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Phase I Study of Capecitabine, Oxaliplatin, Bevacizumab, and Everolimus in Advanced Solid Tumors

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Abstract

Purpose—To define maximum tolerated dose (MTD), toxicities, and pharmacodynamics of capecitabine, oxaliplatin, bevacizumab, and everolimus in advanced solid tumor patients.

Design—This was a standard “3+3” dose-escalation trial. All subjects received bevacizumab 7.5mg/kg on day one of each cycle. Doses for capecitabine, oxaliplatin and everolimus were modified per dose limiting toxicity (DLT). Baseline and on-treatment plasma biomarkers were analyzed. Archived tumor mRNA levels were evaluated for NRP1, NRP2 and VEGF-A isoforms.

Results—Twenty-nine patients were evaluable for toxicity and 30 for efficacy. Two DLTs were observed in cohort 1 and one DLT each was observed in cohort -1 and -1b. Grade 3 toxicities included neutropenia, hypertension, perforation/fistula/hemorrhage, hypertriglyceridemia, diarrhea, and thromboembolism. Twelve subjects experienced partial response (PR); 12 had stable disease as best response. Three of seven chemorefractory metastatic colorectal cancer (mCRC) subjects experienced PR; eight of 15 chemo-naïve mCRC subjects experienced PR. Plasma TβRIII and IL-6 increased on treatment but without correlation to outcome. Increased VEGF₁₆₅ levels significantly correlated with longer progression free survival.

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Conflict of Interest Statement

Dr. Andrew Nixon serves as a consultant for GlaxoSmithKline, Novartis and obtains research support from Amgen, F. Hoffman-La Roche, Pfizer, and Tracoon Pharmaceuticals. Dr. Michael Morse has received honoraria from Genentech and Novartis. Dr. Herbert Hurwitz serves as a consultant for Genentech, Roche, Sanofi, Regeneron, Bristol Meyer Squibb, Lilly, Amgen, Incyte, Novartis, Tracoon Pharmaceuticals, and Pfizer. Dr. Yousuf Zafar serves as a consultant for Genentech. Dr. Hope Uronis has research funding from Genentech. Dr. John Strickler serves as a consultant for Amgen. The remaining authors have no conflicts of interest.

Conclusions—Everolimus with full dose capecitabine, oxaliplatin, and bevacizumab had unacceptable toxicity. MTD was: everolimus 5mg daily; capecitabine 680mg/m² BID days 1-14; oxaliplatin 100mg/m² and bevacizumab 7.5mg/kg, day one. Activity was noted in mCRC.

Keywords

Capecitabine; Oxaliplatin; Bevacizumab; Everolimus; Phase I; Advanced Cancer

Introduction

The phosphatidyl inositol 3-kinase (PI3K)/AKT signaling pathway regulates a variety of basic cellular processes including, cell growth and survival, autophagy, metabolism and angiogenesis. This pathway is inappropriately activated, by multiple different mechanisms, in a broad spectrum of cancers (Engelman, 2009). Temsirolimus and everolimus (RAD001) are rapamycin analogs that inhibit the mammalian target of rapamycin (mTOR), a major downstream effector of the PI3K/AKT network (Meric-Bernstam & Gonzalez-Angulo, 2009). Treatment with rapamycin or its analogs results in cell cycle arrest and a host of indirect antitumor effects including a reduction of vascular endothelial growth factor (VEGF)-stimulated endothelial cell proliferation and migration (Del Bufalo *et al*, 2006; Phung *et al*, 2006).

Inhibition of VEGF and mTOR signaling has distinct effects on tumor vasculature and angiogenesis. In tumor models, inhibition of either VEGF or mTOR results in a potent decrease in blood vessel density. However there are differential effects on tissue permeability. While mTOR inhibition more strongly reduces the number of mature vessels, these agents do not decrease vascular tumor permeability, a classic marker of angiogenesis that is modulated by multiple agents that target VEGF. These important differences are likely accounted for by differential effects on tumor endothelial cells, smooth muscle cells and pericytes (Lane *et al*, 2009). As such, in murine melanoma models, combination treatment with everolimus and the pan-VEGF receptor tyrosine kinase inhibitor, vatalanib, caused synergistic tumor growth inhibition in comparison to either monotherapy. These data suggest that everolimus may be a more effective therapy in combination with targeted inhibitors of VEGF signaling due to more complete inhibition of tumor vascularization (O'Reilly *et al*, 2011).

Bevacizumab is a humanized monoclonal antibody against VEGF and is approved by the Federal Drug Administration for the treatment of colorectal cancer (Hurwitz *et al*, 2004) and non-squamous, non-small cell lung cancer in combination with chemotherapy (Sandler *et al*, 2006). It is also approved in combination with interferon α for the treatment of renal cell cancer (Escudier *et al*, 2007) and as a single agent for progressive glioblastoma (Vredenburgh *et al*, 2007). Multiple studies have reported that the combination of bevacizumab and everolimus is safe (Altomare *et al*, 2011; Bullock *et al*, 2011; Hainsworth *et al*, 2010a; Hainsworth *et al*, 2010b; Strickler *et al*, 2012; Vlahovic *et al*, 2012). Clinically significant toxicities include: fatigue, mucositis, hypertension, vomiting, diarrhea, proteinuria, fistula/abscess/perforation, and hemorrhage. These studies also demonstrated encouraging activity for the combination of bevacizumab with everolimus. In a population

of patients with heavily pretreated solid tumors, the median progression free survival (PFS) was 6.0 months (Bullock *et al*, 2011). In a phase II trial of bevacizumab and everolimus in patients with refractory metastatic colorectal cancer (mCRC), median PFS interval was 2.3 months with 26% of patients achieving prolonged stable disease for >6 months (Altomare *et al*, 2011). 84% of these patients had documented progression on prior bevacizumab suggesting that this combination has modest activity in patients with refractory mCRC.

Capecitabine and oxaliplatin have activity in multiple gastrointestinal tumor types. The primary objective of this study was to define the maximal tolerated dose (MTD) and the recommended phase II dose (RPTD) for the combination of capecitabine, oxaliplatin, bevacizumab, and everolimus in subjects with advanced solid tumors. The secondary objectives were to investigate the pharmacodynamic characteristics of the combination and evaluate for signs of clinical activity. This study also provides additional information regarding the pharmacodynamic properties of bevacizumab and everolimus in patients with advanced solid tumors.

Patients and Methods

Study Design

This was a dose-escalation phase I study to assess the regimen of capecitabine (Genentech, South San Francisco, CA, USA), oxaliplatin, bevacizumab and everolimus (Novartis Pharmaceuticals, East Hanover, NJ, USA) in patients with advanced solid tumors. A standard phase I “3 + 3” design was used to establish the MTD/RPTD of the combination. The MTD was defined around toxicities in the first cycle; the RPTD was selected based upon toxicities occurring in all cycles. A cycle was defined as 21 days. The dose escalation schema is listed in Table 1. Treatment was continued as long as patients were deemed to be clinically benefiting and until: disease progression, intercurrent illness that prevented further treatment, unacceptable toxicity, patient withdrawal from the study, or general or specific changes in the patient’s condition that rendered further treatment inappropriate per judgment of the investigator or treating physician. Maximum time on treatment was capped at two years per protocol.

Patient Selection

Eligible patients were required to have a histologically confirmed solid malignancy refractory to standard therapy or for which standard therapies did not exist or were no longer effective or for whom capecitabine, oxaliplatin, and/or bevacizumab would be considered a standard therapy or therapeutic option. Additional eligibility requirements included: age >18 years; Karnofsky performance status (KPS) ≥70%; previous radiation therapy, hormonal therapy, biologic therapy or chemotherapy for cancer permitted >4 weeks prior to study drug; surgery permitted >4 weeks prior to study drug. Adequate organ and marrow function was defined as: absolute neutrophil count (ANC) >1,500/μl; platelets >100,000/μl; hemoglobin >9 g/dL; total bilirubin <1.5 times the upper limit of normal (ULN); aspartate aminotransferase/alanine aminotransferase (AST/ALT) <2.5 times ULN or <5 times ULN if known hepatic metastases; fasting serum cholesterol <1.5 × ULN; fasting serum triglyceride <2.5 × ULN; fasting blood sugar <160 mg/dL; creatinine clearance >50

mL/min/m²; left ventricular ejection fraction $\geq$ 50% and proteinuria $<$ 1 gram/24hours. Additional exclusion criteria included: pregnancy, breast-feeding, central nervous system metastases, surgically resectable hepatic or pulmonary metastatic colorectal cancer, clinically significant cardiovascular disease with intervention within last twelve months, HIV or hepatitis B or C seropositivity, full dose anti-coagulation other than low molecular weight heparin, tumor invasion or encasement of a major artery, abdominal fistula or gastrointestinal perforation within 6 months of study drug, arterial thrombosis within past twelve months, bleeding diathesis or major bleed within 6 months of study drug, significant vascular or peripheral vascular disease, uncontrolled hypertension (blood pressure $>$ 140/90 mmHg) despite supportive care, history of hypertensive encephalopathy or crisis, chronic treatment with systemic steroids or another immunosuppressive agent, peripheral neuropathy of grade $\geq$ 2, impairment of gastrointestinal function or gastrointestinal disease that may significantly alter drug absorption, evidence of interstitial lung disease, radiation to $>$ 25% of bone marrow at any point. No history of hypersensitivity or intolerance with capecitabine, oxaliplatin, bevacizumab, or everolimus was permitted. Concurrent administration of medications with CYP3A4 or P-glycoprotein interactions (inhibitors, inducers or substrates) was not permitted. Serious medical conditions that might have significantly affected patient safety or toxicity assessment were prohibited. This was a multi-center study (NCT00849550) approved by the institutional review boards of all participating sites and followed the guidelines of the Helsinki Declaration. All patients provided informed written consent prior to any study-related procedure and were treated at Duke University Medical Center (Durham, NC), Sarah Cannon Research Institute (Nashville, TN) and Ingalls Memorial Hospital Cancer Research Center (Chicago, IL). Subject accrual took place from August 2009 to August 2011.

Clinical and Radiographic Assessment

All patients completed an extensive medical history, baseline physical examination and clinical assessment prior to receiving study drug. Toxicity and safety assessments were performed weekly during cycle 1, then every three weeks prior to treatment and as clinically indicated. These assessments included vital signs, KPS, medical history, physical examination including complete blood count (CBC), chemistries including creatinine, alkaline phosphatase, AST, ALT, bilirubin, fasting lipid profile and urinalysis. Serum beta-human chorionic gonadotropin for women of child bearing potential, creatinine kinase (for patients on statin medications) thyroid stimulating hormone and electrocardiograms were assessed at baseline and every three cycles. Cardiac ejection fraction was assessed at baseline and as clinically indicated. General symptom management and supportive care such as anti-diarrheal and anti-emetics agents were provided as clinically indicated to ensure optimal patient care. Computed tomography (CT) scan or magnetic resonance imaging (MRI) and blood tumor markers were completed within four weeks prior to the start of therapy and every three cycles (9 weeks) using RECIST criteria (version 1.0).

Safety

The National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0) was used to grade adverse events. The following adverse events were considered DLT in cycle 1: grade 4 neutropenia or thrombocytopenia lasting over 7 days; nausea/vomiting or diarrhea

grade 3 and lasting 4 days despite adequate supportive measures; febrile neutropenia where ANC <500/ μ l and temperature > 101°F; hand foot syndrome grade 3 lasting 7 or more days; grade 3 neuropathy; grade 3 hypophosphatemia lasting > 24 hours despite adequate supportive measures; grade 3 hyperglycemia lasting > 7 days despite adequate supportive measures; grade 3 hypertriglyceridemia or hyperlipidemia lasting > 28 days despite adequate supportive measures; other non-hematologic treatment related toxicity grade 3, excluding alopecia, anorexia, hypertension, isolated lab abnormalities (not clinically significant); rare, allergic and/or idiosyncratic reactions to any of the study agents of any severity; any treatment-related death or hospitalization; receiving less than 85% of any of the planned study medication due to treatment-related toxicity. Subjects evaluable for DLT toxicity are defined as those subjects who give informed consent, meet inclusion/exclusion screening criteria and complete the full 21-day cycle of both study drug treatment and safety assessments. Subjects with informed consent who met the inclusion/exclusion criteria and received study drug treatment but did not complete the full 21-day cycle of study treatment and safety assessments for primary study end points for reasons other than toxicity (e.g. those subjects who have disease progression or inter-current illness) were not considered evaluable for DLT toxicity. Patients were considered chemo-naïve if they had no prior systemic therapy for metastatic disease and were considered chemorefractory if they had any prior systemic therapy for metastatic disease.

Biomarkers

Real-Time PCR—Archived formalin-fixed paraffin-embedded tumor tissue blocks were obtained for 22 patients. RNA was isolated from six- 10mm cut sections using the Ambion Recoverall Total Nucleic Isolation kit according to manufacturer's protocol (Ambion-Life Technologies, Austin, TX, USA). RNA (200ng) from each sample was reverse transcribed using the High Capacity cDNA Reverse Transcription kit (Applied Biosystems-Life Technologies, Foster City, CA, USA). Taqman quantitative PCR was performed for VEGF-A (Cat# Hs00900055_m1), NRP1 (Cat# Hs01546494_m1), NRP2 (Cat# Hs01033058_m1), and GAPDH (Cat# Hs00266705_g1) expression, using the ABI StepOne PCR System (Applied Biosystems- Life Technologies, Foster City, CA, USA). Primers for specific VEGF-A isoforms were as follows: VEGFA₁₂₁ (forward, ACAACAAATGTGAATGCAGACCAAA; reverse, CTGAGGGAGGCTCCTTCCT), VEGFA₁₄₅ (forward, GCAAGAAATCCCGGTATAAGTCC; reverse, GCTCACCGCCTCGGC), VEGFA₁₆₅ (forward, ACAACAAATGTGAATGCAGACCAAA; reverse, GCTTTCTCCGCTCTGAGCAA), VEGFA₁₈₉ (forward, GCGCAAGAAATCCCGGTATAAGT; reverse, GCTTTCTCCGCTCTGAGCAA), VEGFA₂₀₆ (forward, TGTCTAATGCCCTGGAGCCT; reverse, AATGCTTTCTCCGCTCTGAGC). mRNA expression were normalized to GAPDH mRNA and expressed as $DC_T = [C_T(NRP) - C_T(GAPDH)]$, where C_T is the threshold cycle.

Multiplex ELISA assays—EDTA plasma was obtained at baseline and after the third cycle of treatment. Samples were available from 22 evaluable patients. IL-6, HGF, VEGF, PDGF- β , VEGFR1, and TGF β -2 were measured by ELISA methods SearchLight multiplex platform (Aushon Biosystems, Inc., Billerica, MA) according to the manufacturer's

protocol. The T β R_{III} assay was performed as a stand-alone assay as previously described (Liu *et al*, 2013). Briefly, samples for multiplex analysis were thawed on ice, centrifuged at 20,000 $\times$ g for five minutes to remove any residual precipitate and appropriately diluted before placement onto SearchLight plates. Samples and standards were incubated at room temperature for one hour while shaking. Plates were washed three times using an automated plate washer (Biotek Instruments, Inc., Model ELx405, Winooski, VT), biotinylated secondary antibody was added, and plates were then incubated for an additional thirty minutes. After three more washes, streptavidin-HRP was added to the plates, plates were incubated for thirty minutes, washed again, and SuperSignal substrate was added. Images of the plates were taken within ten minutes, followed by image analysis using the SearchLight array analyst software (Version 2.1). Analyte concentrations were calculated based on a 6-point standard curve performed on each plate. Patient samples were tested in duplicate and the mean value was used for analysis.

Statistical Analysis

The primary objective of this study is to determine the MTD. The DLTs of capecitabine, oxaliplatin, bevacizumab, and everolimus were tabulated by type and grade for all enrolled patients according to dose received. The number and percent of patients achieving complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were summarized. PFS was defined as the time from randomization to progression of disease by RECIST or death, whichever comes first; patients who withdrew from the study for reasons other than progression or death were censored at the time of discontinuation from the study. Kaplan-Meier analyses and plots were used to estimate the PFS of treated patients. The response rate and PFS were to be summarized descriptively for all patients evaluable for efficacy.

Biomarker analyses were considered exploratory. For the plasma data, Wilcoxon signed-rank tests were used to determine significant changes in biomarker on drug. For baseline plasma levels correlation with PFS, the data are limited to chemo-naïve patients with colorectal cancers. The log ratio (L-ratio) defined as $\log_2(\text{on-treatment level/baseline level})$ were also investigated. Univariate biomarker correlations with PFS were evaluated using Cox proportional hazard regression analysis. Spearman's rank correlations were calculated for all pairs of RT-PCR biomarkers using both baseline and L-ratio. Waterfall plots were produced using L-ratios to demonstrate how an analyte changes between the time points. Due to the exploratory nature of all tests, p values were considered descriptive and were not corrected for multiple testing.

Results

Patient Demographics

Patient demographics and tumor type are summarized in Table 2. A total of 32 patients were enrolled and 31 patients were treated. One patient voluntarily withdrew consent prior to being treated due to development of an intercurrent illness. 29 patients were evaluable for toxicity; 30 were considered evaluable for radiographic tumor response. The median age was 58 years (range 25-74). Twenty-three of 31 (74%) patients had metastatic colorectal

cancer. Nine of 31 patients (29%) had no prior chemotherapy treatment for metastatic disease.

Dose Escalation and MTD Determination

The dose escalation schema and corresponding DLTs are listed in Table 1. Dose findings were based on overall safety and tolerability of the investigational drug combination. Two patients had treatment-related DLTs in cohort 1 (n=6). One patient experienced grade 2 intolerable fatigue, anorexia, nausea and vomiting and thus did not receive greater than 85% of planned study medication despite maximal medical management. The second patient experienced transient grade 3 diarrhea and was also unable to receive 85% of planned study medication. In cohort -1 (n=12), one DLT of grade 2 intolerable diarrhea was observed. In cohort -1b (n=13), everolimus was increased from 5mg three times a week to 5 mg daily to maximize dose intensity. One subject in cohort -1b developed a treatment-related DLT, grade 3 rectovaginal fistula, which resulted in protocol discontinuation; this patient was not evaluable for efficacy. Two subjects, one in cohort 1 and one in cohort -1b, were not evaluable for toxicity due to intercurrent illness that was not study treatment related.

Safety

Most adverse events were mild to moderate and resolved with supportive clinical care and protocol- specified dose holdings and reductions. Grade 3 treatment-related toxicities across all cycles is summarized in Table 3. Overall, the most common clinically significant grade 3 adverse events were hypertension (12.9%), GI perforation/fistula (9.7%) and diarrhea (6.5%). There were two treatment related deaths: one due to rectal perforation and one due to GI hemorrhage. Both of these patients had metastatic cholangiocarcinoma, and were in cohort -1b. The patient with the rectal perforation had no prior history of radiation and was concurrently noted to have disease progression. The patient with GI hemorrhage had evidence of a bleeding duodenal ulcer at the site of his prior surgical anastomosis. He had a remote history of adjuvant chemoradiation and his death was complicated by the fact that he declined blood product transfusion.

Efficacy

Patients were considered evaluable for efficacy if they underwent the first planned tumor assessment scan without clinical progression prior to the scan. For assessment of best response across all patients, 12 of 30 patients (40%) had a PR and 12 of 30 patients (40%) had SD (Figure 1). No CRs were noted. Six of 30 patients (20%) had PD at the time of the first response assessment. Median PFS was 8.8 months (95% CI 5.6-12.2 months). Four patients had not demonstrated radiologic or clinical progression at the time of study termination.

Twenty-two patients with colorectal tumors were evaluable for efficacy. Of the 15 patients that were chemonaive, 8 patients had a PR and 6 had SD (Figure 1). Of the 7 patients who had received prior chemotherapy for metastatic disease, three had a PR and 2 had SD. All seven of these patients had been treated with prior 5-fluorouracil or capecitabine, five of seven had been treated with prior oxaliplatin and five of seven had been treated with prior bevacizumab. Three of twenty-two patients had disease progression at the time of first

response assessment. Median PFS for all patients evaluable for efficacy with mCRC was 10.5 months (95% CI 7.2-13.7 months). Median PFS for the chemonaive, mCRC patients was 12.9 months (95% CI 7.2- 20.9 months) and median PFS for the chemorefractory, mCRC patients was 6.8 months (95% CI 1.8-10.5 months). Three patients with colorectal cancer had not demonstrated progression at the time of study termination. Two patients with colorectal cancer were on study therapy for twenty-four months without evidence of progression and thus were discontinued at that time per protocol.

Biomarker analysis

To evaluate biomarker responses to treatment, each subject's baseline biomarker profile was used as his or her reference control. Plasma samples collected at baseline and at the end of three cycles (first re- staging, on treatment) were available for biomarker analysis from 22 of the 31 treated patients. For each patient, seven biomarkers, IL-6, HGF, VEGF, PDGF- β , VEGFR1, TGF β -2, and T β RIII were analyzed at baseline and on-treatment. Statistically significant changes were noted in T β RIII ($p = 0.00001$) and IL-6 ($p = 0.042$) with both markers increasing on treatment (Figure 2A and 2B). In the 11 patients who were evaluated on-treatment, it was noted that the change in PDGF- β levels was associated with PFS ($p = 0.035$; data not shown).

We evaluated the mRNA levels of VEGF-A, VEGF-A isoforms, Neuropilin-1 (NRP1) and Neuropilin-2 (NRP2) by real-time quantitative RT-PCR in archived tissue from 22 patients. There was a correlation between higher levels of VEGF₁₆₅ and longer PFS ($p = 0.0076$). Higher levels of total VEGF-A ($p = 0.094$) and VEGF₁₂₁ ($p = 0.084$) showed trends for a correlation with longer PFS (data not shown). There was no correlation between either NRP1 or NRP2 and outcome. To better understand the potential co- regulation of specific biomarkers, Spearman's rank correlation was used to test pairwise correlations. Pairs of baseline markers that reached statistical significance (correlation coefficients > 0.70 , $P < 0.005$) included VEGF-A and NRP1, VEGF-A and VEGF₁₆₅, VEGF-A and VEGF₁₈₉, and VEGF₁₈₉ and VEGF₁₄₅.

Discussion

The PI3K/Akt/mTOR signaling pathway is a key regulator of hypoxia and plays an important role in tumor angiogenesis (Guba *et al*, 2002). VEGF-dependent and -independent mechanisms for the anti- angiogenic properties of mTOR inhibitors have been proposed. mTOR inhibition abrogates hypoxia- induced, transcription and accumulation of hypoxia-inducible factor alpha (HIF-1 α), thus attenuating expression of the HIF-1 α target gene, VEGF (Bernardi *et al*, 2006; Hudson *et al*, 2002). Accumulation of HIF-1 α has been postulated as a potential resistance mechanism to anti-angiogenic therapies such as bevacizumab (Bergers & Hanahan, 2008; Du *et al*, 2008). Furthermore, platelet derived growth factor (PDGF) signals to stem cell derived factor-1 α (SDF-1 α) via the PI3K/Akt/ mTOR pathway to induce pericyte recruitment during angiogenesis (Song *et al*, 2009). This mechanism is also dependent on HIF- 1 α accumulation and activation. mTOR inhibition dissociates pericytes from the tumor vasculature, thus rendering the tumor more sensitive to anti-VEGF therapies (Lane *et al*, 2009). Finally, the mTOR pathway is a critical for the

differentiation of monocytes to proangiogenic, tumor associated macrophages (TAMs; M2 phenotype). Conversely, inhibition of mTOR modulates the polarity of macrophages to an antitumor M1 phenotype. These findings are independent of VEGF, reinforcing that mTOR inhibitors have effects on angiogenesis that are distinct and non-overlapping with anti-VEGF therapies (Chen *et al*, 2012). Based on this data we hypothesized that bevacizumab and everolimus in combination with chemotherapy would coordinately target parallel angiogenic signaling pathways and circumvent potential resistance mechanisms.

In this phase I study, we demonstrated that everolimus could be safely combined with capecitabine, oxaliplatin and bevacizumab. However, the combination requires dose reductions in everolimus, capecitabine and oxaliplatin as full doses result in unacceptable, gastrointestinal toxicity. The MTD for everolimus in this combination was 5mg daily, lower than the FDA approved monotherapy dose of 10mg daily. It is also lower than other bevacizumab-everolimus combinations, suggesting that the addition of chemotherapy results in overlapping toxicity (Altomare *et al*, 2011; Bullock *et al*, 2011; Hainsworth *et al*, 2010a; Hainsworth *et al*, 2010b). Treatment-related toxicity was consistent with the known toxicity profiles of each of these agents when used separately. Four subjects experienced gastrointestinal fistula, perforation and/or hemorrhage, two of which were grade 5 (fatal) events. Perforation and related wound healing complications are well-described class effects of anti-VEGF therapies and anti-mTOR therapies (Kabbinar *et al*, 2003; Kozloff *et al*, 2009). The frequency of this toxicity was potentially augmented by the combination of these agents, particularly in the setting of chemotherapy with gastrointestinal toxicities or where patients have had prior radiation therapy. The increased rate of fistula, perforation and hemorrhage has been noted in other studies investigating bevacizumab-everolimus combinations (Altomare *et al*, 2011; Bullock *et al*, 2011).

The combination of capecitabine, oxaliplatin, bevacizumab and everolimus demonstrated clinical activity. The partial response rate was 53% in patients with chemo-naïve mCRC and several responses were seen in patients with refractory colorectal cancer and other tumor types. Of the 15 patients with mCRC that were chemo-naïve, two patients were on treatment for two years at which time study treatment was terminated per protocol. In addition, two of eleven chemorefractory patients, one with metastatic pancreatic cancer and the other with mCRC, were on treatment for one year (54.1 and 55.9 weeks respectively). Interestingly, the patient with mCRC had been treated with prior bevacizumab. These results suggest that this combination has sustained clinical activity in a subset of both chemo-naïve and chemorefractory patients with mCRC.

We measured the pharmacodynamic effects of capecitabine, oxaliplatin, bevacizumab and everolimus on several circulating biomarkers. Of the biomarkers analyzed, soluble TβRIII and IL-6 demonstrated statistically significant increases between baseline and the end of cycle 3. TβRIII (also known as betaglycan) is a TGF-β superfamily co-receptor that mediates ligand dependent and independent signaling (reviewed in (Gatza *et al*, 2010)). Regulation of TβRIII occurs at multiple levels with reductions in cell surface TβRIII being due to increased ectodomain shedding, thus producing a soluble TβRIII. Soluble TβRIII functions either by sequestering TGF-β superfamily ligands and suppressing signaling or by binding to extracellular matrix proteins and thus blocking access to cell surface TβRIII. TβRIII

expression may be prognostic, as loss of T β RIII expression increases with clinical stage in multiple tumor types, including ovarian, breast, prostate, and NSCLC (Dong *et al*, 2007; Gatza *et al*, 2010; Gordon *et al*, 2008). More recent data has also demonstrated that in breast and melanoma tumor models, loss of T β RIII expression is associated with decreased tumor infiltrating CD8⁺ T cells and increased regulatory T cells within the tumor microenvironment, markers of more rapid disease progression (Hanks *et al*, 2012). Soluble T β RIII may also have therapeutic benefit as it has been shown to have tumor suppressive effects including inhibition of tumor growth, invasion and migration, angiogenesis and metastasis in multiple tumor types (Bandyopadhyay *et al*, 2002a; Bandyopadhyay *et al*, 2002b; Dong *et al*, 2007; Gordon *et al*, 2008). Increases in soluble T β RIII have not previously been described in response to bevacizumab or everolimus therapy but the lack of a randomized design, in the current study, prevents us from attributing the increase in sT β RIII to bevacizumab, everolimus, capecitabine, oxaliplatin or the combination. Further studies are warranted to explore this relationship.

In this study, plasma IL-6 levels were also noted to significantly increase on therapy but did not correlate with outcome. Elevated IL-6 levels are a well-documented adverse prognostic factor in multiple tumor types suggesting the importance of this pathway in driving tumor biology and clinical outcome (Coward *et al*, 2011; Knupfer & Preiss, 2010; Nixon *et al*, 2011; Tran *et al*, 2012). More recently, IL-6 has also been implicated as a predictive biomarker for both the oral multi-kinase inhibitor, pazopanib, and bevacizumab in patients with metastatic renal cell carcinoma. In the pivotal phase III study of pazopanib versus best supportive care, IL-6 had significant predictive value of PFS benefit. Patients with high IL-6 levels had a greater relative benefit from pazopanib compared with those who received placebo. However a benefit from pazopanib therapy was also noted in the low IL-6 group (Tran *et al*, 2012). Similarly, in CALGB 90206, a phase III trial of patients with advanced renal cell carcinoma randomized to bevacizumab + interferon versus interferon alone, IL-6 and hepatocyte growth factor (HGF) were predictive of overall survival in patients treated with bevacizumab + interferon (Nixon *et al*, 2013). While conclusions regarding the predictive ability of IL-6 must be viewed within the context of a given cancer type and therapeutic agent(s), these data certainly support ongoing study of the role of IL-6 in relation to other anti-angiogenic therapies.

Alternative splicing of the VEGF-A gene results in multiple VEGF-A isoforms that can diffuse over variable distances based on differential interactions with the extracellular matrix. In this study we investigated the role of tumor VEGF-A and VEGF-A isoforms in predicting benefit. We noted a statistically significant correlation between increased levels of tumor VEGF₁₆₅ mRNA and improved PFS. Furthermore, our data suggests coordinate regulation of VEGF-A and VEGF-A isoforms. The potential predictive role of plasma VEGF-A has now been supported by independent biomarker analyses in multiple tumor types. In the AVADO trial, a randomized phase III study of docetaxel +/- bevacizumab or placebo in patients with HER2-negative, metastatic breast cancer, predictive effect to bevacizumab was noted for high plasma VEGF-A and VEGFR-2 and blood mRNA for VEGF₁₂₁ but not VEGF₁₆₅ (Miles *et al*, 2013). The AVAGAST study showed that the addition of bevacizumab to chemotherapy in patients with advanced gastric cancer improved

response rate and PFS, but not OS. Baseline plasma VEGF-A levels and tumor neuropilin-1 expression were identified as potential predictors of bevacizumab efficacy (Van Cutsem *et al*, 2012). The predictive value of VEGF-A to bevacizumab will be evaluated in ongoing, randomized studies. The phase III MERiDiAN trial (GO25632) began recruitment in 2012 and will prospectively evaluate the impact of bevacizumab in patients with metastatic breast cancer stratified by plasma VEGF-A levels.

In conclusion, we have demonstrated that the combination of everolimus at 5mg daily, capecitabine at 680mg/m² BID on days 1-14, oxaliplatin at 100mg/m² and bevacizumab at 7.5mg/kg given every 21 days appears safe and generally well tolerated. Patients should be monitored closely for signs and symptoms of fistula, perforation and/or hemorrhage. This regimen demonstrated activity and our data suggests that tumor levels of VEGF₁₆₅ may correlate with benefit. Furthermore, the combination modulated levels of soluble TβRIII and IL-6 suggesting a potential immunologic or anti-angiogenic mechanism of action.

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References

- Altomare I, Bendell JC, Bullock KE, Uronis HE, Morse MA, Hsu SD, Zafar SY, Blobe GC, Pang H, Honeycutt W, Sutton L, Hurwitz HI. A phase II trial of bevacizumab plus everolimus for patients with refractory metastatic colorectal cancer. *Oncologist*. 2011; 16(8):1131–7. [PubMed: 21795432]
- Bandyopadhyay A, Lopez-Casillas F, Malik SN, Montiel JL, Mendoza V, Yang J, Sun LZ. Antitumor activity of a recombinant soluble betaglycan in human breast cancer xenograft. *Cancer Res*. 2002a; 62(16):4690–5. [PubMed: 12183427]
- Bandyopadhyay A, Zhu Y, Malik SN, Kreisberg J, Brattain MG, Sprague EA, Luo J, Lopez-Casillas F, Sun LZ. Extracellular domain of TGFβ type III receptor inhibits angiogenesis and tumor growth in human cancer cells. *Oncogene*. 2002b; 21(22):3541–51. [PubMed: 12032856]
- Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer*. 2008; 8(8): 592–603. [PubMed: 18650835]
- Bernardi R, Guernah I, Jin D, Grisendi S, Alimonti A, Teruya-Feldstein J, Cordon-Cardo C, Simon MC, Rafii S, Pandolfi PP. PML inhibits HIF-1α translation and neoangiogenesis through repression of mTOR. *Nature*. 2006; 442(7104):779–85. [PubMed: 16915281]
- Bullock KE, Petros WP, Younis I, Uronis HE, Morse MA, Blobe GC, Zafar SY, Gockerman JP, Lager JJ, Truax R, Meadows KL, Howard LA, O'Neill MM, Broadwater G, Hurwitz HI, Bendell JC. A phase I study of bevacizumab (B) in combination with everolimus (E) and erlotinib (E) in advanced cancer (BEE). *Cancer Chemother Pharmacol*. 2011; 67(2):465–74. [PubMed: 21079958]
- Chen W, Ma T, Shen XN, Xia XF, Xu GD, Bai XL, Liang TB. Macrophage-induced tumor angiogenesis is regulated by the TSC2-mTOR pathway. *Cancer Res*. 2012; 72(6):1363–72. [PubMed: 22287548]
- Coward J, Kulbe H, Chakravarty P, Leader D, Vassileva V, Leinster DA, Thompson R, Schioppa T, Nemeth J, Vermeulen J, Singh N, Avril N, Cummings J, Rexhepaj E, Jirstrom K, Gallagher WM,

- Brennan DJ, McNeish IA, Balkwill FR. Interleukin-6 as a therapeutic target in human ovarian cancer. *Clin Cancer Res*. 2011; 17(18):6083–96. [PubMed: 21795409]
- Del Bufalo D, Ciuffreda L, Trisciuglio D, Desideri M, Cognetti F, Zupi G, Milella M. Antiangiogenic potential of the Mammalian target of rapamycin inhibitor temsirolimus. *Cancer Res*. 2006; 66(11):5549–54. [PubMed: 16740688]
- Dong M, How T, Kirkbride KC, Gordon KJ, Lee JD, Hempel N, Kelly P, Moeller BJ, Marks JR, Blobe GC. The type III TGF-beta receptor suppresses breast cancer progression. *J Clin Invest*. 2007; 117(1):206–17. [PubMed: 17160136]
- Du R, Lu KV, Petritsch C, Liu P, Ganss R, Passegue E, Song H, Vandenberg S, Johnson RS, Werb Z, Bergers G. HIF1alpha induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. *Cancer Cell*. 2008; 13(3):206–20. [PubMed: 18328425]
- Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer*. 2009; 9(8):550–62. [PubMed: 19629070]
- Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczyluk C, Chevreau C, Flipeck M, Melichar B, Bajetta E, Gorbunova V, Bay JO, Bodrogi I, Jagiello-Gruszfeld A, Moore N. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007; 370(9605):2103–11. [PubMed: 18156031]
- Gatza CE, Oh SY, Blobe GC. Roles for the type III TGF-beta receptor in human cancer. *Cell Signal*. 2010; 22(8):1163–74. [PubMed: 20153821]
- Gordon KJ, Dong M, Chislock EM, Fields TA, Blobe GC. Loss of type III transforming growth factor beta receptor expression increases motility and invasiveness associated with epithelial to mesenchymal transition during pancreatic cancer progression. *Carcinogenesis*. 2008; 29(2):252–62. [PubMed: 17999987]
- Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med*. 2002; 8(2):128–35. [PubMed: 11821896]
- Hainsworth JD, Infante JR, Spigel DR, Peyton JD, Thompson DS, Lane CM, Clark BL, Rubin MS, Trent DF, Burris HA 3rd. Bevacizumab and everolimus in the treatment of patients with metastatic melanoma: a phase 2 trial of the Sarah Cannon Oncology Research Consortium. *Cancer*. 2010a; 116(17):4122–9. [PubMed: 20564157]
- Hainsworth JD, Spigel DR, Burris HA 3rd, Waterhouse D, Clark BL, Whorf R. Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma. *J Clin Oncol*. 2010b; 28(13):2131–6. [PubMed: 20368560]
- Hanks BA, Holtzhausen A, Gimpel P, Jamieson R, Campbell OM, Sun L, Augustine CK, Tyler DS, Osada T, Morse M, Ling LE, Lysterly HK, Blobe GC. Effect of the loss of the type III TGF{beta} receptor during tumor progression on tumor microenvironment: Preclinical development of TGF{beta} inhibition and TGF{beta}-related biomarkers to enhance immunotherapy efficacy. *ASCO Meeting Abstracts*. 2012; 30(15_suppl):10563.
- Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. *Mol Cell Biol*. 2002; 22(20):7004–14. [PubMed: 12242281]
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004; 350(23):2335–42. [PubMed: 15175435]
- Kabbinavar F, Hurwitz H, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2003; 21(1):60–5. [PubMed: 12506171]
- Knupfer H, Preiss R. Serum interleukin-6 levels in colorectal cancer patients--a summary of published results. *International Journal of Colorectal Disease*. 2010; 25(2):135–40. [PubMed: 19898853]

- Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM, Grothey A. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. *The Oncologist*. 2009; 14(9): 862–70. [PubMed: 19726453]
- Lane HA, Wood JM, McSheehy PM, Allegrini PR, Boulay A, Brueggen J, Littlewood-Evans A, Maira SM, Martiny-Baron G, Schnell CR, Sini P, O'Reilly T. mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. *Clin Cancer Res*. 2009; 15(5):1612–22. [PubMed: 19223496]
- Liu Y, Starr MD, Bulusu A, Pang H, Wong NS, Honeycutt W, Amara A, Hurwitz HI, Nixon AB. Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab. *Cancer Med*. 2013; 2(2): 234–42. [PubMed: 23634291]
- Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol*. 2009; 27(13):2278–87. [PubMed: 19332717]
- Miles DW, de Haas SL, Dirix LY, Romieu G, Chan A, Pivot X, Tomczak P, Provencher L, Cortes J, Delmar PR, Scherer SJ. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. *Br J Cancer*. 2013; 108(5):1052–60. [PubMed: 23422754]
- Nixon AB, Halabi S, Shterev I, Starr M, Brady JC, Dutcher JP, Hopkins JO, Hurwitz H, Small EJ, Rini BI, Febbo PG, George DJ. Identification of predictive biomarkers of overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (I) with or without bevacizumab (B): Results from CALGB 90206 (Alliance). *ASCO Meeting Abstracts*. 2013; 31 suppl; abstr 4520.
- Nixon AB, Pang H, Starr M, Hollis D, Friedman PN, Bertagnolli MM, Kindler HL, Goldberg RM, Venook AP, Hurwitz H. Prognostic and predictive blood-based biomarkers in patients with advanced pancreatic cancer: Results from CALGB 80303. *ASCO Meeting Abstracts*. 2011; 29(15_suppl):10508.
- O'Reilly T, Lane HA, Wood JM, Schnell C, Littlewood-Evans A, Brueggen J, McSheehy PM. Everolimus and PTK/ZK show synergistic growth inhibition in the orthotopic BL16/BL6 murine melanoma model. *Cancer Chemother Pharmacol*. 2011; 67(1):193–200. [PubMed: 20512579]
- Phung TL, Ziv K, Dabydeen D, Eyiah-Mensah G, Riveros M, Perruzzi C, Sun J, Monahan-Earley RA, Shiojima I, Nagy JA, Lin MI, Walsh K, Dvorak AM, Briscoe DM, Neeman M, Sessa WC, Dvorak HF, Benjamin LE. Pathological angiogenesis is induced by sustained Akt signaling and inhibited by rapamycin. *Cancer Cell*. 2006; 10(2):159–70. [PubMed: 16904613]
- Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006; 355(24):2542–50. [PubMed: 17167137]
- Song N, Huang Y, Shi H, Yuan S, Ding Y, Song X, Fu Y, Luo Y. Overexpression of platelet- derived growth factor-BB increases tumor pericyte content via stromal-derived factor-1alpha/CXCR4 axis. *Cancer Res*. 2009; 69(15):6057–64. [PubMed: 19584297]
- Strickler JH, Starodub AN, Jia J, Meadows KL, Nixon AB, Dellinger A, Morse MA, Uronis HE, Marcom PK, Zafar SY, Haley ST, Hurwitz HI. Phase I study of bevacizumab, everolimus, and panobinostat (LBH-589) in advanced solid tumors. *Cancer Chemother Pharmacol*. 2012
- Tran HT, Liu Y, Zurita AJ, Lin Y, Baker-Neblett KL, Martin AM, Figlin RA, Hutson TE, Sternberg CN, Amado RG, Pandite LN, Heymach JV. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. *Lancet Oncol*. 2012; 13(8):827–37. [PubMed: 22759480]
- Van Cutsem E, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol*. 2012; 30(17):2119–27. [PubMed: 22565005]
- Vlahovic G, Meadows KL, Uronis HE, Morse MA, Blobe GC, Riedel RF, Zafar SY, Alvarez-Secord A, Gockerman J, Starodub AN, Ready NE, Anderson EL, Bendell JC, Hurwitz HI. A phase I study

of bevacizumab, everolimus and panitumumab in advanced solid tumors. *Cancer Chemother Pharmacol.* 2012; 70(1):95–102. [PubMed: 22638798]

Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol.* 2007; 25(30):4722–9. [PubMed: 17947719]

Figure 1.

Waterfall plot of best radiographic response. Data from 30 patients evaluable for efficacy are presented. * denotes patient who received prior systemic chemotherapy for metastatic disease.

Figure 2. Change from baseline to the end of cycle three for biomarkers with statistical significance (P value as indicated). * denotes patients who received prior systemic chemotherapy for metastatic disease.

Table 1

Dose Limiting Toxicities by Cohort

Dose level	Everolimus (mg) oral QDay Days 1-21	Capecitabine (mg/m ²) oral BID Days 1-14	Oxaliplatin (mg/m ²) IV Day 1 ^a	Bevacizumab (mg/kg) IV Day 1	Number of Subjects	Dose Limiting Toxicity Events	Dose-Limiting Toxicities
1	5mg three times weekly	850	130	7.5	^b 6	2	Grade 2 fatigue, anorexia, vomitingc Grade 3 diarrhea ^c
-1b	5mg daily	680	100	7.5	13	1	Grade 3 rectovaginal fistula
-1	5mg three times weekly	680	100	7.5	^b 12	1	Grade 2 diarrhea ^c

^a Oxaliplatin administered on day 1 of first 6 cycles only

^b Two subjects, one in cohort 1 and one in cohort -1b, were not evaluable for toxicity due to non-treatment related intercurrent illness.

^c Unable to receive 85% of scheduled doses of study drugs.

Table 2

Clinical Characteristics

Characteristics	Patients (N = 31)
Median age in years (range)	58.2 (50.9-64.3)
Female: Male (N; %)	11 (35.5): 20 (64.5)
Karnofsky Performance Status (N; %)	
100%	15 (48.3)
90%	12 (38.7)
80%	4 (12.9)
Type of Primary Tumor (N; %)	
Colorectal ¹	23 (74.2)
Cholangiocarcinoma	2 (6.5)
Other ²	6 (19.4)
Chemonaive patients ³ (%)	9 (29%)

¹One patient with synchronous primary colon and rectal tumors

²Other consists of 1 patient each with following: appendiceal, bladder, duodenal, gastric, gastroesophageal, pancreatic.

³No prior chemotherapy for metastatic disease.

Table 3

Treatment Related Adverse Events	
Toxicity	Grade 3-5 Treatment-Related Adverse Events (%) N= 31
Hematologic	
Neutropenia	4(12.9)
Lymphopenia	1(3.2)
Thrombocytopenia	1(3.2)
Non-Hematologic	
Hypertension	4(12.9)
GI perforation/fistula	3 (9.7)
Hypertriglyceridemia	3 (9.7)
Diarrhea	2 (6.5)
Arterial Thrombosis	1 (3.2)
Deep Vein Thrombosis	1 (3.2)
Hyperglycemia	1 (3.2)
Hypoalbuminemia	1 (3.2)
Hyponatremia	1 (3.2)
Drug Hypersensitivity Reaction	
GI Hemorrhage	1 (3.2)
Peripheral Neuropathy	1 (3.2)
Mucositis	1 (3.2)
Failure to Thrive	1 (3.2)