker data by dose level and treatment group. Time-to-event variables were analyzed by the Kaplan-Meier method. Reporting of time to PSA response used uncensored values, reporting of patients at risk of progression used censored values.

ANOVA was used for correlative analyses between mean sAA peak and xerostomia grade, and also for assessing trends in change in lymphocyte count during treatment and follow-up. For the latter, baseline lymphocyte count was included as a covariate, with analysis day and dose level as the main effects, and day-dose interaction terms. The Kruskal-Wallis test was used to assess differences in best PSA percentage change from baseline based on baseline SUV mean groups. Logistic models were used to assess lymphopenia AE onset by baseline lymphocyte levels and PSA50 response by baseline SUVmean groups. The Jonckheere-Terpstra test was used to assess the presence of a monotonic increasing trend in salivary glands absorbed dose per cycle across ordered dose cohorts (75, 100, 125, 150 kBq/kg).^{57,58} Further details of the statistical analyses are provided in the **Supplementary Information** and **Supplementary Tables 1–7**. $P < 0.05$ was taken to be significant.

Standard noncompartmental methods were used to estimate the PK parameters for each patient.

FIGURES AND TABLES

Table 1. Baseline characteristics

Characteristic	Dose escalation N=50
Median age, years (range)	71 (46–85)
≥65 years, n (%)	36 (72)
Race, n (%)	
Asian	3 (6)
Black or African American	2 (4)
White	44 (88)
Not reported	1 (2)
ECOG PS, n %	
0 – Fully active	22 (44)
1 – Restricted active	28 (56)
Median time since initial diagnosis of prostate cancer, months (range)	79 (17–279)
Median time since initial diagnosis of metastases, months (range)	46 (4–235)
Extent of disease, n (%)	
Bone with or without lymph node metastases	39 (78)
Non-regional lymph node metastases only	2 (4)
Visceral metastases with or without either lymph node and/or bone metastases	9 (18)
PSA at baseline, µg/L, median (range)	43 (0.1–5,500)
ALP at baseline, U/L, median (range)	91 (17–898)
LDH at baseline, U/L, median (range)	212 (130–460)
Measurable disease at baseline, n (%)	24 (48)
RECIST v1.1 soft tissue lesions, n (%)	
Target only	4 (8)
Non-target only	8 (16)
Target and non-target	20 (40)
None	18 (36)
Radical prostatectomy, ^a n (%)	7 (14)
Radical radiotherapy, n (%)	39 (78)

Number of prior systemic anti-cancer therapy regimens, ^b n (%)	
1	1 (2)
2	13 (26)
3	11 (22)
≥4	25 (50)
Prior lines of ARPI, n (%)	
1	43 (86)
2	6 (12)
≥3	1 (2)
Prior lines of taxanes, n (%)	
0	11 (22)
1	24 (48)
2	14 (28)
≥3	1 (2)

^aIncludes 'prostatectomy' (n=3), 'radical prostatectomy' (n=2), and 'transurethral prostatectomy' (n=2).

^bIncluding androgen deprivation therapy.

Data cutoff: 13 March 2026

ALP, alkaline phosphatase; ARPI, androgen receptor pathway inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Table 2. Overall safety summary

Event	Dose escalation				
	75 kBq/kg (n=12)	100 kBq/kg (n=13)	125 kBq/kg (n=12)	150 kBq/kg (n=13)	All doses (N=50)
TEAE, n (%)	12 (100)	13 (100)	12 (100)	13 (100)	50 (100)
Grade 3	5 (42)	2 (15)	6 (50)	9 (69)	22 (44)
Grade 4	0	0	1 (8)	1 (8)	2 (4)
Serious	2 (17)	1 (8)	1 (8)	4 (31)	8 (16)
Leading to dose modification	0	1 (8)	1 (8)	4 (31)	6 (12)
Leading to dose interruption	0	1 (8)	1 (8)	2 (15) ^a	4 (8)
Leading to permanent discontinuation	1 (8)	1 (8)	1 (8)	0	3 (6)
Treatment-related TEAE, n (%)	12 (100)	13 (100)	12 (100)	12 (92)	49 (98)
Grade 3–4	0	2 (15)	7 (58)	8 (62)	17 (34)
Serious	0	1 (8)	1 (8)	3 (23)	5 (10)
Leading to dose modification	0	1 (8)	1 (8)	2 (15)	4 (8)
Leading to permanent discontinuation	0	1 (8)	1 (8)	0	2 (4)
Dose-limiting toxicities, n (%)	0	0	0	0	0

^aNot considered related to treatment

Data cutoff: 13 March 2026

TEAEs, treatment-emergent adverse events

Table 3. Efficacy

Event	Dose escalation				
	75 kBq/kg (n=12)	100 kBq/kg (n=13)	125 kBq/kg (n=12)	150 kBq/kg (n=13)	All doses (N = 50)
PSA50 response, n (%)	5 (42)	8 (62)	10 (83)	8 (62)	31 (62)
PSA90 response, n (%)	3 (25)	5 (39)	8 (67)	5 (39)	21 (42)
Median time to PSA response, months (range)	NE (0.7–2.8)	2.4 (0.7–2.8)	1.5 (0.7–4.2)	1.4 (0.7–2.8)	2.2 (0.7–4.2)
Median duration of PSA50 response, months (range)	NE (3.3–14.5)	8.9 (1.9–13.9)	7.7 (4.9–9.9)	7.4 (3.5–11.3)	8.9 (1.9–14.5)
Median time to PSA progression, months (range)	8.2 (1.4–21.7)	8.1 (2.6–15.2)	9.7 (1.4–13.5)	8.7 (3.5–12.7)	8.3 (1.4–21.7)
PSA progression-free at 6 months, rate (95% CI)	0.65 (0.31– 0.85)	0.58 (0.27– 0.80)	0.82 (0.44– 0.95)	0.69 (0.37– 0.87)	0.68 (0.53– 0.80)
Patients with measurable disease at baseline, ^a n (%)	3 (25)	8 (62)	7 (58)	6 (46)	24 (48)
Overall response rate, n (%) ^b	1 (33)	4 (50)	5 (71)	2 (33)	12 (50)
cPR	1 (33)	4 (50)	4 (57)	2 (33)	11 (46)
uPR	0	0	1 (14)	0	1 (4)
Disease control rate, n (%) ^b	3 (100)	7 (88)	5 (71)	5 (83)	20 (83)

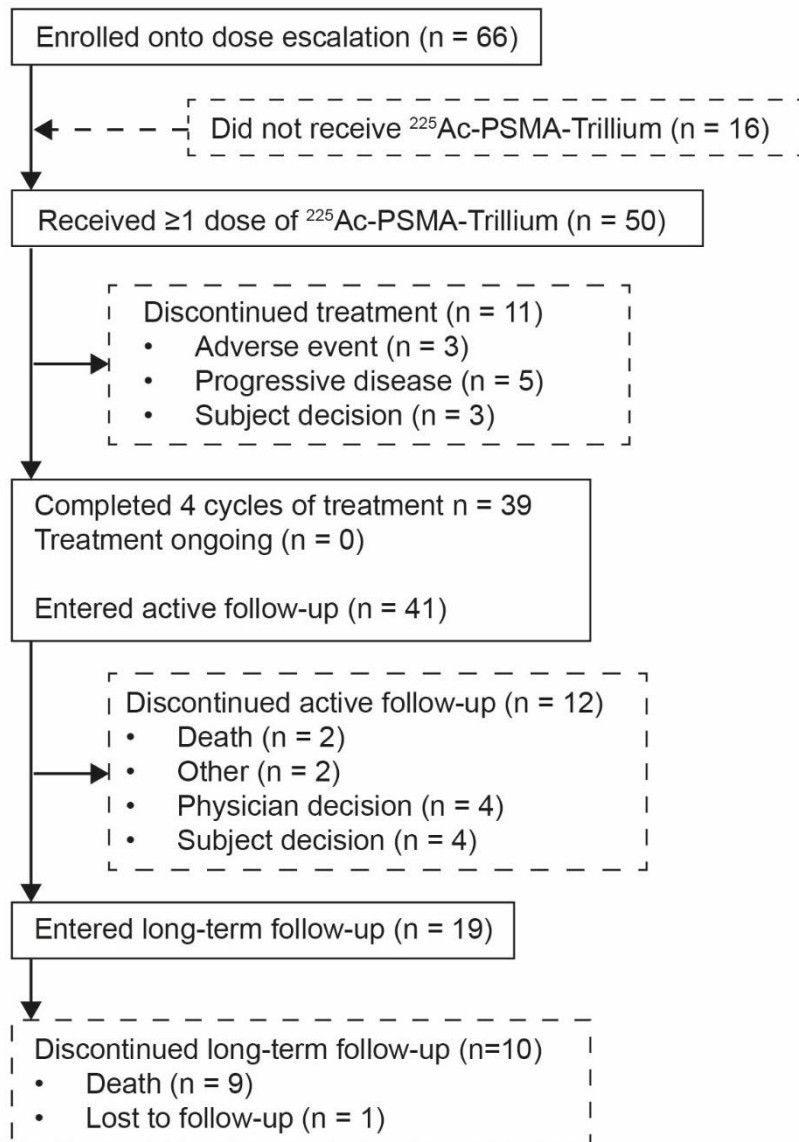
^aPatients included in these analyses had measurable target lesions at baseline

^bOverall response rates and disease control rates were per Prostate Cancer Working Group 3 guidelines

Data cutoff: 13 March 2026

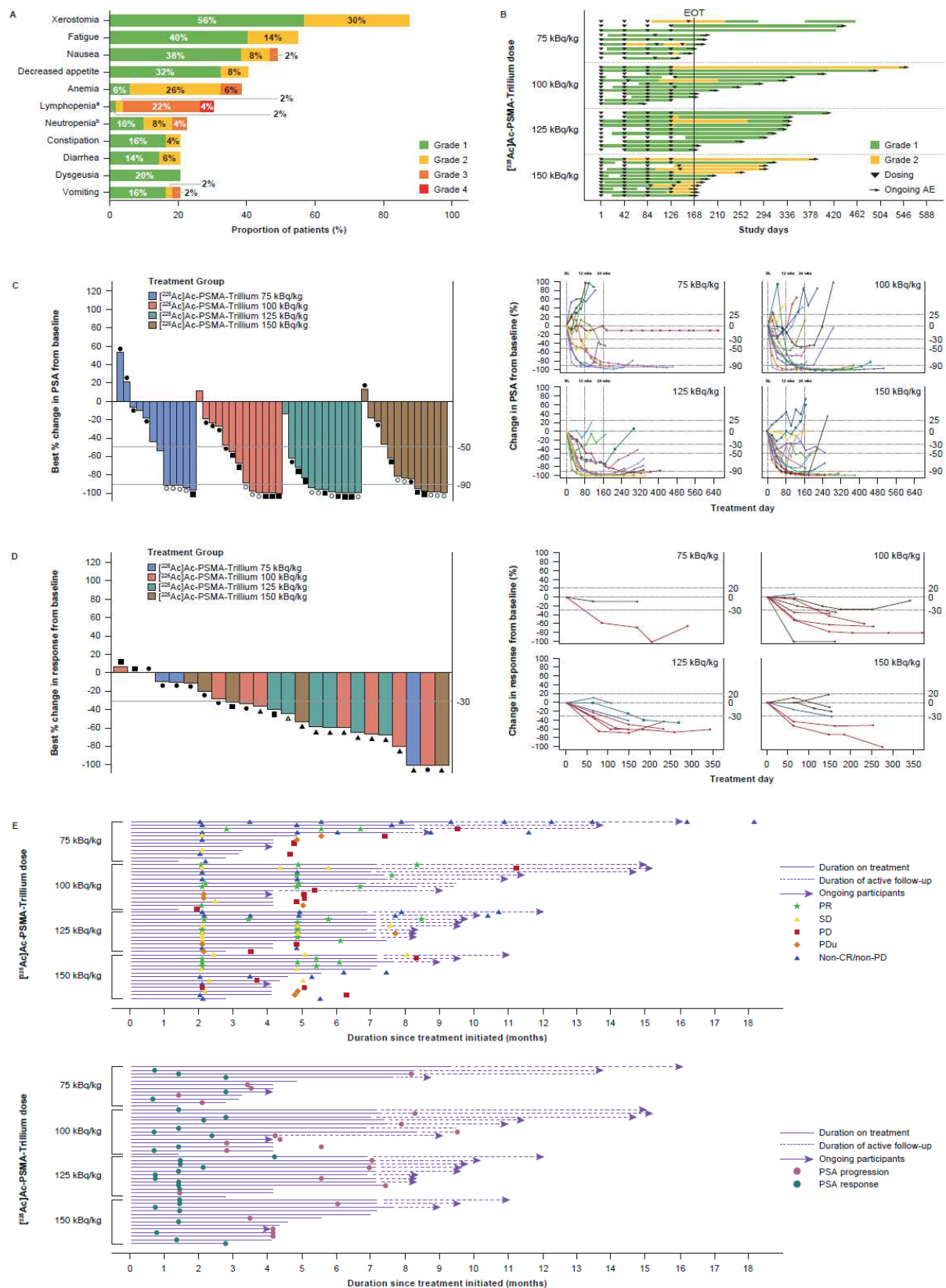
CI, confidence interval; cPR, confirmed partial response; NA, not available; NE, not estimable; PSA, prostate specific antigen; PSA50/PSA90 response, proportion of patients with ≥50%/90% decline in PSA levels; uPR, unconfirmed partial response

Figure 1. Patient disposition



²²⁵Ac, 225-actinium; PSMA, prostate-specific membrane antigen.

Figure 2. Safety and efficacy



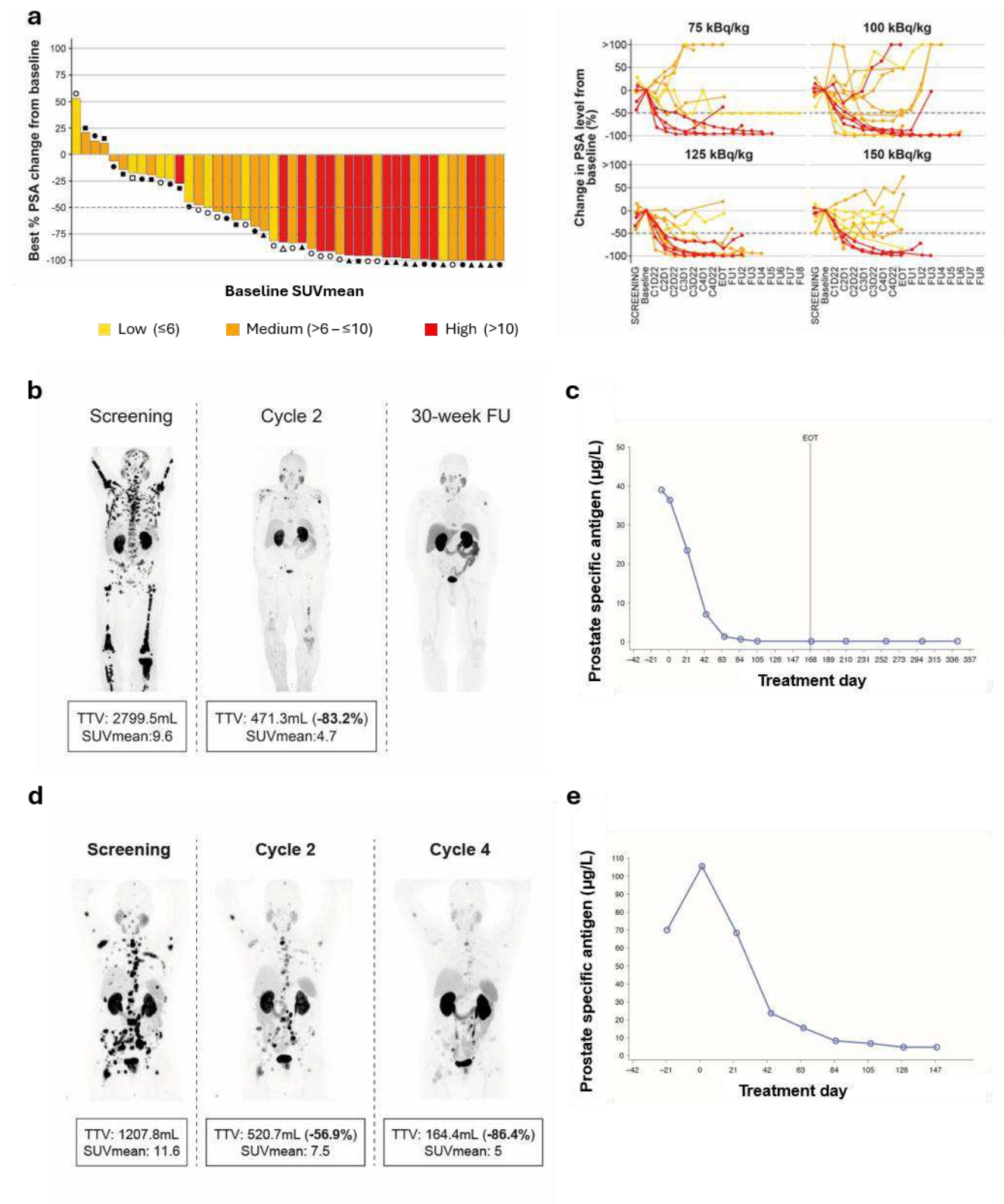
a, Treatment-emergent adverse events seen in $\geq 20\%$ of patients. **b**, Time to onset and resolution of xerostomia. **c**, Changes in PSA levels by (left) best % change from baseline, and (right) over time by dose level; open circle, confirmed PSA response, solid square, confirmed PSA response followed by progression, solid circle, PSA progression. **d**, For patients with measurable disease at baseline (left) best overall response and (right) response over time; solid triangle, confirmed partial response, solid square, progressive disease, solid circle, stable disease, open triangle, unconfirmed partial response. **e**, Time-dependent radiographic and PSA responses.

^aIncludes lymphocyte count decreased

^bIncludes neutrophil count decreased

AE, adverse event; EOT, end of treatment; non-CR/non-PD, non-complete response, and non-progressive disease; PD, progressive disease; PDu, unconfirmed progressive disease; PR, partial response; PSA, prostate specific antigen; SD, stable disease.

Figure 3. Imaging and PSA responses



a, Patients were grouped according to whether they had low (<6 ; yellow), medium $>6 - \geq 10$; orange) or high (>10 ; red) mean standardized uptake value (SUVmean) based on PSMA-PET imaging. (Left) best overall change in PSA and (right) change in PSA levels per dose

level were plotted; solid triangle, confirmed partial response, open circle, non-complete response/non-progressive disease, solid square, progressive disease, solid circle, stable disease, open triangle, unconfirmed partial response, open square, unconfirmed progressive disease. For patient 1, **b**, whole body MIP images of PSMA-PET at screening (left), after cycle 2 (middle) and at 30 weeks FU with total tumor volume (TTV) (including percentage change from baseline after cycle 2) and SUVmean measured at each timepoint, and **c**, change in PSA levels over time. For patient 2, **d**, MIP images of PSMA-PET at SCN (left), after cycle 2 (middle) and cycle 4 (right), with TTV and SUVmean for each timepoint, and **e**, change in PSA levels over time.

C, cycle; D, day; EOT, end of treatment; FU, follow-up; MIP, Maximum Intensity Projection; PSA, prostate specific antigen; PSMA-PET, prostate-specific membrane associated positron-emission tomography; SCN, screening; SUVmean, mean standardized uptake value; TTV, total tumor volume

Supplementary Files

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