Anti-tumor 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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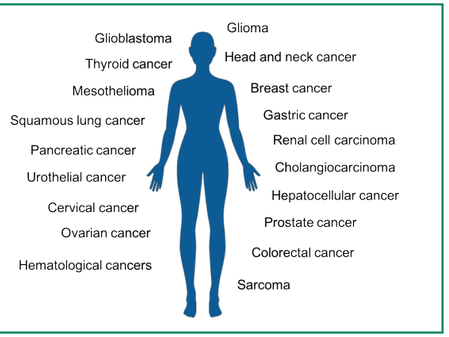
#2206

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.
- Under normal conditions, fibroblast growth factor receptors (FGFRs) 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 cholangiocarcinoma, glioblastoma, bladder, lung, breast, thyroid and prostate cancers (Figure 1).

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



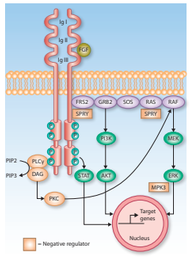
- *FGFR* fusions are the result of *FGFR* gene rearrangements involving a variety of fusion partners (Table 1).

Table 1. A large number of partners have been identified in *FGFR1/2/3* fusions

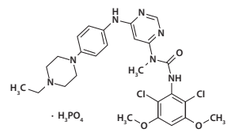
FGFR1 fusions	*FGFR2* fusions			*FGFR3* fusions
BAG4-FGFR1	FGFR2-AFF3	FGFR2-INA	FGFR2-RASAL2	FGFR3-BAIAP2L1
ERLIN2-FGFR1	FGFR2-AFF4	FGFR2-KCTD1	FGFR2-SLC45A3	FGFR3-TACC3
FGFR1-TACC	FGFR2-AHCYL1	FGFR2-KIAA1217	FGFR2-SLMAP2	FGFR3-TNIP2
FGFR1-TRP	FGFR2-BICC1	FGFR2-KIAA1598	FGFR2-SORBS1	FGFR3-WHSC1
FGFR1-NTM	FGFR2-C10orf68	FGFR2-KIAA1967	FGFR2-STK26	FGFR3-JAKMIP1
	FGFR2-C7	FGFR2-MGEA5	FGFR2-STK3	
	FGFR2-CASC15	FGFR2-NCALD	FGFR2-TACC1	
	FGFR2-CASP7	FGFR2-NOL4	FGFR2-TACC2	
	FGFR2-CCDC6	FGFR2-NPM1	FGFR2-TACC3	
	FGFR2-CELF2	FGFR2-OFD1	FGFR2-TBC1D1	
	FGFR2-CIT	FGFR2-OPTN	FGFR2-TFEC	
	FGFR2-COL14A1	FGFR2-PARK2	FGFR2-TRA2B	
	FGFR2-CREB5	FGFR2-PCMI	FGFR2-UBQLN1	
	FGFR2-DNAJC12	FGFR2-PDHX	FGFR2-WAC	
	FGFR2-ERLIN2	FGFR2-PPAPDC1A	FGFR2-ZMYM4	
	FGFR2-HOOK1	FGFR2-PPHLN1		

- *FGFR* fusions exhibit constitutive, ligand-independent activation as result of fusion partner-mediated dimerization and are oncogenic drivers that activate receptor kinases and their downstream signaling pathways, leading to uncontrolled cell proliferation and invasion.
- Infigratinib (BGJ398) is an ATP-competitive, FGFR1–3-selective oral tyrosine kinase inhibitor that has shown preliminary single agent clinical activity against tumors with *FGFR* alterations, with a manageable safety profile (Figure 2).[1–3]

Figure 2. Infigratinib: an oral FGFR1–3 selective kinase inhibitor



- Infigratinib is an orally-available, selective, ATP-competitive FGFR1–3 inhibitor
- Infigratinib has proven activity in tumor models with *FGFR* alterations



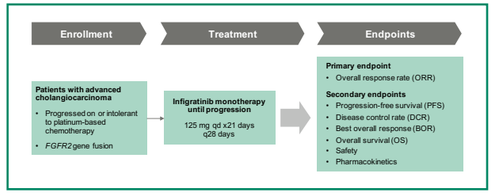
Biochemical activity ($nM\ IC_{50}$)	
FGFR1	1.1
FGFR2	1.0
FGFR3	2.0
FGFR4	61.0
VEGFR2	210.0

- At biochemical and cellular levels, infigratinib selectively inhibits the activity of FGFR1, FGFR2 and FGFR3 with low nM potency, while sparing FGFR4, VEGFR2 and other kinases.

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 *KLK2-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 *KLK2-FGFR2* fusion.
- *FGFR* fusion+ patient-derived xenograft (PDX) models were identified based on NGS of the early passage tumor samples in collaboration with various contract research organizations (CROs).
- Tumor growth inhibition studies were performed in subcutaneous tumor-bearing immunocompromised rats or mice following IACUC approved protocols. Treatment started when average tumor size was about 150 mm^3. Vehicle and infigratinib were given orally at the indicated doses, once daily for 3 weeks. 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).[3]

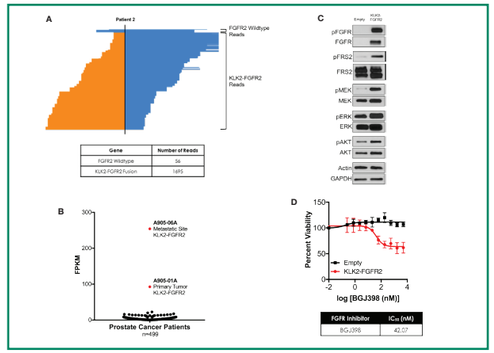
Figure 3. Open-label, phase II study design[3]



Results

- Although numerous *FGFR2* 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 4).

Figure 4. Identification and characterization of a novel *FGFR2* fusion in a prostate cancer patient



KLK2-FGFR2 fusion was identified in a prostate cancer patient and was sensitive to FGFR inhibition by infigratinib.

A. Expression of FGFR2 in a patient harboring the *KLK2-FGFR2* gene fusion. A pileup of all reads is shown with the black vertical line representing the fusion breakpoint (FGFR2: blue; KLK2: orange). The total number of reads supporting *WT FGFR* or the *KLK2-FGFR2* fusion is listed in the table.

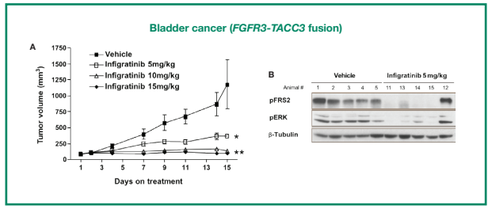
B. FGFR2 expression (FPKM) for all TCGA prostate cancer patients (N=499) assayed using exome capture (exact capture regions vary). Data were downloaded from the Genomic Data Commons (gdc.cancer.gov).

C. Total cell lysates from NIH3T3 empty and NIH3T3 KLK2-FGFR2 cells were prepared and subjected to Western analysis with antibodies against: pAKT, AKT, pMEK, MEK, pFGFR, FGFR, pMAPK, MAPK, pFRS2, FRS2, b-actin and GAPDH.

D. Inhibition of cell proliferation by infigratinib in NIH3T3 empty and NIH3T3 KLK2-FGFR2 cells.

- Anti-tumor efficacy of infigratinib was observed in a bladder cancer (*FGFR3-TACC3*) xenograft model (Figure 5).

Figure 5. Infigratinib inhibits tumor growth and FGFR signaling in a bladder cancer model harboring *FGFR3-TACC3* fusion

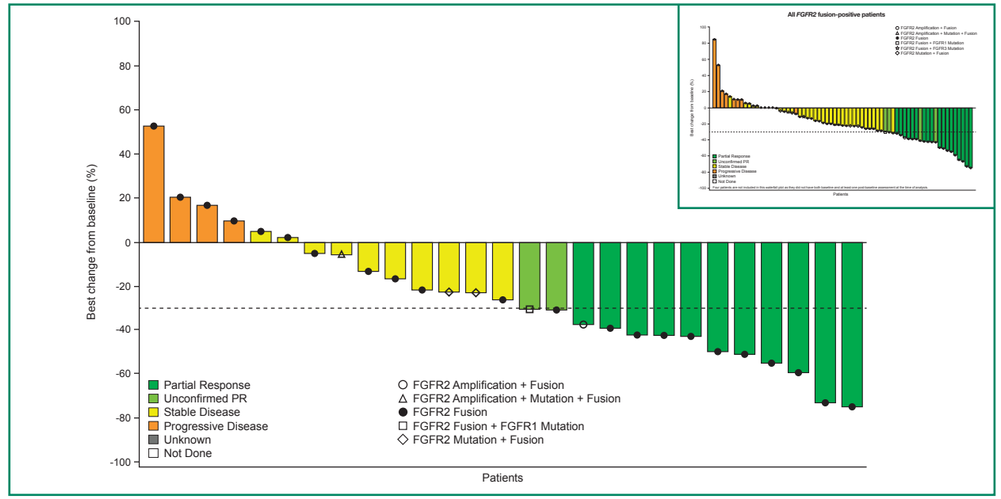


A. Subcutaneous tumors were established in female nude rats with RT112 cells (bladder cancer with *FGFR3-TACC3* fusion). Treatment started when average tumor size was 100 mm^3. Vehicle and infigratinib were given orally at the indicated doses, once a day for 14 days. Data are presented as mean ± SEM. * p<0.05; ** p<0.01 by one-way ANOVA with post-hoc Dunnett's.

B. Randomly selected tumors (5 mg/kg) were dissected 3 hours post treatment and analyzed for pFRS2 and pERK, with β-tubulin as loading control.

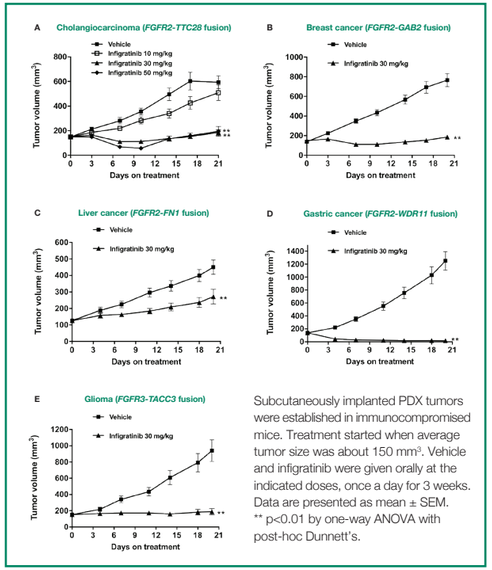
- Infigratinib has also demonstrated efficacy in *FGFR* fusion+ PDX models of cholangiocarcinoma, breast cancer, liver cancer, gastric cancer and glioma (Figure 6).
- Clinically, in an open-label phase II trial, infigratinib demonstrated a confirmed overall response rate (cORR) of 39.3% in *FGFR2* fusion-positive cholangiocarcinoma patients who received infigratinib as second-line therapy (Figure 7).[3] Additionally, clinical benefit was observed in non-cholangiocarcinoma solid tumors tested positive for *FGFR* fusions (data on file).

Figure 7. Efficacy of infigratinib in second-line patients who received prior systemic therapy for metastatic or unresectable disease



All patients received prior antineoplastic therapy; however, 3 patients only received prior antineoplastic therapy as neoadjuvant or adjuvant treatment, not first-line treatment.

Figure 6. Efficacy of infigratinib in *FGFR* fusion+ PDX models of cholangiocarcinoma, breast cancer, liver cancer, gastric cancer and glioma



Subcutaneously implanted PDX tumors were established in immunocompromised mice. Treatment started when average tumor size was about 150 mm^3. Vehicle and infigratinib were given orally at the indicated doses, once a day for 3 weeks. Data are presented as mean ± SEM. ** p<0.01 by one-way ANOVA with post-hoc Dunnett's.

Conclusions

- Infigratinib is an oral, FGFR1–3 selective TKI that has demonstrated unequivocal clinical benefit and a favorable safety profile in molecularly-selected patients exemplified by *FGFR2* fusion+ chemotherapy-refractory cholangiocarcinoma.
- Infigratinib exhibits potent anti-tumor activity in cell line- and patient-derived xenograft models driven by *FGFR* fusions, regardless of the fusion partner or the tissue of origin.
- The results presented here provide robust evidence and rationale for advancing infigratinib as a potential tumor-agnostic treatment for patients with *FGFR* fusion+ cancers.

References

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