FP-1039/GSK3052230, an FGF ligand trap, enhances VEGF antagonist therapy in preclinical models of RCC and HCC

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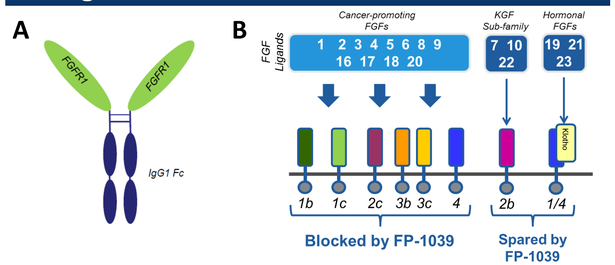
Abstract

An increasing body of evidence has implicated FGF2 as one of the drivers of resistance to various inhibitors of VEGF-mediated angiogenesis. This resistance may play a role as a key limitation to the efficacy of therapies targeted at VEGF and its receptors. We investigated the potential for FP-1039/GSK3052230, a ligand trap that sequesters FGFs and inhibits their signaling, to enhance the activity of VEGF antagonist therapies in certain preclinical models of renal cell (RCC) and hepatocellular (HCC) carcinomas. First, we examined whether FP-1039/GSK3052230 has single agent efficacy against human RCC and HCC xenografts that express relatively high levels of FGF2, a profile that would mimic FGF2-driven resistance to VEGF therapy. We determined that this expression profile represents 34% of clear cell RCC (ccRCC) and 31% of HCC patients, based on the cancer genome atlas (TCGA) data. Human ccRCC xenografts with high FGF2 expression and low VEGFA expression demonstrated a significant inhibition in tumor growth when treated with FP-1039/GSK3052230 alone (TGI: 39-81%). In addition, we show that the high FGF2 expression profile is similarly predictive for the anti-tumor response of a human HCC model to single-agent FP-1039/GSK3052230 (TGI: 31-55%). In contrast, RCC models with low FGF2 expression, representing 66% of all ccRCC in the TCGA, are relatively insensitive to FP-1039/GSK3052230 as a single agent. However, combination therapy of FP-1039/GSK3052230 with pazopanib in these tumors is significantly more effective than either agent alone. FP-1039/GSK3052230 not only slows tumor growth, but can induce ~25% tumor regression when administered to mice bearing ccRCC xenografts that have become resistant to pazopanib. Together, our data demonstrate that FP-1039/GSK3052230 may be an effective therapy against RCC and HCC, both as a single agent in disease driven by FGF2 and in combination with VEGF antagonist therapies that represent the current standards of care for advanced disease.

Background

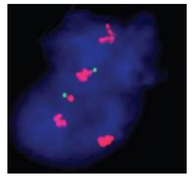


- FP-1039/GSK3052230 consists of the extracellular domain of FGFR1c, linked to the Fc of human IgG1
- FP-1039/GSK3052230 binds to multiple members of the classical FGF ligand family.
- Hormonal FGFs are not blocked by FP-1039/GSK3052230.
- Suppresses pro-cancer FGF signaling without toxicities common to small molecule FGFR inhibitors.

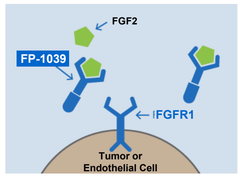
*** Harding T.C. et al. *Sci. Transl. Med.* 2013; 5:1-9**

Rationale

***FGFR1* Gene Amplification**

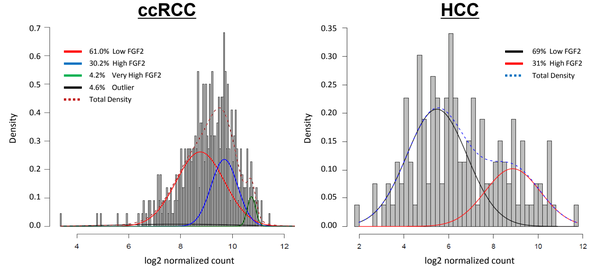


FGF-Driven Disease

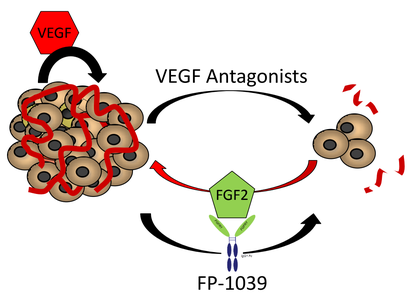


- FP-1039/GSK3052230 is currently being assessed in a Phase 1b clinical trial in squamous NSCLC patients with amplified *FGFR1* and in mesothelioma, a tumor in which FGF2 is over-expressed.
- Here, we explore FP-1039/GSK3052230 as a therapeutic against kidney and liver malignancies driven by the ligand FGF2.

Distribution of FGF2 Expression in Human Cancer Patients



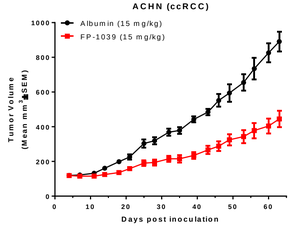
- Approximately 34% of human clear cell renal cell carcinoma (ccRCC) possess high FGF2 mRNA expression, as assessed from the TCGA.
- High FGF2 was also detected in 31% of human hepatocellular carcinoma (HCC).

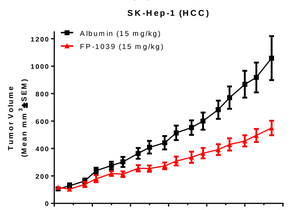


- Tumors that become resistant to VEGF antagonist therapies may up-regulate FGF2 as a mechanism of resistance.
- FGF2 driven resistance to VEGF antagonist therapy can be blocked by treatment with FP-1039.
- Patients demonstrating disease progression following VEGF antagonist therapy may represent a novel population that would benefit from FP-1039 therapy.

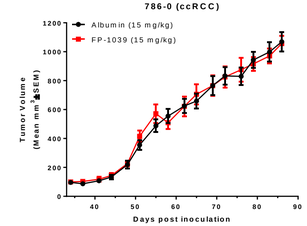
Results

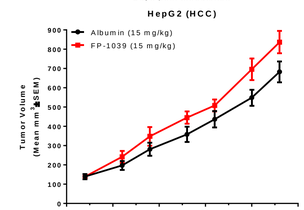
High FGF2, Low VEGFA





Low FGF2, High VEGFA

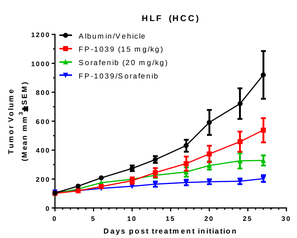


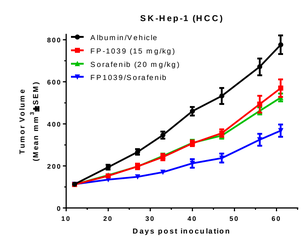


Tissue	Cell Line	FGF2 *	VEGFA *	FGF2/VEGFA Ratio	Prediction	%TGI#
Clear Cell Renal Cell Carcinoma (ccRCC)	Caki-1	10.67	7.53	1.42	FP1039 single agent sensitive	81%
	ACHN	9.79	7.19	1.36		50-57%
	A-498	9.85	9.77	1.01	Not sensitive to single agent FP-1039	7-28%
	Caki-2	8.26	8.61	0.96		27%
	786-0	7.20	9.39	0.77		0%
Hepatocellular Carcinoma (HCC)	SK-Hep-1	9.45	7.03	1.34	FP1039 single agent sensitive	48%
	HLF	9.74	7.90	1.23		24%
	Hep3B	5.17	8.33	0.62	Not sensitive to single agent FP-1039	9%
	HepG2	4.62	8.60	0.54		3%
	Huh7	4.19	7.83	0.53		18%

* FGF2 and VEGFA expression are obtained from CCLE (RMA values, log2 transformed).
** %TGI = 100 x (1-(ΔTumor Volume/ΔTumor Volume Control))

- Single agent FP-1039 significantly reduces tumor growth in human ccRCC models with high FGF2 and low VEGFA expression.
- Human HCC models with high FGF2 and low VEGFA expression are also significantly inhibited when administered FP-1039 alone.

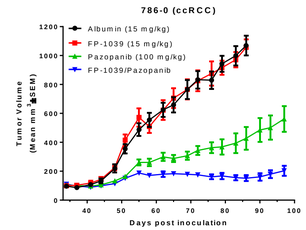




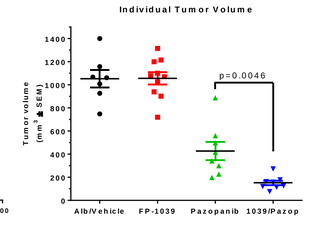
- FP-1039 is additive with the small molecule inhibitor sorafenib in HCC models that are sensitive to the ligand trap as a single agent therapy.

Results

786-0 (ccRCC)

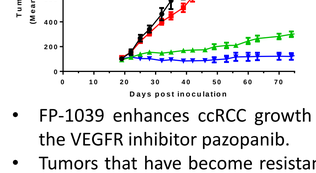


Individual Tumor Volume

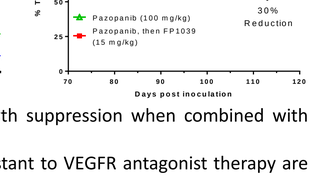


- Human ccRCC models demonstrate additive tumor suppression when treated in combination with the VEGR inhibitor pazopanib, even in models that are not sensitive to single-agent FP-1039.

A498 (ccRCC)



Pazopanib-Resistant Tumors



- FP-1039 enhances ccRCC growth suppression when combined with the VEGFR inhibitor pazopanib.
- Tumors that have become resistant to VEGFR antagonist therapy are sensitive to FP-1039, demonstrating an immediate reduction in tumor volume of 25-30%, followed by persistent, stable tumor size.

Conclusions

- Preclinical human ccRCC and HCC models with high FGF2 and low VEGFA expression demonstrate significant growth suppression when treated with FP-1039 alone.
  - ccRCC and HCC models with low FGF2 and high VEGFA have limited growth inhibition when treated with single agent FP-1039.
- FP-1039 is additive with sorafenib, the current standard of care, in HCC models that are sensitive to FP-1039 as a single agent.
- In ccRCC, FP-1039 significantly enhances tumor inhibition in combination with the VEGF receptor inhibitor pazopanib.
  - Additivity occurs even in tumor models that are not sensitive to FP-1039 as a single agent therapy.
- Long-term treatment of ccRCC reveals a pazopanib-resistant population that is sensitive to FP-1039.
  - FP-1039 can be an effective therapy for tumors that may rely upon FGF2 as a mechanism of resistance to VEGF antagonist therapy.