Phase II Trial of Pemigatinib in Combination With Atezolizumab and Bevacizumab for Treatment of Advanced Cholangiocarcinoma With FGFR2 Fusion (NCT06439485)

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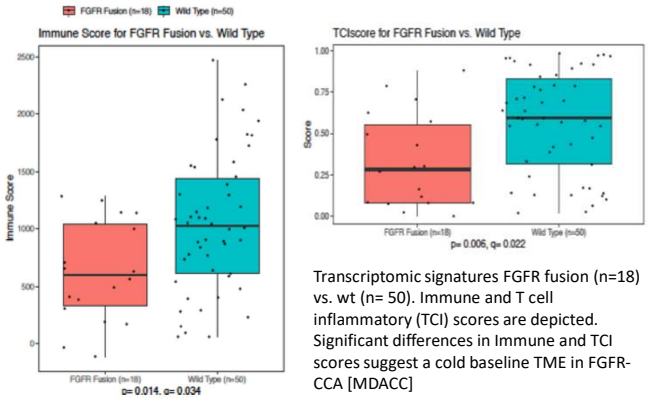
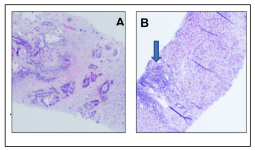
Background & Rationale

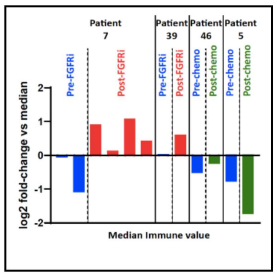
- Fibroblast growth factor receptor (FGFR) alterations: 10-15% of intrahepatic cholangiocarcinoma (CCA)
- Oncogenic signaling promoting angiogenesis and EMT
- FGFR alterations result in an immunosuppressed tumor microenvironment
- FGFR inhibition: Overall response rates range from 20-35% and progression-free survival ranges 6–9 months.
- Therefore, there is an unmet need to improve efficacy in addition to anti-FGFR alone.



Transcriptomic signatures FGFR fusion (n=18) vs. wt (n= 50). Immune and T cell inflammatory (TCI) scores are depicted. Significant differences in Immune and TCI scores suggest a cold baseline TME in FGFR-CCA [MDACC]



Moderately differentiated carcinoma (A) before and (B) after FGFR inhibition with tumor infiltrating lymphocytes present in tumor bed

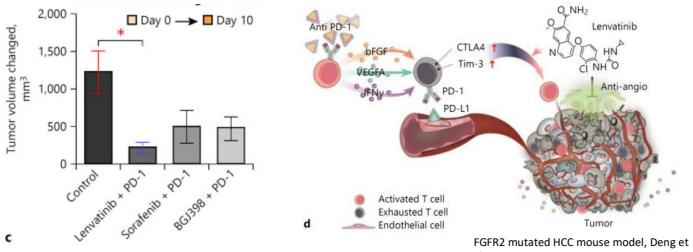


FGFR-CCA Pre and post chemotherapy or FGFRi. Nanostring. PANCancer, 770 genes innate and acquired immune response show upregulation after FGFRi

- VEGF, highly expressed in CCA (Lenvatinib, regorafenib, ramucirumab studies).
- FGFR pathway has also been shown to play an important role in angiogenesis.

- VEGF/VEGFR, FGF/FGFR, and FGFR/VEGFR inhibitors invert immunologically 'cold' into 'hot' tumors

← Immune-supportive effects by suppressing immunosuppressive cells and enhancing infiltration of mature dendritic cells and cytotoxic T lymphocytes.



FGFR2 mutated HCC mouse model, Deng et al, 2020

Dual blockade of FGFR and VEGFR pathways has a potential synergic anti-tumor activity.

Based on the above data, we hypothesize that the combination of **pemigatinib** with **atezolizumab** and **bevacizumab** may be safe and improve the antitumor effect of pemigatinib alone in cholangiocarcinoma with *FGFR2* fusion that has progressed on gemcitabine-based therapy.

Study Population & Objectives

Study Population: Patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusion or rearrangement who have progressed on gemcitabine-based therapy.

Primary Objective: To determine safety and maximum tolerated dose (MTD)

Secondary Objectives: Objective response rate (ORR), Disease control rate (DCR), Duration of response (DOR), Progression-free survival (PFS), Overall survival (OS), Changes in immune TME – RNA sequencing, flow cytometry, multiplexed IHC

Dosing and Schedule

Pemigatinib 13.5 mg PO
+
Bevacizumab 15 mg/kg IV
+
Atezolizumab 1,200 mg IV

Dosing Table

Dose Level	Pemigatinib	Bevacizumab	Atezolizumab
0	13.5 mg daily PO [14 days on and 7 days off]	15 mg/kg IV [D1]	1,200 mg IV [D1]
-1	9 mg daily PO [14 days on and 7 days off]	15 mg/kg IV [D1]	1,200 mg IV [D1]

Cycle Length: 21 days

Inclusion & Exclusion Criteria

Key Inclusion Criteria:
- Patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusion or rearrangement who have progressed on gemcitabine-based therapy

Key Exclusion Criteria:
- Previous treatment with FGFR inhibitors or bevacizumab

Correlative Studies:
- Pre-treatment and 9 week tumor biopsy samples, pre- and post-treatment ctDNA
  → Mandated biopsy to assess tumor evolution
- Optional biopsy on progression

This trial adds immunotherapy and anti-VEGF to address FGFR inhibitor resistance and improve the limited survival outcomes seen with treatments like pemigatinib.