Published in final edited form as:

Cancer Treat Res Commun. 2017 ; 10: 21–26. doi:10.1016/j.ctarc.2016.12.002.

Phase II Study of Dovitinib in Patients Progressing on Anti-Vascular Endothelial Growth Factor Therapy

Thomas J. Semrad, MD, MAS¹, Edward J. Kim, MD, PhD¹, Michael S. Tanaka, MD¹, Jacob Sands, MD², Chris Roberts³, Rebekah A. Burich, MS¹, Yu Li, MS¹, David R. Gandara, MD¹, Primo Lara Jr., MD¹, and Philip C. Mack, PhD¹

¹Division of Hematology/Oncology, University of California, Davis Comprehensive Cancer Center, Sacramento, California

²Lahey Clinic, Boston, MA

³HTG Molecular Diagnostics, Inc., Tucson, AZ

Abstract

Background—Prior work identified the fibroblast growth factor (FGF) pathway as a mediator of resistance to anti-vascular endothelial growth factor (VEGF) therapy. We tested dovitinib, an inhibitor of both FGF and VEGF receptors, in patients progressing on anti-VEGF treatment.

Methods—Patients with measurable advanced colorectal or non-small cell lung cancer with progression despite anti-VEGF treatment within 56 days, good performance status and adequate organ function were eligible. A research tumor biopsy was followed by treatment with dovitinib 500 mg on a 5-day on/2-day off schedule for 28-day cycles. The primary endpoint of tumor response was evaluated every 2 cycles. Secondary endpoints included toxicity and 8-week disease control rate. Intratumor mRNA expression of angiogenic mediators was analyzed using a next generation sequencing based expression array.

Results—Ten patients treated previously with bevacizumab or ziv-aflibercept enrolled. The study closed with termination of dovitinib development. No responses were observed in 7 evaluable patients. The best response was stable disease in 1 patient. Common toxicities included gastrointestinal, metabolic, and biochemical derangements. All patients experienced at least one grade 3 treatment-related adverse event, most commonly fatigue, elevated GGT, and lymphopenia. Expression of multiple angiogenic mediators was common in tumors progressing on anti-VEGF therapy including high levels of FGFR1 and VEGFA.

Conclusions—We found no evidence for the activity of dovitinib in patients who had recently progressed on anti-VEGF therapy and toxicities were significant. In tumors progressing despite

*Correspondence to: Thomas J. Semrad MD, MAS, Division of Hematology/Oncology, Department of Internal Medicine, University of California Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817. Phone: (916) 734-3771; Fax: (916) 734-7946, tsemrad@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

anti-VEGF therapy, a multitude of pro-angiogenic mediators are expressed, including members of the FGF pathway.

Keywords

Dovitinib; Vascular Endothelial Growth Factors; Fibroblast Growth Factors; Angiogenesis Inhibitors

INTRODUCTION

Since the landmark study demonstrating a survival advantage for the addition of bevacizumab to irinotecan, 5-fluorouracil (5-FU), and leucovorin therapy for the treatment of advanced colorectal cancer (CRC) (1), several agents have been developed that target vascular endothelial growth factor (VEGF) pathway signaling. The list of approved agents now includes those that target VEGF ligands (bevacizumab, ziv-aflibercept) and the VEGF receptor 2 (ramucirumab). The approval of the multi-kinase inhibitor regorafenib, which targets VEGFR2 amongst other targets, may also be an extension of this paradigm (2). Moreover, two of these agents have demonstrated modest improvements in treatment outcome when combined with chemotherapy in advanced non-small cell lung cancer (NSCLC) (3, 4). Despite the promise of anti-VEGF therapy-based combinations in the treatment of advanced CRC and NSCLC, intrinsic and acquired resistance to anti-VEGF therapy results in the absence of benefit for some patients and a reduced duration of benefit for others.

The fibroblast growth factor (FGF) signaling pathway is an alternative pro-angiogenic pathway that may be an important mediator of resistance to anti-VEGF therapy (5). FGF signaling is highly polymorphic with 22 potential ligands and 4 FGF receptor (FGFR) tyrosine kinases identified (6). Preclinical models suggest that up-regulation of components of the FGF pathway may contribute to tumor growth and anti-angiogenic resistance. For example, in a mouse model of pancreatic islet cell tumors treated with a VEGFR-antibody, vasculature regrowth was observed 10–14 days into treatment and associated with increased mRNA expression of FGF1 and FGF2 (7). The addition of an FGF antibody slowed revascularization in this model. Furthermore, in a phase II trial the VEGFR tyrosine kinase inhibitor cediranib (Recentin, AstraZenaca) in malignant gliomas, circulating levels of FGF2 were found to be higher in the presence of resistant tumors than in the same patients during the responsive phase (8). While FGF pathway activation may be important for some tumors prior to any treatment, anti-VEGF therapy may select for FGF pathway activation as a resistance mechanism. Indeed, investigators studying dynamic changes in circulating angiogenic factors in patients treated with irinotecan, 5-fluorouracil (5-FU), leucovorin and bevacizumab demonstrated that FGF2 levels were strikingly elevated immediately prior to progression compared to baseline (9). Taken together, these data suggest that the FGF pathway may be an important mediator of anti-VEGF therapy resistance.

Dovitinib (TKI258, Novartis Pharmaceuticals) is an orally available investigational agent that is an inhibitor of multiple tyrosine kinases. Included in its spectrum of targets are FGFR1 (IC₅₀ 8 nM), FGFR2 (IC₅₀ 40 nM) and FGFR3 (IC₅₀ 9 nM), as well as VEGF

receptors (VEGFR) 1 to 3 (10). Potent tumor growth inhibition and anti-angiogenic activity has been observed in preclinical models of multiple tumor types (11–14). In this study, we tested the hypothesis that dovitinib would induce responses in patients whose tumors progressed within 8-weeks of an anti-VEGF strategy and explored the baseline expression of angiogenic mediators in these tumors.

PATIENTS AND METHODS

Patients

This investigator initiated study was reviewed and approved by the University of California Davis institutional review board and was performed at the University of California Davis Comprehensive Cancer Center. Written informed consent was obtained from each enrolled patient. The study was registered at clinicaltrials.gov under identifier NCT01676714.

Patients 18-years of age or older with histologically-confirmed Response Evaluation Criteria In Solid Tumors (RECIST) v1.1-measurable advanced CRC or NSCLC with < 50% squamous-cell component whose immediate prior treatment regimen included an anti-VEGF agent administered not more than 56-days from enrollment were eligible (15). Willingness to participate in a pre-treatment research biopsy and tumor site amenable to core needle biopsy were required. Further inclusion criteria included the ability to give informed consent, Zubrod performance status 0–1, and acceptable end-organ function defined by an absolute neutrophil count > 1,500/mm³, platelet count > 100,000/mm³, hemoglobin > 9 g/dL, total bilirubin < 1.5 times the institutional upper limit of normal (ULN), ALT and AST < 3 times the ULN, and serum creatinine < 1.5 times the ULN or calculated creatinine clearance > 30 mL/min using the Cockcroft-Gault formula if the serum creatinine was 1.5 – 3 times the ULN.

Exclusion criteria included ongoing side effects of prior treatment that had not resolved to grade 1 or less, known brain metastases, major surgery within 4 weeks, minor surgical procedures within 1 week, radiotherapy within 4 weeks, and prior malignancy within 3 years except for completely treated in-situ carcinoma of the uterine cervix or non-melanoma skin cancer. Further exclusion criteria included clinically significant and uncontrolled cardiac dysrhythmia, reduced left ventricular ejection fraction (LVEF) by echocardiogram or multiple gated acquisition (MUGA), systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg, and myocardial infarction, congestive heart failure, cerebrovascular ischemia, or pulmonary embolism within the prior 6 months. Pregnant or breast-feeding women were ineligible, and those biologically able to conceive were required to use highly effective barrier contraception.

Study Procedures

Prior to registration, patients underwent a history and physical examination and baseline laboratory studies, including a pregnancy test for women of child bearing potential. Assessment of LVEF by echocardiogram or MUGA was performed within 56 days of treatment, and repeated at week 12 and 24 of the study. Radiographic tumor assessment by CT or MRI was required within 4 weeks of study entry. Tumor measurements were

subsequently repeated every 8 weeks. History and physical examination were performed along with assessment of hematology and chemistry profiles on day 1 and 12 of the first two 4-week cycles, then once per cycle.

At the time of enrollment, the study team including the relevant interventional radiologists selected an appropriate site for biopsy. The biopsy procedure was scheduled at least 3-weeks after the last infusion of bevacizumab or ziv-aflibercept and at least 1-week from last any anti-VEGF tyrosine kinase inhibitor. The preferred method was a core biopsy system to obtain at least 2 core biopsies not less than 20 gauge in diameter and 1 cm in length. A focused history and examination were performed after completion of the biopsy to ensure recovery from any adverse events.

Treatment Plan

Treatment began between 4 and 7 days after completion of the tumor biopsy. Dovitinib was administered with or without food at an initial dose of 500 mg for 5 days on then 2 days off continuously during 28-day cycles. Up to 2 dose reductions according to a pre-specified scale were allowed for clinically relevant toxicities, with a maximum of 14 days allowed for dose interruptions. Hormonal contraception was not allowed and barrier contraception required during the study due to potential cytochrome P450 (CYP) interactions of dovitinib and oral contraceptives. Similarly, concomitant medications with potential for interaction via CYP1A1/2, CYP2C9, and CYP2C19 were reviewed and used with caution if no alternative was available. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Treatment was continued unless there was a biopsy complication until unacceptable adverse event(s), disease progression, pregnancy, the patient withdrew consent, or the investigator felt that continued treatment was no longer in the patient's best interest.

Correlative Studies

Archival tumor specimen was requested on all patients. Research tumor biopsies were formalin fixed and 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 (HTG Molecular Diagnostics, Inc.). 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.

Selected circulating angiogenic factors were analyzed at baseline, day 12 of cycle 1, day 1 of cycle 2, 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). Values for each patient and each time point are reported as the mean of three replicates.

Statistical Analysis

The trial was conducted using a two-stage Simon optimal design (Simon, 1989). The primary endpoint of the trial was overall response rate using RECIST 1.1 criteria. Under the assumption that a response rate of 5% or less is not worthy of further study and an

alternative response rate of at least 25% or more would be of considerable interest, the initial phase was to enroll 9 evaluable patients. If 1 or more of the first 9 patients has a response, then accrual would continue until a total of 30 evaluable patients have been treated. Demographic and other baseline data were summarized descriptively. Secondary endpoints included disease control rate at 8 weeks, progression free survival (PFS), and toxicity (NCI CTCAE version 4). Gene expression values are reported as the median normalized value. Expression of circulating angiogenic factors are expressed as the mean and standard error. Given the small number of patients included and the number of tests performed, no comparative statistics were performed and the results are considered descriptive.

RESULTS

Patient Characteristics

Between March 2013 and June 2014 we enrolled ten patients with a median age of 63 years who had recently progression on anti-VEGF treatment for advanced CRC or NSCLC. The median time from administration of the last anti-VEGF treatment was 48 days and all but one patient had advanced CRC. A median of 4 prior lines of systemic treatment had been administered; the prior anti-VEGF regimen contained bevacizumab in 80% of enrolled patients and ziv-aflibercept in the remaining 20%. The study closed to new accrual in February 2015 with the termination of dovitinib development programs. Demographics of the cohort are summarized in Table 1.

Treatment and Response

The study closed after enrolling 10 patients, three of whom were not eligible for response assessment due to withdrawal of consent for treatment and response assessment in the first cycle of therapy. The population of evaluable patients included only those with CRC, amongst whom no RECIST 1.1 response was observed in 7 evaluable patients. The overall best response was stable disease in 1 patient. The median time on treatment for the entire cohort was 40 days. For those patients who did not withdraw from therapy in cycle 1, the median time on treatment was 57 days. The median progression free survival was 1.9 months. Tumor responses for the cohort are summarized in Table 2.

Adverse Events

There were no complications from the pre-treatment study biopsies. Treatment related toxicities were substantial; all patients had grade 3 or higher toxicities attributed to drug treatment (Table 3). Grade 3 or higher toxicities experience by 2 or more patients included fatigue (40%), elevated GGT (40%), lymphopenia (40%), elevated alkaline phosphatase (30%), elevated aspartate aminotransferase (20%), hypoalbuminemia (20%) and generalized muscle weakness (20%). Common all grade toxicities included anorexia, nausea, hypoalbuminemia, liver function test abnormalities, generalized muscle weakness, and weight loss. There was one death after extensive bilateral pulmonary emboli that was attributed as potentially related to drug treatment.

Molecular Correlates

Although archival tumor was requested, no samples with sufficient tissue for further analysis were available from archived specimens. All enrolled patients underwent a pre-treatment study biopsy procedure. Sufficient tumor tissue for gene expression analysis was available in 9 specimens. As one specimen was NSCLC, expression data from the CRC cohort with available specimens (n=8) is reported. Expression of multiple angiogenic mediators was common in CRC tumors progressing on anti-VEGF therapy (Figure 1). Prominent expression of all four FGFRs was detected, along with prominent expression of FGF ligands commonly implicated in tumor angiogenesis. Additionally high expression of VEGF pathway ligands was noted along with detectable but lower expression of VEGFR2.

Plasma FGF2 increased continuously during treatment and at progression (Figure 2). Similarly, IL-8 values increased continuously on treatment and at progression (Supplemental Figure 1A). The VEGF family ligands VEGF-A and placenta growth factor (PlGF) peaked in early treatment and returned to near baseline upon progression. Soluble VEGFR2 levels decreased during therapy. There was no significant change in soluble Tie2 and HGF (Supplemental Figure 1).

DISCUSSION

In this study, we did not confirm the activity of combined FGFR and VEGFR inhibition in tumors with resistance to anti-VEGF therapy. Dovitinib was associated with significant toxicities in this heavily pretreated patient population and although the number of treated patients was small, we observed no evidence for meaningful clinical benefit from dovitinib treatment. Nonetheless, the pre-treatment tumor biopsies that were collected shortly after progression on prior anti-VEGF therapy provide a unique opportunity to assess the expression status of angiogenic mediators in this situation.

Potential mechanisms of resistance to anti-VEGF therapy include selection for or upregulation of alternative pro-angiogenic pathways, recruitment of bone marrow derived vascular progenitors and pro-angiogenic monocytes, increased involvement of pericytes in blood vessel stability, and increased capacity for invasion without metastasis (16–18). Based on pre-clinical and translational data, the FGF pathway has been proposed as a major alternative pro-angiogenic escape mechanism (7, 9). In this study, we confirmed significant levels of expression of FGF ligands and receptors in tumor biopsies obtained after recent progression on treatment containing an anti-VEGF agent. We requested archival specimens from all patients on this study but sufficient tumor was not available for comparison of expression profiles prior to anti-VEGF therapy to those obtained from the study research biopsy. Nevertheless, the pattern of expression does support the potential for activation of the FGF pathway in this context. A key finding of our study is the observation of relevant levels of continued expression of VEGF pathway components as well as other pro-angiogenic factors. Based on these data, we speculate that the angiogenic factor milieu in tumors growing despite VEGF pathway inhibition is robust and perhaps not dependent on a single alternative angiogenic pathway.

There are a number of limitations of this study that warrant comment. Enrollment was aborted prior to completion of the first stage of the Simon 2-stage design. Nonetheless, it is unlikely that accrual of additional patients would have significantly altered the efficacy and toxicity conclusions presented. We allowed both advanced CRC and NSCLC patients to be enrolled on this study; however, enrollment was largely restricted to CRC patients. We could not confirm that dovitinib was acting as a potent FGF pathway inhibitor in this study despite preclinical and clinical data supporting potent FGF inhibition in other contexts (10, 19). Indeed, we demonstrated that FGF pathway mediators are amongst the most expressed angiogenic mediators in patients recently progressing on anti-VEGF therapy. Thus, caution should be exercised for the extrapolation of our results to other anti-FGF strategies. Additionally, we defined anti-VEGF resistance as progression on a treatment regimen that includes an anti-VEGF agent. In the period since this study was designed, clinical data in advanced CRC demonstrated a survival advantage to the continuation of an anti-VEGF agent while changing the concomitant chemotherapy backbone (20). This suggests that progression on an anti-VEGF therapy containing regimen is distinct from anti-VEGF therapy resistance. Moreover, the expression of VEGF pathway mediators in post-anti-VEGF therapy tumors suggests the potential for ongoing VEGF-mediated angiogenesis in these patients. Just as molecular selection of patients for anti-VEGF strategies remains an unachieved goal, the molecular and clinical definitions of resistance to anti-VEGF therapy strategies are unknown.

In conclusion, we observed significant toxicities and no meaningful activity when dovitinib was administered to a small number of CRC patients progressing on anti-VEGF therapy. While there was evidence of VEGF pathway modulation through altered circulating angiogenic mediators, we did not confirm evidence of FGF pathway modulation. In tumors progressing despite anti-VEGF therapy, a multitude of pro-angiogenic mediators are expressed, including members of the FGF and VEGF pathways. Future studies are required to understand the interplay of multiple proangiogenic pathways active in tumors exposed to anti-VEGF therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The research reported was supported by Novartis Pharmaceuticals. Additional support was provided by the National Cancer Institute of the National Institutes of Health under Award Number K12CA138464 and the UC Davis Cancer Center Support Grant, P30CA093373-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors would also like to thank Stephanie H. Astrow, PhD, and Miriana Moran, PhD from Response Genetics, Inc. for support of correlative studies on this protocol. **Study Identifier:** NCT01676714. Presented in part at the 2016 Gastrointestinal Cancers Symposium (Abstract 616)

References

1. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004; 350(23):2335–42. [PubMed: 15175435]

2. Troiani T, Martinelli E, Orditura M, De Vita F, Ciardiello F, Morgillo F. Beyond bevacizumab: new anti-VEGF strategies in colorectal cancer. Expert opinion on investigational drugs. 2012; 21(7): 949–59. [PubMed: 22612461]
3. Garon EB, Ciuleanu TE, Arrieta O, Prabhaskar K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014; 384(9944):665–73. [PubMed: 24933332]
4. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006; 355(24):2542–50. [PubMed: 17167137]
5. Dieci MV, Arnedos M, Andre F, Soria JC. Fibroblast growth factor receptor inhibitors as a cancer treatment: from a biologic rationale to medical perspectives. Cancer discovery. 2013; 3(3):264–79. [PubMed: 23418312]
6. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer. 2010; 10(2):116–29. [PubMed: 20094046]
7. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer Cell. 2005; 8(4):299–309. [PubMed: 16226705]
8. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell. 2007; 11(1):83–95. [PubMed: 17222792]
9. Kopetz S, Hoff PM, Morris JS, Wolff RA, Eng C, Glover KY, et al. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. J Clin Oncol. 2010; 28(3):453–9. [PubMed: 20008624]
10. Lee SH, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, et al. In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. Clin Cancer Res. 2005; 11(10):3633–41. [PubMed: 15897558]
11. Porta C, Giglione P, Liguigli W, Paglino C. Dovitinib (CHIR258, TKI258): structure, development and preclinical and clinical activity. Future oncology. 2015; 11(1):39–50.
12. Lee CK, Lee ME, Lee WS, Kim JM, Park KH, Kim TS, et al. Dovitinib (TKI258), a multi-target angiokinase inhibitor, is effective regardless of KRAS or BRAF mutation status in colorectal cancer. Am J Cancer Res. 2015; 5(1):72–86. [PubMed: 25628921]
13. Eucker J, Zang C, Zhou Y, Li X, Habbal P, Neumann C, et al. The multi-tyrosine kinase inhibitor TKI258, alone or in combination with RAD001, is effective for treatment of human leukemia with BCR-ABL translocation in vitro. Anticancer research. 2014; 34(9):4909–14. [PubMed: 25202073]
14. Andre F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, et al. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. Clin Cancer Res. 2013; 19(13):3693–702. [PubMed: 23658459]
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92(3):205–16.
16. Abdollahi A, Folkman J. Evading tumor evasion: current concepts and perspectives of anti-angiogenic cancer therapy. Drug Resist Updat. 2010; 13(1–2):16–28. [PubMed: 20061178]
17. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer. 2008; 8(8):592–603. [PubMed: 18650835]
18. Ellis LM, Hicklin DJ. Pathways mediating resistance to vascular endothelial growth factor-targeted therapy. Clin Cancer Res. 2008; 14(20):6371–5. [PubMed: 18927275]
19. Kim KB, Chesney J, Robinson D, Gardner H, Shi MM, Kirkwood JM. Phase I/II and pharmacodynamic study of dovitinib (TKI258), an inhibitor of fibroblast growth factor receptors and VEGF receptors, in patients with advanced melanoma. Clin Cancer Res. 2011; 17(23):7451–61. [PubMed: 21976540]

20. Bennouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *The lancet oncology*. 2013; 14(1):29–37. [PubMed: 23168366]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.
Median Normalized Expression of Selected Angiogenic Mediators in Pretreatment Tumor Specimens (CRC patients, n=8)

Figure 2. Mean Circulating A) FGF2, B) soluble VEGFR2, C) VEGF-A, and D) PlGF at baseline and during treatment. Error bars depict the standard error.

Table 1

Patient Demographic, Clinical, and Treatment Characteristics (n = 10)

Characteristic	n (%)
<u>Age, years</u>	
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

Duration of Treatment and Disease Response

Characteristic	n (%)
Tumor Response	
Evaluable	7 (70)
Partial Response	0
Stable Disease	1 (10)
Disease Control Rate	1 (10)
Progressive Disease	6 (60)
Not Evaluable – Withdrew Consent	3 (30)
Days on Treatment	
Median (range)	40 (7–123)

Table 3**Major Treatment-Related Toxicities**

Adverse Event (CTCAE term)	Any Grade ¹		Grade 3–5 ²	
	N	%	N	%
Any	10	100	10	100
Blood and Lymphatic System Disorders				
Anemia	3	30	1	10
Skin and Subcutaneous tissue Disorders				
Dry Skin	2	20	0	0
Gastrointestinal Disorders				
Abdominal Pain	2	20	1	10
Bloating	2	20	0	0
Diarrhea	4	40	1	10
Esophageal pain	1	10	1	10
Nausea	6	60	1	10
Vomiting	3	30	1	10
General disorders				
Edema limbs	2	20	0	0
Fatigue	9	90	4	40
Malaise	2	20	0	0
Infections and infestations				
Sepsis	1	10	1	10
Investigations				
ALT increased	5	50	1	10
Alkaline phosphatase increased	8	80	3	30
AST increased	5	50	2	20
Blood bilirubin increased	5	50	0	0
Cholesterol high	2	20	1	10
GGT increased	6	60	4	40
Lymphocyte count decreased	4	40	4	40
Other – LDH increased	2	20	0	0
Weight loss	5	50	0	0
Metabolism and Nutrition Disorders				
Anorexia	8	80	1	10
Dehydration	2	20	1	10
Hypoalbuminemia	6	60	2	20
Hyponatremia	4	40	0	0
Hypertriglyceridemia	4	40	0	0
Musculoskeletal and connective tissue disorders				
Generalized muscle weakness	5	50	2	20
Psychiatric Disorders				
Insomnia	2	20	0	0

Adverse Event (CTCAE term)	Any Grade ¹		Grade 3–5 ²	
	N	%	N	%
Respiratory, thoracic and mediastinal disorders				
Dyspnea	2	20	1	10
Vascular Disorders				
Hypertension	1	10	1	10
Hypotension	2	20	0	0
Thromboembolic event	1	10	1	10

¹Toxicities of any grade occurring in 2 or more individuals

²Grade 3–5 toxicities occurring in 1 or more individuals