**Antitumor activity of infigratinib, a potent and selective inhibitor of FGFR1, FGFR2 and FGFR3, in FGFR fusion-positive cholangiocarcinoma and other solid tumors**

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**Introduction**

Abnormal expression and constitutive activation of receptor tyrosine kinases, such as ALK, ROS1 and TRK, as a result of gene rearrangements have been clinically validated as therapeutic targets for cancer. FGFRs are also frequently altered and their ligands regulate a wide range of biological processes, such as development, differentiation, proliferation, survival, migration, and angiogenesis. Ligand binding results in receptor dimerization, which leads to the propagation of downstream signaling cascades.

Recently, fusions involving the FGFR family, especially FGFR1, FGFR2 and FGFR3, have been identified in diverse solid tumors such as cholangiocarcinomas, glioblastomas, bladder, lung, breast, thyroid and prostate cancers (Figure 1).

![Figure 1](image1.png)

**Figure 1.** FGFR fusions have been identified in a variety of tumor types

**Methods**

- The landscape of FGFR fusions was compiled based on published data and internally generated data from patients screened for enrollment into infigratinib clinical trials.
- A novel KLU-FGFR2 fusion gene was identified in a patient’s prostate tumor biopsy by next-generation sequencing (NGS). Biochemical analysis of FGFR2 signaling and inhibition of cell proliferation by infigratinib were performed in NIH3T3 cells expressing the KLU-FGFR2 fusion.
- Infigratinib patient-derived xenograft (PDX) models were identified based on NGS of the early passage tumor samples in collaboration with various commercial and academic research organizations (CROs).
- Tumor growth studies were performed in subcutaneous tumor-bearing immunocompetent male mice following ACUC-approved protocols. Tumor treatment started when average tumor size was about 150 mm3. Average tumor dimensions were measured by digital caliper twice a week.
- The open-label phase II study of infigratinib in cholangiocarcinoma patients with FGFR2 fusions was performed as described previously (Figure 3).

**Results**

- Although numerous FGFR fusions have already been found in multiple tumor types, novel fusions are continuously being identified.
- A novel FGFR2 fusion was identified and characterized in a prostate cancer patient (Figure 6).

**Conclusions**

- Infigratinib is an orally available, selective, ATP-competitive FGFR-3 inhibitor.
- Infigratinib has proven activity in tumor models with FGFR2 alterations.

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