

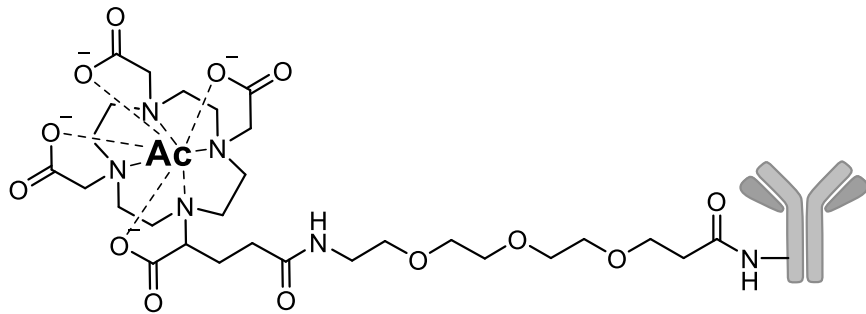


Combination of IGF-1R targeted alpha therapy with olaparib results in synergistic efficacy against colorectal and lung cancer xenografts.

M Hu, J Forbes, R Simms, Y Storozhuk, J Valliant, E Burak
Fusion Pharmaceuticals, Hamilton, Ontario, Canada

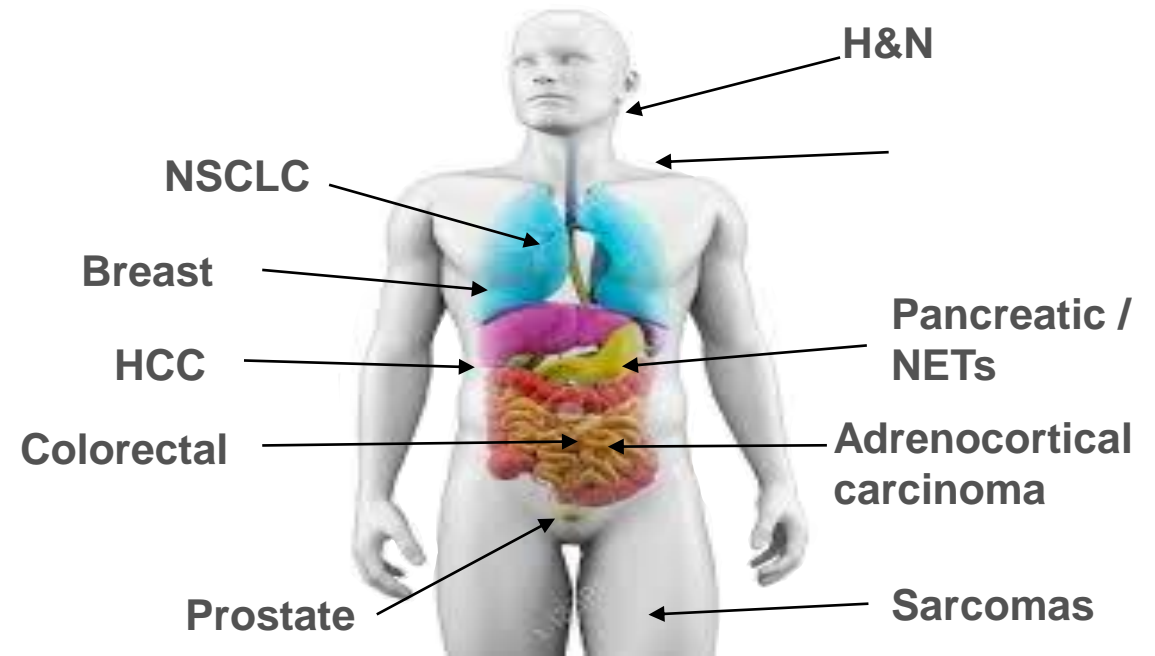
FPI-1434: IGF-1R Targeted Alpha Therapeutic

- IGF-1R: Ideal alpha therapeutic delivery mechanism
 - Overexpressed on the surface of cancer cells
 - Low expression on surface of normal tissue
 - Rapidly internalizing receptor to concentrate alpha-particles inside tumor cells



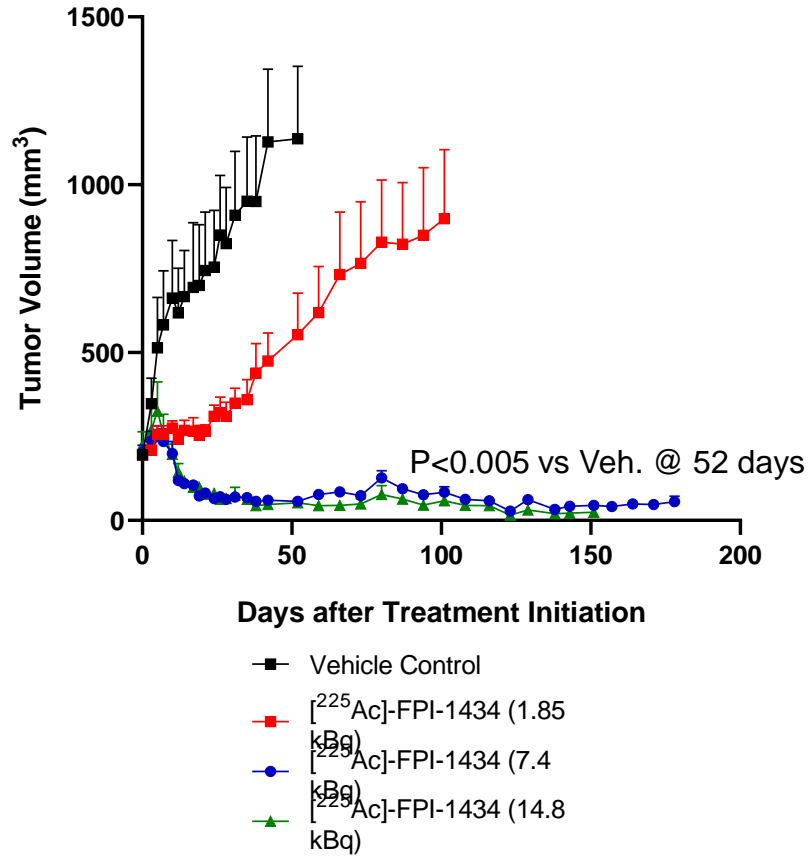
**[²²⁵Ac]-FPI-1434
(Therapeutic)**

**Attractive Therapeutic Potential:
IGF-1R is expressed on nearly all tumor
types**

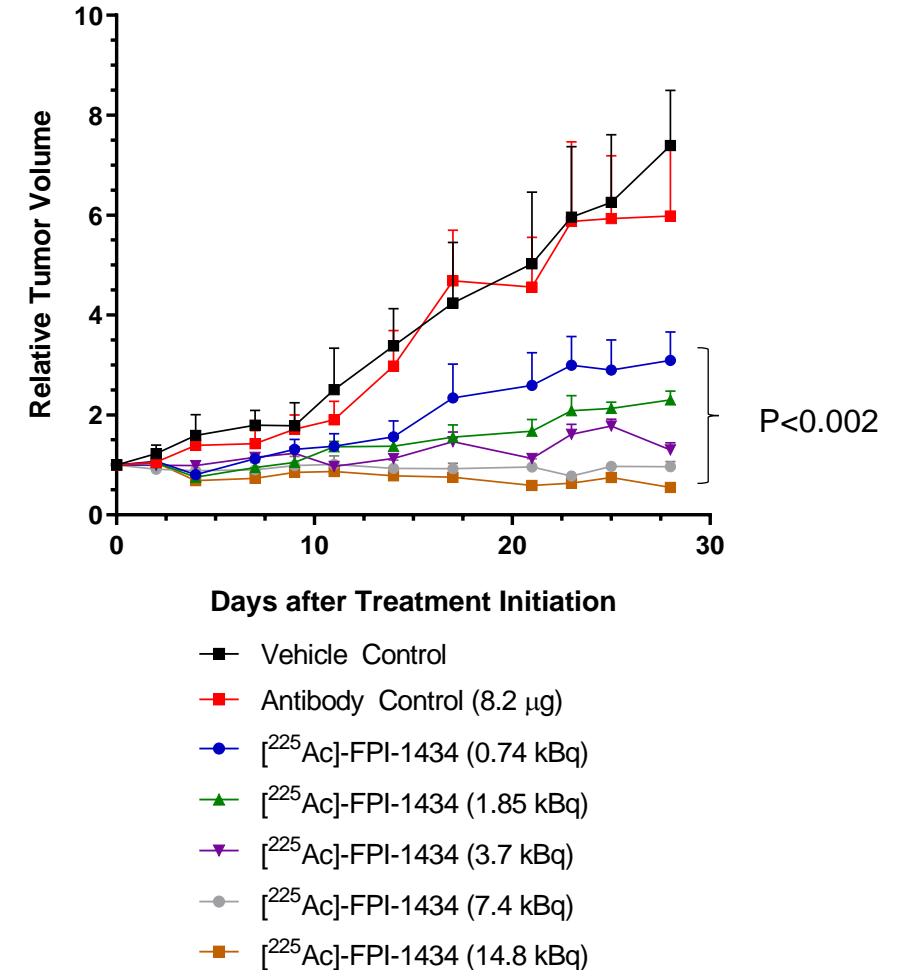


Single Dose Therapeutic Efficacy in a Colorectal Cancer (Colo-205) and NSCLC Tumor (A549) Xenograft Models

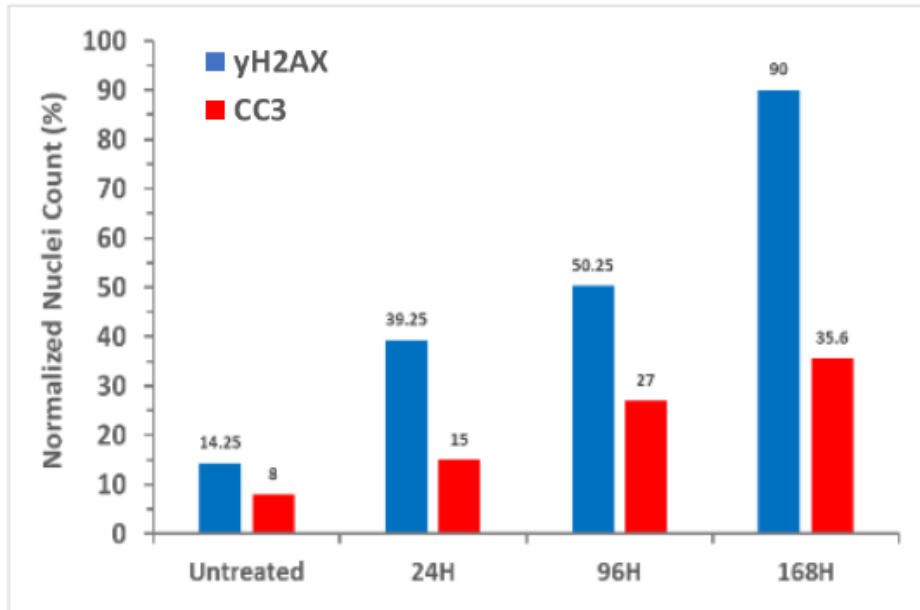
Colo-205



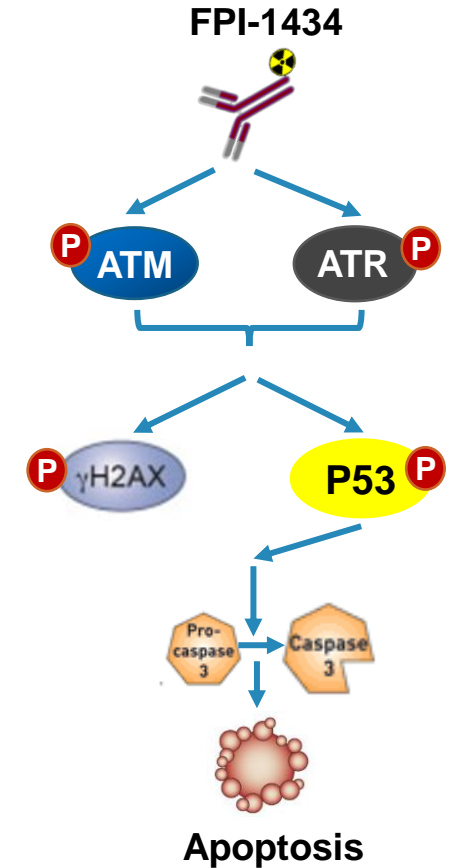
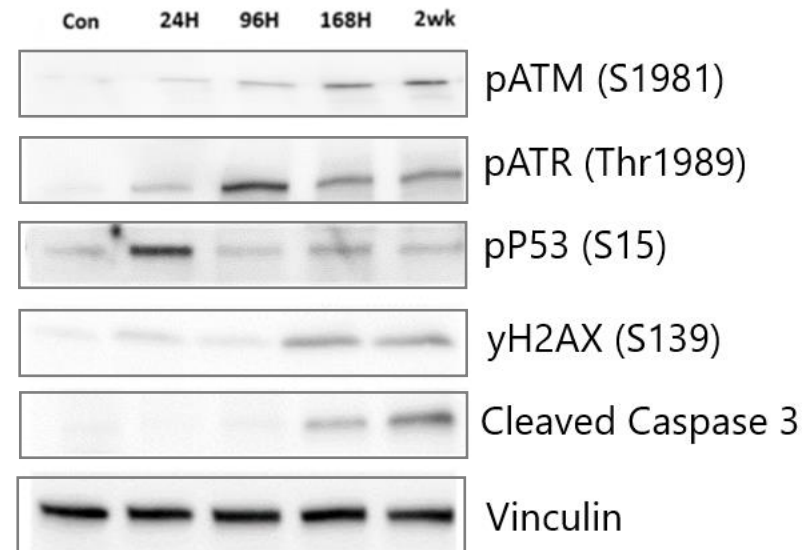
A549 (External Beam Radiation Resistant)



Time course at 14.8 kBq- IHC



Time course at 14.8 kBq- WB

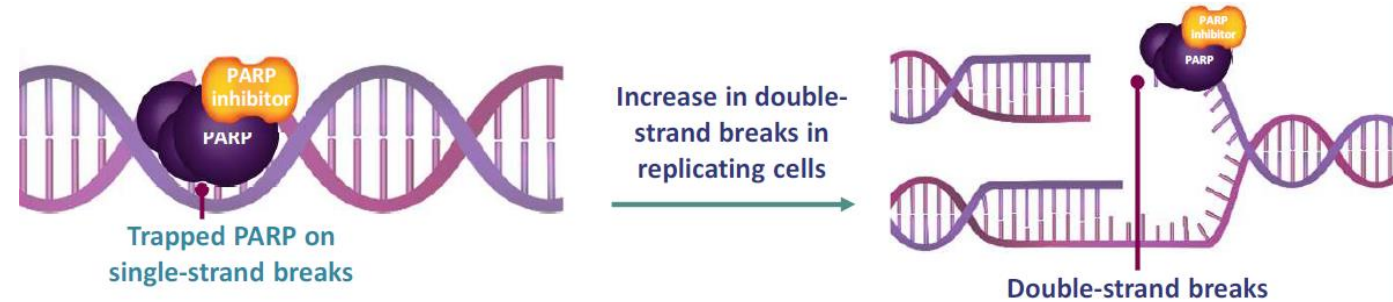
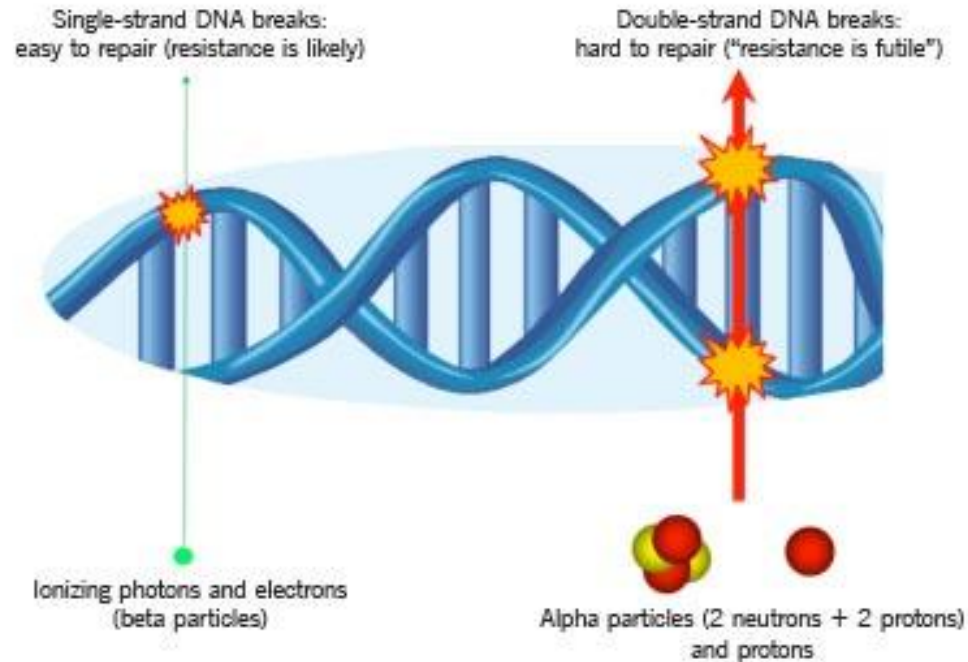


- Increase in DSBs and apoptosis was demonstrated in a dose- & time-dependent manner
- Involvement of cell death mechanisms other than apoptosis cannot be ruled out

Investigating Therapeutic Combinations Between FPI-1434 and the Double Stranded DNA Repair Inhibitor Olaparib (PARPi)

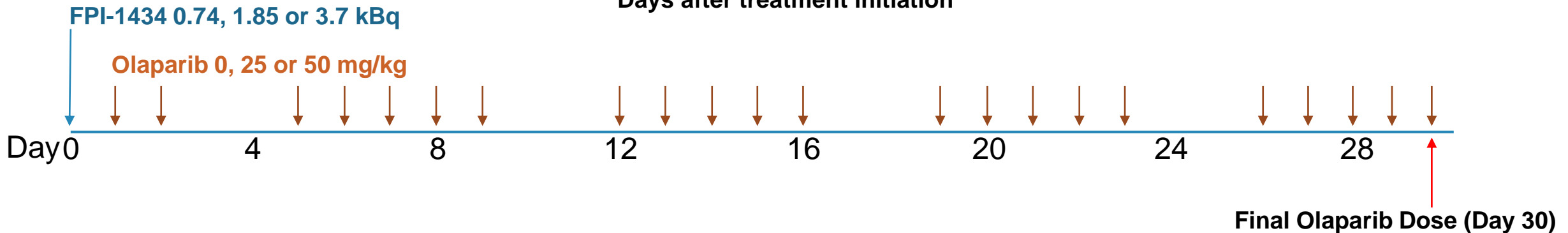
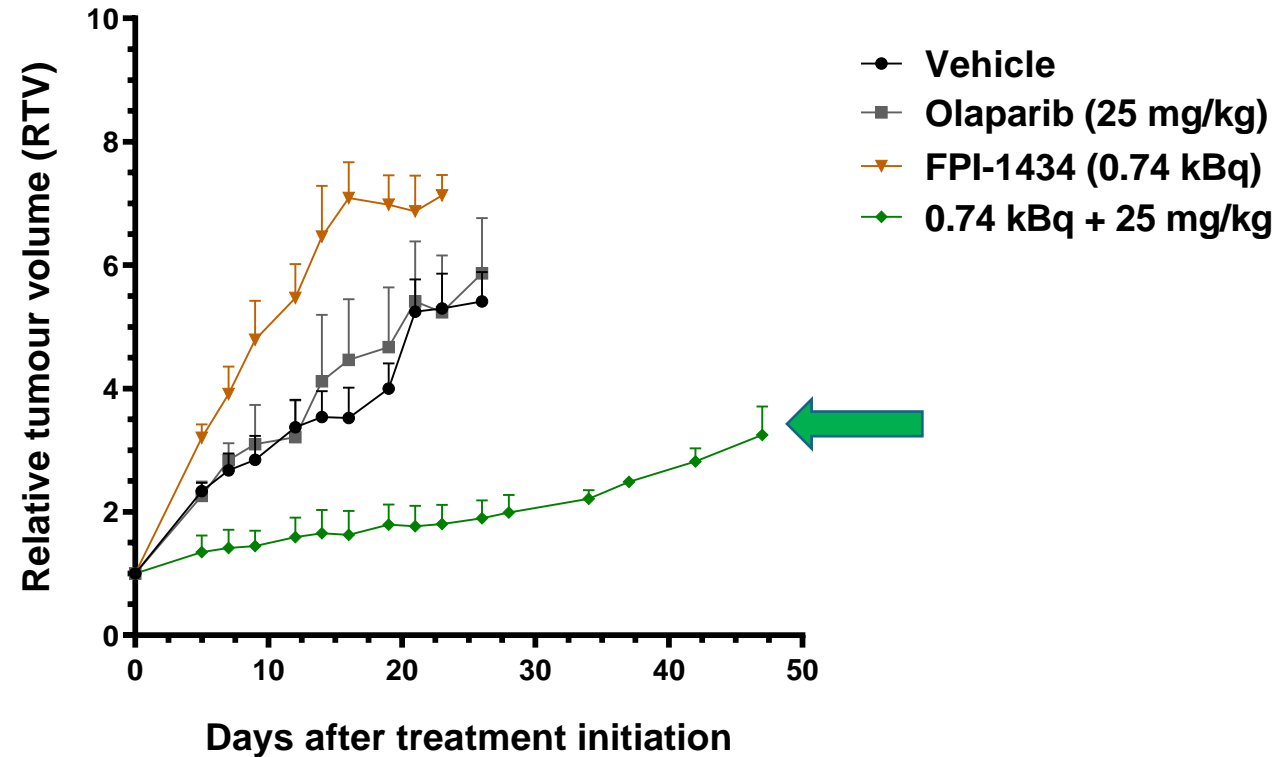
Alpha-particles cause the breakage of tumor DNA that starts the process of tumor kill

DDRi that inhibit the repair of DNA damage may synergize with FPI-1434 to amplify tumor kill (eg. olaparib)



Combination of No-Effect Single Agent Doses of FPI-1434 and Olaparib Resulted in Enhanced Efficacy (Colo-205 Model)

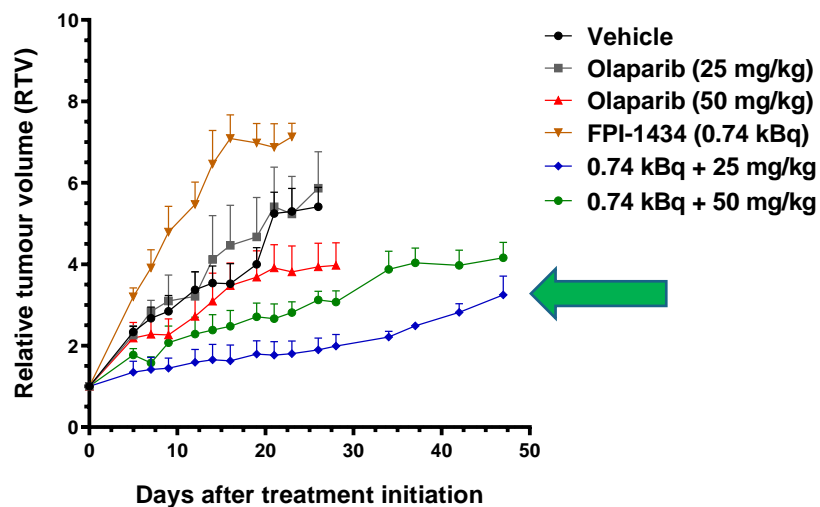
0.74 kBq FPI-1434 + 25 mg/kg Olaparib



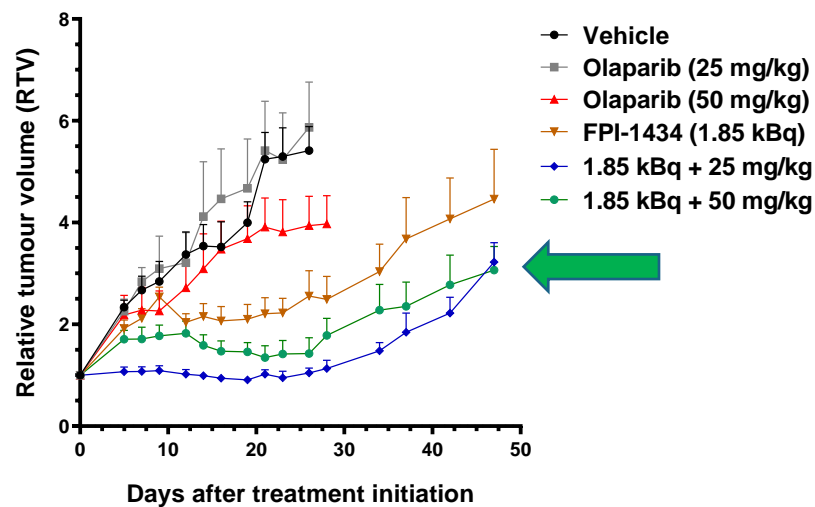
FPI-1434 + Olaparib; Combination Therapy at Multiple Dose Levels (Colo-205 Model)

FPI-1434 Dose Level

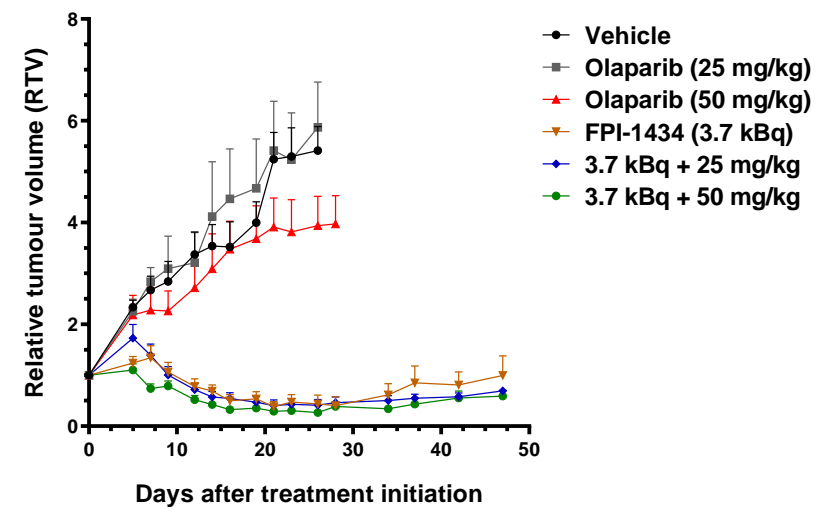
0.74 kBq FPI-1434 + Olaparib



1.85 kBq FPI-1434 + Olaparib



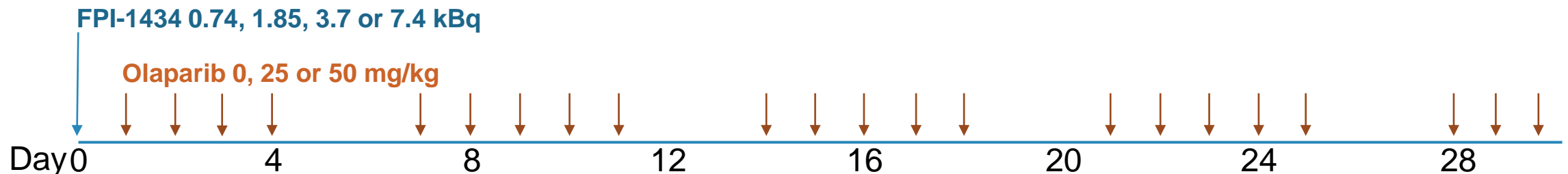
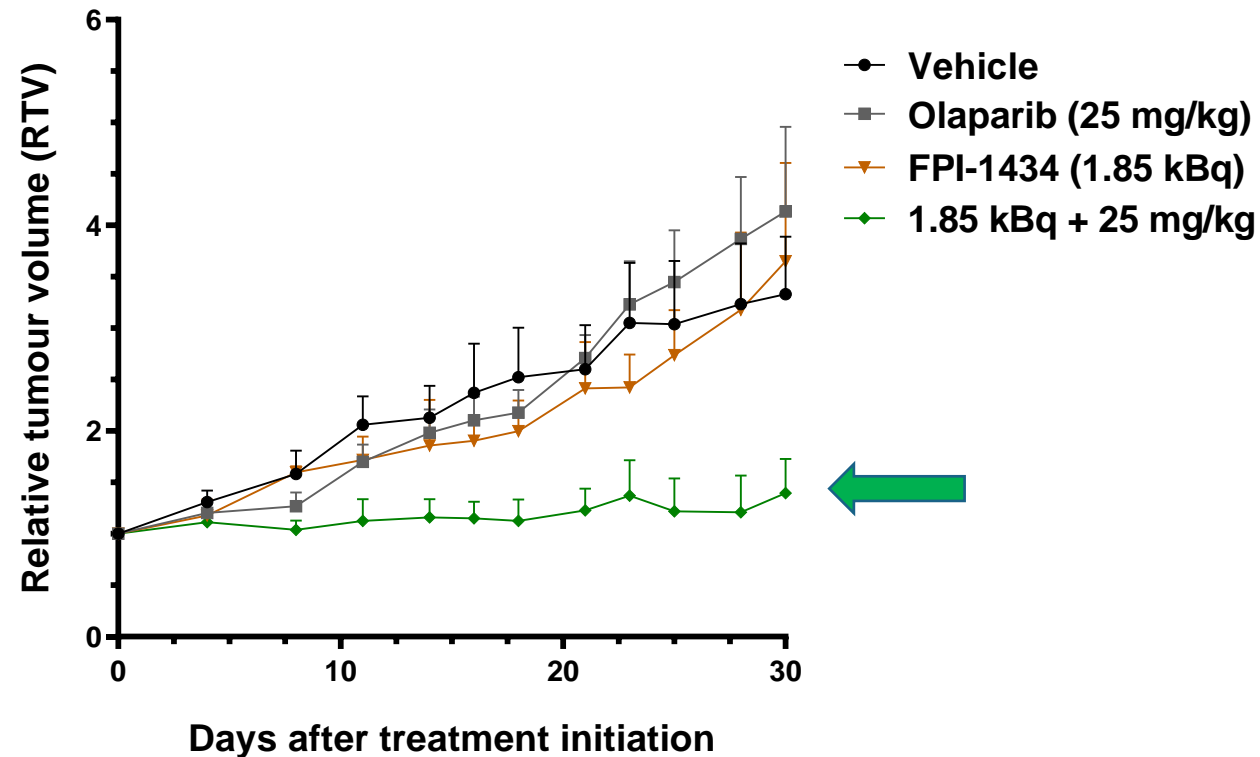
3.7 kBq FPI-1434 + Olaparib



Strongest Combination Effect at the Lowest Single Agent Doses

Combination of No-Effect Single Agent Doses of FPI-1434 and Olaparib Resulted in Enhanced Efficacy (A549 Model)

1.85 kBq FPI-1434 + 25 mg/kg Olaparib



FPI-1434 + Olaparib; Combination Therapy at Multiple Dose Levels (A549 Model)

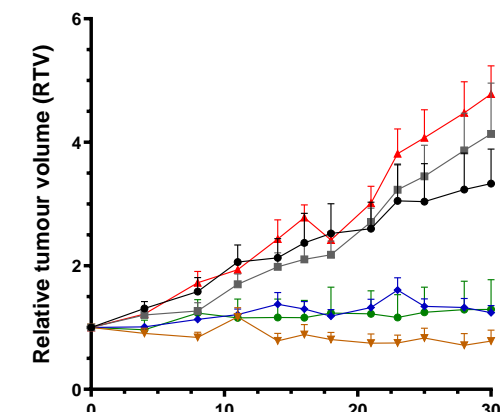
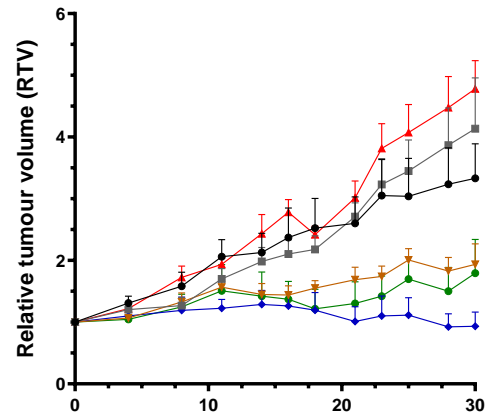
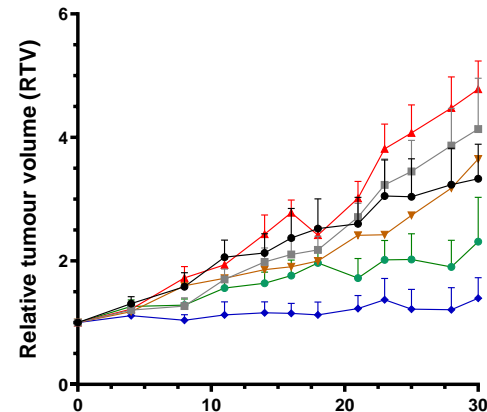
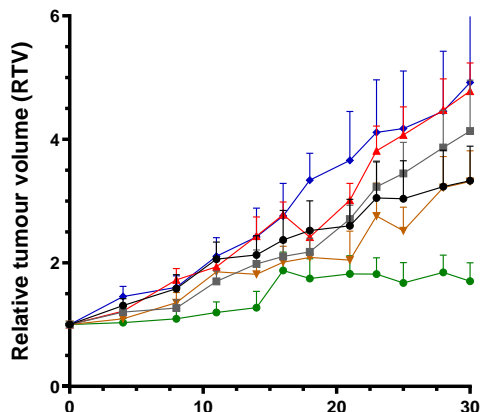
FPI-1434 Dose Level ➔

0.74 kBq FPI-1434 + Olaparib

1.85 kBq FPI-1434 + Olaparib

3.7 kBq FPI-1434 + Olaparib

7.4 kBq FPI-1434 + Olaparib



Days after treatment initiation

- Vehicle
- Olaparib (25 mg/kg)
- ▲ Olaparib (50 mg/kg)
- ▼ FPI-1434 (0.74 kBq)
- ◆ 0.74 kBq + 25 mg/kg
- 0.74 kBq + 50 mg/kg

Days after treatment initiation

- Vehicle
- Olaparib (25 mg/kg)
- ▲ Olaparib (50 mg/kg)
- ▼ FPI-1434 (1.85 kBq)
- ◆ 1.85 kBq + 25 mg/kg
- 1.85 kBq + 50 mg/kg

Days after treatment initiation

- Vehicle
- Olaparib (25 mg/kg)
- ▲ Olaparib (50 mg/kg)
- ▼ FPI-1434 (3.7 kBq)
- ◆ 3.7 kBq + 25 mg/kg
- 3.7 kBq + 50 mg/kg

Days after treatment initiation

- Vehicle
- Olaparib (25 mg/kg)
- ▲ Olaparib (50 mg/kg)
- ▼ FPI-1434 (7.4 kBq)
- ◆ 7.4 kBq + 25 mg/kg
- 7.4 kBq + 50 mg/kg

Strongest Combination Effect at Low Single Agent Doses

Summary of Studies with FPI-1434 + Olaparib Combinations

- Olaparib combination gave additional benefit to FPI-1434 therapy alone
- Combination of no-effect single agent doses resulted in enhanced efficacy in the Colo-205 model
 - 0.74 kBq FPI-1434 + 25 mg/kg Olaparib
 - Strongest combination effect appeared to occur at the lowest single agent doses
 - FPI-1434 effect dominates as the dose level escalates
- Combination of no-effect single agent doses resulted in enhanced efficacy in the radioresistant A549 model
 - 1.85 kBq FPI-1434 + 25 mg/kg Olaparib
 - Strongest combination effect appeared to occur at the low single agent doses
 - FPI-1434 effect dominates as the dose level escalates