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IGF-1R Targeted Alpha Therapeutic FPI-1434 causes DNA double-stranded breaks and induces regression in preclinical models of human cancer

Objectives:
Insulin-like growth factor-1 receptor (IGF-1R) is an oncogenic protein that is over-expressed in multiple solid tumors. IGF-1R targeted therapeutics have not demonstrated clinical efficacy for treating cancers either as stand-alone agents or in combination with other therapies. Despite this, targeted alpha therapeutic agents (TATs) may be ideal for treating IGF-1R expressing cancers due to their high potency and lower protein mass dose. Herewith we describe the preclinical efficacy of FPI-1434 in several solid tumor models and provide insight into its mechanism of action.
Methods: FPI-1434 was produced by conjugating with a lysine directed bifunctional chelated to AVE1642 and radiolabeled with Ac-225. Single dose radiotherapeutic efficacy studies were carried out using Colo-205 (colorectal), A549 (radioresistant lung), or LNCaP (prostate) xenografts inoculated into immunodeficient mice. Animals received single doses ranging from 0.05 μCi to 0.4 μCi with a corresponding dose of total protein typically less than 10 μg (0.5 mg/kg). Study endpoints included tumor volume measurement and/or impact to animal health status.
Results: Colo-205 xenograft bearing mice received single doses of FPI-1434 at 0.05, 0.2, and 0.4 μCi or vehicle and radiotherapeutic efficacy was followed for 178 days. FPI-1434 caused suppression of tumor growth at the 0.05 μCi dose and the 0.2 and 0.4 μCi doses caused durable tumor regression. In addition, FPI-1434 caused regression in large Colo-205 tumors grown to a volume of greater than 400 mm prior to dosing. FPI-1434 was also efficacious in the LNCaP and A549 models following single doses of radioimmunoconjugate. To elucidate the mechanism of action, COLO205 tumors treated with 400 nCi FPI-1434 were isolated at 24h, 96h and 168h post treatment, fixed, paraffin-embedded and stained with γH2AX (S139), a marker of double-stranded DNA breaks and Cleaved Caspase 3 (CC3), an early/intermediate apoptosis marker. γH2AX phosphorylation (S139) was almost undetectable at 24h but became more prominent at 96h and 168h post treatment. CC3 followed a similar pattern to yH2AX, highlighting cell nuclei actively undergoing apoptosis because of double-stranded DNA breaks. Current efforts are focusing on confirming the role of apoptosis and investigating the contribution of necrosis, autophagy and senescence to FPI-1434 mechanism of action.
Conclusion: Single doses of FPI-1434 as a standalone agent in pre-clinical models demonstrate a high degree of durable anti-tumor efficacy in multiple tumor xenograft types. The mechanism of action involves induction of DNA double-stranded breaks and progression into apoptosis. These results strongly support the use of FPI-1434 in IGF-1R overexpressing cancers.

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