Preliminary Dosimetry Results from a First-in-Human Phase 1 Study Evaluating the Efficacy and Safety of [^{225}Ac]-FPI-1434 in Patients with IGF-1R Expressing Solid Tumors

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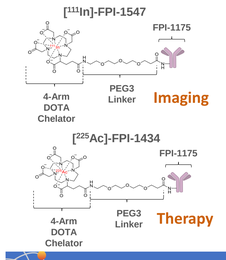
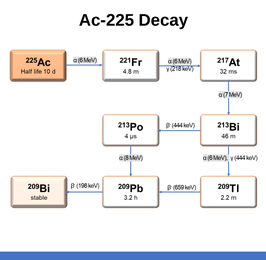
Background

[^{225}Ac]-FPI-1434 is a radioimmunoconjugate consisting of a humanized monoclonal antibody, a proprietary bifunctional chelate, and the alpha-emitting radionuclide actinium-225 (Ac-225) which binds to the external domain of the insulin-like growth factor type 1 receptor (IGF-1R), a receptor tyrosine kinase expressed by a majority of cancer cells. Internalization of the radioimmunoconjugate causes tumor cell death primarily through double stranded DNA breaks induced by alpha particles emitted from the decay of Ac-225. An indium-111 imaging analog, [^{111}In]-FPI-1547, with the identical antibody and bifunctional chelate as [^{225}Ac]-FPI-1434 is used for patient selection based on quantification of IGF-1R expressing targets and organ-based dosimetry prior to therapy.



IGF-1R Expression in Solid Tumors	
100%	Ovarian
100%	Bladder
90%	Sarcomas
62%	Head & Neck
62%	Prostate
59%	NSCLC
57%	Pancreatic
50%	Colorectal
50%	Liver
47%	Breast
43%	Small Cell Lung
40%	Esophagus
36%	Renal
36%	ACC

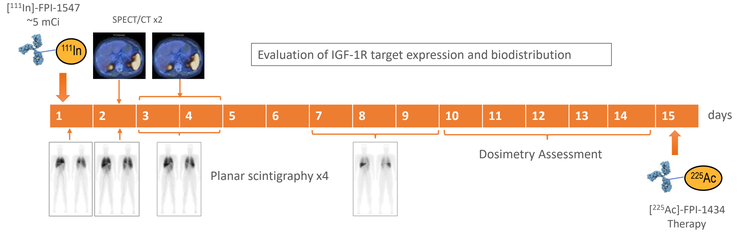


Ac-225 Decay

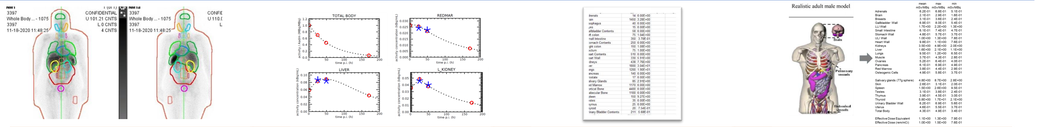
Objectives

The aim of this phase 1 study (NCT03746431) is to evaluate the safety and tolerability of [^{111}In]-FPI-1547 and [^{225}Ac]-FPI-1434 in patients with advanced refractory solid tumors that express IGF-1R based on imaging assessment and to determine the Recommended Phase 2 Dose (RP2D) of [^{225}Ac]-FPI-1434. Patient-specific dosimetry is employed for treatment planning to confirm the protocol-specified administered activity does not exceed radiation absorbed dose limits for selected organs of interest.

Imaging Procedure

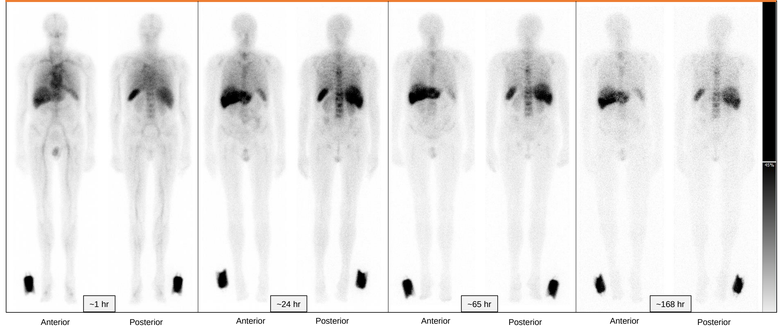


Dosimetric Methodology

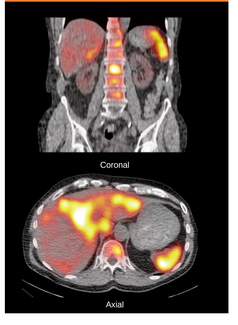


Regions of Interest CT-based organ volume → Time Activity Curves and Time-integrated Activity → Residence Time Calculation In-111 to Ac-225 values → OLINDA/EXM 2.1-2.2 (Hermes Medical Solutions)

[^{111}In]-FPI-1547 Whole Body Planar Scintigraphy



[^{111}In]-FPI-1547 SPECT/CT



- Radiation absorbed doses estimated in "real-time" for the planned therapeutic activity based on time-integrated activity from [^{111}In]-FPI-1547 planar biodistribution converted to values for [^{225}Ac]-FPI-1434
  - Administered activity was not to exceed protocol-defined thresholds of 18 Gy (kidneys), 31 Gy (liver), and 16.5 Gy (lungs) using an RBE value of 3.4 for all calculations

Demographics

Table 1. Study FPX-01-01: Patient Characteristics Safety Population Treated with [^{225}Ac]-FPI-1434 [N=12]

Median Age (range)	61.0 (36-78) years
Gender, n (%)	
Male	9 (75%)
Female	3 (25%)
Race, n (%)	
White	10 (83%)
Asian	1 (8%)
Not reported	1 (8%)
Tumor type, n (%)	
Prostate cancer	6 (50%)
Colorectal cancer	3 (25%)
Adrenocortical carcinoma	1 (8%)
Fibromyxoid sarcoma	1 (8%)
Ovarian cancer	1 (8%)
Baseline ECOG, n (%)	
0	7 (58%)
1	5 (42%)

Therapeutic Administration

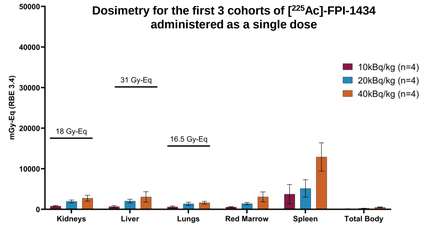
Patients with evaluable [^{111}In]-FPI-1547 Image Data for Dosimetry N=13 → Patients treated with [^{225}Ac]-FPI-1434 N=12

Eligible per imaging but not treated due to rapid disease progression N=1

Table 2. [^{225}Ac]-FPI-1434 Administration (kBq)

	Mean	Min	Max
Cohort 1 (10 kBq/kg) N=4	884	797	984
Cohort 2 (20 kBq/kg) N=4	1840	1290	2290
Cohort 3 (40 kBq/kg) N=4	3394	2400	4179

Dosimetry for the first 3 cohorts of [^{225}Ac]-FPI-1434 administered as a single dose



- Patients received ~5mCi (185 MBq) [^{111}In]-FPI-1547 for imaging
- Therapeutic administrations of [^{225}Ac]-FPI-1434 were 10, 20 and 40 kBq/kg body-weight with a protein mass-dose range ~0.01-0.04 mg/kg.

Radiation Absorbed Doses

Table 3. Study FPX-01-01: [^{225}Ac]-FPI-1434 Radiation Absorbed Dose Estimates by Target Organ (Dosimetry-Evaluable Subjects, N=13)

Target Organ	Mean* (mGy-Eq/MBq)	Minimum* (mGy-Eq/MBq)	Maximum* (mGy-Eq/MBq)	Standard Deviation* (mGy-Eq/MBq)
Adrenals	78	56	102	14
Brain	94	56	169	34
Esophagus	75	54	99	14
Eyes	74	53	98	14
Gallbladder Wall	77	55	100	14
Left colon	81	59	104	14
Small Intestine,	75	54	99	14
Stomach Wall	76	54	99	14
Right colon	78	57	102	14
Rectum	81	59	104	14
Heart Wall	1,190	690	2,040	392
Kidneys	988	615	1,820	305
Liver	934	556	1,660	319
Lungs	626	328	910	175
Pancreas	76	54	99	14
Salivary Glands	1,520	900	2,370	452
Red Marrow	807	398	1,450	303
Osteogenic Cells	1,280	922	1,860	227
Spleen	3,668	1,740	9,060	1881
Thymus	75	54	99	14
Thyroid	693	315	1,510	347
Urinary Bladder Wall	76	55	99	14
Total Body	*140*	*111*	*167*	*16*

* mGy-Eq to denote a relative biologic effectiveness (RBE) value of 3.4 for alpha emitters has been applied.

Safety

Table 4. Study FPX-01-01: Post-Treatment Safety Events Safety Population – Cohorts 1-3 (N=12)

Patients, n (%)	
Any Adverse Events (AEs)	12 (100%)
Serious Adverse Events (SAEs)	1 (8%)
FPI-1434-related AEs	8 (67%)
FPI-1547-related AEs	1 (8%)
FPI-1434-related SAEs	0 (0%)
FPI-1547-related SAEs	0 (0%)

No DLTs, treatment-related SAEs, or dose interruption/modification were reported in Cohorts 1-3

Table 5. Study FPX-01-01: Most Common FPI-1434-related AEs

All Grades (≥2pts) , n (%)	
Thrombocytopenia	5 (42%)
Neutropenia	4 (33%)
Fatigue	4 (33%)
Lymphocyte count decrease	3 (25%)
White blood cell count decrease	3 (25%)
Nausea	2 (17%)
Grade 3, n (%)	
*Neutropenia	1 (8%)
*Lymphocyte count decrease	1 (8%)
*White blood cell count decrease	1 (8%)
No Grade 4 AEs observed	

* Gr 3 WBC decrease , neutropenia, lymphopenia were attributed to the same patient.

Conclusions

- 100% of patients imaged were eligible based on imaging to receive [^{225}Ac]-FPI-1434.
- Prospective and personalized treatment planning for targeted alpha therapy of IGF-1R expressing tumors is an important safety checkpoint to estimate risk to critical organs.
- Dosimetric results well within pre-specified limits in a single-dose regimen up to 40 kBq/kg.
- [^{225}Ac]-FPI-1434 demonstrated a manageable safety profile with no drug-related serious adverse events and/or dose limiting toxicity in administered activity up to 40 kBq/kg body-weight.
- Recruitment to multi-dose and cold antibody cohorts ongoing.