FGFR3 Targeted Alpha Therapeutic [^{225}Ac]-FPI-1966 Induces Regression in Preclinical Bladder Xenograft Model

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FGFR3 is a Promising Target for Bladder and Head & Neck Cancers

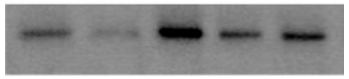
- Member of FGFR family of receptor tyrosine kinases
  - Plays a key role in embryogenesis and tissue homeostasis (cellular proliferation and migration)
- FGFR3 is overexpressed in multiple cancer types, including bladder and head & neck cancers, where there is a large unmet medical need
  - Targeted alpha therapy (TAT) enables cancer targeting wherever FGFR3 is expressed, independent of genetic mutations
  - Potential to address new indications, larger patient populations
- Fusion has in-licenced vofatamab, a FGFR3-specific fully human mAb:
  - Cross-reacts with mouse, rat, cynomolgus monkey, human
  - Blocks FGF binding and activation of both WT and mutant FGFR3
  - Demonstrated safety and good tolerability in patients with advanced bladder cancer (tested in >150 patients)

FGFR3 Expression in Solid Tumors	
60%	Gastric Carcinoma
59%	H&N - Oropharyngeal SCC, advanced
50%	Skin - Cutaneous malignant melanoma (metastatic)
49%	Bladder - Metastatic
48%	H&N - Oral SCC, advanced
47%	Liver - HCC (Advanced)
29%	Bladder - Primary
16%	Colorectal
10-25%	Hematological - Multiple Myeloma

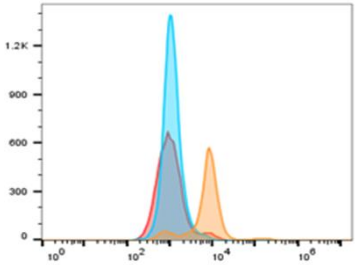
Evaluation of [^{177}Lu]-FPI-1965 and [^{225}Ac]- FPI-1966 - Overview

Model development

Western blot

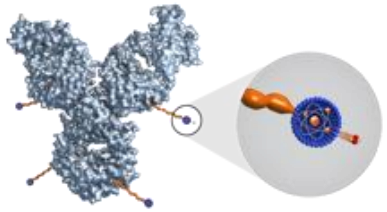


Flow cytometry



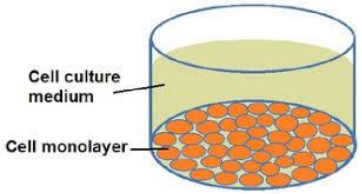
FGFR3$^+$ Bladder cell lines:
RT4, **RT112**, UM-UC-1

Conjugation and Radiolabeling



- Conjugate - **FPI-1964**
- ^{177}Lu-construct - **FPI-1965**
  - **In vitro characterization**
  - **Tissue biodistribution**
- ^{225}Ac-construct - **FPI-1966**
  - **Therapeutic Efficacy**

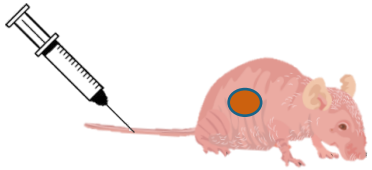
In vitro evaluation



[^{177}Lu]-FPI-1965

- Saturation binding: Kd = 1.9-4.8 nM
- Residualization: % residualized @ 24h = 74.8 ± 1.8

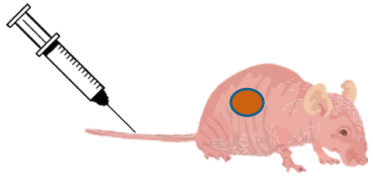
Biodistribution



[^{177}Lu]-FPI-1965

- Tumor-bearing nude mice are injected with [^{177}Lu]-FPI-1965 i.v.
- Selected organs are dissected at various time points and measured for radioactivity using a gamma counter.

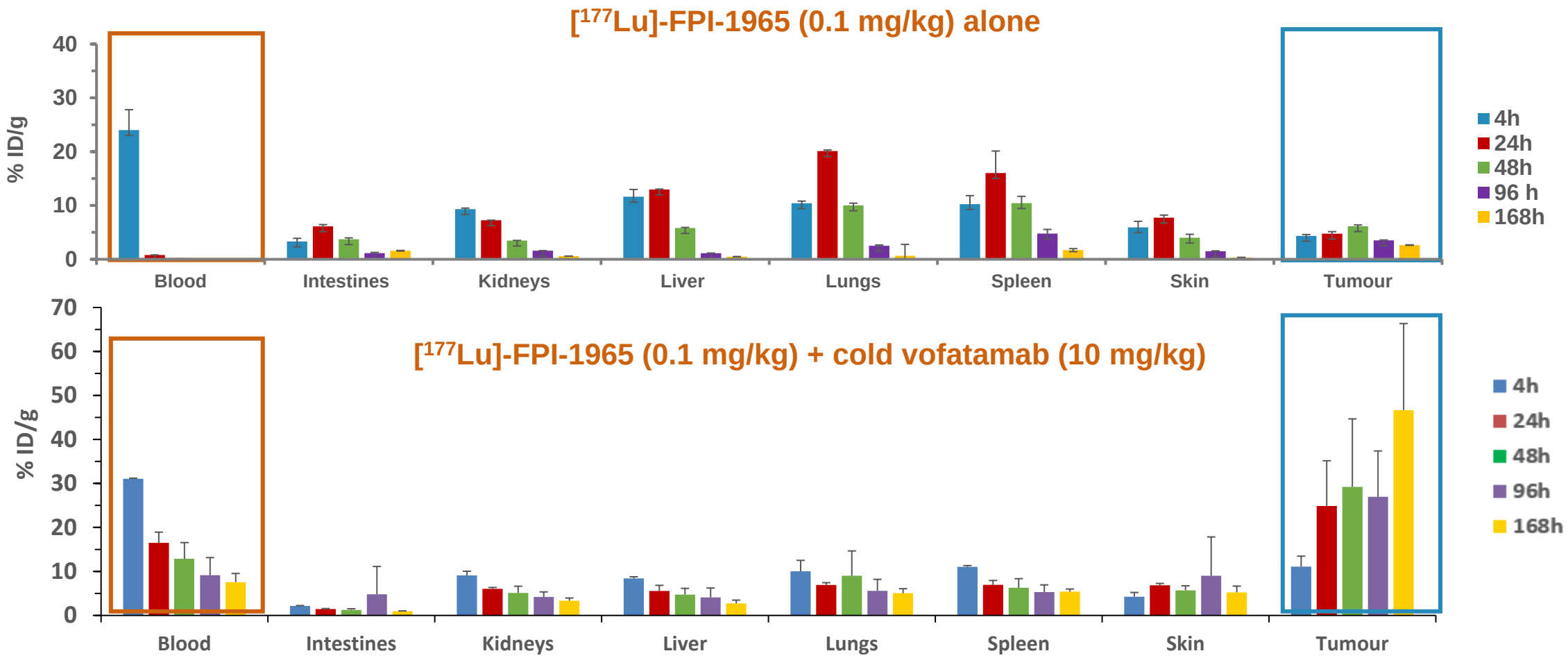
Therapeutic efficacy



[^{225}Ac]-FPI-1966

- Tumor-bearing nude mice are injected with different doses of [^{225}Ac]-FPI-1966 i.v.
- Tumor growth and mouse weight are monitored over 54 days.

Biodistribution Profile of [^{177}Lu]-FPI-1965 is Improved with the Addition of Cold Vofatamab



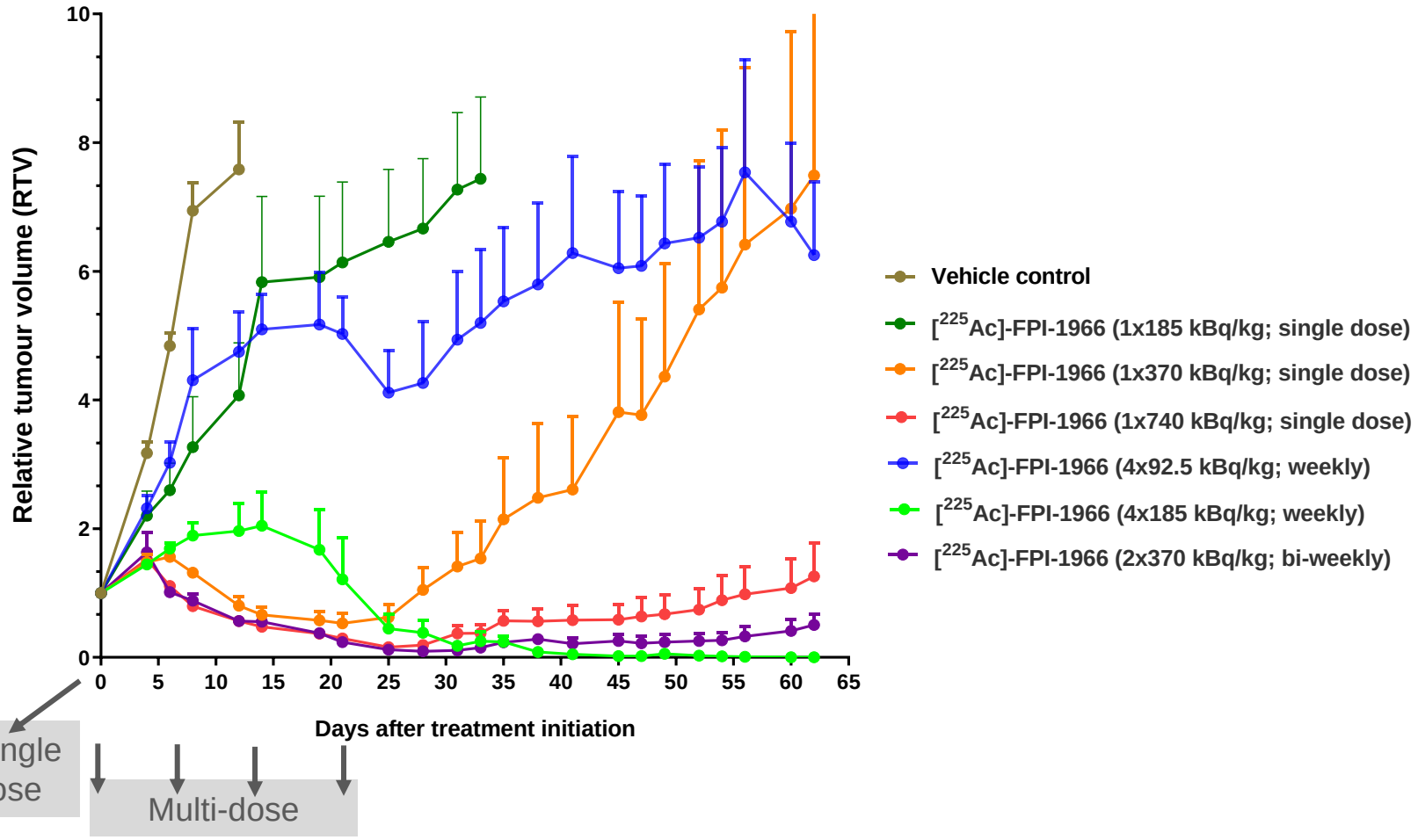
Improved tumor (47% ID/g @ 168h) and low normal tissue uptake was demonstrated in RT112 model with the addition of cold vofatamab.

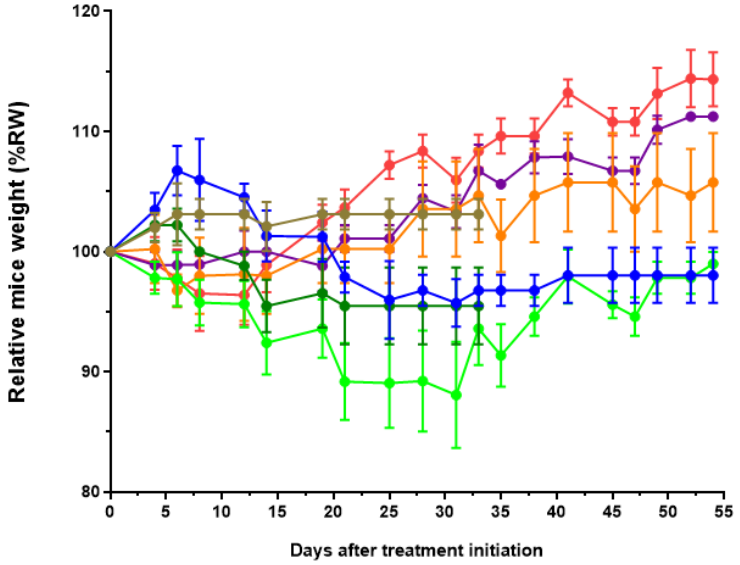
Single Dose vs Fractionated Dose Therapeutic Efficacy Studies - Design

- Head-to-head comparative study of [^{225}Ac]- FPI-1966 single dose vs fractionated dose was performed in bladder RT112 xenograft model
- Dosing Regimen was as follows:

Group	Cold Vofatamab (mg/kg)	Total Dose Administered (nCi)	Total Dose Administered (kBq/kg)
Single dose	10	50 nCi	92.5 kBq/kg
Single dose	10	100 nCi	185 kBq/kg
Single dose	10	200 nCi	370 kBq/kg
Single dose	10	400 nCi	740 kBq/kg
Multi-dose	40 (4 weekly doses)	50 x 4 weekly doses = 200 nCi	92.5 x 4 weekly doses = 370 kBq/kg
Multi-dose	40 (4 weekly doses)	100 x 4 weekly doses = 400 nCi	185 x 4 weekly doses = 740 kBq/kg
Multi-dose	20 (2 bi-weekly doses)	200 x 2 bi-weekly doses = 400 nCi	370 x 2 bi-weekly doses = 740 kBq/kg

Treatment with Single or Fractionated Doses of [^{225}Ac]-FPI-1966 Induces Tumor Regression in RT112 Bladder Cancer Model





Conclusions

- FGFR3 is a promising target for Targeted Alpha Therapy, specifically for bladder cancer and head & neck tumors due to frequent overexpression
- Co-dosing with cold vofatamab improves blood retention and tumor uptake with minimal normal tissue uptake
- Durable tumour regression was observed in RT-112 model as a result of single and multi-dose administration of FPI-1966.
  - No signs of toxicity were observed in preclinical studies with doses up to 740 kBq/kg as a single dose.
- Fusion announced FDA clearance to proceed with evaluation of [^{225}Ac]-FPI-1966 in patients with solid tumors
- Clinical trial will initiate around the end of 2021 and will evaluate the safety, tolerability, dosimetry and pharmacokinetics of [^{225}Ac]-FPI-1966 +/- cold vofatamab