BATON-CRC: a phase II randomized trial comparing tivozanib plus mFOLFOX6 with bevacizumab plus mFOLFOX6 in stage IV metastatic colorectal cancer

Al B. Benson III[1], Igor Kiss[2], John Bridgewater[3], Ferry A.L.M. Eskens[4], Carolyn Sasse[5], Sandra Vossen[5], Jihong Chen[5], Chip Van Sant[5], Howard Ball[5], Anne Keating[5], Andrew Krivoshik[5]

[1]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois. [2]Masaryk Memorial Cancer Institute, Brno, Czech Republic. [3]University College London Cancer Institute, London, United Kingdom. [4]Eramus MC Cancer Institute, Rotterdam, The Netherlands. [5]Astellas Pharma Global Development, Northbrook, Illinois.

Corresponding Author:
Al B. Benson III, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 676 N. St. Clair, Suite 850, Chicago IL 60611. Phone: 312-695-6180; Fax: 312-695-6189; E-mail: a-benson@northwestern.edu

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This phase II study of untreated patients with metastatic colorectal cancer compared efficacy and safety of tivozanib plus folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6) vs. bevacizumab plus mFOLFOX6. The combination of tivozanib/mFOLFOX6 was tolerable and adverse events were comparable to both bevacizumab/mFOLFOX6 and previous tivozanib studies. Following a prespecified interim futility analysis, which demonstrated that the futility boundary for superiority of tivozanib over bevacizumab for progression-free survival (PFS) in the intent-to-treat population was crossed in this study, tivozanib/mFOLFOX6 resulted in PFS and overall response rates comparable to bevacizumab/mFOLFOX6. At the time of interim analysis, no significant association was found between biomarkers and PFS. Post hoc final analyses demonstrated a statistical difference in PFS in patients with low neuropilin-1 (NRP-1), favoring the tivozanib combination arm, and no difference in patients with high NRP-1. NRP-1 is a potential predictive biomarker for tivozanib activity and this biomarker association warrants further study.

Author Contributions:

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Abstract

Background: Tivozanib, a selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3, plus mFOLFOX6 in an advanced gastrointestinal cancer phase Ib study had encouraging antineoplastic activity and a tolerable safety profile. This randomized, open-label, phase II trial of tivozanib/mFOLFOX6 vs. bevacizumab/mFOLFOX6 in patients with previously untreated metastatic colorectal cancer (mCRC) evaluated tivozanib activity vs. bevacizumab.

Methods: Treatment-naïve patients received mFOLFOX6 every 2 weeks of each 28-day cycle plus either tivozanib orally 1.5 mg once daily for 21 days or bevacizumab intravenously 5 mg/kg every 2 weeks. Investigator-assessed progression-free survival (PFS) was the primary endpoint; some secondary endpoints included safety, overall survival, overall response rate (ORR), duration of response, time to treatment failure, and biomarker subgroup analyses.

Results: A prespecified interim futility analysis demonstrated that the futility boundary for superiority of tivozanib/mFOLFOX6 over bevacizumab/mFOLFOX6 for PFS in the intent-to-treat population was crossed; median PFS was 9.4 vs. 10.7 months (HR=1.091; CI 0.693–1.718; *P* = 0.706). Tivozanib/mFOLFOX6 resulted in PFS and ORR comparable to bevacizumab/mFOLFOX6; interim analyses biomarker results revealed no significant PFS association. Post hoc final analyses demonstrated a statistical difference in tivozanib-specific PFS in patients with low neuoropilin-1 (NRP-1), but not in patients with high NRP-1. Tivozanib/mFOLFOX6 was tolerable and adverse events were comparable to both bevacizumab/mFOLFOX6 and previous tivozanib studies.

Conclusions: The efficacy of tivozanib/mFOLFOX6 was comparable to bevacizumab/mFOLFOX6 in patients with previously untreated mCRC; safety and tolerability profile of tivozanib/mFOLFOX6 was consistent with other tivozanib trials. NRP-1 is a potential predictive biomarker for tivozanib activity.

Introduction

Colorectal cancer (CRC) is a prevalent and deadly cancer with an estimated 136,830 new cases and 50,310 deaths in the United States in 2014 (1). Although 5-year survival rates remain low (9.8% to 17.7% across major racial/ethnic population and age groups), survival time for metastatic CRC (mCRC) has been improving (2). Additional therapeutic options including combination therapy and therapies with agents targeting the epidermal growth factor receptor (EGFR)- and vascular endothelial growth factor receptor (VEGFR)-signaling pathways have created a significant change in CRC therapy over the last decade, particularly for mCRC (3, 4). In particular, the addition of bevacizumab has become a standard in combination therapy for mCRC (5).

Tivozanib is an oral VEGFR tyrosine kinase inhibitor (TKI) with selective inhibition of VEGFR-1, -2, and -3 (6). It is more selective and potent than other VEGFR TKIs and was designed to optimize blockade of VEGFR while minimizing off-target toxicities (6–8). Tivozanib has a long half-life of approximately 4.5 days, which allows once-daily dosing to maintain serum concentrations (7, 9).

In a phase III trial in patients with renal cell carcinoma, tivozanib met its primary endpoint of progression-free survival (PFS), but failed to meet the overall survival (OS) secondary endpoint (10). One possibility is that crossover to sorafenib may have confounded the survival results (11). Tivozanib has also shown single-agent activity in patients with other solid tumors, including CRC (7, 12–14) and in combination with temsirolimus in patients with renal cell carcinoma (15), with paclitaxel in patients with metastatic breast cancer (16), and with everolimus in patients with metastatic colon cancer (17). Preclinical data demonstrated additive antitumor activity of tivozanib when combined with fluorouracil. A pharmacokinetic drug-drug interaction study showed that dosing of tivozanib with a CYP3A4 pathway inhibitor had no influence on tivozanib concentrations; however, a strong CYP3A4 inducer reduced tivozanib plasma concentration (9).

Tivozanib plus mFOLFOX6 (modified treatment regimen of: **FOL**inic acid, **F**luorouracil, and **OX**aliplatin) was evaluated in a phase Ib study in patients with advanced gastrointestinal (GI) cancers, including mCRC (18). Results from this study showed that tivozanib can be safely combined at the recommended dose with mFOLFOX6 in patients with advanced GI tumors and also demonstrated encouraging antineoplastic activity with 30.8% of all patients achieving a partial response (18). A randomized, open-label, phase II trial of tivozanib/mFOLFOX6 (Arm A) vs. bevacizumab/mFOLFOX6 (Arm B) in patients with previously untreated mCRC (BATON [Biomarker Assessment of Tivozanib in ONcology] -CRC; NCT01478594) was initiated to evaluate tivozanib activity vs. bevacizumab and to evaluate a predefined set of biomarkers for potential prediction of clinical response following tivozanib therapy.

Materials and Methods

Patients

Male or female patients ≥18 years with histologically or cytologically confirmed mCRC, ≥1 measurable lesions by RECIST (Version1.1), no prior systemic chemotherapy, no fluorouracil-containing adjuvant therapy in the previous 6 months, and an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 were included in the study. Patients were excluded if they had prior VEGF therapy (including bevacizumab) or a history of significant thromboembolic or vascular disorders within 6 months of study entry. Patients with any of the following were also excluded: hematologic abnormalities; significant cardiovascular disease; history of serious GI toxicity, diarrhea, or stomatitis within 6 weeks of study entry; a GI condition with increased risk of perforation; history of abdominal fistula, GI perforation, or intraabdominal abscess within 4 weeks prior to study entry; and peripheral neuropathy ≥Grade 2.

All patients provided informed consent prior to performing any study-related procedures. Approval was obtained by the research ethics committee at each participating institution for the protocol, informed consent, patient information, and amendments. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice with the ethical principles of the current version of Declaration of Helsinki.

Study design

This was a randomized, open-label, phase II trial designed to evaluate superiority of tivozanib/mFOLFOX6 over bevacizumab/mFOLFOX6 in patients with mCRC. Patients were randomized 2:1 to tivozanib/mFOLFOX6 (Arm A) or bevacizumab/mFOLFOX6 (Arm B) and stratified by lactate dehydrogenase (LDH), origin of cancer, and number of metastatic sites. Patients received mFOLFOX6 every 2 weeks on days 1 and 15 of each 28-day cycle with either tivozanib orally 1.5 mg once daily for 21 days followed by 7 days off treatment (Arm A) or bevacizumab intravenously 5 mg/kg every 2 weeks on days 1 and 15 (Arm B).

PFS by investigator-assessed radiological disease progression was the primary endpoint. Assessed secondary endpoints included safety, OS, overall response rate (ORR), duration of response (DOR), and time to treatment failure (TTF). PFS subgroup analyses and biomarker analyses of lactate dehydrogenase (LDH); VEGF A, C, D, and their ratios; CD68; myeloid-derived gene signature; and serum soluble cytokines were evaluated for any potential to predict response to tivozanib therapy. The trial initiated on December 20, 2011 and interim efficacy analyses were based on a September 13, 2013 data analysis cut off, which led to the termination of the study due to futility. Secondary endpoints of PFS by independent radiological review and health-related quality of life were not assessed due to early termination of the study. Disposition, safety, and biomarker analyses include data through trial follow-up to February 28, 2014.

Safety and efficacy assessment

Safety and tolerability was assessed by monitoring vital sign measurements, physical examinations, 12-lead electrocardiograms (ECG), clinical laboratory tests (including hematology, urinalysis, serum chemistry, thyroid, coagulation, and pregnancy tests), cardiac biomarkers (troponin, creatine phosphokinase), ECOG PS, and adverse events (AEs) which were coded using NCI-CTCAE (v4.03). Dose reduction for toxicity was allowed for tivozanib and mFOLFOX6, but not for bevacizumab. Dose interruptions for all agents were allowed; however, interruption for longer than 2 weeks could result in treatment discontinuation as determined by the study investigator. Dose reductions of tivozanib and mFOLFOX6 could have occurred independently. Tivozanib was reduced to 1.0 mg/day for patients with Grade ≥3 AEs, and could not be re-escalated.

Disease progression was assessed based on radiologic imaging (e.g., diagnostic computed tomography scans, magnetic resonance imaging scans) of the chest, abdomen, and pelvis every 8 weeks from the start of study medication for the first 18 months on study and then every 12 weeks until study end, disease progression, or death. PFS was defined as the time from the date of randomization until objective tumor progression (defined by RECIST v1.1) or death. Secondary efficacy variables were defined as follows: OS from the date of randomization until death from any cause, ORR was the proportion of patients with confirmed complete response (CR) or partial response (PR), DOR from the date of first documented CR or PR to the date of progression, and TTF from randomization to treatment discontinuation for any reason.

Serum Biomarker Analysis

A secondary objective to identify biomarkers that potentially could predict clinical response following tivozanib/mFOLFOX6 therapy or preferential response vs. bevacizumab/mFOLFOX6, included analysis of VEGF A, C, D, and their ratios; CD68; myeloid-derived gene signature; serum soluble cytokines; and

neuropilin-1 (NRP-1). Serum protein measurement for the biomarker analyses were measured using the Myriad Rules-Based Medicine system (Myriad RBM, Austin, TX). These multiplexed assays are based on the capture-sandwich format using capture antibodies attached to fluorescently encoded microspheres. After capture of antigen from a biological sample, such as serum, the antigen is then detected using specific detection antibodies coupled to a fluorescent probe. Biomarker measurement was categorized as below or above the median.

Statistical analysis

A total of 166 PFS events were planned for the study to provide 80% power at a one-sided type I error of 0.2 to detect a statistically significant treatment effect of tivozanib/mFOLFOX6 over bevacizumab/mFOLFOX6 using a log-rank test assuming a median PFS for bevacizumab/mFOLFOX6 of 9.4 months (19) and a 3-month improvement for tivozanib/mFOLFOX6. An interim futility analysis for superiority was planned for when approximately 83 PFS events (50% of the total) were observed with a futility boundary of hazard ratio (HR)>1.0581. The actual number of PFS events (95, 57.2% of the required 166 events) changed the futility stopping boundary to an HR>1.004 according to the prespecified Lans-DeMets beta spending function for O'Brien-Fleming boundary. The full analysis set was defined as all randomized patients and was used for primary analyses of efficacy as well as demographic and baseline characteristics. The safety analysis set consisted of all patients who received ≥1 dose of study drug. The distribution of the primary endpoint, PFS, was estimated for each treatment arm using the Kaplan-Meier method and compared between arms using a stratified log-rank test. A Cox proportional hazard model along with the 95% confidence interval (CI) was used to assess PFS, OS, TTF, and DOR as well as the association between potential serum biomarkers and PFS with treatment arms as the covariate. ORR and corresponding CIs were calculated for each treatment arm and compared

between 2 arms using a stratified Cochran-Mantel-Haenszel test. All data processing, summarization, and analyses were performed using SAS® Version 9.2 or above in a UNIX environment.

Results

Patients

The study was conducted at 73 sites in 12 countries including Australia (8), Austria (3), Belgium (4), Canada (5), Czech Republic (2), Finland (2), Hungary (4), Italy (4), the Netherlands (1), Spain (6), United Kingdom (7), and the United States (27). From December 2, 2011 through April 28, 2013, 265 subjects were randomized, 177 to tivozanib/mFOLFOX6 (Arm A) and 88 to bevacizumab/mFOLFOX6 (Arm B) (**Supplementary Figure S1**). In Arm A, all 177 patients were included in both the full and safety analysis set and 158 patients (89%) discontinued study treatment (61 patients [38.6%] primarily because of an AE and 55 [34.8%] because of progressive disease). In Arm B, 88 patients were included in the full analysis set, but one patient did not receive study drug and was not included in the safety analysis set; 81 patients [92%] discontinued study treatment (28 patients [34.6%] primarily due to an AE and 34 [42.0%] due to progressive disease). Median dose intensity for the combination dose was similar between the 2 arms at 83% in Arm A and 86% in Arm B. Likewise, median duration of treatment was similar (168.0 days Arm A and 162.0 days Arm B). Patient baseline demographic and disease characteristics are presented in **Table 1** and are generally balanced between the two treatment groups except that Arm A had a higher proportion of patients with an ECOG PS of 1 (46.3 vs. 34.1%).

Safety

The overall safety profile was comparable between treatment arms. In both treatment arms, the most common all grade treatment emergent adverse event (TEAE) was diarrhea (58.2% Arm A and 57.5% Arm B) and the most common Grade 3/4 TEAE was neutropenia (39.5% Arm A and 24.1% Arm B) (**Table 2**). The most common treatment-related AE in both arms was hypertension (39.5% Arm A and 25.3% Arm B). An AE led to permanent discontinuation in 41.2% of patients in Arm A and 34.5% of patients in Arm B (although not necessarily the primary reason for discontinuation). Pulmonary embolism and deep vein thrombosis were the most common AEs leading to discontinuation for Arm A and Arm B, respectively.

Serious AEs (SAEs) were reported for 46.3% of patients in Arm A compared with 48.3% in Arm B. The two most common SAEs in Arm A were diarrhea (4.0% Arm A, 5.7% Arm B) and pulmonary embolism (4.0% Arm A, 0% Arm B), and in Arm B were pyrexia (2.3% Arm A, 8.0% Arm B) and diarrhea (as reported above). Serious treatment-related AEs were reported in 21.5% of patients for tivozanib (most common being pulmonary embolism at 2.8%) and in 17.2% patients for bevacizumab (most commonly abdominal pain at 3.4%).

A total of 9 patients died while on treatment or within 30 days of last dose. There were 7 deaths (4.0%) in Arm A with 3 patients having at least one fatal AE considered to be probably related to tivozanib (pulmonary hemorrhage, gastrointestinal hemorrhage, and duodenal neoplasm) or possibly related (asthenia). There were 2 deaths (2.3%) in Arm B patients, both of which were due to AEs probably related to bevacizumab (hepatic hemorrhage and large intestine perforation).

Efficacy

A prespecified interim analysis included 95 PFS events and met the prespecified futility criteria. Median PFS (Arm A vs. Arm B) was 9.4 vs. 10.7 months (HR = 1.091; CI 0.693–1.718; *P* = 0.706) (**Table 3, Figure 1**). Complete responses were achieved for 4 patients (2.3%) in Arm A and 1 patient (1.1%) in Arm B and

ORR (Arm A vs. Arm B) was 45.2% vs. 43.2% (*P* = 0.718) (**Table 3**). In addition, Arm A vs. Arm B median DOR was 7.4 vs. 9.3 months (HR = 1.389; CI 0.604–3.194; *P* = 0.437), median TTF was 5.5 vs. 5.4 months (HR = 1.006; CI 0.764–1.358; *P* = 0.967), and median OS was not reached for either arm. Because the data from the prespecified interim analysis demonstrated futility for superiority, the study was discontinued. Post hoc analysis of final data of 91 and 50 events for Arm A and Arm B, respectively showed a median PFS of 9.8 vs 9.5 months (HR = 0.908; CI 0.624–1.301; *P* = 0.598) and an ORR of 46.9% in Arm A vs. 43.2% in Arm B. Subgroup analysis did not show significant differences in PFS (**Figure 2A**). A trend of benefit was observed in the predefined LDH high (>1.5 upper limit of normal [ULN]) subgroup.

A secondary objective of the study was to evaluate the value of potential predefined biomarkers for preferential response of tivozanib/mFOLFOX6 vs. bevacizumab/mFOLFOX6. None of the biomarker analyses showed significant differences at the time of the interim analysis. Post hoc exploratory biomarker analyses were conducted on 164 (62%) patient samples based on final efficacy data collected through February 28, 2014. The PFS HR along with the 95% confidence interval is presented for each biomarker subgroup (**Figure 2B**).

NRP-1, the biomarker found to be most associated with increased PFS, was analyzed further to determine if it had potential prognostic value for tivozanib and bevacizumab and potential predictive value for tivozanib over bevacizumab in the low NRP-1 selected population. In both treatment arms, there was an increase in PFS in patients with NRP-1 below the median (NRP-1 low) (**Figure 3A and 3B**), consistent with other studies (20, 21) and suggesting a potential prognostic biomarker. Additionally, there is a statistically significant difference in PFS in patients with low NRP-1 in favor of Arm A with no difference in high NRP-1 (above median NRP-1), suggesting that NRP-1 could be a potential predictive marker as well as a prognostic marker (Figure 3C and D); for NRP-1 low patients, PFS was 17.9 months in

the tivozanib-treated patients and 11.2 months in the bevacizumab-treated patients (HR =0.38; unstratified *P* value 0.0075).

Discussion

In this randomized, open-label, phase II trial of tivozanib/mFOLFOX6 vs. bevacizumab/mFOLFOX6 in patients with previously untreated mCRC, a prespecified interim futility analysis demonstrated that the futility boundary for superiority of tivozanib over bevacizumab for PFS in the intent-to-treat (ITT) population was crossed, resulting in discontinuation of the study. At this interim analysis, the combination of tivozanib/mFOLFOX6 resulted in PFS, ORR, TTF, and DOR comparable to that of bevacizumab/mFOLFOX6. Also at this interim analysis, subgroup and biomarker analyses revealed no significant association with PFS, although LDH-1 and NRP-1 showed a trend of PFS benefit. At the post hoc final analysis, NRP-1 low (below the median) did demonstrate a statistical difference in PFS favoring the tivozanib/mFOLFOX6 arm. The safety profile of the combination of tivozanib/mFOLFOX6 was consistent with the safety profile reported to date in other tivozanib studies of patients with advanced disease (7, 10, 15, 16, 18) and comparable to that of bevacizumab/mFOLFOX6.

Bevacizumab plus chemotherapy has been shown to improve OS compared with chemotherapy alone in patients with mCRC (3, 4). Specifically, bevacizumab added survival benefits when added to treatment with various FOLFOX therapies (19, 22), although the benefits may be specific to PFS according to a recent meta-analysis (23). Bevacizumab/mFOLFOX6 is considered to be a standard treatment for mCRC, and the combination has been used as a comparison arm in several first-line mCRC clinical trials, including those involving panitumumab (24), cediranib (25), axitinib (26), cetuximab (19, 27), and XELOX (capecitabine and oxaliplatin)/SOX (oxaliplatin and S-1) (28, 29). In the current study at the interim futility analysis, the efficacy of tivozanib/mFOLFOX6 was comparable to that of bevacizumab/mFOLFOX6

with a PFS of 9.4 vs. 10.7 months (HR = 1.091; CI 0.693–1.718; *P* = 0.706) and ORR 45.2% vs. 43.2%; the post hoc final analysis of PFS was 9.8 vs. 9.5 months (HR = 0.908; CI 0.624–1.301; *P* = 0.598). Furthermore, the bevacizumab/mFOLFOX6 results were comparable to those previously observed in recent comparison studies in similar patient populations treated with first-line therapy, which reported a bevacizumab/FOLFOX6 PFS range of 10.1 to 15.9 months and an ORR range of 47.3% to 63% (21, 24–26, 28, 29).

In the current study, none of the subgroup analyses revealed significant differences in PFS. However, a trend of PFS benefit was observed in the predefined LDH high (≥1.5 ULN) subgroup (HR = 0.67; CI 0.37–1.19). LDH levels were investigated in this study based on previous studies demonstrating increased efficacy associated with high LDH in patients treated with vatalanib combined with FOLFOX4 (30, 31). High LDH levels have been associated with survival in patients with mCRC treated with bevacizumab. Yin and colleagues (2014) reported an improvement in PFS in patients treated with first-line bevacizumab associated with high serum LDH levels (32). Similarly, high LDH level was designated a factor for improved prognosis in patients treated with first-line bevacizumab (33) and in patients treated with FOLFIRI (irinotecan, fluorouracil, and folinic acid) or XELOX plus anti-VEGF therapy (34). Additionally, a high level of LDH was reported to be one of only 5 parameters associated with survival in ≥3 studies included in a systematic review of 29 bevacizumab studies (35). However, the association is not definitive. High LDH levels were associated with worse prognosis in the HORIZON I study (36) and in a large single-center analysis (37).

PFS was not significantly changed in this study in the ITT population. It is possible that the high percentage of AEs leading to permanent discontinuation seen in the current study (41.2% Arm A and 34.5% Arm B), which led to a median duration of treatment of 168 and 162 days, may have confounded the estimate of median PFS in both study arms. Previous studies with bevacizumab suggest high

discontinuation observed for reasons other than disease progression could have potentially affected survival endpoints, but not the treatment response (19, 38).

In light of the move toward personalized treatments in mCRC, potential biomarkers are an important aspect of treatment investigation. RAS is the only established predictive biomarker in the treatment of mCRC (39). To date, although LDH and NRP-1 levels have been shown to be prognostic for antiangiogenesis therapy (32–35, 40), no predictive factor for anti-VEGF therapy has been identified (39). In the current study, the biomarkers that were investigated were largely based on tivozanib mechanism (VEGF-C, VEGF-A, sVEGFR2, and sVEGFR3) and antiangiogenic properties (interleukin 8). These biomarkers were investigated to find a potential predictor of clinical response following tivozanib therapy based on the premise that reduced ligand and their respective soluble receptor levels have been associated with longer PFS and ORR in previous sunitinib studies (41, 42). RNA expression levels from patient archival formaldehyde fixed-paraffin embedded tumor samples and circulating serum protein levels were evaluated for VEGF-A, -C, -D and placental growth factor ligand levels as well as VEGF C/ VEGF A ratios. Additionally, circulating NRP-1 protein, which was reported to be highly correlated with PFS following treatment of renal cancer with tivozanib (40), was also evaluated in serum. NRP-1 is a VEGFR-2 coreceptor and is involved in the regulation of VEGFR-2–mediated angiogenesis (43, 44). Although there was no statistical difference in the ITT analysis, the results presented here following the preplanned, post hoc biomarker efficacy analysis suggest that serum NRP-1 could identify a subset of patients who would benefit from treatment with tivozanib rather than bevacizumab in combination with chemotherapy. A PFS HR of 0.38 for tivozanib compared with bevacizumab, both in combination with FOLFOX chemotherapy, was observed in patients with serum NRP-1 levels below the median for the patients included in the trial analysis. A second detection antibody was subsequently evaluated resulting in qualitatively similar data. Additional efforts are underway to screen antibodies suitable for

use as a companion diagnostic to further validate serum NRP-1 as a biomarker to identify those patients most likely to respond to tivozanib.

This study has demonstrated that the tivozanib/FOLFOX6 combination treatment is tolerable in patients with mCRC. The AEs noted with the combination were comparable to those observed in previous studies with tivozanib in combination with other therapies (15– 17) and with tivozanib alone (7, 10). The safety of the tivozanib/FOLFOX6 combination was also comparable to the bevacizumab/FOLFOX6 combination. The most common treatment-related AE in both study arms was hypertension, which is characteristic of VEGF-targeted therapy (45).

In conclusion, although data from the prespecified interim analysis demonstrated futility for superiority and resulted in discontinuation of this study, the efficacy of tivozanib/mFOLFOX6 was comparable to that of bevacizumab/mFOLFOX6 in patients with previously untreated mCRC. Moreover, the safety profile of tivozanib/mFOLFOX6 was consistent with that seen with other trials with tivozanib in similar patient populations. Notably, low NRP-1 emerged as a potential predictive biomarker for tivozanib activity which may warrant further study.

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References:

1) Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. CA Cancer J Clin 2014;64:9–29.
2) Sineshaw HM, Robbins AS, Jemal A. Disparities in survival improvement for metastatic colorectal cancer by race/ethnicity and age in the United States. Cancer Causes Control 2014;25:419–23.
3) Bergsland EK. Combination therapies in colorectal cancer treatment. Hematol Oncol Clin N Am 2015;29:85–116.
4) Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer 2015;14:1–10.
5) Akhtar R, Chandel S, Sarotra P, Medhi B. Current status of pharmacological treatment of colorectal cancer. World J Gastrointest Oncol 2014;6:177–83.
6) Nakamura K, Taguchi E, Miura T, Yamamoto A, Takahashi K, Bichat F, et al. KRN951, a highly potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, has antitumor activities and affects functional vascular properties. Cancer Res 2006;66:9134–42.
7) Eskens FALM, de Jonge MJA, Bhargava P, Isoe T, Cotreau MM, Esteves B, et al. Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1, -2, and -3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors. Clin Cancer Research 2011;17:7156–63.
8) Haberkorn BCM, Eskens FALM. Structure, development, preclinical and clinical efficacy of tivozanib (KRN-951, AV-951). Future Oncol 2013;9:13–20.
9) Cotreau MM, Siebers NM, Miller J, Strahs AL, Slichenmyer W. Effects of ketoconazole or rifampin on the pharmacokinetics of tivozanib hydrochloride, a vascular endothelial growth factor receptor tyrosine kinase inhibitor. Clin Pharm Drug Dev 2014;DOI: 10.1002/cpdd.145.

10) Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: Results from a phase III trial. J Clin Oncol 2013;31: 3791–9.

11) Mehta A, Sonpavde G, Escudier B. Tivozanib for the treatment of renal cell carcinoma: results and implications of the TIVO-1 trial. Future Oncol 2014;10:1819–26.

12) Moore K, Infante JR, Cotreau MM, Wilson L, Strahs AL, Vargo DL, et al. A phase I cardiac safety and pharmacokinetic study of tivozanib hydrochloride in patients with advanced solid tumors. Clin Pharm Drug Dev 2014;3:284–9.

13) Berge EM, Bowles DW, Flaig TW, Lam ET, Jimeno A. Tivozanib: Practical implications for renal cell carcinoma and other solid tumors. Drugs Today 2013;49:303–15.

14) Pal SK, Bergerot PG, Figlin RA. Tivozanib: Current status and future directions in the treatment of solid tumors. Expert Opin Investig Drugs 2012;21:1851–9.

15) Fishman MN, Srinivas S, Hauke RJ, Amato RJ, Esteves B, Cotreau MM, et al. Phase Ib study of tivozanib (AV-951) in combination with temsirolimus in patients with renal cell carcinoma. Eur J Cancer 2013;49:2841–50.

16) Mayer EL, Scheulen ME, Beckman J, Richly H, Duarte A, Cotreau MM, et al. A phase I dose-escalation study of the VEGFR inhibitor tivozanib hydrochloride with weekly paclitaxel in metastatic breast cancer. Breast Cancer Res Treat 2013;140:331–9.

17) Wolpin BM, Ng K, Zhu AX, Abrams T, Enzinger PC, McCleary NJ, et al. Multicenter phase II study of tivozanib (AV-951) and everolimus (RAD001) for patients with refractory, metastatic colorectal cancer. Oncologist 2013;18:377–8.

18) Oldenhuis CN, Loos WJ, Esteves B, van Doorn L, Cotreau MM, Strahs AL, et al. A phase 1b study of the VEGF receptor tyrosine kinase inhibitor tivozanib and modified FOLFOX-6 in patients with advanced gastrointestinal malignancies. Clin Colorectal Cancer 2015;14:18–24.

19) Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–9.

20) Benson AB, Krivoshik A, Van Sant C, Gyuris J, Feng B. Poster A24: Neuropilin-1 as a potential biomarker of progression-free survival benefit for tivozanib + FOLFOX6 versus bevacizumab + FOLFOX6 in metastatic colorectal cancer: post-hoc biomarker analysis of BATON-CRC Phase 2 trial. AACR Annual Meeting; March 6, 2015; Orlando, Florida.

21) Benson AB, Krivoshik A, Van Sant C, Needle M. Abstract O-007: Neuropilin--1 may be prognostic and identify a subgroup of patients with metastatic colorectal cancer who benefit from tivozanib + mFOLFOX6 compared to bevacizumab + mFOLFOX6. 17th World Congress on Gastrointestinal Cancer; July 1-4, 2015; Barcelona, Spain.

22) Giantonio BJ, Catalono PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539–44.

23) Chen Y, Yang Q, Kuang J, Chen SY, Wei Y, Jiang ZM, et al. Efficacy of adding bevacizumab in the first-line chemotherapy of metastatic colorectal cancer: Evidence from seven randomized clinical trials. Gastroenterol Res Pract 2014:594930.

24) Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32:2240–7.

25) Schmoll HJ, Cunningham D, Sobrero A, Karapetis CS, Rougier P, Koski SL, et al. Cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as first-line treatment for patients with

advanced colorectal cancer: a double-blind, randomized phase III study (HORIZON III). J Clin Oncol 2012;30:3588–95.

26) Infante JR, Reid TR, Cohn AL, Edenfield WJ, Cescon TP, Hamm JT, et al. Axitinib and/or bevacizumab with modified FOLFOX-6 as first-line therapy for metastatic colorectal cancer: a randomized phase 2 study. Cancer 2013;119:2555–63.

27) Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Mahoney MR, O'Neil B, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-fu/leucovorin (FOLFIRI) or oxaliplatin/5-fu/leucovorin (FOLFOX6) with bevacizumab (bv) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon. Ann Oncol 2014;25(suppl 2):ii105–17.

28) Buchler T, Pavlik T, Melichar B, Bortlicek Z, Usiakova Z, Dusek L, et al. Bevacizumab with 5-fluorouracil, leucovorin, and oxaliplatin vers bevacizumab with capecitabine and oxaliplatin for metastatic colorectal carcinoma: results of a large registry-based cohort analysis. Cancer. 2014;14:323.

29) Yamada Y, Takahari D, Matsumoto H, Baba H, Nakamura M, et al. Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomized phase 3 trial. Lancet Oncol 2013;14:1278–86.

30) Van Cutsem EV, Bajetta E, Valle J, Köhne CH, Hecht JR, Moore M, et al. Randomized, placebo-controlled, phase III study of oxaliplatin, fluorouracil, and leucovorin with or without PTK787/ZK 222584 in patients with previously treated metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:2004–10.

31) Hecht JR, Trarbach T, Hainsworth, JD, Major P, Jäger E, et al. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral

vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:1997–2003.

32) Yin C, Jiang C, Liao F, Rong Y, Cai X, Guo G, et al. Initial LDH level can predict the survival benefit from bevacizumab in the first-line setting in Chinese patients with metastatic colorectal cancer. Onco Targets Ther 2014;7:1415–22.

33) Silvestris N, Scartozzi M, Graziano G, Santini D, Lorusso V, Maiello E, et al. Basal and bevacizumab-based therapy-induced changes of lactate dehydrogenases and fibrinogen levels and clinical outcome of previously untreated metastatic colorectal cancer patients: a multicentric retrospective analysis. Expert Opin Biol Ther 2015;15:155–62.

34) Cetin B, Kaplan MA, Berk V, Ozturk SC, Benekli M, Isikdogan A, et al. Prognostic factors for overall survival in patients with metastatic colorectal carcinoma treated with vascular endothelial growth factor-targeting agents. Asian Pac J Cancer Prev 2012;13:1059–63.

35) Petrelli F, Coinu A, Cabiddu M, Borgonovo K, Lonati V, Ghilardi M, et al. Prognostic factors for survival with bevacizumab-based therapy in colorectal cancer patients: a systematic review and pooled analysis of 11,585 patients. Med Oncol 2015;32:456.

36) Bar J, Spenser S, Morgan S, Brooks L, Cunningham D, Robertson J, et al. Correlation of lactate dehydrogenase isoenzyme profile with outcome in patients with advanced colorectal cancer treated with chemotherapy and bevacizumab or cediranib: Retrospective analysis of the HORIZON I study. Clin Colorectal Cancer 2014;13:46–53.

37) Scartozzi M, Giampieri R, Maccaroni E, Del Prete M, Faloppi L, Bianconi M, et al. Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first-line bevacizumab-based therapy in metastatic colorectal cancer patients. Br J Cancer 2012;106:799–804.

38) Whyte S, Pandor A, Stevenson M, Rees A. Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer. Health Technol Assess 2010;14 (suppl. 2):47–53.

39) Stintzing S, Stremitzer S, Sebio A, Lenz H-J. Predictive and prognostic markers in the treatment of metastatic colorectal cancer (mCRC): Personalized medicine at work. Hematol Oncol Clin N Am 2015;29:43–60.

40) Lin J, Needle M, Gyuris J, Feng B. Abstract A-17: Circulating neuropilin-1 as a potential biomarker of progression-free survival benefit for tivozanib in metastatic clear cell renal cell carcinoma (RCC): post-hoc biomarker analysis of tivozanib RCC trials. 17th Annual Symposium on Anti-Angiogenesis and Immune Therapies for Cancer. 2015; February 19-21; La Jolla, CA.

41) Rini BI, Michaelson MD, Rosenberg JE, Bukowski RM, Sosman JA, Stadler WM, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol 2008;26:3743–8.

42) Harmon CS, DePrimo SE, Raymond E, Cheng AL, Boucher E, Douillard JY, et al. Mechanism-related circulating proteins as biomarkers for clinical outcome in patients with unresectable hepatocellular carcinoma receiving sunitinib. J Transl Med 2011;9:120.

43) Cagnoni G, Tamagnone L. Semaphorin receptors meet receptor tyrosine kinases on the way of tumor progression. Oncogene 2014;33:4795–802.

44) Pan Q, Chanthery Y, Liang W-C, Stawicki S, Mak J, Rathore N, et al. Blocking neuropilin-1 function has an additive effect with anti-VEGF to inhibit tumor growth. Cancer Cell 2007;11:53–67.

45) Small HY, Montezano AC, Rios FJ, Savola C, Touyz RM. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. Can J Cardiol 2014;30:534–43.

Table 1. Baseline Patient Characteristics

	Tivozanib +mFOLFOX6 (*n* = 177)	**Bevacizumab +mFOLFOX6 (*n* = 88)**	**Total (*n* = 265)**
Sex, n (%)			
Male	118 (66.7)	55 (62.5)	173 (65.3)
Female	59 (33.3)	33 (37.5)	92 (34.7)
Age, mean (SD)	61.9 (9.6)	62.6 (11.2)	62.2 (10.1)
Age group, n (%)			
<65 years	101 (57.1)	48 (54.5)	149 (56.2)
≥65 years	76 (42.9)	40 (45.5)	116 (43.8)
Race, n (%)			
White	169 (95.5)	85 (96.6)	254 (95.8)
Black	2 (1.1)	0	2 (0.8)
Asian	3 (1.7)	2 (2.3)	5 (1.9)
ECOG performance score, n (%)			
0	95 (53.7)	58 (65.9)	153 (57.7)
1	82 (46.3)	30 (34.1)	112 (42.3)
LDH status, n (%)			
<1.5 x ULN	127 (71.8)	64 (72.7)	191 (72.1)
≥1.5 x ULN	50 (28.2)	24 (27.3)	74 (27.9)
Origin of cancer, n (%)			
Rectal	53 (29.9)	24 (27.3)	77 (29.1)
Colon	124 (70.1)	64 (72.7)	188 (70.9)
No. of metastatic sites/organs, n (%)			
1	56 (31.6)	30 (34.1)	86 (32.5)
2	80 (45.2)	34 (38.6)	114 (43.0)
3	29 (16.4)	21 (23.9)	50 (18.9)
≥4	12 (6.8)	3 (3.4)	15 (5.7)
KRAS mutation status, n (%)			
Wild-type	33 (18.6)	21 (23.9)	54 (20.4)
Mutant	23 (13.0)	16 (18.2)	39 (14.7)
Unknown	121 (68.4)	51 (58.0)	172 (64.9)
Time since initial diagnosis in months, mean (SD)	9.4 (20.5)	10.9 (21.1)	9.9 (20.6)
No. metastatic sites at screening, mean (SD)	2.0 (1.02)	2.0 (0.85)	2.0 (0.97)
Prior therapy, n (%)			
Adjuvant therapy	29 (16.4)	19 (21.6)	48 (18.1)
Surgery or procedure	115 (56.0)	54 (61.4)	169 (63.8)
Radiation	18 (10.2)	13 (14.8)	31 (11.7)

ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal

Table 2. All-Grade Treatment Emergent AEs ≥20% Patients in Either Treatment and Grade 3/4

Treatment Emergent AEs

	Tivozanib/mFOLFOX6 (Arm A) (*n* = 177)		**Bevacizumab/mFOLFOX6 (Arm B) (*n* = 88)**	
Adverse Event, n (%)	**All-Grade**	**Grade 3/4**	**All-Grade**	**Grade 3/4**
Diarrhea	103 (58.2)	19 (10.7)	50 (57.5)	9 (10.3)
Nausea	99 (55.9)	5 (2.8)	47 (54.0)	2 (2.3)
Fatigue	97 (54.8)	20 (11.3)	46 (52.9)	8 (9.2)
Neutropenia	95 (53.7)	70 (39.5)	37 (42.5)	21 (24.1)
Hypertension	79 (44.6)	29 (16.4)	25 (28.7)	9 (10.3)
Peripheral neuropathy	75 (42.4)	18 (10.2)	34 (39.1)	11 (12.6)
Decreased appetite	64 (36.2)	2 (1.1)	25 (28.7)	2 (2.3)
Vomiting	60 (33.9)	10 (5.6)	24 (27.6)	1 (1.1)
Thrombocytopenia	54 (30.5)	10 (5.6)	13 (14.9)	2 (2.3)
Constipation	50 (28.2)	1 (0.6)	32 (36.8)	1 (1.1)
Paresthesia	46 (26.0)	2 (1.1)	20 (23.0)	3 (3.4)
Abdominal pain	45 (25.4)	7 (4.0)	17 (19.5)	5 (5.7)
Dysphonia	42 (23.7)	1 (0.6)	13 (14.9)	0
Mucosal inflammation	40 (22.6)	5 (2.8)	29 (33.3)	6 (6.9)
Asthenia	39 (22.0)	5 (2.8)	17 (19.5)	1 (1.1)
Stomatitis	37 (20.9)	3 (1.7)	14 (16.1)	2 (2.3)
Epistaxis	34 (19.2)	0	25 (28.7)	0
Dysgeusia	26 (14.7)	0	18 (20.7)	0

Table 3. Summary of Efficacy and Response

Efficacy Endpoint	Tivozanib/mFOLFOX6 (Arm A) (*n* = 177)	Bevacizumab/mFOLFOX6 (Arm B) (*n* = 88)	HR (95% CI)	*P* Value
Progression-free survival (Investigator-assessed)				
Disease progression, n (%)	58 (32.8)	26 (29.5)	1.091 (0.693, 1.718)	0.706
Death, n (%)	8 (4.5)	3 (3.4)		
Median, months (95% CI)	9.4 (8.5, 10.1)	10.7 (7.5, 12.8)		
Overall survival				
Event, n (%)	26 (14.7)	12 (13.6)	1.116 (0.561, 2.218)	0.754
Median, months (95% CI)	NA (NA, NA)	NA (12.8, NA)		
Duration of response				
Event, n (%)	28 (35.0)	10 (26.3)	1.389 (0.604, 3.194)	0.437
Median, months (95% CI)	7.4 (5.6, 11.3)	9.3 (7.3, 10.7)		
Time to treatment failure				
Event, n (%)	138 (78.0)	65 (73.9)	1.006 (0.746, 1.358)	0.967
Median, months (95% CI)	5.5 (4.9, 7.1)	5.4 (3.7, 6.7)		
Best overall response, n (%)				
Complete response	4 (2.3)	1 (1.1)	NA	
Partial response	76 (42.9)	37 (42.0)	NA	
Stable disease	80 (45.2)	38 (43.2)	NA	
Progressive disease	6 (3.4)	5 (5.7)	NA	
Not evaluable	11 (6.2)	7 (8.0)	NA	
Confirmed overall response rate	80 (45.2)	38 (43.2)	NA	0.718

Figure 1: Survival probability of PFS

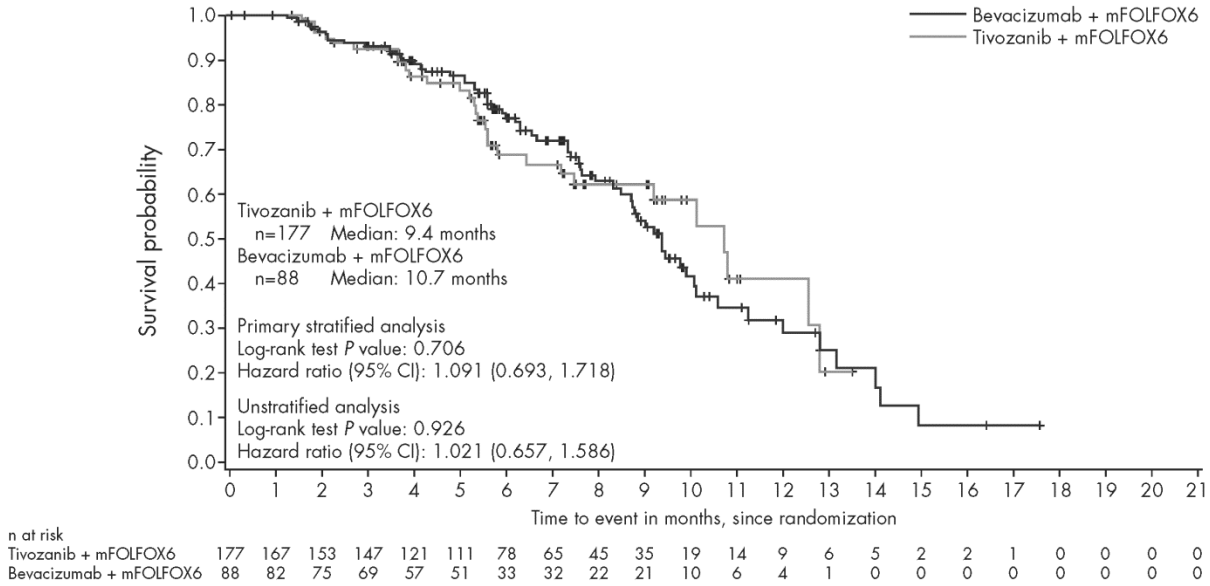
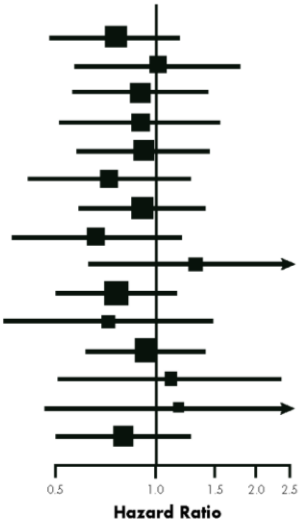


Figure 2: Subgroup Analyses (A) and biomarker Analysis (B) of PFS[a].

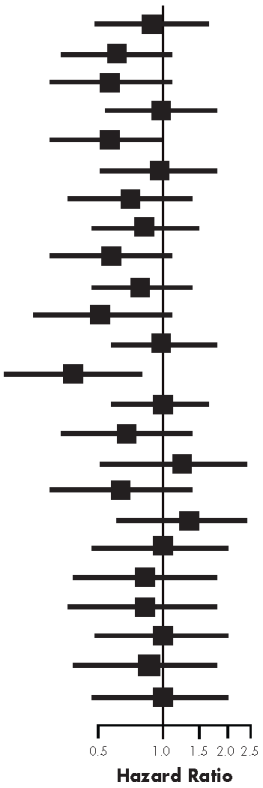
(A)

Subgroups	Tivozanib Event/N	Bevacizumab Event/N	HR [95% CI]
AGE<65	53/101	32/48	0.75 [0.48, 1.17]
AGE≥65	38/76	18/40	1.01 [0.57, 1.78]
Male	57/118	27/55	0.9 [0.56, 1.42]
Female	34/59	23/33	0.9 [0.52, 1.55]
Baseline ECOG=0	49/95	31/58	0.92 [0.58, 1.45]
Baseline ECOG=1	42/82	19/30	0.72 [0.42, 1.25]
LDH<1.5 ULN	59/127	32/64	0.91 [0.59, 1.4]
LDH≥1.5 ULN	32/50	18/24	0.67 [0.37, 1.19]
Rectal Cancer	28/53	11/24	1.3 [0.63, 2.69]
Colon Cancer	63/124	39/64	0.76 [0.51, 1.14]
1 Metastatic Site	25/56	12/30	0.72 [0.35, 1.47]
≥2 Metastatic Sites	66/121	38/58	0.93 [0.62, 1.39]
KRAS Wild Type	19/33	11/21	1.1 [0.52, 2.37]
KRAS Mutant	10/23	11/16	1.17 [0.47, 2.9]
KRAS Unknown	62/121	28/51	0.8 [0.51, 1.25]



(B)

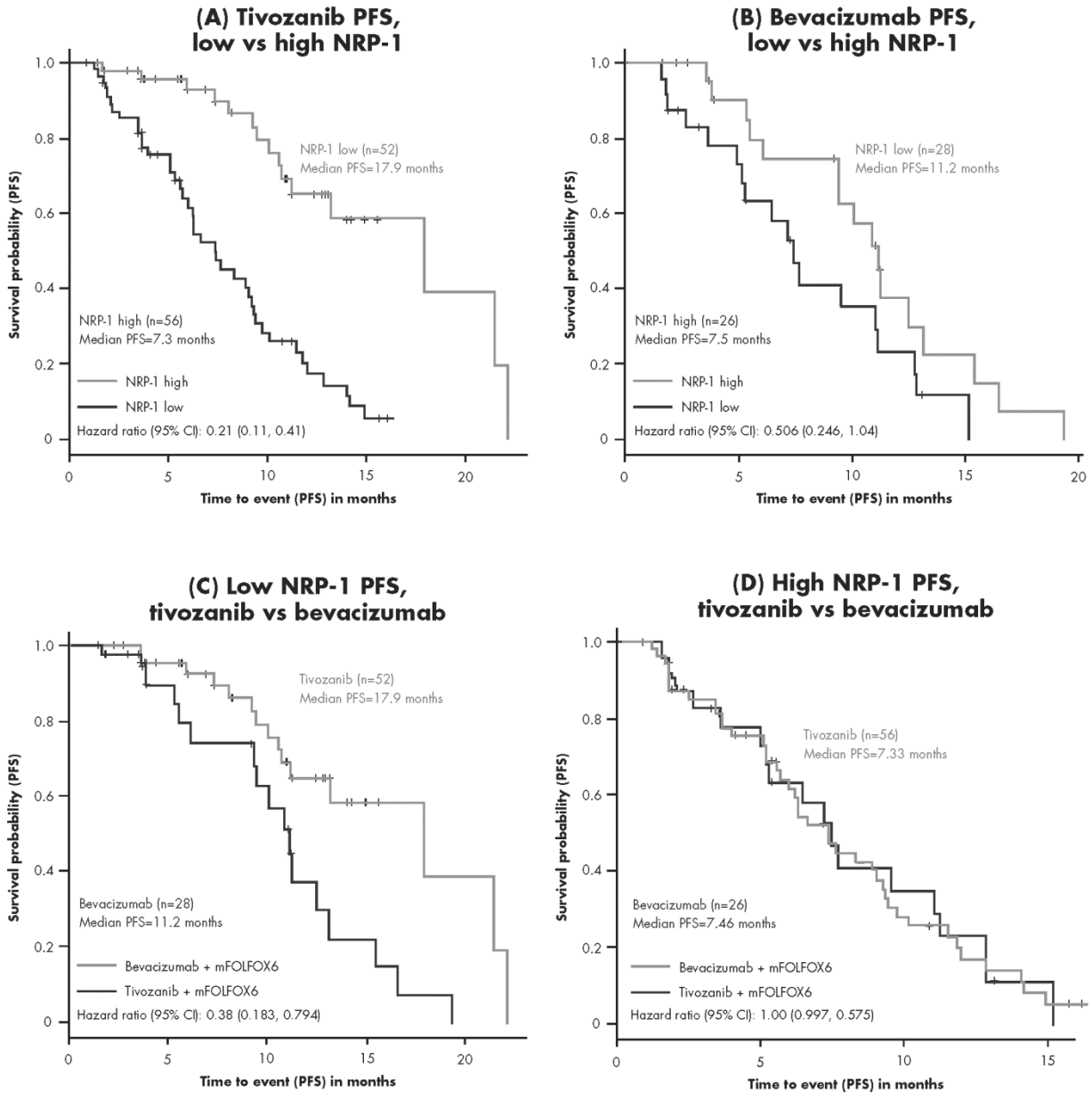
Subgroups	Tivozanib Event/N	Bevacizumab Event/N	HR [95% CI]
Serum VEGF–A < Median	27/54	16/27	0.88 [0.47, 1.65]
Serum VEGF–A ≥ Median	29/54	18/27	0.62 [0.34, 1.12]
Serum VEGF–C < Median	23/52	16/26	0.57 [0.3, 1.1]
Serum VEGF–C ≥ Median	33/56	18/28	0.99 [0.55, 1.81]
Serum VEGF–C/A < Median	31/56	15/25	0.56 [0.3, 1.05]
Serum VEGF–C/A ≥ Median	25/52	19/29	0.96 [0.52, 1.79]
Serum sVEGFR–2 < Median	23/53	14/28	0.71 [0.36, 1.4]
Serum sVEGFR–2 ≥ Median	33/55	20/26	0.81 [0.46, 1.43]
Serum sVEGFR–3 < Median	20/51	16/30	0.58 [0.3, 1.14]
Serum sVEGFR–3 ≥ Median	36/57	18/24	0.78 [0.44, 1.38]
Serum IL–8 < Median	22/53	14/26	0.52 [0.26, 1.04]
Serum IL–8 ≥ Median	34/55	20/28	0.97 [0.55, 1.71]
Serum Neuropilin < Median	15/52	16/28	0.38 [0.18, 0.79]
Serum Neuropilin ≥ Median	41/56	18/26	1 [0.58, 1.75]
Tumor VEGF–A < Median	18/38	13/18	0.67 [0.33, 1.37]
Tumor VEGF–A ≥ Median	24/37	7/16	1.21 [0.51, 2.87]
Tumor VEGF–C < Median	20/39	11/16	0.63 [0.3, 1.34]
Tumor VEGF–C ≥ Median	22/36	9/18	1.33 [0.61, 2.9]
Tumor VEGF–C/A < Median	22/37	9/15	0.99 [0.45, 2.18]
Tumor VEGF–C/A ≥ Median	20/38	11/19	0.83 [0.39, 1.73]
Tumor VEGF–D < Median	23/41	8/13	0.82 [0.36, 1.85]
Tumor VEGF–D ≥ Median	19/34	12/21	1.01 [0.49, 2.09]
Tumor PIGF < Median	20/38	9/16	0.85 [0.38, 1.89]
Tumor PIGF ≥ Median	22/37	11/18	0.98 [0.47, 2.04]



[a]Serum values indicate protein levels in circulation and the categories for tumor biomarkers indicate RNA expression.

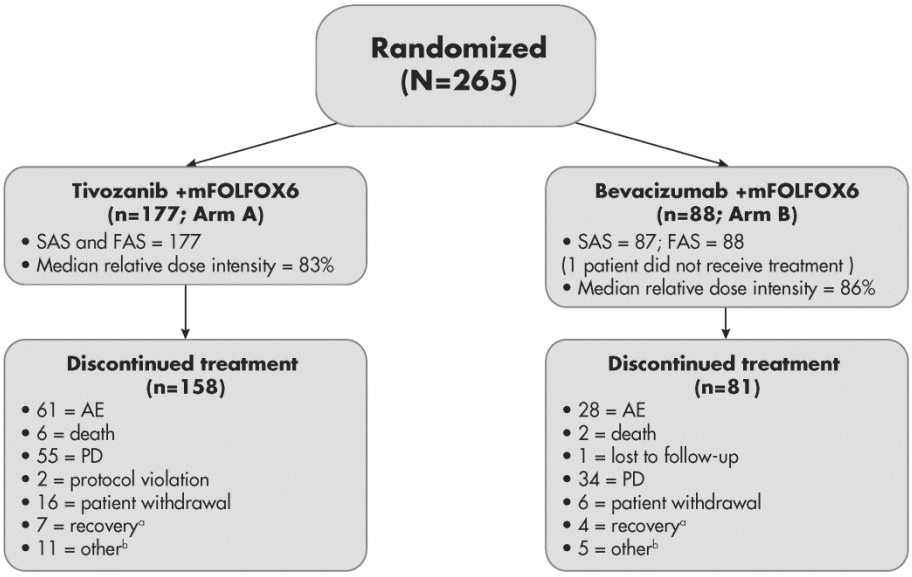
ECOG, Eastern Cooperative Oncology Group;IL-8, interleukin-8; LDH, lactate dehydrogenase; PFS, progression-free survival; PIGF, placental growth factor; sVEGFR, serum vascular endothelial growth factor receptor; VEGF, vascular endothelial growth factor.

Figure 3: Low vs. high NRP-1 PFS (A, tivozanib; B, bevacizumab) and tivozanib vs. bevacizumab PFS in patients with low NRP-1 (C) or high NRP-1 (D)



CI, confidence interval; HR, hazard ratio, NRP, neuropilin, PFS, progression-free survival.

Supplemental Figure 1. Patient Disposition



[a]The "recovery" category consisted of patients who had tumor shrinkage sufficient to discontinue treatment in order to have resection/curative surgery.
[b]"Other" included physician decision, complete treatment response, patient wanted to pursue other treatment options, etc.
AE, adverse event; FAS, full analysis set; PD, progressive disease; SAS, safety analysis set.