Dose-Escalation Study of [^{225}Ac]-FPI-1434 (FPI-1434) in Patients With IGF-1R-Expressing Advanced Solid Tumors: Preliminary Pharmacology and Dosimetry Results (NCT03746431)

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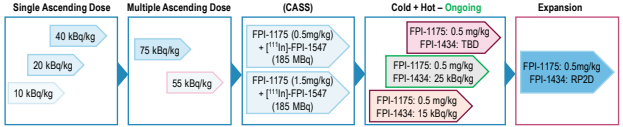
BACKGROUND

- The insulin-like growth factor 1 receptor (IGF-1R) promotes cancer cell proliferation, migration, and invasion. It is associated with tumor metastasis, treatment resistance, and poor prognosis.
- IGF-1R is overexpressed in several malignancies, including lung, breast, ovarian, colorectal, head and neck, and sarcomas.
- Alpha particles are highly cytotoxic, cause direct double-strand DNA breaks with subsequent apoptosis, and produce indirect local damage (bystander effect) and a systemic/vaccine-like response (activation of antigen-specific CD8+ T cells).
- Fusion has developed an IGF-1R-based theranostic pair: an α-emitting therapeutic ([^{225}Ac]-FPI-1434) and a γ-emitting diagnostic ([^{111}In]-FPI-1547) agent. FPI-1434 is a radioimmunoconjugate consisting of a humanized monoclonal antibody (Ab) FPI-1175 that binds to the external domain of IGF-1R, a proprietary bifunctional chelate, and the alpha-emitting radionuclide Ac-225. The In-111 analog, FPI-1547, with the identical Ab and bifunctional chelate, is used for patient selection.
- Pre-administration of "Cold" Ab may improve tumor uptake of the therapeutic ("Hot") agent by saturation of natural sinks and blocking Ab-binding sites in normal tissue and by increasing circulation time.

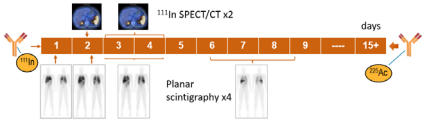
The phase 1 study is designed to determine the safety, tolerability, pharmacokinetics, biodistribution, dosimetry, and preliminary antitumor activity of different dosing regimens of FPI-1434.

- Dose escalation follows a 3+3 design; dose-limiting toxicities (DLTs) are assessed during the first cycle (56 days in the single ascending dose; 42 days in all other segments)



Screening and Treatment

- Eligibility includes adequate hematologic, renal, hepatic, and cardiovascular function and sufficient tumor uptake defined as a tumor to background ratio (skeletal muscle) of 2:1 in at least 1 lesion



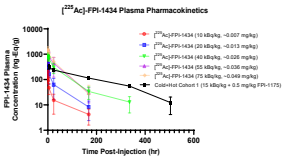
- Cumulative radiation dose to critical organs should not exceed 18 Gray (Gy) for kidneys, 31 Gy for liver, and 16.5 Gy for lungs by more than 10%

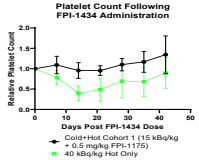
Demographics and Baseline Characteristics

Variable		N=36 (54 patients consented; 7 did not meet imaging eligibility)
Gender	Male / Female	21 / 15
ECOG	0 / 1	17 / 19
Median age	59 years (range 34-78)	
Race[a]	White / Asian	31 / 2
Number of prior systemic treatment regimens** Media: 4 (range: 1-13)	1-2 3-5 ≥6	7 17 10
Tumor indications (>3 patients)	Prostate (9); colorectal cancer (7); ovarian (4); adenoid cystic (3)	

[a] 3 not reported. ** 2 pending.

Plasma PK, Platelet Counts, and Radiation Absorbed Doses





- Cold + Hot demonstrates increased exposure but minimizes thrombocytopenia compared to Hot only

Study FPX-01-01: [^{225}Ac]-FPI-1434 Radiation Absorbed Dose Estimates for Dosimetry-Evaluable Patients

Target Organ	Hot Only (N=19) Mean [Range] mGy-Eq/MBq	Cold + Hot (N=5) Mean [Range] mGy-Eq/MBq
Kidneys	1,060 [615-1820]	1,060 [890-1,290]
Liver	905 [535-1660]	1580 [929-1,840]
Lungs	588 [328-910]	629 [333-1,380]
Spleen	4,115 [1,740-9,060]	2,190 [686-3,430]
Red marrow	776 [398-1,450]	950 [785-2770]

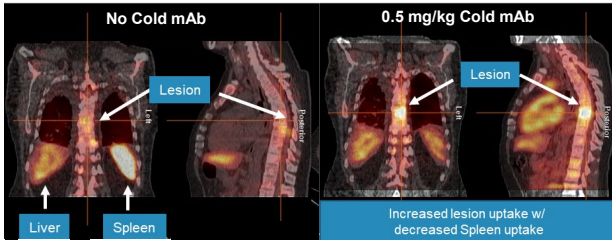
Note: Radiation doses are presented in units of mGy-Eq to denote a relative biologic effectiveness value of 3.4 for alpha emitters. Absorbed dose estimates performed by CDE.

Mean Cumulative Lesion Dose[a] at [225Ac]-FPI-1434 Dosimetric Limit

Hot Only	Cold + Hot
29.3 Gy	59.2 Gy

[a] Relative biologic effectiveness = 3.4 for alpha emissions applied. 70 kg body weight assumed.

Within prespecified critical organ limits, the Cold + Hot regimen is estimated to deliver ~2x the radiation dose compared to the Hot only regimen,



The Most Common (≥3 Patients) Treatment-Related Adverse Events[a]

Preferred Term	All n=30 (%)		FPI-1434 (only) 10-20 kBq n=9		FPI-1434 (only) 40 kBq n=9 (incl. CASS=5)		FPI-1434 (only) 55-75 kBq n=9		FPI-1434 (15 kBq) + FPI-1175 (0.5 mg) n=3	
	Any grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Thrombocytopenia	14 (47%)	5 (17%)	2 (22%)	0	5 (56%)	1 (11%)	6 (67%)	4 (44%)	1 (33%)	0
Anemia	6 (20%)	4 (13%)	0	0	1 (11%)	0	5 (56%)	4 (44%)	0	0
Leukopenia	8 (27%)	2 (7%)	1 (11%)	0	2 (22%)	1 (11%)	4 (44%)	1 (11%)	1 (33%)	0
Neutropenia	10 (33%)	5 (17%)	0	0	4 (44%)	1 (11%)	5 (56%)	4 (44%)	1 (33%)	0
Lymphopenia	5 (17%)	3 (10%)	1 (11%)	0	2 (22%)	1 (11%)	2 (22%)	2 (22%)	0	0
Fatigue	9 (30%)	0	2 (22%)	0	2 (22%)	0	4 (44%)	0	1 (33%)	0
Decreased appetite	4 (13%)	0	0	0	0	0	4 (44%)	0	0	0
Nausea	5 (17%)	0	2 (22%)	0	1 (11%)	0	2 (22%)	0	0	0
Diarrhea	3 (10%)	0	0	0	1 (11%)	0	2 (22%)	0	0	0

[a] Percentage is based on safety population that includes all patients who received at least 1 dose of FPI-1547 (FPI-1547 ± FPI-1434 ± FPI-1175).
- FPI-1547-related adverse events regardless of grade were fatigue and constipation in 1 patient each; FPI-1175 + FPI-1547-related adverse event was adrenal insufficiency in 1 patient; all 3 patients received FPI-1434.
- 16 patients received FPI-1175 as part of their imaging/treatment regimens, and no FPI-1175-related adverse events were reported.

Conclusion

- The Cold + Hot regimen (pre-administration of FPI-1175 at 0.5 mg/kg with FPI-1434 at the 15 kBq/kg dose level) demonstrated:
  - Decreased rate of systemic clearance from plasma, leading to increase exposure (area under the curve) at 15 kBq/kg (Cold + Hot) compared to the 40 kBq/kg (Hot only) dose level
  - There were no related DLTs, serious adverse events, or grade ≥3 adverse events at 15 kBq (Cold + Hot) compared to 40+kBq (Hot)
- The Cold + Hot regimen demonstrated potential to improve the therapeutic index
  - No significant impact on organ-absorbed doses (kidney, lung, bone marrow), except in the liver (increased) and spleen (decreased)
  - Per-cycle organ-absorbed doses at 15 kBq/kg FPI-1434 + 0.5 mg/kg FPI-1175 levels were ≤7% of protocol-defined limits
  - Doubling of tumor absorbed dose
- Exploration of FPI-1434 at 25 kBq/kg (with pre-administration of FPI-1175 at 0.5 mg/kg) dose level is ongoing

References: **1.** Juergens RA, et al. *JCO*. May 1, 2019;37(suppl. 15)TPS 3152. **2.** Juneau D, et al. *JNM*. May 2021;62(suppl. 1):74. **3.** Scott et al. *JNM*. June 2022;63(supp. 2):2275.

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