# #461 - KIN-3248, a next-generation pan-FGFR inhibitor, is active against FGFR gatekeeper and molecular brake drug resistance mutations

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## BACKGROUND

- Oncogenic FGFR2 alterations are observed in ~10-20% of cholangiocarcinoma (CCA) and to a lesser extent in other gastrointestinal (GI) cancers, including gastroesophageal and pancreatic tumors (<1%)[1]
- Pemigatinib and infigratinib are FDA-approved for the treatment of locally advanced or metastatic CCA patients harboring FGFR2 gene fusions / rearrangements
- FGFR2 kinase domain (KD) resistance mutations are observed in > 50% CCA patients treated with approved & clinical-stage FGFR inhibitors (FGFRi)[2]
- KIN-3248 is a next-generation, irreversible pan-FGFRi designed to target primary oncogenic FGFR alterations as well as secondary KD drug resistance mutations

## IN VITRO RESULTS

**Table. 1.** Biochemical activity of KIN-3248 against wild-type and kinase domain FGFR mutants.

| FGFR Status | Kinase Domain Mutation | Erdafitinib IC50 (nM) | Pemigatinib IC50 (nM) | Futibatinib IC50 (nM) | **KIN-3248 IC50 (nM)** |
|---|---|---|---|---|---|
| FGFR1 WT | - | 0.2 | 0.4 | 2.1 | **3.9** |
| FGFR2 WT | - | 0.15 | 0.4 | 1.4 | **5.3** |
| V565F | Gatekeeper | 330 | >500 | >500 | **20.8** |
| N550H | Molecular Brake | 4.1 | 19.8 | 36.4 | **22.8** |
| FGFR3 WT | - | 0.7 | 1.5 | 5.3 | **9.7** |
| V555M | Gatekeeper | 137 | >500 | 324 | **24.3** |
| K650M | Activating Mutation | 3.5 | 20 | 8.3 | **4.6** |

Inhibition FGFR family kinases was determined using a fluorescence-based microfluidic mobility shift assay in multiple independent experiments.

**Table. 2.** KIN-3248 activity against FGFR2 fusion and kinase domain mutants in CCA cell lines.

| Cell Line | FGFR Status | Kinase Domain Alteration | Pemigatinib | Infigratinib | Futibatinib | **KIN-3248** |
|---|---|---|---|---|---|---|
| CCLP-1 (FGFR2-PHGDH) | WT | - | | | | |
| | V565F | Gatekeeper | | | | |
| | V565I | | | | | |
| | V565L | | | | | |
| | N550H | Molecular Brake / Regulatory Triad | | | | |
| | N550K | | | | | |
| | E566A | | | | | |
| | K642R | | | | | |
| | C492F | Other | | | | |
| | K660M | Activating Mutation | | | | |
| | L618F | | | | | |
| | L618V | | | | | |
| | M538I | | | | | |
| | M538I / M539L | | | | | |
| ICC13-7* (FGFR2-PHGDH) | WT | - | | | | |
| | V565F | Gatekeeper | | | | |
| | N550K | Molecular Brake | | | | |
| | L618V | Activ. Mut. | | | | |

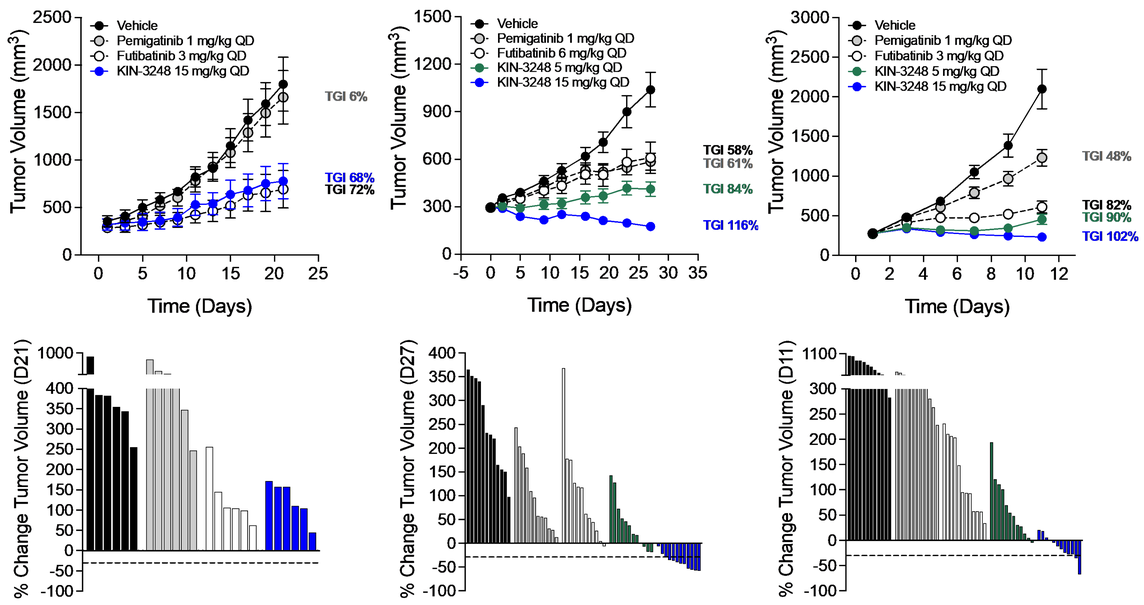
*ICC13-7 express endogenous FGFR2-OPTN fusion
Cell viability was measured by MTT in multiple independent experiments.

Fold change in activity versus WT: 0 10 20 30 40 > 50

## IN VIVO RESULTS

**Figure 1.** KIN-3248 efficacy in cell line- and patient-derived xenograft models with FGFR2 kinase domain resistance mutations.

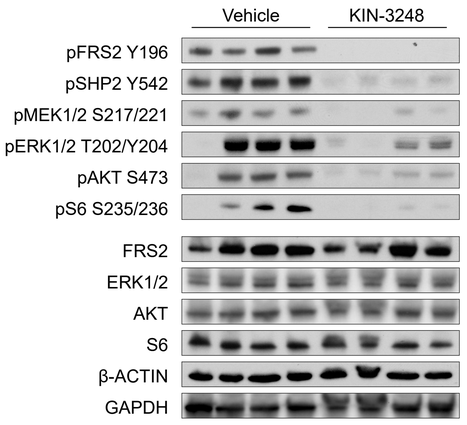
| Kinase Domain Mutant CCA FGFR2-CBX5 + M538I / M539L | Gatekeeper Mutant Gastric Cancer FGFR2 amp + V565L | Mol. Brake Mutant Endometrial Cancer FGFR2 N550K |
|---|---|---|




Tumor growth inhibition (TGI) was calculated as follows: TGI = (1 –(TVf-TVi)treated/ (TVf-TVi)control)) x 100%, where TVf the final tumor volume and TVi the initial tumor volume.

- KIN-3248 showed improved inhibition of FGFR2 and FGFR3 gatekeeper and molecular brake mutations when compared to FDA-approved and clinical-stage FGFR inhibitors in biochemical and cell-based assays (Tables 2 and 3)
- KIN-3248 demonstrated comparable or superior activity against clonally distinct FGFR2 resistance mutations compared to approved and clinical-stage FGFR inhibitors in P/CDX models (Figure 1)
- KIN-3248 led to deeper tumor responses and regressions – including partial responses in P/CDX models harboring FGFR2 gatekeeper and molecular brake mutations (Figure 1)
- KIN-3248 ablated FGFR signaling as measured by western blot analysis of proximal and distal pharmacodynamic biomarkers (e.g., phosphorylated FRS2 and phosphorylated ERK, respectively) in a patient-derived CCA xenograft model harboring KD resistance mutations (Figure 2)

**Figure 2.** KIN-3248 modulation of FGFR signaling in a patient-derived CCA xenograft model harboring KD resistance mutations.




Three-day PK / PD study conducted in CCA PDX model harboring FGFR2-CBX5 and secondary M538I / M539L resistance mutations Animals treated with 15 mg/kg QD KIN-3248 and tumors harvested 4 hours post-final dose to evaluate FGFR pathway activation

## SUMMARY & CONCLUSION

- The emergence of on-target acquired FGFR resistance mutations limits the duration of response to approved and clinical-stage FGFR inhibitors
- KIN-3248 has pronounced *in vitro* and *in vivo* activity against clinically-relevant FGFR2 resistance mutations including those associated with progressive disease
- A phase 1 / 1b dose escalation and expansion clinical trial evaluating KIN-3248 in patients with advanced tumors harboring *FGFR2* and *FGFR3* gene alterations is expected to initiate in 1H-2022*

REFERENCES: 1) Krook 2020 Br. J. Cancer; 2) Goyal 2020 EORTC-NCI-AACR Symposium.

*Subject to IND clearance by FDA