

ProTACT: A first-in-human, phase 1 study evaluating the safety, tolerability, and anti-tumor activity of [²²⁵Ac]Ac-FL-020, a PSMA-targeted radioconjugate in patients with mCRPC – Dose escalation results

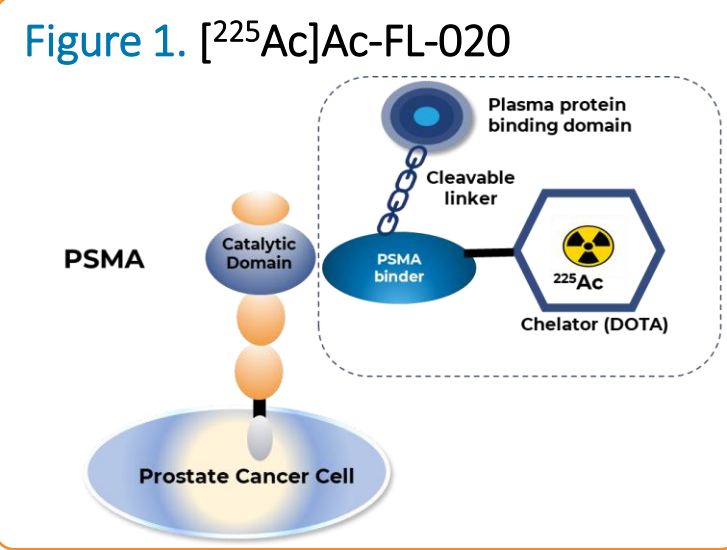
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Background

- Alpha-emitting [²²⁵Ac]Ac-FL-020 (Figure 1) represents a new generation of PSMA-targeted RDCs with potential improvements in PK and pharmacodynamics compared with a beta-emitting RDC indicated for mCRPC.¹
- Discovered using the UniRDC™ technology platform, [²²⁵Ac]Ac-FL-020 is designed to enhance tumor uptake while minimizing healthy tissue exposure, including to the salivary glands.
- ProTACT is an ongoing Phase 1, first-in-human, open-label, multicenter global study evaluating [²²⁵Ac]Ac-FL-020 in patients with mCRPC (NCT06492122).
- The FDA granted Fast Track Designation for [²²⁵Ac]Ac-FL-020 in mCRPC.



Aims and Objectives

- Primary objectives:** RP2D (incidence of DLTs), safety, and tolerability of [²²⁵Ac]Ac-FL-020.
- Secondary objectives:** Anti-tumor activity of [²²⁵Ac]Ac-FL-020 (based on PSA response, ORR, DCR, BOR per PCWG3/RECIST v1.1), PK profile, and dosimetry.

Methods

Patient eligibility

- Patients must have progressive mCRPC, with PSMA PET/CT-positive lesions, prior androgen receptor signaling inhibitors or CYP17 inhibitors, ≥1 prior taxane regimen (patients who declined taxane may be eligible), and adequate organ function.
- Exclusion criteria include extensive PSMA-negative disease, a superscan, untreated brain metastases, and prior radionuclide treatment other than [¹⁷⁷Lu]Lu-PSMA-617/I&T and Ra-223.

Study design

- The study consists of dose escalation to determine the MTD and/or RP2D, and expansion to confirm safety of the RP2D and to evaluate preliminary antitumor activity; the study design is shown in Figure 2.
- Patients receive [²²⁵Ac]Ac-FL-020 every 6 weeks for up to 6 cycles. Patients who benefit from treatment after 6 cycles of [²²⁵Ac]Ac-FL-020 may receive up to a maximum of 2 additional cycles.
- PK sampling is performed in all patients.
- Approximately 10 patients will receive [¹¹¹In]In-FL-020 and serial SPECT/CT for dosimetry prior to [²²⁵Ac]Ac-FL-020.
- The trial is enrolling patients in Australia, the United States, Turkey, and China.

Safety Results

- As of 9 Oct 2026, 39 patients have received [²²⁵Ac]Ac-FL-020 at up to 10 MBq per cycle. Of these, 15 remain on treatment, 4 completed ≥6 cycles (2 received additional cycles), and 20 discontinued (12 due to disease progression, 5 due to AEs, and 1 withdrew consent). Time on treatment and patient status are shown in Figure 4.
- No DLTs were observed up to the highest dose administered (10 MBq); the MTD was not reached.
- Frequency and severity of TEAEs are shown in Table 1.
- Grade ≥3 TEAEs occurred in 22 patients (56.4%). The most common (≥2 patients) Grade ≥3 TEAEs were lymphocyte count decreased (8 patients); anaemia (7 patients); platelet count decreased (5 patients); white blood cell count decreased (4 patients); neutrophil count decreased (3 patients); and decreased appetite (2 patients).
- Dry mouth was reported in 32 patients (82.1%): 23 (59.0%) Grade 1 and 9 (23.1%) Grade 2.
- TESAEs occurred in 11 patients (28.2%); 3 patients (7.7%) had a TESAE considered related to [²²⁵Ac]Ac-FL-020. No individual TESAE occurred in more than 1 patient.
- There were 8 deaths on study, all of which were related to disease progression.

Figure 2. Study Design

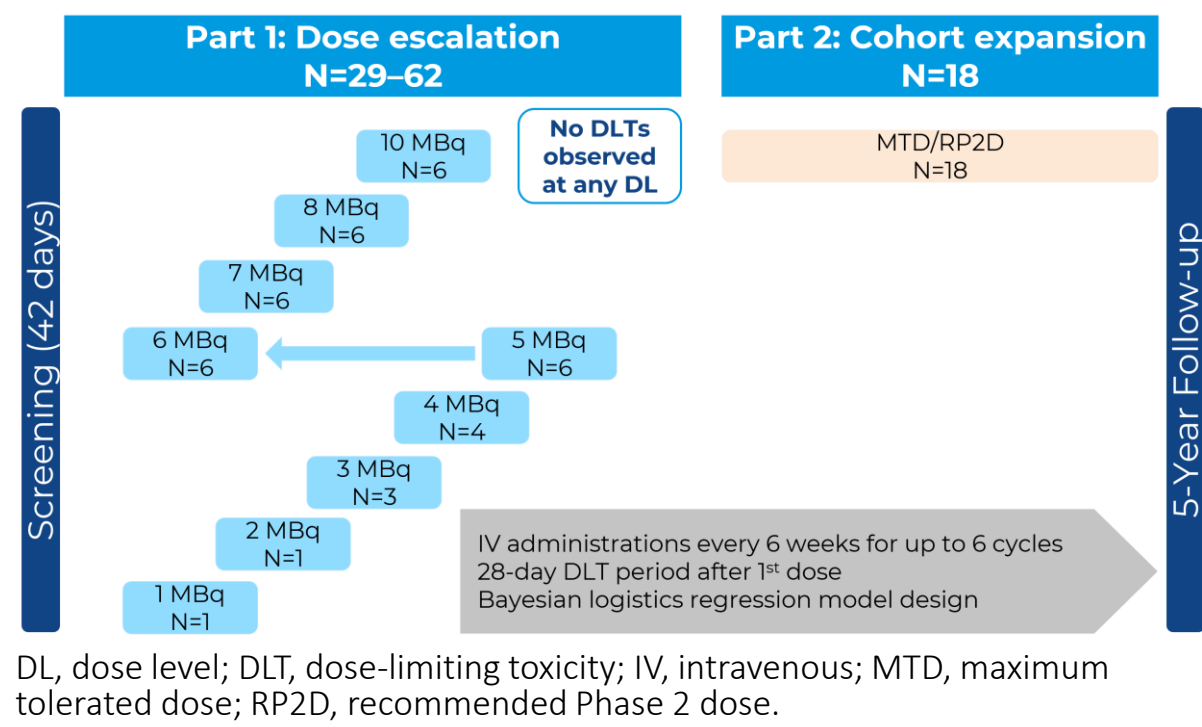


Table 1. Most Frequent (≥30%) TEAEs by Highest CTCAE Grade

Adverse Event, preferred term	1 to 5 MBq (N=15)	6 MBq (N=6)	7 MBq (N=6)	8 MBq (N=6)	10 MBq (N=6)	Total (N=39)
Any AE, any Grade	15 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	39 (100%)
Grade 1 - Mild	0	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (50.0%)	6 (15.4%)
Grade 2 - Moderate	6 (40.0%)	0	1 (16.7%)	1 (16.7%)	3 (50.0%)	11 (28.2%)
Grade 3 - Severe	8 (53.3%)	4 (66.7%)	3 (50.0%)	3 (50.0%)	0	18 (46.2%)
Grade 4 - Life-threatening	1 (6.7%)	1 (16.7%)	0	1 (16.7%)	0	3 (7.7%)
Grade 5 - Death	0	0	1 (16.7%)*	0	0	1 (2.6%)
Dry mouth (any Grade)	11 (73.3%)	6 (100%)	6 (100%)	5 (83.3%)	4 (66.7%)	32 (82.1%)
Grade 1 - Mild	8 (53.3%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	3 (50.0%)	23 (59.0%)
Grade 2 - Moderate	3 (20.0%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	9 (23.1%)
Fatigue (any Grade)	13 (86.7%)	6 (100%)	2 (33.3%)	3 (50.0%)	2 (33.3%)	26 (66.7%)
Grade 1 - Mild	5 (33.3%)	5 (83.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	16 (41.0%)
Grade 2 - Moderate	8 (53.3%)	1 (16.7%)	0	0	0	9 (23.1%)
Grade 3 - Severe	0	0	0	1 (16.7%)	0	1 (2.6%)
Nausea (any Grade)	10 (66.7%)	5 (83.3%)	4 (66.7%)	1 (16.7%)	2 (33.3%)	22 (56.4%)
Grade 1 - Mild	9 (60.0%)	4 (66.7%)	4 (66.7%)	0	2 (33.3%)	19 (48.7%)
Grade 2 - Moderate	1 (6.7%)	0	0	1 (16.7%)	0	2 (5.1%)
Grade 3 - Severe	0	1 (16.7%)	0	0	0	1 (2.6%)
Decreased appetite (any Grade)	8 (53.3%)	3 (50.0%)	4 (66.7%)	2 (33.3%)	1 (16.7%)	18 (46.2%)
Grade 1 - Mild	5 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	10 (25.6%)
Grade 2 - Moderate	2 (13.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0	6 (15.4%)
Grade 3 - Severe	1 (6.7%)	1 (16.7%)	0	0	0	2 (5.1%)
Anaemia (any Grade)	8 (53.3%)	2 (33.3%)	4 (66.7%)	2 (33.3%)	1 (16.7%)	17 (43.6%)
Grade 1 - Mild	1 (6.7%)	0	0	1 (16.7%)	1 (16.7%)	3 (7.7%)
Grade 2 - Moderate	4 (26.7%)	1 (16.7%)	2 (33.3%)	0	0	7 (17.9%)
Grade 3 - Severe	3 (20.0%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0	7 (17.9%)
Lymphocyte count decr. (any Grade)	2 (13.3%)	2 (33.3%)	2 (33.3%)	3 (50.0%)	3 (50.0%)	12 (30.8%)
Grade 1 - Mild	0	0	0	0	1 (16.7%)	1 (2.6%)
Grade 2 - Moderate	0	0	0	1 (16.7%)	2 (33.3%)	3 (7.7%)
Grade 3 - Severe	2 (13.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0	8 (20.5%)

*Grade 5 intracranial hemorrhage related to disease progression proven by bone marrow biopsy and not related to [²²⁵Ac]Ac-FL-020. AEs that occurred in 20-30% of patients included: dizziness and dysgeusia (28.2% each); diarrhea, white blood cell count decreased, and platelet count decreased (25.6% each); neutrophil count decreased, weight decreased, and constipation (23.1% each); and vomiting (20.5%).

Efficacy Results

- As of 9 Oct 2026, PSA50 responses were observed in 15/17 (88.2%) evaluable patients receiving effective doses (6-8 MBq). Of these, 13/17 (76.5%) patients had PSA80 responses, and 8/17 (47.1%) went on to have PSA90 responses (Table 2).
- PSA responses (Figures 5a and 5b) were observed at 6-8 MBq for 100% of patients naïve and 75% of patients exposed to prior ¹⁷⁷Lu (Table 2).
- All 13 PSMA-PET-evaluable patients at 6-8 MBq had a decrease in SUV in subsequent scans (data not shown).
- One patient (7 MBq) with best response to prior ¹⁷⁷Lu of PD had CR by PSMA-PET after 2 cycles. One patient (8 MBq) had near-complete disappearance of all tumors by PSMA-PET after 2 cycles and 97% decrease in PSA after 1 cycle (Figure 3).

Figure 3 Pre- and Post-Lutetium Responses

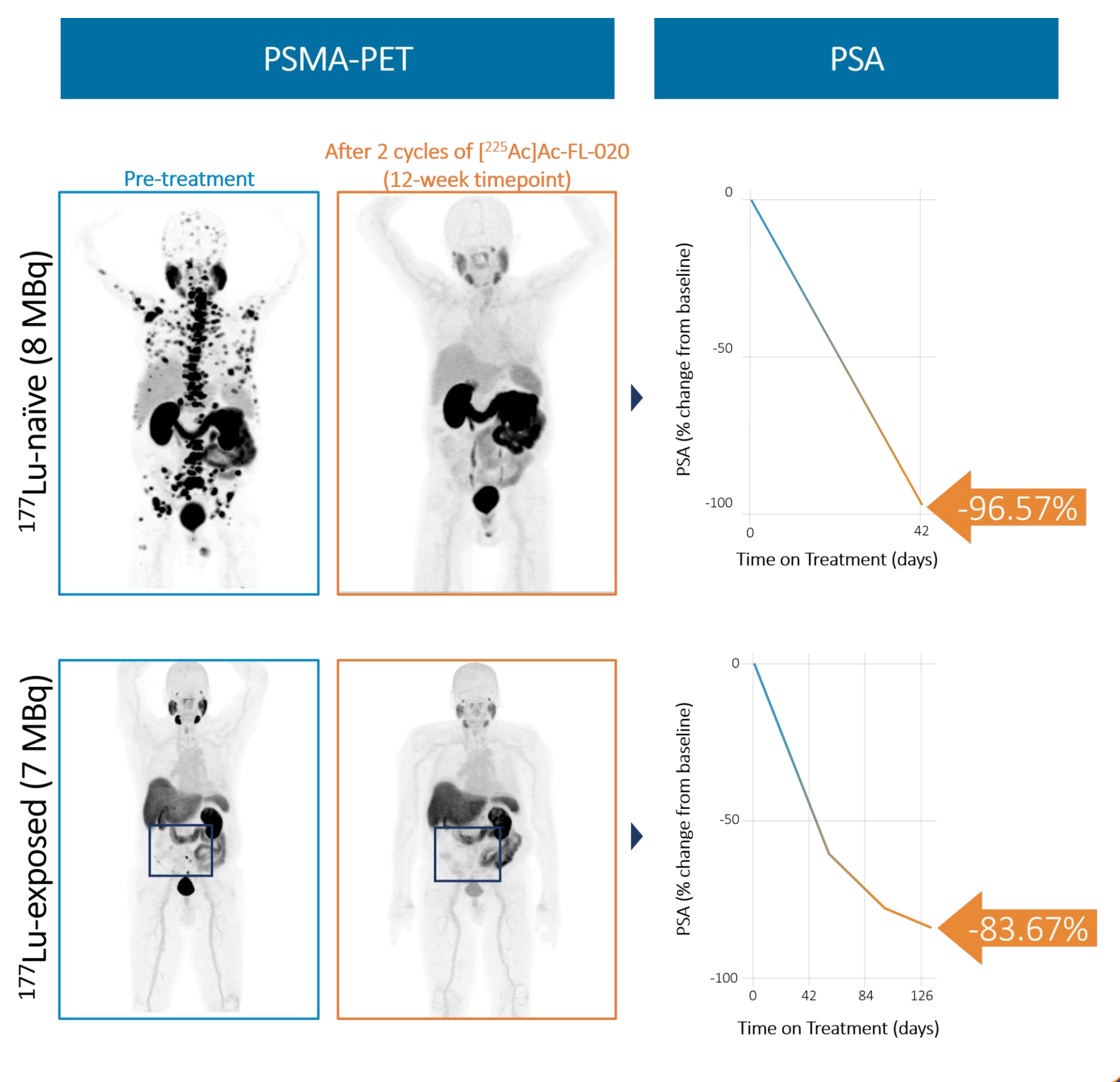


Table 2. PSA Responses at 6-8 MBq by Prior ¹⁷⁷Lu Exposure

PSA response	¹⁷⁷ Lu-naïve (N=9)	¹⁷⁷ Lu-exposed (N=8)	Total (N=17)
PSA50	9 (100%)	6 (75.0%)	15 (88.2%)
PSA80	8 (88.9%)	5 (62.5%)	13 (76.5%)
PSA90	6 (66.7%)	2 (25.0%)	8 (47.1%)

One ¹⁷⁷Lu-naïve patient (8 MBq) had no post-baseline PSA measurement and is not evaluable. Data cutoff: 9 Oct 2026.

Conclusions

- [²²⁵Ac]Ac-FL-020 has been well tolerated, with no DLTs or treatment-related deaths. The observed safety profile thus far is consistent with expectations for this patient population receiving alpha therapies in a Phase 1 clinical trial.
- Overall, 56.4% of patients had Grade ≥3 TEAEs (most commonly lymphocyte count decreased), 28.2% of patients had TESAEs (7.7% had TESAEs considered related to [²²⁵Ac]Ac-FL-020), and 12.8% discontinued due to AEs; all after receiving ≥2 cycles.
- Most discontinuations (60%) were due to disease progression, predominantly (75%) at dose levels <6 MBq.
- Dry mouth was reported in 82.1% of patients (59% Grade 1 and 23.1% Grade 2).
- PSA50 responses were observed in 88.2% of evaluable patients who received 6-8 MBq, including 100% of ¹⁷⁷Lu-naïve and 75% of ¹⁷⁷Lu-exposed patients.
- PSA80 responses were observed at 8 MBq after 1 to 3 cycles and at 6 and 7 MBq after 2 to 3 cycles. PSA90 responses were observed at 8 MBq after 1 to 3 cycles, at 7 MBq after 2 cycles, and at 6 MBq after 4 to 5 cycles. This suggests superior anti-tumor activity with higher cumulative doses.
- By the data cutoff date, dose level 10 MBq enrolled 6 patients and was cleared by the DRC with no DLTs observed.
- These data support the continued development of [²²⁵Ac]Ac-FL-020.

Figure 4. Time on Treatment

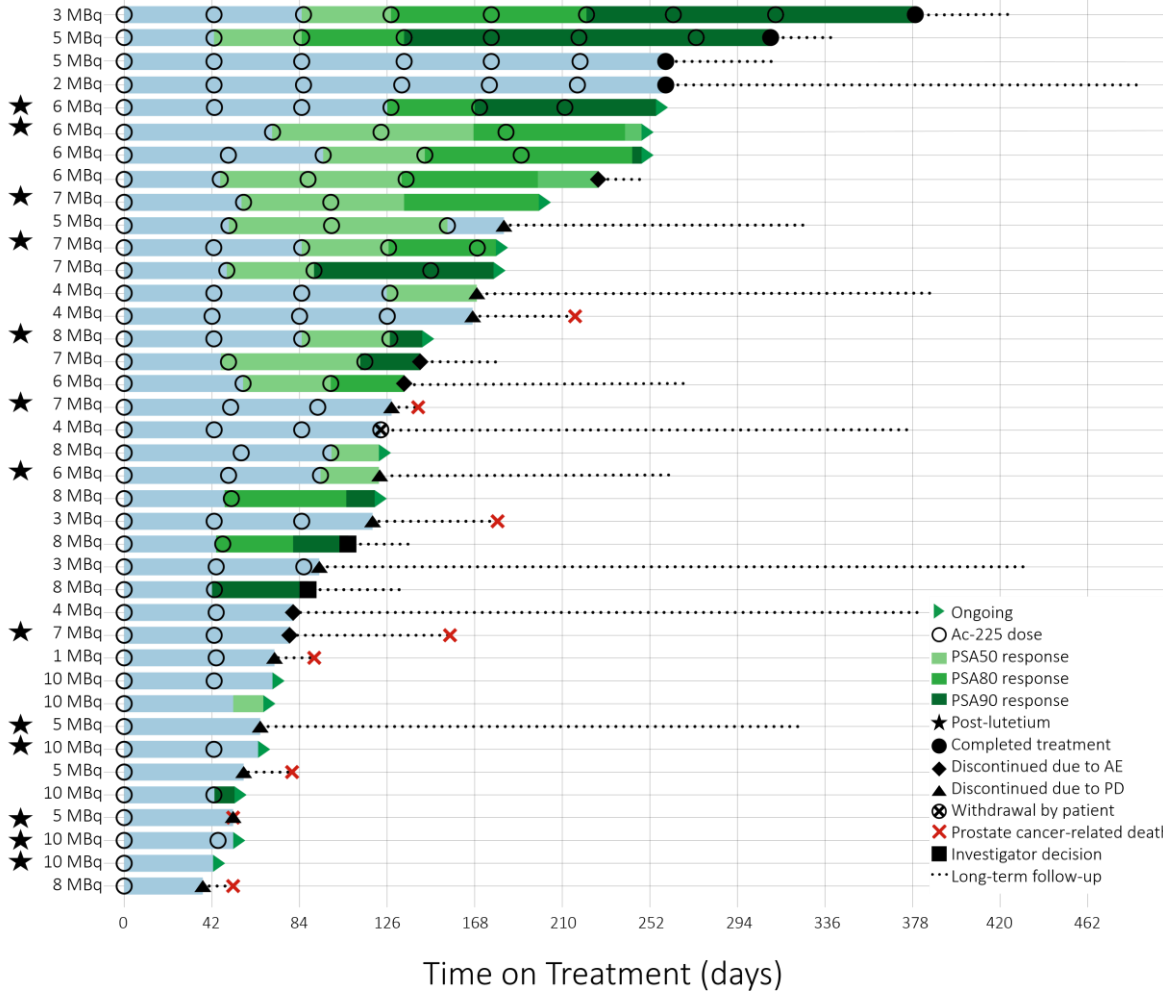


Figure 5a. Individual PSA Changes from Baseline (6-8 MBq)*

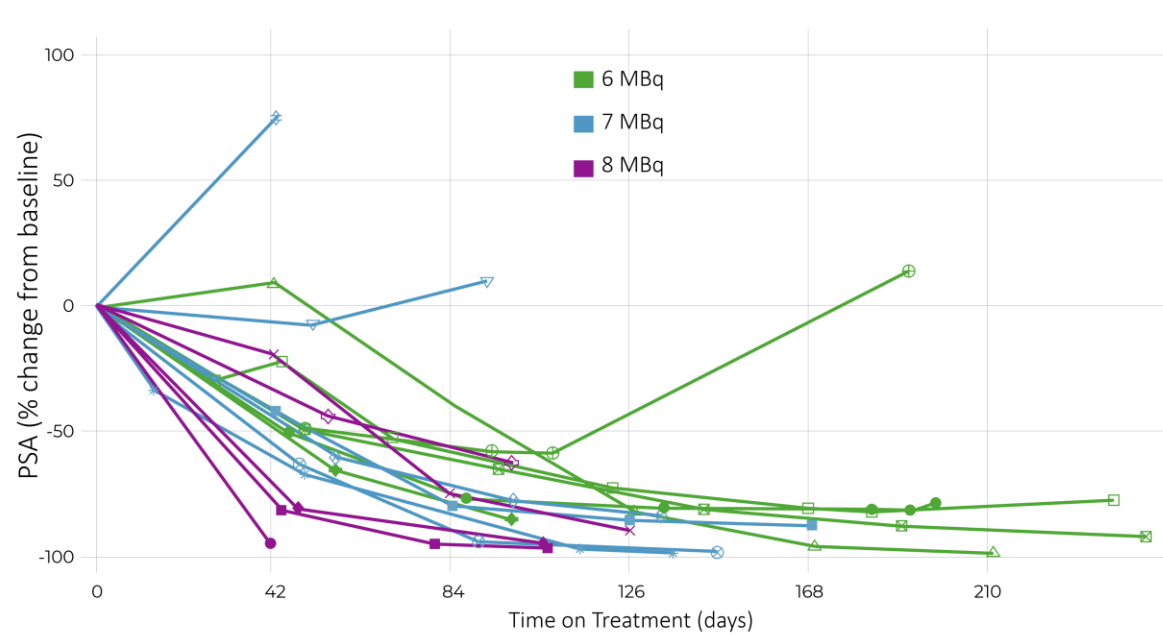
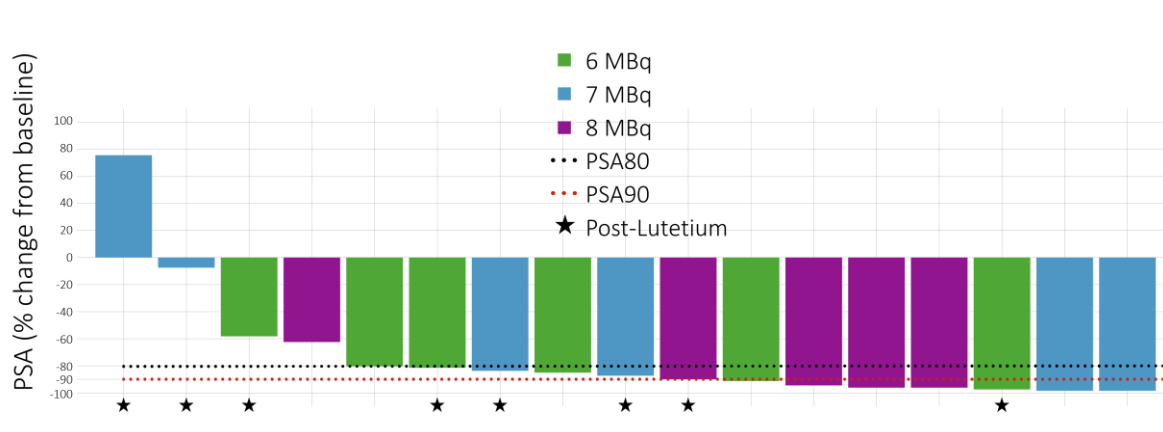


Figure 5b. Best PSA Response (6-8 MBq)*



*As of 9 Oct 2026, 6 patients have been enrolled and treated at 10 MBq; related PSA data are immature.

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Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; DRC, Data Review Committee; FDA, Food and Drug Administration; I&T, imaging and therapy; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetics; PSA, prostate-specific antigen; PSA50, decrease in prostate-specific antigen levels of ≥50%; PSA80, decrease in prostate-specific antigen levels of ≥80%; PSA90, decrease in prostate-specific antigen levels of ≥90%; PSMA, prostate-specific membrane antigen; RDC, radionuclide drug conjugate; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SPECT, single-photon emission computed tomography; SUV, standardized uptake value; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event