Phase II study of dovitinib in patients (Pts) progressing on anti-vascular endothelial growth factor (VEGF) therapy.

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Abstract 612

BACKGROUND

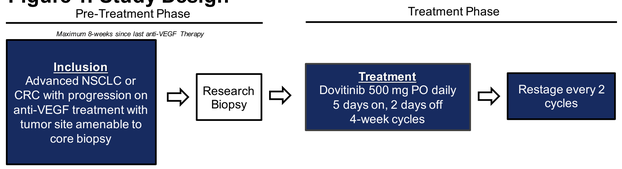
- The FGF-FGFR signaling pathway is involved in regulating cellular proliferation, survival, migration and differentiation.[1]
- Signaling through FGFRs is involved in vessel assembly and sprouting.[1, 2]
- Because circulating FGF is increased in patients with metastatic CRC progression on anti-VEGF therapy, activation of FGF-FGFR signaling has been proposed as a mechanisms of resistance to anti-VEGF agents.[3, 4]
- Dovitinib is an orally available investigational drug that is a potent inhibitor of FGFR1-3 and VEGFR2 amongst other kinases.[5]
- We tested the hypothesis that dovitinib would induce responses in patients whose tumors progressed within 8 weeks of an anti-VEGF strategy.

METHODS

Key Inclusion Criteria

- Pretreated advanced non-squamous NSCLC or CRC
- Progression on anti-VEGF therapy containing regimen (bevacizumab or ziv-aflibercept) within 8 weeks
- Willingness to undergo research biopsy
- Adequate organ function
- Zubrod PS 0-1

Figure 1. Study Design



Simon 2-Stage Phase II Design

Primary Objective: Overall Response Rate

Secondary Objectives: Expression of Angiogenic Mediators, Disease Control Rate, Progression Free Survival, Toxicity

Biomarker Analyses

Tumor: Formalin fixed paraffin embedded (FFPE) tumor samples were micro-dissected to reduce non-tumor components. RNA was isolated and gene expression was assessed using a next generation sequencing based panel with probe sequences for 2,560 genes. Raw counts from the Illumina MiSeq output for each gene were filtered from background using the median negative control. Normalized expression values were then generated from expression across all samples. One sample had insufficient specimen for analysis.

Circulating: Selected circulating angiogenic factors were analyzed at baseline, Cycle 1 Day 12, Cycle 2 Day 1, and at progression using multiplex bead based array (VEGF-A, VEGF-C, PlGF, IL-8, HGF, and soluble Tie2; R&D Luminex®) or ELISAs (FGF2, and soluble VEGFR2)

The study closed February 2015 with termination of dovitinib development programs

RESULTS

Table 1. Baseline Characteristics (n=10)

	n (%)
Age, years	
Median (range)	63 (48-77)
Time From Last Anti-VEGF Treatment, days	
Median (range)	48 (28-58)
ECOG Performance Status	
0	3 (30)
1	7 (70)
Tumor Site	
Colorectal	9 (90)
Non-Small Cell Lung Cancer	1 (10)
Prior Anti-VEGF Agent	
Bevacizumab	8 (80)
Ziv-Aflibercept	2 (20)
Gender	
Female	5 (50)
Male	5 (50)
Race/Ethnicity	
White	9 (90)
Black	1 (10)

Table 2. Response and Treatment Duration

Response (RECIST v1.1)	n (%)
Evaluable	7 (70)
Partial Response	0
Stable Disease	1 (10)
Progressive Disease	6 (60)
Not Evaluable – Withdrew Consent	3 (30)
Days on Treatment	
Median (range)	40 (7-123)

Figure 2. Median Expression of FGF Ligands in Pretreatment Tumor Specimens (CRC patients, n=8)

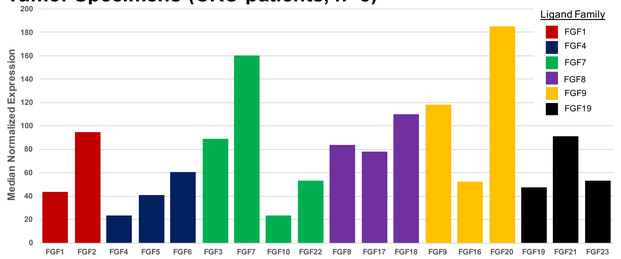


Table 3. Major Treatment Related Toxicities

Category	CTCAE term	Any Grade[1] N (%)	Grade 3-5[2] N (%)
Blood	**Anemia**	3 (30)	1 (10)
Gastrointestinal	**Abdominal Pain**	2 (20)	1 (10)
	Diarrhea	4 (40)	1 (10)
	Esophageal pain	1 (10)	1 (10)
	Nausea	6 (60)	1 (10)
	Vomiting	3 (30)	1 (10)
General	**Fatigue**	9 (90)	4 (40)
Infections	**Sepsis**	1 (10)	1 (10)
Investigations	**ALT/AST increased**	5 (50)	2 (20)
	Alkaline phosphatase	8 (80)	3 (30)
	Bilirubin increased	5 (50)	0
	Cholesterol high	2 (20)	1 (10)
	GGT increased	6 (60)	4 (40)
	Lymphopenia	4 (40)	4 (40)
	Weight loss	5 (50)	0
Metabolism and Nutrition	**Anorexia**	8 (80)	1 (10)
	Dehydration	2 (20)	1 (10)
	Hypoalbuminemia	6 (60)	2 (20)
	Hyponatremia	4 (40)	0
	Hypertriglyceridemia	4 (40)	0
Musculoskeletal	**Generalized muscle weakness**	5 (50)	2 (20)
Respiratory	**Dyspnea**	2 (20)	1 (10)
Vascular	**Hypertension**	1 (10)	1 (10)
	Thromboembolic event	1 (10)	1 (10)

[1] Toxicities of any grade occurring in 4 or more individuals [2] Grade 3-5 toxicities occurring in 1 or more individuals

Figure 3. Median Expression of Selected Angiogenic Mediators Pretreatment Tumor Specimen (CRC patients, n=8)

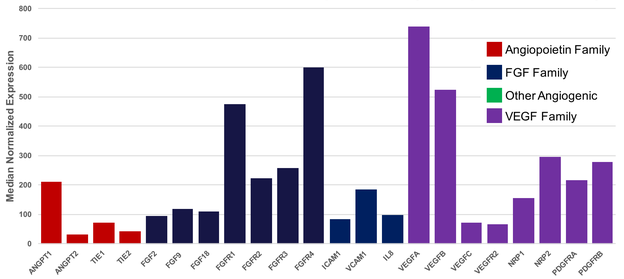
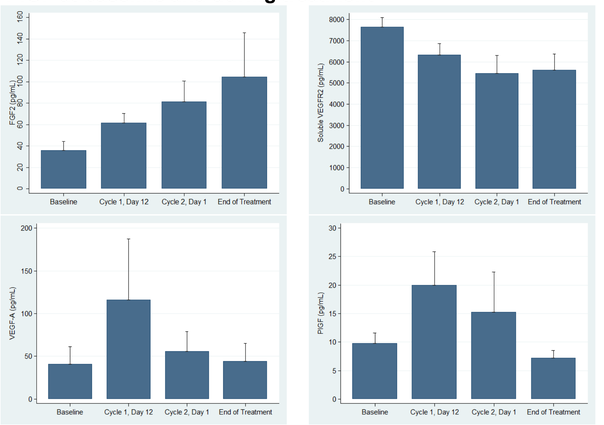


Figure 4. Circulating FGF2, soluble VEGFR2 , VEGF-A, and PlGF at baseline and during treatment*



* IL-8 values increased continuously on treatment and at progression. There was no change in soluble Tie2 and HGF (not shown)

CONCLUSIONS

- Dovitinib was not active in CRC patients progressing on anti-VEGF therapy
- There was evidence of VEGF pathway modulation through altered circulating angiogenic mediators
- We did not confirm evidence of FGF pathway modulation through treatment-induced hyperphosphatemia. Circulating FGF2 increased during treatment.
- In tumors progressing despite anti-VEGF therapy, a multitude of pro-angiogenic mediators are expressed, including members of the FGF and VEGF pathways.

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