Update on Antiangiogenic Therapy for Metastatic Colorectal Cancer

Metastatic colorectal cancer (mCRC) is the third leading cause of cancer-related deaths in the United States. More than 143,460 new cases and 51,690 deaths from the disease are expected in 2012.1 Mortality from mCRC overall has been decreasing due to the routine use of colonoscopy as a screening tool and vehicle for excising precursor lesions, as well as an improvement in therapy that leads to a higher percentage of patients being candidates for surgery and, thus, having a curative chance with therapy. For patients with mCRC, who are not surgical candidates, refinements to standard chemotherapy regimens have incrementally improved median life expectancy over the past decade. These gains, however, have come at the cost of considerable toxicities, and overall prognosis remains poor for this patient population, which represents over 50% of patients diagnosed with disseminated disease.2,3 A substantial change in the therapeutic outlook for patients with mCRC came in 2004, when the U.S. Food and Drug Administration (FDA) approved bevacizumab (BV), a fully humanized monoclonal antibody against vascular endothelial growth factor (VEGF) and the first biologic agent targeting angiogenesis, for use in combination with intravenous 5-fluorouracil (5-FU) -based chemotherapy for this patient population.4 Since then, numerous clinical trials have demonstrated efficacy for BV in combination with various chemotherapeutic backbones, such as leucovorin/5-FU/oxaliplatin (FOLFOX) and infusional leucovorin/5-FU/irinotecan (FOLFIRI) regimens, in the front-line and subsequent treatment settings.5-7

Another change in the therapeutic landscape of mCRC occurred recently with the FDA approval of ziv-aflibercept for use in combination with FOLFIRI in patients with progressive disease after prior treatment with an oxaliplatin-containing regimen, and regorafenib as monotherapy for patients who have failed previous treatment with 5-FU-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if the tumor is KRAS wild-type, anti-epidermal growth factor receptor (EGFR) therapy. Treatment algorithms must be updated to accommodate all three agents as potential therapy for patients with mCRC.

In addition to the three antiangiogenic agents that have already gained approval by the FDA, numerous other agents with varying mechanisms of action are currently under investigation as potential therapy for patients with mCRC. Monoclonal antibodies, engineered proteins, tyrosine kinase inhibitors (TKIs) and other small molecule agents target members of the VEGF signaling cascade, most notably VEGFR-2, as well as the action of other growth factor signaling pathways including those downstream of platelet-derived growth factor (PDGF), placental growth factor (PIGF) and basic fibroblast growth factor (bFGF; please see figure).8,9

VEGF Suppression: FDA Approved Antiangiogenic Agents for CRC

Of the many known endogenous growth factors involved in angiogenesis within tumors, VEGF and its associated signaling cascade have been the most extensively studied and is known to be critical for initiating and maintaining vasculature throughout tumorigenesis and dissemination of disease characteristic of CRC.9,10 Not only is VEGF a potent stimulator of endothelial cell proliferation, migration and survival, but also controls the overall structure of tumor vasculature by stimulating new capillary buds and directing their growth toward VEGF-overexpressing tumor cells to form new vascular tubes and loops. VEGF is also the major vascular permeability factor, and high expression levels cause excessive vascular permeability. VEGF binding and activation leads to receptor dimerization, phosphorylation of tyrosine residues on its intracellular tail, and activation of numerous downstream signaling pathways.8,11 Two activated pathways that play an important role in endothelial and tumor cell survival and growth are the Raf-MEK-ERK and phosphotyrosylinositol-3-kinase (PI3K)-Akt pathways.8 Each member of these proangiogenic pathways represents potential targets for drug development and mechanisms of action for the treatment of cancer.

This comprehensive review includes clinical trial data regarding the role of BV as standard chemotherapy for first-line and beyond, the utility of ziv-aflibercept and regorafenib as newly approved antiangiogenic agents, and the potential role of agents still undergoing clinical development as therapy for patients diagnosed with mCRC.

Bevacizumab was approved by the FDA as first-line therapy for mCRC based on results from the randomized AVF 2107 phase 3 trial comparing bolus 5-FU/leucovorin/irinotecan (IFL) in combination with BV or placebo as treatment for patients with mCRC. The addition of BV to IFL prolonged median overall survival (OS) by approximately 5 months compared with patients who received IFL alone (20.3 vs. 15.6 months; HR 0.66, P < 0.001). Progression-free survival (PFS) was 4.4 months longer in BV-treated patients compared to those who received placebo (10.6 vs. 6.2 months; HR 0.54, P < 0.001). This study was the first to demonstrate that the combination of an antiangiogenic agent with cytotoxic chemotherapy was superior to chemotherapy alone. Bevacizumab-associated increases in adverse events were grade 3 hypertension (11.0% vs. 2.3%) and gastrointestinal perforation (1.5% vs. 0).

A subsequent phase 3 study comparing the irinotecan-containing regimens IFL, FOLFIRI, and CapeIRI (capcitabine/irinotecan) was amended to add BV to IFL and FOLFIRI subsequent to the results

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Targeting Cells and Pathways in Metastatic Colorectal Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells, which in turn, release growth factors that sustain angiogenesis. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

Targeted Agents (Targets shown in diagram above)
- Bevacizumab
- Brivanib
- Remotumab
- VEGF Trap
- Regorafenib
- BBF 1120

Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to acquired gene mutations and hypoxia.

Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation.

Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

Tumor blood vessels are characteristically tortuous, saccular, and leaky; blood flow is uneven and chaotic, with areas of tumor necrosis, hypoxia, and acidosis.

Angiogenesis in CRC liver metastases is initiated when a tumor co-opts sinusoidal endothelial cells lining the periphery of the lesion. The liver contributes abundant proangiogenic factors to the metastatic lesion.

Inflammatory cells and stromal cells also release growth factors.
of AVF 2107.12 The BICC-C study established FOLFIRI as superior to IFL in terms of efficacy. There are no randomized data directly comparing FOLFIRI/BV and FOLFIRI alone that demonstrate superiority for the addition of BV, but updated survival data from period 2 of the study indicated that patients treated with FOLFIRI/BV survived significantly longer than those treated with IFL/BV (28.0 vs. 19.2 months; HR for death 1.79, P = 0.037).4 Despite the fact that treatment with FOLFIRI/BV was associated with higher rates of grade 3 or higher toxicities than IFL/BV, such as febrile neutropenia (5.4% vs. 1.7%) and hypertension (12.5% vs. 1.7%), its clear superiority in terms of survival led FOLFIRI to become the preferred irinotecan-based regimen for combination with BV. The preference of FOLFIRI/BV over IFL/BV as first-line therapy for patients with mCRC was further validated when a secondary analysis of the BICC-C trial found no significant differences in efficacy or safety when used in an older patient population.13

Concomitant with the clinical development of combination therapy with irinotecan-containing regimens, BV was assessed as a potential combination partner with oxaliplatin-containing chemotherapy. The randomized phase 3 trials ECOG 3200 and NO16966 evaluated the use of BV and oxaliplatin in the second-line chemotherapy-intensive regimen, folinic acid/5-FU/oxaliplatin/irinotecan therapy for patients with mCRC. A Spanish phase 3 study of patients who had already failed treatment with 5-FU/irinotecan.6 After FOLFOX, FOLFOX/BV and BV alone as second-line therapy in patients who had already failed treatment with 5-FU/irinotecan.6 The NO16966 phase 3 trial, a 2 x 2 randomized trial assessing the addition of BV to FOLFOX significantly improved survival (12.9 vs. 10.8 months; HR for death 0.75, P = 0.0011) and median PFS (7.3 vs. 4.7 months; HR for progression 0.61, P < 0.0001) when compared with FOLFOX alone as treatment for patients with previously treated mCRC. Bevacizumab treatment was associated with grade 3/4 hypertension, bleeding and vomiting.

ECOG 3200 was originally designed to compare the efficacy of FOLFOX/BV and BV alone as second-line therapy in patients who had already failed treatment with 5-FU/irinotecan.6 After the BV monotherapy arm was terminated due to inferiority to the control arm of the trial, the study demonstrated that the addition of BV to FOLFOX significantly improved survival (12.9 vs. 10.8 months; HR for death 0.75, P = 0.0011) and median PFS (7.3 vs. 4.7 months; HR for progression 0.61, P < 0.0001) when compared with FOLFOX alone as treatment for patients with previously treated mCRC.

The NO16966 phase 3 trial, a 2 x 2 randomized trial assessing non-inferiority of capecitabine/oxaliplatin (XELOX) compared with FOLFOX and the superiority of the addition of BV to an oxaliplatin-based regimen compared with placebo as first-line therapy, demonstrated that PFS was significantly prolonged among patients who received BV compared with placebo in a pooled analysis (9.4 vs. 8.0 months; HR 0.83, P = 0.0023).7 It should be noted, that approximately 26.8% of enrolled patients discontinued primary treatment due to toxicity and, when taking into account only patients who remained on treatment until disease progression, the PFS benefit from BV (10.4 vs. 7.9 months; HR 0.63, P < 0.0001) was more pronounced. Unlike previous studies, there was no statistically significant difference in OS in the treatment arms and treatment was discontinued previous to PD in the majority of patients in both arms of this trial. The authors hypothesized that treatment with BV could require continuation through to disease progression to maximize BV-associated clinical benefit. Results from the AVF2107, ECOG 3200 and NO16966 firmly established the survival benefit of adding BV to chemotherapy in the first-line or second-line treatment settings and established its use as standard care for patients with newly diagnosed or BV-naïve mCRC.

Two ongoing phase 3 studies of BV address its potential use in combination with new cytotoxic chemotherapy partners as first-line therapy for patients with mCRC. A Spanish phase 3 study comparing the efficacy and toxicity of FOLFOX/BV and the more chemotherapy-intensive regimen, folinic acid/5-FU/oxaliplatin/irinotecan (FOLFOXIRI)/BV in the first-line therapeutic setting for mCRC was planned in response to favorable results of a phase 2 study.14 In the multi-institutional phase 2 study, patients were treated first-line with FOLFOXIRI/BV and achieved a 10-month PFS rate of 74%.15 It was concluded that BV could be safely administered in combination with FOLFOXIRI. The ongoing phase 3 trial began in July 2012, and the estimated enrollment is 350 patients. The primary outcome measure of the trial is PFS, and secondary outcome measures include overall survival, response, R0 resection rate, and adverse events. Biomarkers, including baseline circulating tumor cells, KRAS, BRAF, and PI3K, will be correlated with efficacy measures. With the notion that patients with multiple metastases or ineligible for surgery may not benefit from intensive standard first-line therapy, a German study was initiated in December 2010 to comparing the safety and efficacy of CAPEIRI/BV and the less intensive capecitabine/BV (Cap/BV).16 The primary endpoint of the trial is time-of-failure strategy (TFS), and patients in the Cap/BV arm will be treated until progression of disease, when they will then crossover to CAPEIRI/BV treatment. Secondary outcome measures for this trial are objective response rates, OS, and quality of life.

Several clinical trials have addressed the administration of BV according to schedules other than as a combination partner for a single discreet line of therapy. The BRITE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) observational cohort study was initiated to assess the utility of BV in a large, unrestricted population of patients with treatment-naïve mCRC.17 An unexpectedly prolonged median OS for the entire cohort (25.1 months) led to ad hoc analysis of pre- and post-treatment factors of BRITE. The investigators found that median OS varied considerably between patients who, after progression on first-line therapy containing BV, had received no treatment (12.6 months), chemotherapy without BV (19.9 months) and chemotherapy with BV (31.8 months). Multivariate analyses comparing patients who received chemotherapy with and without BV after first progression indicated that prolonged BV exposure was independently associated with improved survival (HR, 0.48; P = 0.001). Results of an interim analysis of another large observational study assessing post-progression treatment with BV, ARIES, confirmed findings of the BRITE study.18 Median OS was significantly longer in patients who received BV after first progression on standard therapy than in those who did not (18.7 vs. 27.5 months; HR 0.52, P < 0.001).

To address this data in prospective trial structure, the randomized phase 3 ML18147 study was undertaken to assess the benefit of continuing BV treatment beyond first progression in patients with mCRC.19 Patients with unresectable mCRC who had progressed on first-line standard chemotherapy (irinotecan- or oxaliplatin-containing regimen) plus BV were randomized to second-line chemotherapy (crossover to irinotecan- or oxaliplatin-containing regimen) ± BV. Consecutive treatment with BV in first- and second-line therapy was associated with a survival benefit (11.2 vs. 9.8 months; HR 0.81, P = 0.0062) when compared to treatment with BV in first-line therapy only. Median PFS was also significantly longer in patients who received BV across two lines of therapy (5.7 vs. 4.1 months; HR 0.68, P < 0.0001). It is notable that although a survival benefit was confirmed for BV treatment past first progression, the benefit was considerably less than that reported for observational studies. Based upon the results of the ML18147 study, the FDA recently approved BV in combination with fluoropyrimidine–irinotecan- or fluoropyrimidine–oxaliplatin-based chemotherapy for the treatment of mCRC patients whose disease progressed while on first-line BV or irinotecan- or oxaliplatin-containing regimens.

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Another question regarding the duration of BV therapy, similar BV past progression, is whether patients who respond to a front-line BV-containing regimen, or induction therapy, would benefit from continuing BV as maintenance therapy. Updated results from a multicenter phase 3 trial comparing the efficacy front-line therapy with XELOX/BV until progression and 6 cycles of XELOX/BV followed by maintenance capecitabine/BV without oxaliplatin until progression in patients with mCRC indicated that maintenance therapy is non-inferior to XELOX/BV treatment to progression.20 While maintenance therapy was associated with an improvement in median PFS (9.9 vs. 8.3 months) and ORR (69.2% versus 57.4%) compared to XELOX/BV, statistical significance was not reached. Tolerability was comparable in both treatment groups.

Results from another phase 3 trial assessing the efficacy of single agent BV maintenance therapy following XELOX/BV induction as first-line therapy in patients with mCRC, the MACRO trial, did not establish its non-inferiority to XELOX/BV induction followed by XELOX/BV maintenance.21 Previously untreated mCRC patients were randomized to receive 6 cycles of induction XELOX/BV followed by maintenance therapy with XELOX/BV or BV alone. Median PFS was comparable between the two arms, at 23.4 months and 21.7 months, respectively. Several other trials evaluating maintenance BV in mCRC are recruiting patients, including CAIRO-3 and AIO-ML21768.22,23 These trials will further evaluate the continuation or reintroduction of BV in mCRC patients following successful induction chemotherapy, both as a single agent and paired with chemotherapy.

Clinical trials investigating a potential role for BV in the adjuvant treatment setting have yielded data that do not support ongoing interest. Updated results from the phase 3 NSABP C-08 trial comparing the efficacy FOLFFOX/BV and FOLFOX alone in patients with stage II/III disease indicated that adding BV to chemotherapy did not improve disease free survival (DFS) or OS in the overall study population compared with chemotherapy alone.24 After a median follow-up of 55 months, no BV-associated improvement in DFS (HR 0.93, P = 0.34) or OS (HR 0.96, P = 0.64) was noted. Using a 15-month landmark for analysis, DFS was improved for the BV combination treatment group prior to cut-off (HR 0.61, P < 0.0001), but marginally worse after the 15-months (HR 1.20, P = 0.052). Although statistically non-significant, patients who received BV had poorer survival following relapse and a longer time to recurrence compared with those who did not. It should be noted that during BV therapy, a transient positive effect was observed. One hypothesis is that BV therapy delayed, but did not prevent, disease recurrence. The investigators reported that exposure to BV was not associated with development of more aggressive tumor behavior upon disease recurrence. Additionally, the AVANT adjuvant trial conducted in Europe confirmed these results when no improvement in DFS in patients with stage III disease, the primary endpoint, was found when BV was added to FOLFFOX or XELOX.25 This final efficacy analysis also found that BV in combination with chemotherapy yielded a higher number of relapses and shorter survival than chemotherapy alone. These findings do not support the use of BV in the adjuvant setting for patients with stage II or III. In light of the negative results from trials of antiangiogenic agents as potential adjuvant therapy, the E5202 and QUASAR2 trials have been closed.

Ziv-aflibercept, the second FDA-approved antiangiogenic agent for treatment of mCRC, is a fusion protein made from two VEGF-binding domains from VEGFR-1 and VEGFR-2 linked to the Fc portion of IgG, can bind all human isoforms of VEGF-A, VEGF-B and PIGF and prevent their interaction with VEGFR-1 and -2.26 The pivotal VELOUR study, a randomized, placebo-controlled phase 3 trial, evaluated ziv-aflibercept as second-line therapy in combination with FOLFOXIRI.27 Results from the VELOUR study demonstrated that adding ziv-aflibercept to FOLFIRI yielded a modest, significant increase in median PFS (6.9 vs. 4.7 months; HR 0.758, P < 0.0001) and median OS (13.5 vs. 12.1 months; HR 0.817, P = 0.0032).27 Treatment with ziv-aflibercept was also associated with an increase in the ORR (19.8% versus 11.1%, P = 0.0001). Importantly, previously BV-treated and BV-naïve patients benefited similarly from the addition of ziv-aflibercept to FOLFIRI in terms of OS (HR 0.862 and HR 0.788, respectively) and PFS (HR 0.661 and HR 0.797, respectively). The results of the VELOUR study led to the FDA approval on August 3, 2012 of ziv-aflibercept in combination with FOLFIRI for second line therapy for metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.28

The AFFIRM trial is a randomized phase 2 trial that studied modified FOLFOX6 in combination with ziv-aflibercept or placebo as first-line therapy for metastatic colorectal cancer.29 In the experimental arm, a total of 119 patients were treated with ziv-aflibercept 4 mg/kg plus mFOLFOX6 every two weeks. The primary outcome measure was PFS at 12-months. In the experimental arm, PFS12 was 25.8% (95% CI: 17.2-34.4) and 21.2% (95% CI: 12.2-30.3) for the placebo arm. Response rate was 49.1% (95% CI: 39.7-58.6) in the experimental arm and 45.9% (95% CI: 36.4-55.7) in the placebo, and median PFS was 8.48 months (95% CI: 7.89-9.92) in the experimental arm and 8.77 months (95% CI: 7.62-9.27) in the placebo arm. Grade 3 or 4 adverse events in the experimental arm with a greater than 5% incidence than in the placebo arm were hypertension, proteinuria, neutropenia, diarrhea, and infections. The study was not powered to compare the 2 arms.

On September 27, 2012, regorafenib became the third antiangiogenic agent approved by the FDA to treat metastatic colorectal cancer.30 Reforafenib is approved for patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Regorafenib is an oral TKI of angiogenic (VEGFR-1, -2, -3, TIE-2), stromal (PDGFR-β, FGFR1), and oncogenic kinases (KIT, RET, BRAF). Its antitumor activity was established in preclinical studies that demonstrated its ability to suppress tumor growth and decrease microvessel area in colorectal xenografts.31 A subsequent phase 1 study assessed the efficacy and safety of regorafenib in 38 patients with heavily pretreated metastatic colorectal cancer.32 The patients had a median of 4 previous lines of systemic therapy for metastatic disease, with a range of 0 to 7 lines. In the 27 patients evaluable for response, there was one confirmed PR (4%) and 19 patients with SD (70%), giving a disease control rate at 2 months (PR or SD) of 74%. PD was best response in 7 patients (26%). Of the 20 patients who achieved either PR or SD, 45% had received previous treatment with cetuximab or panitumumab, 45% with bevacizumab, 85% with oxaliplatin and 80% with irinotecan. Median PFS was 107 days (95% CI, 66–161), and 13 patients experienced tumor shrinkage of any percentage.

The randomized, placebo-controlled phase 3 trial of regorafenib, the CORRECT trial, compared its efficacy and tolerability with best
supportive care (BSC) in patients with mCRC who have failed all previous standard therapy. Results from an interim analysis indicated that treatment with regorafenib 160 mg (3 weeks on, 1 week off) was associated with a higher disease control rate than with BSC (41.0% vs. 15%, P < .0001).31 Although modest, a significantly longer median PFS (1.9 vs. 1.7 months; HR 0.49, P < .0001) and median OS (6.4 vs. 5.0 months; HR 0.77, P = 0.0052) was noted in patients who had received regorafenib. The regorafenib-associated survival benefit was comparable for most sub-groups analyzed and KRAS mutation status (Y or N), with the exception that patients having primary, including prior lines of therapy (≤ 3 vs. > 3) tumor sites in the colon benefitted more (HR 0.70) than those with primary tumors in the rectum (HR 0.95) or in both colon and rectum (HR 1.09). KRAS subgroup analysis (wt vs. mutant) demonstrated that there was a considerable OS (HR 0.65 vs. HR 0.87) and PFS benefit (HR 0.48 vs. HR 0.53) associated with regorafenib treatment. Regorafenib-related grade 3/4 adverse events reported for the trial were hand-foot skin reaction (17% vs. < 1%), fatigue (10% vs. 5%), hypertension (7% vs. 1%), diarrhea (7% vs. 1%), and rash/desquamation (6% vs. 0%). The percentage of patients who suffered treatment-related grade 5 adverse events (bleeding) was higher in regorafenib-treated patients (1.0% vs. 0%).

**Antiangiogenic Agents in Clinical Development for CRC**

There are several antiangiogenic agents currently undergoing clinical development as potential therapy for patients with mCRC. Another fully human monoclonal antibody, ramucirumab, functions as an antiangiogenic agent by targeting VEGFR-2 and preventing its interaction with VEGF. In contrast to BV, which targets VEGF-A and prevents it from interacting with VEGFR-1 or -2, ramucirumab specifically disrupts VEGFR-2 ligand binding, and blocks all isoforms of VEGF from binding to VEGFR-2.8,9 In preclinical studies, ramucirumab showed anti-tumor activity in animal models of colorectal cancer, lung, mammary, glioblastoma, and renal cell cancer.45,46 A phase 1 dose-finding study of single agent ramucirumab found that it could elicit disease control in 30% (PR and SD; 11 of 37 patients with measureable disease) of patients with advanced solid tumors that lasted at least 6 months across a range of doses (2 to 16 mg/kg).46 Although the study found a maximum tolerable dose of 13 mg/kg, PK clearance appeared saturated at 8 mg/kg. As a result, the 8 mg/kg dose was selected for subsequent clinical trials.

Results were recently presented from an open-label phase 2 trial assessing the safety and efficacy of ramucirumab in combination with FOLFIRI in 48 patients with treatment-naïve mCRC.37 The median PFS was 11.5 months with a 48% one-year PFS rate and a 85% one-year OS rate. Additionally the ORR was 67%, disease control rate was 94%, and the duration of response was 11.0 months. The most frequently observed ramucirumab-related grade 3/4 adverse events were hypertension (15%) and diarrhea (2%). Two patients on therapy died due to acute MI or cardiopulmonary arrest.

A randomized, double-blind phase 3 has been initiated to compare the efficacy of FOLFIRI in combination with ramucirumab or placebo as second-line therapy for mCRC following first line BV plus chemotherapy. The primary objective of the trial is OS and secondary objectives include PFS, ORR and safety.48

Despite the success of regorafenib, results from clinical trials of small molecule TKIs in mCRC have been disappointing. Published results of the HORIZON 3, a randomized phase 3 trial of the VEGFR TKI cediranib comparing mFOLFOX6 (modified dosing regime of leucovorin/S-FU/oxaliplatin) /cediranib and mFOLFOX6/ BV as first-line therapy for patients with mCRC, demonstrated no significant difference in median PFS (HR, 1.10, P = 0.119) and median OS (HR, 0.95, P = .541) between the two groups and failed to meet the predetermined value for non-inferiority.49 Results from a second front-line phase 3 trial comparing FOLFIRI/CAPOX (capcitabine and oxaliplatin) with cediranib and FOLFOX/CAPOX with placebo in patients with mCRC, HORIZON 2, mirrored those from HORIZON 3.40 Brivanib, a small molecule TKI that inhibits the signaling of VEGF and FGF, exhibited antitumor activity in vitro and in a phase 1 study in combination with cetuximab.41-43 Brivanib/cetuximab in combination is currently under investigation in a phase 3 trial for previously treated patients with KRAS wild type, advanced mCRC.44 Recently reported results, however, indicated that despite a significantly longer median PFS (5.0 vs. 3.4 months; HR 0.72, P < 0.0001) and higher PR rate (13.6% vs. 7.2%; P = 0.004) for patients treated with brivanib/cetuximab compared to placebo/cetuximab, brivanib was associated with no significant impact on median OS (HR 0.88, P = 0.12), the trial’s primary endpoint.45 Sunitinib, another small molecule TKI inhibitor of PDGFR, VEGFR1-3, KIT, FLT3 and RET, also failed to demonstrate activity in treating mCRC when combined with mFOLFOX6 or FOLFIRI as first-line therapy. A phase 2b study revealed that addition of sunitinib to mFOLFOX6 led to shorter median PFS when compared to mFOLFOX6/BV (9.1 vs. 11.2 months, HR = .96), and a phase 3 trial found that treatment with FOLFIRI/sunitinib was associated with shorter median PFS than FOLFIRI/placebo (7.8 vs. 8.4, P = .807).46

Numerous agents currently in clinical development for mCRC target the VEGF/VEGFR signaling pathway and its downstream effectors, PI3K and Ras/Raf. New agents with novel mechanisms of action and molecular targets are also being evaluated for activity in this disease and treatment setting.

BIBF 1120 is a novel kinase inhibitor that concurrently blocks the activity of three families of growth factor receptors, VEGFR-1, -2, -3, PDGFR- and -8, and FGF-1, -2, -3 and was evaluated in combination with mFOLFOX6 and compared with BV plus mFOLFOX6 as first-line treatment in 126 patients with mCRC.48,49 Interim results from this randomized, open label phase 2 trial showed a median PFS of 10.6 months for both treatment arms. At 9 months, the PFS rate was 63% for the BIBF arm versus 69% for the BV arm, while the ORR was 61.2% for the BIBF arm and 53.7% in the BV arm. There was a lower frequency of serious adverse events in the BIBF 1120 arm (34.1%) versus the BV arm (53.7%).

Tas-102, a novel formulation of the fluorinated pyrimidine analogue triflurorothymidine and an inhibitor of the angiogenic enzyme thymidine phosphorylase, was found to stabilize disease in patients with refractory solid tumors after heavy pretreatment with 5-FU.50,51 In a double-blind, randomized, placebo-controlled phase 2 trial, patients who received Tas-102 (35 mg/m² twice a day in a 28-day cycle [2-week cycle of 5 days of treatment followed by a 2-day rest period], and then a 14-day rest period) survived significantly longer than those who received placebo (9.0 vs. 6.6 months; HR 0.56, P = 0.0011).52 In terms of survival, patients with tumors having either wild type or mutant KRAS benefitted from Tas-102 (HR 0.70
and 0.44, respectively). Median PFS was longer for patients who received Tas-102 (2.0 vs. 1.0 months; HR 0.41, P < 0.0001) and the rate of disease control was higher as well (43% vs. 11%, P < 0.0001). Serious adverse events were reported for 19% of patients treated with Tas-102, compared to 9% in the placebo group, and no treatment-related deaths were noted for either group. The phase 3 placebo-controlled trial of Tas-102 in patients with refractory mCRC, RECOURSE, is currently underway and a primary completion date is estimated for June 2014.\textsuperscript{4}

Tivozanib, a selective inhibitor of VEGFR-1, -2, -3, has exhibited antitumor activity colon xenografts and in patients with mCRC at 1.5 mg daily four weeks on/two weeks off dosing regimen.\textsuperscript{5,6} Results from a phase 1b dose-escalation trial of tivozanib in combination with FOLFOX in patients with advanced gastrointestinal cancers concluded that tivozanib 1.5 mg/day was safe and tolerable.\textsuperscript{6} A phase 2 study comparing tivozanib and BV head-to-head as first-line combination partners with FOLFOX has been implemented in patients with mCRC.\textsuperscript{57} The primary outcome measure for the trial is PFS and secondary measures include OS, ORR, duration of response, and time to treatment failure. The combination of tivozanib and capcitabine is being explored in a phase 1 trial in patients with advanced solid tumors.\textsuperscript{58}

CT-322 is a novel antiangiogenic composed of human portions of human fibronectin that interfere with the action of VEGFR-2.\textsuperscript{59} CT-322 is able to block VEGF-induced phosphorylation of VEGFR-2 and significantly inhibit tumor growth and normalize vasculature in CRC xenografts.\textsuperscript{60} A phase 1 study of CT-322 in patients with advanced solid tumors demonstrated that at the MTD of 2 mg/kg per week, it had promising antitumor activity with an acceptable tolerability profile.\textsuperscript{61} Results are awaited from a recently completed randomized, double-blind phase 2 study comparing CT-322 in combination with FOLFIRI and BV/FOLFIRI as second-line therapy for patients with mCRC.\textsuperscript{62}

Axitinib, a TKI that inhibits VEGFR1-3, has demonstrated antiangiogenic activity and is an FDA approved for treating patients with advanced renal cell carcinoma after prior failure of TKI therapy.\textsuperscript{53} A phase 1 study of axitinib in combination with FOLFOX/BV in patient with solid tumors indicated that there was no pharmacokinetic interaction between axitinib and its combination partners, and the authors recommended axitinib 5mg in combination with BV 1 or 2 mg/kg with FOLFOX for future analyses based upon tolerability.\textsuperscript{64} An open-label, randomized phase 2 trial was comparing the efficacy of axitinib 5 mg twice daily and BV 5 mg/kg every two weeks in combination with either FOLFOX or FOFIGI failed to meet is primary endpoint of PFS.\textsuperscript{65} No significant difference in median PFS or OS between the axitinib and BV arms, with FOLFOX or FOFIGI, was found. Another randomized phase 2 study comparing FOLFOX/BV 5 mg/kg every two weeks, FOLFOX/axitinib 5 mg twice daily starting dose, and FOLFOX/BV 2 mg/kg every two weeks/axitinib 5 mg twice daily as first-line therapy for patients with mCRC has been initiated and is currently ongoing.\textsuperscript{66}

Dovitinib (TKI258) is TKI that suppresses the signaling activity of VEGFR1/2, FGFR1/3, PDGFRα, FLT3, and KIT.\textsuperscript{67} A phase 1/2 trial of dovitinib in patients with advanced melanoma found that dovitinib 400 mg/day had an acceptable toxicity profile and inhibited FGFR and VEGFR signaling.\textsuperscript{68} A phase 2 trial of dovitinib has been planned for the treatment of advanced lung and CRC and includes a pilot study of FGFR biomarkers to assess activity in treated patients.\textsuperscript{69}

IMC-18F1 is a human monoclonal antibody that targets VEGFR-1 and has demonstrated ability to inhibit tumor growth in breast cancer xenograft models concomitant with suppression of Akt activation.\textsuperscript{70} A phase 1 dose-finding study of IMC-18F1 in patients with advanced solid malignancies that have failed standard therapy identified 15 mg/kg every two weeks and 20 mg/kg every three weeks as the schedules with supportive PK and toxicity profiles.\textsuperscript{71} The most commonly reported adverse events were fatigue and nausea. An open-label, randomized phase 2 study comparing the efficacy and safety of IMC-1121B and IMC-18F1 in combination with FOLFOX as second-line therapy after failure on an irinotecan-containing regimen in patients with mCRC has been initiated and is currently ongoing.\textsuperscript{72}

A novel targeted agent, MEGF0444A, is a human monoclonal antibody that binds and inhibits epidermal growth factor-like domain 7 (EGF7L) extracellular matrix protein that promotes endothelial cell differentiation, proliferation and migration in proliferating, and not mature, tissue.\textsuperscript{73} A phase 1a open-label, dose-escalation study of single agent MEGF0444A to evaluate its tolerability in patients with advanced solid tumors found a low rate of transfusion reactions but no tumor response or dose-limiting toxicities associated with up to the highest planned dose, 15 mg/kg.\textsuperscript{74} Interestingly, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) revealed a decrease in circulating progenitor cells (CPCs), suggesting potential vascular targeting. A randomized, double-blind phase 2 trial comparing MEGF0444A and placebo in combination with BV and FOLFOX as first-line therapy for patients with mCRC, CONGO, is currently ongoing.\textsuperscript{75} The primary endpoint for the trial is PFS and the estimated completion date is March 2015.

Ornatuzumab is a monoclonal antibody that binds to and suppresses the Met receptor and hepatocyte growth factor (HGF) associated signaling.\textsuperscript{76} It is postulated that overactivation of the HGF/Met pathway in tumor cells might promote angiogenesis by non-physiologic secretion of HGF-associated proteins, such as VEGF-A, into the tumor microenvironment.\textsuperscript{77} A phase 1 study of ornatuzumab in combination with BV in patients with advanced solid malignancies found that single agent ornatuzumab and ornatuzumab/BV were well tolerated and in the patients treated with combination therapy, no pharmacokinetic interaction between the two agents was noted.\textsuperscript{78} A placebo-controlled phase 2 trial has been implemented to evaluate the addition of ornatuzumab to first-line FOLFOX/BV therapy in patients with mCRC.\textsuperscript{79}

Several other agents in clinical development involve non-classical molecular targets as potential antiangiogenic agents. Recently reported results from a phase 1 study of EMD 525797, an antibody targeting avb integrins, in combination with cetuximab and irinotecan as second-line therapy for patients with KRAS wild-type mCRC concluded that the combination was well-tolerated and exhibited anti-tumor activity in this patient population.\textsuperscript{80} A randomized phase 2 study is currently underway.\textsuperscript{81} E7820, a novel antiangiogenic oral sulfonamide derivative, inhibits a2-integrin expression and vascular morphogenesis in a dose-dependent manner.\textsuperscript{82} After a phase 1 study demonstrated tolerability in patients with advanced malignancies,\textsuperscript{83} a phase 2 trial was initiated that assessed its activity in combination with cetuximab in patients with refractory mCRC.\textsuperscript{84} Early reports from this trial indicate the combination has a tolerable toxicity profile and led to a median OS of 9.6 months and an ORR of 3.6%. An ongoing phase 1/2 study compares E7820/FOLFIRI and FOLFIRI as second-line therapy in patients with advanced CRC.\textsuperscript{85}
A phase 1 dose-escalation study has been initiated to evaluate the safety of VGX-100, a monoclonal antibody that blocks VEGF-C, when combined with BV in patients with advanced solid tumors.96,97

Biomarkers for Anti-Angiogenic Therapy in Colorectal Cancer

The majority of clinical studies of antiangiogenic agents have identified potential prognostic rather than predictive biomarkers. Numerous biomarkers associated with angiogenesis have been correlated with patient outcome in clinical trials of mCRC. Elevated serum VEGF levels have been associated with tumor size and volume as well as poorer prognosis.98 Microvessel density measured using CD31 or CD34 immunohistochemistry has been associated with poor prognosis in CRC.99

The current use of KRAS mutational status as a predictive biomarker for response to EGFR-targeted agents, such as cetuximab and erlotinib, is a powerful example of a predictive biomarker; patients with activating mutations in KRAS do not benefit from treatment with EGFR-targeted agents.90 KRAS, and its signaling partner downstream of receptor tyrosine kinase activation, BRAF, are associated with poor prognosis, but plays no role in predicting benefit from antiangiogenic and other types of agents.91 Indeed, patients with wild-type and mutant KRAS benefitted from treatment with BV (HR 0.44 and 0.41) and regorafenib (HR 0.48 and 0.53).33,92

Along these lines, although BV/chemotherapy is standard clinical practice for first-line therapy for mCRC, identifying patients who will most benefit, or who will not benefit, from antiangiogenic agents will be an important advancement in the management of mCRC. The search for predictive biomarkers is currently underway in clinical trials of antiangiogenic agents in treating patients with CRC, but predictive markers have yet to be clinically validated. Serum levels of VEGF have been studied extensively across tumor types since high levels of serum VEGF have correlated with metastasis and dissemination of disease. Plasma levels of VEGF are often substantially elevated after exposure to anti-VEGF therapy and drop once therapy is discontinued.93 This finding has been observed with BV, and a meta-analysis assessed the value of circulating VEGF level as a prognostic biomarker for outcome and a predictive biomarker of benefit from BV-containing treatment across five randomized trials, including four phase 3 studies.94 The analysis included VEGF ELISA of archived baseline plasma samples from 1,816 patients with metastatic colorectal cancer, NSCLC, and renal cell carcinoma. The researchers found that higher baseline levels of circulating VEGF was associated with shortened PFS and OS in all tumor types regardless of exposure to BV, suggesting that VEGF levels are a prognostic and not predictive in this treatment setting. In a subset of matched archival tumor samples analyzed for VEGF-A expression using in situ hybridization, baseline circulating plasma levels of VEGF did not correlate with tumor expression of VEGF.

Hypertension has been proposed as a noninvasive biomarker of response to anti-angiogenic therapy. A primary hypothesis for this effect is that VEGF inhibition by these agents reduces the synthesis of nitric oxide in the capillary walls, leading to increased vasoconstriction and elevated blood pressure.95 A number of clinical trials in breast, colorectal, pancreatic, lung, and kidney cancer have found that patients who experience higher levels of hypertension show improved response rates and increased PFS and OS.96 However, a recent meta-analysis that included approximately 5,900 patients across six studies of metastatic cancer treated with bevacizumab failed to confirm a correlation between higher blood pressure and PFS or OS in most of the studies.97 Only one study in patients with colorectal cancer showed that hypertension occurring in the first 60 days of treatment predicted superior PFS and OS in the bevacizumab-treated group, and worse OS in the control group. At the same time, more recent studies involving the TKIs axitinib (in a variety of solid tumors) and sunitinib (in metastatic renal cell carcinoma) have found that increases in systolic and/or diastolic blood pressure were significantly correlated with improved PFS and OS.98

Changes in serum cytokine levels from baseline after the initiation of treatment with antiangiogenic therapy have been extensively studied. A phase 2 study with 43 patients followed changes in serum levels of 37 circulating angiogenic factors (CAF) from baseline after initiation of first-line therapy with FOLFI/IV in patients with mCRC.99 Baseline elevated interleukin-8 (IL-8; > 3.7 pg/mL) was associated with shorter median PFS (11.0 vs. 15.1 months; HR 2.05, P = .03) and correlated with increased tumor volume (Spearman r = 0.62; P < .001). Another study reported that baseline CA19.9 levels (> vs. < normal) were independently associated with PFS in patients treated with FOLFI/IV as first-line therapy for mCRC.100 Patients with abnormal CA19.9 benefitted significantly from BV and patients with normal levels did not.

Numerous studies have approached identifying potential predictive biomarkers for antiangiogenic therapy from the genetic perspective and have focused on differences in the DNA sequence of candidate biomarker genes. In a retrospective analysis conducted in 119 patients treated between 2004 and 2009 with BV/FOFIFOX or BV/XELOX as first-line therapy for mCRC in multiple institutions, SNPs in 26 candidate genes of VEGF-dependent and -independent angiogenesis pathways were assessed for association with PFS and RR. This study identified the CXCR1 rs2234671 SNP as a potential predictive marker for response to BV.101 However, a subsequent international, prospective study of SNPs in patients treated with BV/ FOLFI/IV failed to validate any previously identified variants, leading the investigators to conclude that future studies of angiogenic biomarkers be assessed using various approaches rather than focusing on differences in genetic sequence.102

Antiangiogenic Escape Mechanisms and Clinical Management

Antiangiogenic escape—the resumption of tumor growth and revascularization in the presence of sustained VEGF inhibition—has been well documented and may be attributed to the induction of alternate hypoxia-dependent proangiogenic factors and signaling pathways among other physiological mechanisms.103 The alternate angiogenic factors besides VEGF that cause this re-establishment of angiogenesis have not been definitively identified, but there have been several studies suggesting the association of several proangiogenic cytokines with acquired resistance to BV. Importantly, results from a prospective phase 2 study of FOLFI/IV indicated that circulating factors that play a role in angiogenesis and myeloid recruitment increased prior to radiologic progression of disease.99 Serum levels of FGF (P = 0.046), HGF (hepatocyte growth factor) (P = 0.046), PlGF, SDF-1 (stromal-derived factor-1) (P = 0.04), and macrophage chemo-attractant protein-3 (P < 0.001) increased from baseline at the time of antiangiogenic escape. Mounting evidence
Antiangiogenic Combination Strategies for Colorectal Cancer

An enduring strategy to treating metastatic disease and overcoming escape from angiogenic suppression is to pair antiangiogenic agents, sequentially or in series, with other targeted biologics to disrupt multiple pathways necessary for tumor growth and survival. In the treatment of mCRC, clinical investigation of dual biologic therapy originally focused on the combination of BV with the EGFR-targeted antibody, cetuximab, but clinical trials have yielded primarily negative results and currently are not being pursued as a potential therapeutic strategy for patients with mCRC. Despite initially promising results from the BOND-2 phase 2 trial, which found that the dual biologic regimen was able to elicit a response in patients both with and without irinotecan (37% vs. 20%), this did not translate to phase 3 clinical trials.106 The PACCE phase 3 trial evaluating first line oxaliplatin- or irinotecan-based chemotherapy regimens containing BV (Ox/BV and Iri/BV, respectively) in combination with placebo or panitumumab, a fully human monoclonal antibody that targets the EGFR, was discontinued after a planned interim revealed that the addition of panitumumab to Ox/BV was associated with shorter median PFS (HR 1.27) and median OS (HR 1.43).107 Adding panitumumab to Iri/BV also led to shorter median PFS (HR 1.19) and median OS (HR 1.42). A second phase 3 trial of dual biologics as first-line therapy for mCRC, the CAIRO-2 trial comparing CAPOX/BV with and without cetuximab, yielded results similar to PACCE.108 The investigators found that median PFS and OS were shorter in patients treated with CAPOX/BV plus cetuximab than in those treated with CAPOX/BV (HR 1.22). Grade 3 or 4 serious events were increased in the anti-EGFR/BV combination arms in both studies.

A different approach to therapy with dual VEGF/EGFR blockade was undertaken in a French phase 3 trial (GERCOR DREAM), that assessed the efficacy and tolerability of BV plus erlotinib, a small molecule inhibitor of EGFR, vs. BV alone as maintenance therapy for patients with mCRC who did not progress on standard first-line BV-based induction therapy (FOLFOX/BV, XELOX2/BV or FOLFIRI/BV).109 The investigators found that patients treated with BV/erlotinib maintenance therapy were progression-free for significantly longer after randomization than those treated with BV maintenance therapy (5.7 vs. 4.6 months; HR 0.73, P = .005). Median PFS from inclusion was also significantly longer in patients treated with BV/erlotinib maintenance therapy (10.2 vs. 9.2 months; HR 0.73, P = 0.0045). Toxicity profiles for both maintenance therapies were comparable, with a substantially higher incidence of grade 3 – 4 diarrhea and grade 3 skin toxicity in patients who received BV/erlotinib. Overall survival data are not yet available.

Several other combination strategies of targeted therapies have been investigated in patients with mCRC who have failed prior lines of therapy with BV-containing or anti-EGFR antibody-containing regimens. Two approaches explored include combining dual VEGF inhibitors or combining a VEGF inhibitor with an inhibitor of mammalian target of rapamycin (mTOR). The N054C phase 2 trial evaluated BV plus sorafenib, a small molecule multi-kinase inhibitor that targets VEGFR-1, -2, -3, PDGFR, RAF, KIT, and RET, as salvage therapy for patients with mCRC.110 Although the combination showed initial signs of activity, toxicities were fairly high. Among 73 patients with available toxicity data, 55% experienced at least one grade 3 or 4 adverse event. In the second phase 2 study, 50 patients with heavily pretreated mCRC received a combination of BV plus the mTOR inhibitor, everolimus, until progression.111 Median PFS and OS for the trial were 2.3 and 8.1 months, respectively. Twenty-six percent of patients achieved disease control for over 6 months. Serious adverse events (grade ≥3) included hypertension (14%), fistula/abscess/perforation (8%), mucositis (6%), and hemorrhage (2%). This toxicity profile may indicate that the BV/everolimus combination therapy may have wound healing or mucosal damage risk.

Combining therapies to block multiple pathways downstream of VEGF is an approach that is gaining momentum. Studies are underway to evaluate the dual targeting of the RAF/MEK/ERK and PI3K/AKT signaling pathways, as both pathways can be disregulated in CRC. MK-2206, an inhibitor of AKT, is currently being investigated in combination with selumetinib (AZD6244), a MEK inhibitor, as therapy for patients with advanced CRC.112 A preliminary report of this combination therapy in patients with disease refractory to standard therapy resulted in stabilized disease in 2 of 9 patients. Of note, when used in combination, dose reductions of both agents were necessary due to toxicity. Only half of the treated patients experienced biologically significant inhibition of one pharmacodynamic biomarker, and no patient had >70% inhibition of both pathways when biochemical targets were tested, indicating that adequate inhibition of both pathways may be limited by the toxicity of combining the two agents.113

An interesting antiangiogenic combination therapy currently beginning clinical evaluation for the treatment of advanced solid malignancies includes both BV and the VEGF-C-targeted monoclonal antibody, VGX-100. VEGF-C binds and activates both VEGF-R2 and -3 and therefore plays a role in angiogenesis/vasculogenesis and lymphangiogenesis.114 Studies of VEGF-C have suggested that loss of its activity in colon cancer cell lines decelerates tumor growth and inhibits metastasis, and that VEGF-C blockade suppresses both blood and lymphatic vessel growth.115 A phase 1 dose-escalation trial of VXG-100 with targeted enrollment of 40 patients was initiated in January 2012 to assess the tolerability of VXG-100 and VXG-100/BV in patients with advanced solid tumors.116

Side Effects of Antiangiogenic Therapy in Colorectal Cancer

Antiangiogenic treatments are well tolerated relative to cytotoxic chemotherapy and their duration of use is not typically limited by toxicities. Nonetheless, agents that function via blocking VEGF-related signaling are associated with a number of distinct adverse effects that require careful monitoring and medical management. Hypertension is the primary side effect of systemic VEGF inhibition and can usually be effectively managed with standard anti-hypertensive medications. In phase 3 trials in mCRC, 11-16% of patients treated with first-line BV plus chemotherapy developed grade 3 hypertension requiring aggressive medical therapy.117 The true
incidence of hypertension, however, may be considerably higher depending on the chemotherapy paired with BV and the hypertension criteria used.116

There is some evidence that onset of hypertension during anti-VEGF therapy may be predictive of clinical response. Two small retrospective analyses found improved outcomes in mCRC patients who developed hypertension while on BV.117,118 In one of these studies, patients who developed arterial hypertension during treatment had a significant improvement in PFS compared with those who did not (15.1 vs. 8.3 months; P = 0.04).119 In a much larger analysis involving approximately 5,900 patients across six clinical trials of BV in various metastatic cancers (CRC, breast, non-small cell lung, and renal cell carcinoma), in five of six studies, hypertension during treatment was not predictive of clinical benefit nor disease course for either BV or control treatment arms.97 However, in the one study that found a positive correlation—a phase 3 trial in mCRC (AVF2107g)—hypertension predicted longer PFS and OS in the BV arm, and shorter OS in the control arm.

Proteinuria, in a dose-dependent manner, is the second most common adverse event associated with systemic VEGF inhibition therapy, with an overall incidence of 23-38% in mCRC patients treated with BV.119 A recent report documented several cases of renal thrombotic microangiopathy in patients receiving VEGF inhibitors.120 This side effect appears to be an on-target effect of VEGF inhibition on the glomerular endothelium, and although it is sometimes reversible upon discontinuation of treatment, proteinuria persistence in not uncommon.

Other serious but less frequent adverse events documented in patients on BV include thromboembolic (primarily arterial) and bleeding events, gastrointestinal perforation, delayed wound healing, and nasal septum perforation. A large meta-analysis of randomized clinical trials of BV as therapy for advanced solid tumors found that compared to chemotherapy alone, the addition of BV was associated with an increased risk (relative risk 1.33) of FAEs (fatal adverse events). The associations between BV use and dose or tumor type were not statistically significant.121 However, the associated risk of a FAEs and chemotherapy partners was statistically significant, and treatment with BV in combination with taxanes or platinum agents carried a much higher relative risk than when in combination with other chemotherapy agents (RR, 3.49 vs. 0.85). This meta-analysis reported that the most common causes of FAEs were hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%).

A recently reported meta-analysis from the 2012 Annual Meeting of the American Society of Clinical Oncology evaluated the incidence of adverse events in 2,662 patients with metastatic colorectal, lung and pancreatic cancer treated with ziv-aflibercept in combination with chemotherapy in three double-blind, placebo-controlled phase 3 trials.122 Compared to placebo, treatment with ziv-aflibercept was associated with statistically significant increased risk of grade 3 hypertension (RR, 9.21; P < 0.05), proteinuria (RR, 8.37; P < 0.05), hemorrhage (RR, 2.04; P < 0.05), proteinuria (RR, 2.04; P < 0.05). Additionally, patients treated with ziv-aflibercept experienced grade 4 hypertension (0.4%) and nephrotic syndrome (0.5%). Ziv-aflibercept was not associated with an increase in venous thromboembolic events compared to patients who received placebo.

Future Directions

Antiangiogenic agents represent an important part of therapeutic regimens across all lines of treatment for mCRC. Standard first-line therapy for mCRC includes BV and the FDA has newly approved the addition of ziv-aflibercept to second-line therapy in combination with FOLFIRI and single agent regorafenib as salvage therapy for refractory patients. In contrast, it is notable that antiangiogenic therapy has no role in the adjuvant treatment setting of CRC. Ongoing questions regarding the use of antiangiogenic agents in the treatment of advanced CRC include 1) can we find and clinically validate predictive biomarkers for patient selection; 2) what is the appropriate duration of VEGF suppression as part of first-line, maintenance, and second-line therapy and 3) how do we identify and target pathways involved in resistance to therapy using these agents? The laboratory and clinical investigation that will help answer these questions remains ongoing.

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colorectal cancer. There is a large
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review all of this important information in this rapidly expanding field. Clinicians
are not educating patients about the side
effects of antiangiogenic therapy and
referring patients to specialists to optimize
management of side effects and increasing
patient outcomes. There are many clinical
trials out there researching several new
targeted therapies, providing clinicians
with this updated information will help
increase enrollment in these clinical trials
and can lead to an increase in the number of
treatment options with fewer side effects.
New treatment approaches are therefore
urgently required to improve outcome in
this disease and one promising strategy
to have emerged has been the study of
angiogenesis in colorectal cancer and the
role of modulators of angiogenesis in its
treatment.

PROGRAM LEARNING OBJECTIVES
At the completion of this activity, participants should be able to:

• Describe the role of tumor angiogenesis as both a disease mechanism and therapeutic target in mCRC.
• Explain how antiangiogenic therapies may be integrated into current mCRC treatment regimens, including front-line, second-line, maintenance, and adjuvant therapy settings.
• Discuss clinical efficacy and safety data from recent studies on antiangiogenic therapies for mCRC.
• Describe common safety concerns of antiangiogenic cancer therapy and their management.
• Explain strategies for addressing progressive disease, including the use of combination antiangiogenic treatment or new therapy targets under investigation.

ACTIVITY GOAL
This activity is designed to address the following ABMS / IOM competencies: Patient Care and Medical Knowledge

METHOD OF PARTICIPATION
There are no fees for participating in and receiving credit for this online educational activity. The participant should, in order, read the objectives and faculty disclosures, review the educational content, answer
the multiple-choice post-test and complete the evaluation. This program is available in PDF format accessible from the Angiogenesis Foundation’s website (http://www.angio.org) in the CME section. A print version is also available; for more information contact outreach@angio.org. After reviewing the material, CME credits are available through the Angiogenesis Foundation’s website (http://www.cmeonline.org) by selecting the name of the program (registration required). Course code: 2013CRC

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COURSE FACULTY
William Li, MD
Dartmouth Medical College

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Medical writer.
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Erin Grothey, M.S.
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DISCUSSION OF UNLABELLED USE
This CME activity contains discussion of published and/or investigational use of: aflibercept (Zaltrap®), Axitinib (Inlyta®), bevacizumab (Avastin®), BIBF 1120 (Vargatef®), brivanib, cediranib, CT-322 (Adnectin®), Dovitinib (TKI258), EMD 525797, IMC-18F1, MEGF0444A, MM-2206, Onatzumab (MetMab), ramucirumab, regorafenib (Stivarga®), sorafenib ( Nexavar®), sunitinib (Sutent®), Tas-102, and Tivozanib.

TOPICS AND EDUCATIONAL CONTENT
Antiangiogenic therapy for advanced colorectal cancer:
• FDA Approved Antiangiogenic Agents for CRC
• Antiangiogenic Agents in Clinical Development for CRC
• Biomarkers for Anti-Angiogenic Therapy in Colorectal Cancer
• Antiangiogenic Escape Mechanisms and Clinical Management
• Antiangiogenic Combination Strategies for Colorectal Cancer
• Side Effects
• Future directions

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