Preliminary efficacy and safety results from the TATCIST trial: A PSMA-directed targeted alpha therapy with FPI-2265 (^{225}Ac-PSMA-I&T) for the treatment of metastatic castration-resistant prostate cancer

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Highlights

- The efficacy and safety profile of FPI-2265 is consistent with data from the published literature, which includes almost 500 patients treated with PSMA-targeted Ac radiopharmaceuticals
- In this heavily pretreated population, PSA50 was 50%, and was 69% when a PSMA PET SUV_{mean} cutoff of 6 was used
- Durable PSA response by week 24 was observed in participants with PSMA SUV_{mean} >6
- No discontinuations occurred owing to xerostomia
- Safety signals were consistent with the literature, where higher grades of hematologic toxicity were observed mainly in participants with superscan or who had received multiple lines of chemotherapy
- A registration-enabling phase 2/3 trial will further evaluate the efficacy/safety of FPI-2265

Introduction

Targeted radiopharmaceuticals are designed to deliver radiation specifically to cancer cells by combining a radionuclide with a ligand that binds with high affinity to a membrane antigen (e.g., prostate-specific membrane antigen [PSMA], somatostatin receptor).[1,2]

β-emitting radioligand therapies (RLTs), such as lutetium-177 (^{177}Lu)-PSMA-therapy, have been shown to prolong radiographic progression-free (PFS) and overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC); however, almost 50% of patients do not respond to this treatment, therefore identifying a further unmet medical need.[2,3]

Targeted α-therapies have the potential to overcome limitations of β-therapies in that α-emitting radioisotopes have i) a higher probability of causing catastrophic double-strand DNA breaks and ii) a shorter radiation path length that may lessen unwanted exposure of surrounding healthy cells (**Table 1**).[2,4]

Table 1. Comparison of radiotherapy approaches

	Composition	Primary Mechanism of Cell Death	Penetrating Power in the Body (Emission Travel Distance)
Alpha particles	2 protons and 2 neutrons	Double-strand DNA breaks	50–100 µm (~ few cells)
Beta particles	1 electron	Single-strand DNA breaks	Up to 12 mm
External beam	**X-rays:** High-energy electromagnetic radiation **Gamma rays:** High-energy photons	Single-strand DNA breaks	Several cm

Treatment with actinium-225 (^{225}Ac)-PSMA-RLT including ^{225}Ac-PSMA-I&T, a small molecule comprising PSMA-targeting ligand coupled with the multi-alpha emitter ^{225}Ac radionuclide, has shown strong clinical activity in mCRPC across multiple studies.[4,5] Decreased prostate-specific antigen (PSA) levels have been observed in 79% of treated patients, as well as a ≥50% decline in PSA (PSA50) in 50% of patients, including those previously treated with ^{177}Lu-PSMA-617.[5]

This herein described TATCIST study was designed to confirm the safety and efficacy results of ^{225}Ac-PSMA-I&T (renamed FPI-2265) to results published to date.

FPI-2265 (^{225}Ac-PSMA-I&T)

- FPI-2265 is a small molecule containing a PSMA-targeting ligand coupled with an ^{225}Ac radionuclide that is currently being evaluated in the phase 2 TATCIST study (**Figure 1** and **Figure 2**)

Figure 1. Chemical structure of ^{225}Ac-PSMA-I&T

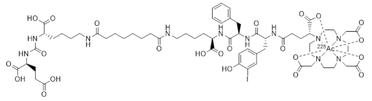
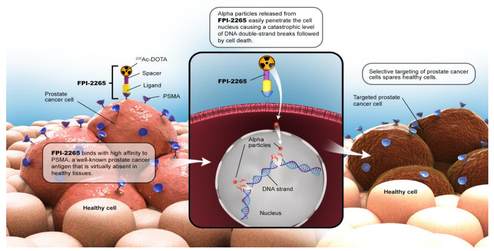


Figure 2. Mechanism of action of ^{225}Ac-PSMA-I&T



Methods

Figure 3. TATCIST open-label trial in participants with mCRPC

Participant population: Progressive mCRPC based on serum PSA, soft tissue, and/or bone progression; positive PSMA PET/CT[a] scans to confirm PSMA expression; ECOG PS 0–2/0–1[b]

Enrolling in the US

Key Inclusion Criteria
- **Progressive mCRPC**
- **Positive PSMA PET/CT**
- **Must have received ≥1 ARPI**
- **Prior Lu-PSMA RLT permitted**
- **Prior taxanes were allowed**

Key Exclusion Criteria
- **<6 weeks from prior myelosuppressive therapy**
- **Skeletal metastases presenting as superscan[b,d]**
- **Known CNS or liver metastases[b]**
- **>4 prior therapies[b]**

FPI-2265
100 kBq/kg (± 10%) IV
every 8 weeks
for up to 4 cycles[c]

Dose could be de-escalated based on PSA response:
- PSA ≥50% decline: dose should be de-escalated to 87 kBq/kg
- PSA >85% decline: additional de-escalation to 75 kBq/kg, then 50 kBq/kg

Primary endpoint:
- PSA50 (≥50% decline in PSA by 12 weeks after first treatment)

Secondary endpoints include:
- Safety and tolerability
- Maximum % PSA decline
- Response based on RECIST v1.1 criteria
- Non-progression by PCWG3

NCT05219500: Trial Currently Enrolling Participants

[a]The TATCIST PSMA ligand study included both diagnostic gallium-68 (^{68}Ga) and 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL) PET/CT. [b]Revised per a protocol amendment. [c]Treatment was continued until radiographic or clinical progression; serious or intolerable adverse events; completion of 4 RLT cycles; subject withdrawal or noncompliance; required use of prohibited treatment; sponsor/investigator decision; or death. [d]Superscan is a bone scan that demonstrates markedly increased skeletal radioisotope uptake relative to soft tissues in association with absent or faint renal activity (absent kidney sign).
ARPI, androgen receptor pathway inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; Lu, lutetium; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PET/CT, positron emission tomography/computed tomography; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

Exploratory Analysis: Mean Standardized Uptake Value (SUV_{mean})

- Quantifying ^{68}Ga-labeled PSMA PET uptake may predict response in patients with prostate cancer who receive RLT
- Some studies have shown that SUV_{mean} may predict improved outcomes in patients with mCRPC[6]
  - SUV_{mean}, a measure of PSMA PET uptake, is the average SUV within a region of interest[7]
  - Lower SUV_{mean} has been associated with worse radiographic PFS and OS in patients treated with ^{177}Lu-PSMA-617[8]
- In this exploratory analysis, PSA50 was evaluated by PSMA SUV_{mean} >6 or ≤6

Results

Participant Disposition

- As of the data cutoff of March 1, 2024, 35 participants received ≥1 dose of FPI-2265 (**Table 2**), with 25 participants having ≥12 weeks follow-up
  - 4 participants were identified as superscan
    - Superscan participants are excluded from the efficacy analyses and reported separately in the safety analysis
  - 1 participant was excluded from the PSA endpoint analysis due to uninterpretable PSA response

Table 2. Participant disposition

Participant Disposition	N
Participants received ≥1 dose of FPI-2265	35[a]
Participants with ≥12 weeks of follow-up assessments after first administration	25
Safety population	25
Non-superscan participants	21
Superscan participants	4
Participants included in efficacy analysis	20[b]

[a]As of the March 1, 2024, data cut, 5 additional participants received the first treatment dose after January 30, 2024. [b]4 participants with skeletal metastases presenting as superscan were excluded from efficacy analyses following a protocol amendment; 1 participant with uninterpretable PSA data was excluded from all analyses.

Results

- Baseline participant demographics and disease characteristics are presented in **Table 3**

Table 3. Baseline demographics and disease characteristics

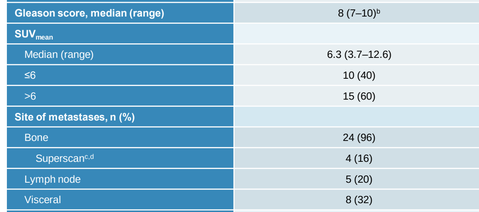
Clinical Characteristics	Total Number of Participants N=25
Age, y, median (range)	70 (52–84)
PSA, ng/mL, median (range)	37.9 (0.14–4729)
ECOG performance status, n (%)	
0–1	24 (96)
2[a]	1 (4)
Gleason score, median (range)	8 (7–10)[b]
SUV_{mean}	
Median (range)	6.3 (3.7–12.6)
≤6	10 (40)
>6	15 (60)
Site of metastases, n (%)	
Bone	24 (96)
Superscan[c,d]	4 (16)
Lymph node	5 (20)
Visceral	8 (32)
Lines of prior anticancer therapy, n (%)	
Median (range)	4 (1–6)
ARPI	25 (100)
≥2	18 (72)
1	7 (28)
Chemotherapy	20 (80)
Taxane	19 (76)
≥2	10 (40)
1	9 (36)
Docetaxel	14 (56)
Cabazitaxel	10 (40)
Carboplatin[e]	11 (44)
^{177}Lu-PSMA RLT	9 (36)
6 cycles	5 (20)
1–3 cycles	4 (16)
Radium-223	4 (16)
Other (sipuleucel-T, olaparib)	6 (24)

[a]Participants enrolled based on an earlier protocol version. Following a protocol amendment, only participants with ECOG performance status 0–1 are eligible for enrollment. [b]Data are missing for 3 participants. [c]Participants enrolled based on an earlier protocol version. Following an amendment, superscan participants are excluded. [d]Superscan status was determined via Technetium-99m bone scan. [e]Carboplatin was given as part of a taxane regimen.

Primary Endpoint: PSA50 Response

- PSA50 was achieved in 10/20 participants (50%), regardless of prior Lu treatment (**Figure 4**)
  - PSA50 was achieved by 7/13 (54%) of Lu-naïve participants and by 3/7 (43%) of Lu-treated participants

Figure 4. Maximum percent PSA change from baseline during the treatment period (weeks 0–28) by prior Lu treatment

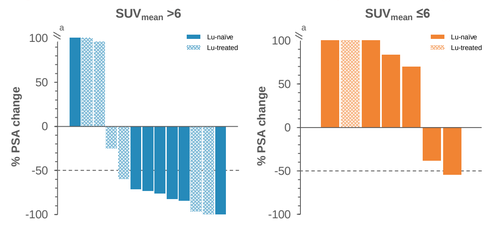


[a]% maximum PSA increase shown to 100%.

Exploratory Analysis: SUV_{mean}

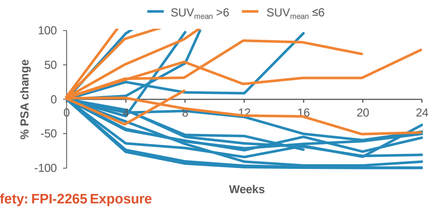
- In participants with baseline PSMA SUV_{mean} >6 (n=13, overall; post-Lu, n=6), PSA50 was achieved in 9 participants (69%; **Figure 5A**)
- Durable PSA response by week 24 was observed in participants with PSMA SUV_{mean} >6 (**Figure 5B**)

Figure 5A. Percent change in PSA from baseline by baseline SUV_{mean}



[a]% maximum PSA increase shown to 100%.

Figure 5B. PSA changes over 24 weeks by SUV_{mean} status



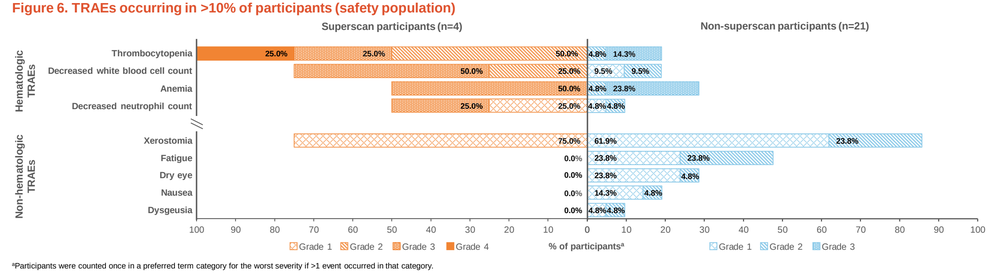
Safety: FPI-2265 Exposure

- As of the March 1, 2024, data cut, participants received a total of 71 cycles of treatment, with a median of 3 cycles
- 7/10 participants had dose de-escalation due to a biochemical response of ≥PSA50

Safety: Treatment-Related Adverse Events

- In non-superscan participants, most hematologic and non-hematologic treatment-related adverse events (TRAEs) were grade 1 or 2 (**Figure 6**)
- 1 treatment-related death due to cerebral hemorrhage secondary to thrombocytopenia was reported in a superscan participant
- 2 (8%) participants discontinued treatment due to TRAEs, including 1 participant in the superscan group
- **All incidences of xerostomia were grade 1–2 in severity (Figure 6)**
- **There were no discontinuations due to xerostomia**

Figure 6. TRAEs occurring in >10% of participants (safety population)



[a]Participants were counted once in a preferred term category for the worst severity if >1 event occurred in that category.

Secondary Endpoint: PCWG3 and RECIST v1.1 Criteria

- 14/20 (70%) of participants had non-progressive disease per PCWG3 criteria
- Per RECIST v1.1 criteria
  - Objective response rate was 3/9 (33%); all 3 participants had a partial response (PR; **Table 4**)

Table 4. Independent reviewer response by RECIST v1.1 criteria

Best Response by RECIST v1.1	Participants Evaluable by RECIST 1.1 (n=9)
PR, n (%)	3 (33)
SD, n (%)	4 (44)
PD, n (%)	2 (22)

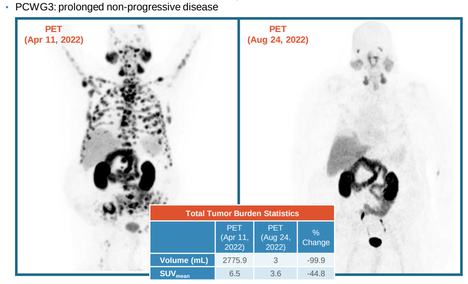
PD, progressive disease; SD, stable disease.

Case Study

A 72-year-old male with an 8-year history of prostate cancer (Gleason score 9) with extensive skeletal disease was enrolled into the TATCIST study and received 4 cycles of treatment with FPI-2265. The participant had bone-only mCRPC.

Initial treatment for mCRPC included prostatectomy and external-beam radiation therapy. Subsequently, the participant received bicalutamide, enzalutamide, apalutamide, abiraterone, Radium-223, olaparib, and cabazitaxel + carboplatin. The participant continued treatment with leuprolide during the study.

Disease response to treatment:
- Biochemical response: reduction of PSA by 99.8% (from 1119 to 2.43 ng/mL)
- PSMA-PET/CT: PSMA-tumor volume decrease by 99.9%
- PCWG3: prolonged non-progressive disease



Total Tumor Burden Statistics	PET (Apr. 11, 2022)	PET (Aug. 24, 2022)	% Change
Volume (mL)	2775.9	3	-99.9
SUV_{mean}	6.5	3.6	-44.8

Conclusions

- Data from this prospective study support prior clinical reports on the safety and efficacy of ^{225}Ac-PSMA-I&T (FPI-2265) despite enrolling a more heavily pretreated patient population
- Preliminary efficacy data suggest that FPI-2265 has activity in heavily pretreated participants with progressive mCRPC, including those participants who had received prior ^{177}Lu-PSMA therapy
  - PSA50 was achieved by 50% of participants overall, including 54% in the ^{177}Lu-naïve population and 43% in the ^{177}Lu-treated population
- Safety and tolerability were consistent with other published studies of ^{225}Ac-PSMA RLTs
  - The majority of TRAEs were grade 1 or 2
  - Xerostomia was the most common TRAE, and the majority of occurrences were grade 1
    - Incidences of grade 1 and 2 xerostomia were 61.9% and 23.8%, respectively
    - No participants discontinued because of this particular AE
  - Hematologic toxicity was observed at an expected rate; the extent of bone marrow involvement (i.e., superscan or multiple sites of bone disease) appears to correlate with a higher rate of myelotoxicity
- In an exploratory analysis, PSA50 was achieved by 69% of participants with a baseline PSMA PET SUV_{mean} >6
- These initial results support further investigation of FPI-2265
  - An upcoming registration-enabling phase 2/3 trial will further examine the efficacy and tolerability of FPI-2265

References

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Disclosures

ESD: Chairman and Medical Director (Excel Diagnostics and Nuclear Oncology Center) and CEO (RadioMedix, licensing drug to Fusion); **MJH:** Employment (Excel Diagnostics and Nuclear Oncology Center); **JK:** Employment (Fusion); **ON:** Employment (Fusion); **GG:** Employment (Fusion); **JS:** Employment (Fusion); **LN:** Nothing to disclose

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