Update on Antiangiogenic Therapy for Metastatic Colorectal Cancer

In the United States, metastatic colorectal cancer (mCRC) is the third-leading cause of cancer-related deaths. More than 136,830 new cases and 50,310 deaths from the disease are expected in 2014.1 Deaths from mCRC overall have been decreasing due to the routine use of colonoscopy as a screening tool and as a method for excising precursor lesions. Furthermore, there has been an improvement in therapies, meaning that a higher percentage of patients now have a curative chance with therapy and are candidates for surgery. However, for patients with mCRC who are not surgical candidates, improvements in the standard chemotherapy regimens have incrementally improved the median life expectancy over the past ten years, but at the cost of considerable toxicities. Overall prognosis remains poor for this group of non-surgical mCRC candidates, which represents over 50% of patients diagnosed with disseminated disease.2,3

In 2004, there was a significant change in the therapeutic outlook for patients with mCRC 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, various clinical trials have demonstrated efficacy for BV in combination with several chemotherapeutic backbones, such as leucovorin/5-FU/oxaliplatin (FOLFOX) and infusional leucovorin/5-FU/irinotecan (FOLFIRI) regimens; these regimens can function in both front-line and subsequent treatment settings.4-7

Additional changes in the therapeutic landscape of mCRC have occurred with the FDA’s recent approval of two other medications: (1) ziv-aflibercept, for use in combination with FOLFIRI in patients with progressive disease after prior treatment with an oxaliplatin-containing regimen, and (2) 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. The current treatment algorithms need to be updated to accommodate BV, ziv-aflibercept and regorafenib as components of potential therapy regimens for patients with mCRC.

In addition to these three antiangiogenic agents currently approved by the FDA, numerous other agents with different mechanisms of action are under investigation at this time as potential therapy for patients with mCRC. Monoclonal antibodies, engineered proteins, tyrosine kinase inhibitors (TKIs), and other small molecule agents target components 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 (PlGF) and basic fibroblast growth factor (bFGF; see Figure).8-10

VEGF Suppression: FDA Approved Antiangiogenic Agents for mCRC

VEGF and its associated signaling cascade have been the most extensively studied growth factor of the many known endogenous growth factors that are involved in angiogenesis within tumors. VEGF has been found to be vital for the initiation and maintenance of vasculature throughout tumorigenesis and the dissemination of disease that is characteristic of CRC.11-13 While VEGF is a potent stimulator of endothelial cell proliferation, migration and survival, the growth factor 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 of VEGFR leads to receptor dimerization, phosphorylation of key tyrosine residues on its intracellular tail, and the activation of numerous downstream signaling pathways.12,13 Two activated pathways that have an important role in endothelial and tumor cell growth and survival are the Raf-MEK-ERK and phosphotyridinositol-3-kinase (PI3K)-Akt pathways.14 Each component of these proangiogenic pathways represents possible targets for drug development and mechanisms of action for the treatment of cancer.

This comprehensive review includes clinical trial data concerning the role of BV as a standard chemotherapy for first-line therapy and beyond, the usefulness of ziv-aflibercept and regorafenib as the newly approved antiangiogenic agents, and the potential role of other agents that are still under clinical development as therapy options for patients diagnosed with mCRC.

The FDA approved BV as a first-line therapy for mCRC based on results from the randomized AVF 2107 Phase 3 trial, which compared bolus 5-FU/leucovorin/irinotecan (IFL) in combination with BV or placebo as treatment for patients with mCRC.15 The addition of BV to IFL prolonged the median overall survival (OS) by approximately 5 months compared with patients who received IFL alone (20.3 vs. 15.6 months; Hazard Ratio (HR) = 0.66, p <0.001). The 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). The median duration of response was 10.4 months for the group that received BV and IFL compared with 7.1 months in the group that received placebo and IFL (HR = 0.62, p = 0.001). This study was the first to show that the combination of an antiangiogenic agent with a fluorouracil-based cytotoxic chemotherapy regimen was superior to chemotherapy alone. BV treatment showed increases in adverse events in grade 3 hypertension (11.0% vs. 2.3%) and gastrointestinal perforation (1.5% vs. 0).
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
- Ramucirumab
- Ziv-afibercept
- Cetuximab

Targeting Tumor Angiogenesis

1. 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.

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

3. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αVβ3 integrins.

4. Tumor blood vessels are characterized by tortuous, anastomosing, and lezzy; 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-optis stromal 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.

Metastases exit through the tumor vasculature to the systemic circulation.

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Diagram by Joe Lelievre and Diana Sastre.
Following the results of the AVF 2107 trial, a subsequent Phase 3 study that had originally planned to compare the irinotecan-containing regimens IFL, FOLFIRI, and CapanRI (capcitabine/irinotecan) was altered to add BV to IFL and FOLFIRI. This study, BICC-C, established that FOLFIRI was 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 who were treated with IFL/BV (28.0 vs. 19.2 months; HR for death = 1.79, p = 0.037). The proportion of patients who were still alive at one year was 87% for the FOLFIRI/BV group and 61% for the IFL/BV group. Although the fact that treatment with FOLFIRI/BV was linked with higher rates of grade 3 or higher toxicities than IFL/BV, including febrile neutropenia (5.4% vs. 1.7%) and hypertension (12.5% vs. 1.7%), its clear superiority in terms of survival indicated that FOLFIRI should be the preferred irinotecan-based regimen for combination with BV. The partiality of FOLFIRI/BV over IFL/BV as the first-line therapy for patients with mCRC was further authenticated when a secondary analysis of the BICC-C trial found no significant differences in efficacy or safety when used in a group of older patients.

Simultaneously, with the clinical development of combination therapy with irinotecan-containing regimens, BV was also evaluated as a potential partner in combination regimens with oxaliplatin-containing chemotherapy. Two randomized Phase 3 trials, ECOG 3200 and NO16966, assessed the use of BV and oxaliplatin in second- and first-line treatment settings, respectively.

The ECOG 3200 study was originally intended to compare the efficacy of FOLFOX, FOLFOX/BV, and BV alone as second-line therapy in patients who had already failed treatment with 5-FU/irinotecan. However, the BV monotherapy arm was terminated due to its inferiority to the control arm of the trial. The results of the remaining arms of the study proved 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) in comparison with FOLFOX alone as treatment for patients who had been previously treated for mCRC. The overall response rates (ORRs) were 22.7% for FOLFOX/BV and 8.6% for FOLFOX alone. In this trial, the BV treatment was associated with grade 3/4 hypertension, bleeding and vomiting.

For the NO16966 Phase 3 trial, the researchers established a 2 x 2 randomized study that assessed the non-inferiority of capcitabine/oxaliplatin (XELOX) as compared with FOLFOX, as well as the superiority of the addition of BV to an oxaliplatin-based regimen as compared with placebo as first-line therapy. The findings from a pooled analysis revealed that PFS was significantly prolonged among patients who had received BV compared with placebo (9.4 vs. 8.0 months; HR = 0.83, p = 0.0023). It is important to remember that approximately 26.8% of the registered patients discontinued their primary treatment due to toxicity; therefore, when taking into consideration the patients who stayed on the treatment regimen until disease progression, the PFS benefit from BV (10.4 vs. 7.9 months; HR = 0.63, p < 0.0001) was more marked. In contrast to previous studies, there was no statistically significant difference in OS in the treatment arms and treatment was discontinued prior to PD in most of the patients in both arms of this trial. The toxicity of BV was consistent with the profiles reported in other trials. The authors hypothesized that the clinical benefits associated with BV treatment were maximized when BV treatment was continued through to disease progression. The findings from the AVF2107, ECOG 3200 and NO16966 trials decisively clarified the survival benefit of adding BV to chemotherapy in the first-line or second-line treatment settings and indicated that it should be used as a standard of care for patients with newly diagnosed or BV-naïve mCRC.

There are two ongoing Phase 3 studies that aim to address the potential use of BV in combination with other cytotoxic chemotherapy partners as a first-line therapy for patients with mCRC. A Spanish Phase 3 study that compared 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 after the favorable results of a Phase 2 study. In the multi-institutional Phase 2 study, patients treated with FOLFOXIRI/BV as a first-line therapy achieved a 10-month PFS rate of 74%. The researchers determined that BV could be safely administered in combination with FOLFOXIRI. Subsequently, the ongoing Phase 3 trial began in July 2012, and the enrollment goal is 350 patients. The primary outcome measure for this trial is PFS, with secondary outcome measures including overall survival, response, R0 resection rate, and adverse events. Biomarkers, including baseline circulating tumor cells, BRAF, KRAS, and PI3K, will also be correlated with efficacy measures. Because of the fact that patients who have multiple metastases or who are ineligible for surgery may not benefit from intensive standard first-line therapy, a German study was initiated to compare the safety and efficacy of CAPIRI/BV and the less intensive capcitabine/BV (Cap/BV). The primary endpoint of this trial is time-of-failure strategy (TOF), and the patients in the Cap/BV arm will be treated until progression of disease, at which point, they will crossover to CAPIRI/BV treatment. The secondary outcome measures for this trial are OS, objective response rates, and quality of life.

There may be other avenues of utilizing BV in patients with mCRC. Instead of being used as a combination partner for a single discrete line of therapy, some clinical trials have evaluated the use of BV according to other regimen schedules. The BRiTE (BV Regimens: Investigation of Treatment Effects and Safety) observational cohort study was begun to gauge the utility of BV in a large, unrestricted group of patients with mCRC who had never been treated. The researchers completed an ad hoc analysis of pre- and post-treatment factors of BRiTE due to the unexpectedly prolonged median OS for the entire cohort (25.1 months). After progression on first-line therapy containing BV, the investigators found that the median OS did vary significantly between patients who had received no treatment (12.6 months), who had received chemotherapy without BV (19.9 months) and who had received chemotherapy with BV (31.8 months). Multivariate analyses compared patients who received chemotherapy with and without BV after first progression; these findings showed that prolonged BV exposure was independently associated with improved survival (HR, 0.48; p = 0.001). The results of an interim analysis of another large observational study that assessed post-progression treatment with BV, ARIEFS, validated the findings of the BRiTE study. The 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). A recent analysis of this data verified that BV exposure after the first progression was associated with longer post-progression survival (PPS).

The randomized Phase 3 ML18147 trial was originally started to further gauge the benefit of continuing BV treatment beyond the first progression in patients with mCRC in a prospective trial structure. 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 that included BV in the 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 the first-line therapy regimen only. The median PFS was also significantly longer in patients who had received BV across two lines of therapy (5.7 vs. 4.1 months; HR = 0.68, p < 0.0001). Grade 3-5 bleeding, gastrointestinal perforation, and venous thromboembolisms were more common in the BV/chemotherapy arm than in the chemotherapy alone arm. While a survival benefit was confirmed for BV treatment past the first disease progression, the benefit was considerably less than the benefit that had been reported for observational studies. As a consequence of 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 had progressed while on first-line BV plus irinotecan-/oxaliplatin-containing regimens.

Another area of interest when considering the duration of BV therapy, similar to the use of BV past progression, is whether patients who have responded to a front-line therapy that contained BV, or induction therapy, would derive any benefit from continuing BV as a maintenance therapy. Updated results from a multicenter Phase 3 trial of patients with mCRC that compared the efficacy of front-line therapy with XELOX/BV until progression to 6 cycles of XELOX/BV followed by maintenance capecitabine/BV without oxaliplatin until progression, showed that maintenance therapy was non-inferior to XELOX/BV treatment to progression. While the 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, there were no statistically significant differences between the groups. Tolerability was similar in both treatment groups.

The MACRO trial was another Phase 3 trial that assessed the efficacy of single agent BV maintenance therapy following XELOX/BV induction as a first-line therapy in patients with mCRC; the findings from this study did not establish its non-inferiority to XELOX/BV induction followed by XELOX/BV maintenance. Patients with mCRC who had not been previously treated were randomized to receive 6 cycles of induction XELOX/BV therapy followed by maintenance capecitabine/BV without oxaliplatin until progression, that showed maintenance therapy was non-inferior to XELOX/BV treatment to progression. While the 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, there were no statistically significant differences between the groups. Tolerability was similar in both treatment groups.

One of the studies of BV maintenance in mCRC, CAIRO-3, found that maintenance treatment of capecitabine plus BV significantly delayed progression compared to observation alone in patients with mCRC, and also conveyed an overall survival benefit in a subset of patients. Previously untreated mCRC patients, with stable disease or complete/partial response after six cycles of CAPOX-B, were randomized to observation (arm A) or cap + BV maintenance treatment (arm B). At first progression (PFS1), patients in both arms were treated with CAPOX-B until the second progression (PFS2, the primary endpoint). Over the 48-month period of the trial, CAPOX-B was reintroduced in 60% of patients in arm A and 47% of patients in arm B. PFS2 was 8.5 months in arm A and 11.7 months in arm B (HR = 0.67, p < 0.0001). The total population did not experience a significant benefit in OS as a result of improvement in PFS. However, there was significant improvement in OS with maintenance therapy for patients with synchronous disease who underwent resection of the primary tumor (median OS = 18.0 months for arm A vs. 25.0 months for arm B (p < 0.0001)) and those who attained a complete or partial response to induction therapy (median OS = 18.8 months in arm A and 24.1 months in arm B (p < 0.0001)). These findings demonstrate that maintenance therapy may delay disease progression. Further research is needed to identify which patient populations would reap the greatest benefit from maintenance therapy.

Another study looked at the inclusion of BV or cetuximab (CET) in first line chemotherapy for patients with KRAS wild-type mutation. Recent results from the Phase 3 CALGB/SWOG 80405 trial found similar benefits between BV or CET as first-line therapy in combination with FOLFIRI or mFOLFOX6. Patients with KRAS wild-type tumors (codon 12 and 13) received FOLFIRI or mFOLFOX6 and were randomized to CET or BV. The median OS, which was the primary endpoint, was 29.04 months for the chemotherapy/BV arm and 29.93 months for the chemotherapy/CET arm. The PFS was also comparable between the arms at 10.84 months for chemotherapy/BV and 10.45 months for chemotherapy/CET. No significant differences were found in OS or PFS; this suggested that both biologic agents were appropriate in first-line treatment. While more patients received FOLFIRI chemotherapy, it was difficult to compare the chemotherapy backbones. Future analyses of this data will include outcomes by primary tumor site and gender, impact of lifestyle and diet, and differences in RAS mutations.

Some clinical trials that have investigated a potential role for BV in the adjuvant treatment setting have produced data that do not support further clinical interest. Updated results from the Phase 3 NSABP C-08 trial that compared the efficacy of FOLFOX/BV and FOLFIRI 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. No BV-associated improvement in DFS (HR = 0.93, p = 0.34) or OS (HR = 0.96, p = 0.64) was noted after a median follow-up of 55 months. 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 was marginally worse after the 15-months (HR = 1.20, p = 0.052). Although the data was statistically non-significant, the findings demonstrated that patients who received BV had a longer time to recurrence but poorer survival following relapse compared with those who received chemotherapy alone. It should be noted that during BV therapy, a transient positive effect was observed. One hypothesis is that this BV therapy delayed, but did not prevent, disease recurrence. The investigators also reported that exposure to BV was not related to development of more aggressive tumor behavior upon disease recurrence. Additionally, the AVANT adjuvant trial, conducted in Europe, validated these results when it showed that there was no improvement in DFS, the primary endpoint, in patients with stage III disease when BV was added to FOLFOX or XELOX. This final efficacy analysis also found that BV in combination with chemotherapy produced a higher number of relapses and shorter time of survival than chemotherapy alone. These findings do not support the use of BV in the adjuvant setting for patients with stage II or III disease. While the E5202 (5-FU, leucovorin, oxaliplatin with/without BV) and QUASAR2 (capecitabine vs. capecitabine/BV) trials have been closed in light of their inconsistent results as potential adjuvant therapies, final analyses of the data accumulated from these trials are still pending.

Elderly patients, due to health issues, often are unable to tolerate some of the more stringent chemotherapy regimens, such as oxaliplatin-
based or irinotecan-based therapies. As such, this population of patients may be underrepresented in clinical trials for mCRC. The open-label, randomized, Phase 3 AVEX trial prospectively evaluated the use of BV in the elderly population with mCRC who had not been previously treated. The treatment regimens in this trial were capcitabine (1000 mg/m² orally twice a day on days 1—14) alone or in combination with BV (7.5 mg/kg intravenously on day 1), given in 3-week cycles until disease progression or unacceptable toxicity. PFS was significantly longer with BV/capcitabine than with capcitabine alone (9.1 months vs 5.1 months; HR = 0.53; p < 0.0001). Grade 3 or higher adverse events occurred in 40% patients in the BV/capcitabine arm compared to 22% in the capcitabine group. The findings support the use of BV/capcitabine in elderly patients with mCRC. Subgroup analysis for the elderly population found that the improvements in PFS were present across age groups; adverse events were also consistent across groups as well. Ziv-aflibercept, the second FDA-approved antiangiogenic agent for treatment of mCRC, is a fusion protein that is made from two VEGF-binding domains from VEGFR-1 and VEGFR-2 linked to the Fc portion of IgG, and can bind to all human isoforms of VEGF-A, VEGF-B and PIGF; it also can prevent their interactions with VEGFR-1 and -2. The pivotal VELOUR study was a randomized, placebo-controlled Phase 3 trial that evaluated ziv-aflibercept as a second-line therapy in combination with FOLFIRI. The results from the VELOUR study demonstrated that adding ziv-aflibercept to FOLFIRI yielded a modest, significant increase in the median PFS (6.9 vs. 4.7 months; HR = 0.758, p < 0.0001) and the median OS (13.5 vs. 12.1 months; HR = 0.817, p = 0.0032). Treatment with ziv-aflibercept was also associated with an increase in the ORR (19.8% versus 11.1%, HR = 0.797, p = 0.0001). Importantly, patients who both had and had not been treated previously with BV 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 response rate with ziv-aflibercept and FOLFIRI was 19.8% compared to 11.1% for placebo plus FOLFIRI (p = 0.0001). After the results of the VELOUR study, the FDA approved ziv-aflibercept in combination with FOLFIRI, on August 3, 2012, for second-line therapy for metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

The AFFIRM trial was a randomized Phase 2 trial that studied modified FOLFOX6 in combination with ziv-aflibercept or placebo as first-line therapy for metastatic colorectal cancer. 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, the PFS was 25.8% (95% CI: 17.2-34.4), compared to 21.2% (95% CI: 12.2-30.3) for the placebo arm. In the experimental arm, the response rate was 49.1% (95% CI: 39.7-58.6), while in the placebo arm, the response rate was 45.9% (95% CI: 36.4-55.7). Finally, the 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. The grade 3 or 4 adverse events that had a greater than 5% incidence in the placebo arm were hypertension, proteinuria, neutropenia, diarrhea, and infection. The study was not designed to compare the two arms. A recent analysis of the VELOUR study’s overall (ITT) population has shown benefit from adding ziv-aflibercept to FOLFIRI in mCRC patients, and was consistently observed across a range of pre-specified patient subgroups based on demographic variables and baseline clinical characteristics, including the stratification factors identified at randomization (prior BV treatment and ECOG PS). The subgroup analyses based on the patients’ baseline characteristics identified a significant association between treatment and factors found in patients who were grouped according to the presence of liver metastases; patients with liver-only metastases at baseline had a greater ziv-aflibercept treatment effect when compared to patients who either did not have liver metastases or who had metastases to the liver and other organs.

While the subgroup analysis study was not powered to show differences between the treatment arms for OS within the specific subgroups, the lack of a significant interaction between the treatment arm and the presence or lack of prior BV treatment indicated that the efficacy of ziv-aflibercept was not lessened by prior BV treatment. A post hoc analysis of VELOUR evaluated the potential for subgroups that might derive greater benefits from treatment with ziv-aflibercept. The results of this subset analysis suggested that patients who had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of PS0, with any number of metastases, or PS1, with less than 2 metastatic sites, might receive enhanced efficacy benefits in OS, PFS, and ORR when treated with the combination of ziv-aflibercept and FOLFIRI compared to FOLFIRI alone. These and other subgroup findings may help physicians select patients for maximal benefits.

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

The CORRECT trial, which was the randomized, placebo-controlled Phase 3 trial for regorafenib, compared its efficacy and tolerability with best supportive care (BSC) in patients with mCRC who had failed all previous standard therapy. The 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 treatment with BSC (41.0% vs. 15%, p < 0.0001). Although the differences were modest, a significantly longer median PFS (1.9 vs. 1.7 months; HR = 0.49, p < 0.0001) and median OS (6.4 vs. 5.0 months; HR = 0.77, p = 0.0052) was found in patients who had received regorafenib. The survival benefit that was associated with regorafenib was comparable for most sub-groups analyzed, including prior lines of therapy (≤ 3 vs. > 3) and KRAS mutation status (Y or N), with the exception that patients who had primary tumor sites in the colon benefited 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) showed 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. The grade 3/4 adverse events that were associated with regorafenib
were hand-foot skin reaction (17% vs. < 1%), fatigue (10% vs. 5%), diarrhea (7% vs. 1%), hypertension (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 the regorafenib-treated group (1.0% vs. 0%).

A Phase 3 trial (CONCUR) in Asian patients with mCRC showed increased OS and PFS in those with prior regorafenib treatment compared to placebo. The median OS in the regorafenib group was 8.8 months compared to 6.3 months with placebo (HR = 0.550, p = 0.0002). The secondary endpoint showed an increase in PFS of 3.2 months for patients receiving regorafenib compared to 1.7 months for placebo (HR = 0.311, p < 0.0001). The most common adverse events were hypertension (15%) and diarrhea (2%). Two patients who received regorafenib showed anti-tumor activity in animal models of different carcinomas such as colorectal cancer, lung, mammary, glioblastoma, and renal cell cancer. In pre-clinical studies, ramucirumab showed anti-tumor activity in combination with VEGF. Unlike BV, which targets VEGF-A and prevents it from interacting with VEGFR-1 or -2, ramucirumab specifically disrupts VEGF-2 ligand binding, and blocks all isoforms of VEGF from binding to VEGFR-2. In clinical studies, ramucirumab showed anti-tumor activity in animal models of different carcinomas such as colorectal cancer, lung, mammary, glioblastoma, and renal cell cancer. In a Phase 1 dose-finding study of single agent ramucirumab, it was found that the maximum tolerable dose was 13 mg/kg, the PK clearance appeared saturated at 8 mg/kg, and the PK clearance was selected for ensuing clinical trials.

Results were recently presented from an open-label Phase 2 trial that evaluated the safety and efficacy of ramucirumab in combination with FOLFIRI in 48 treatment-naïve patients with mCRC. The median PFS was 11.5 months with a 48% one-year PFS rate and an 85% one-year OS rate. In addition, the ORR was 67%, the disease control rate was 94%, and the duration of response was 11.0 months. The most frequently observed grade 3/4 adverse events related to treatment included hand-foot skin reaction and hypertension. The occurrence of these adverse effects was consistent with other reports of regorafenib in patients of Asian descent.

### Antiangiogenic Agents in Clinical Development for CRC

There are numerous antiangiogenic agents currently undergoing clinical development as prospective therapies for patients with mCRC. Another fully human monoclonal antibody, ramucirumab, functions as an antiangiogenic agent by targeting VEGFR-2 and inhibiting its interaction with VEGF. Unlike BV, which targets VEGF-A and prevents it from interacting with VEGFR-1 or -2, ramucirumab specifically disrupts VEGF-2 ligand binding, and blocks all isoforms of VEGF from binding to VEGFR-2. In pre-clinical studies, ramucirumab showed anti-tumor activity in animal models of different carcinomas such as colorectal cancer, lung, mammary, glioblastoma, and renal cell cancer. A Phase 1 dose-finding study of single agent ramucirumab found that it could produce disease control in 30% (PR and SD; 11 of 37 patients with measureable disease) of patients with advanced solid tumors; this effect lasted for at least 6 months across a range of doses (2 to 16 mg/kg). Although the study found that the maximum tolerable dose was 13 mg/kg, the PK clearance appeared saturated at 8 mg/kg. Consequently, the 8 mg/kg dose was selected for ensuing clinical trials.

To compare the efficacy of FOLFIRI in combination with ramucirumab or placebo as second-line therapy for mCRC following the use of first line BV plus chemotherapy, researchers began a randomized, double-blind Phase 3 trial. The primary objective of this study is OS and the secondary objectives include ORR, PFS, and safety.

Notwithstanding the success of regorafenib, the results from clinical trials of small molecule TKIs in mCRC have been unsatisfactory. The published results of HORIZON 3, a randomized Phase 3 trial of the VEGFR TKI cediranib that compared mFOLFOX6 (modified dosing regimen of leucovorin/5-FU/oxaliplatin/cediranib) and mFOLFOX6/BV as first-line therapy for patients with mCRC, revealed no significant difference in the median PFS (HR = 1.10, p = 0.119) and median OS (HR = 0.95, p = .541) between the two groups; while the activity of cediranib was comparable to BV in terms of PFS and OS, the study drug failed to meet the predetermined value for non-inferiority. The results from a second front-line Phase 3 trial, HORIZON 2, that compared FOLFOX/CAPOX (capcitabine and oxaliplatin) with cediranib and FOLFOX/CAPOX with placebo in patients with mCRC, echoed findings from HORIZON 3; the addition of cediranib did provide a small PFS prolongation but there was no difference in OS. Brivanib, a small molecule TKI that inhibits the signaling of FGFR and VEGF, displayed antitumor activity in vitro and in, a Phase 1 study, in combination with cetuximab. The combination of brivanib/cetuximab has been investigated in a Phase 3 trial for patients with KRAS wild-type, advanced mCRC who had been previously treated with combination chemotherapy. The results from this trial, however, showed that although there was 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 who were treated with brivanib/cetuximab compared to placebo/cetuximab, treatment with brivanib had no significant impact on the median OS (HR = 0.88, p = 0.12), the trial’s primary endpoint. Another small molecule TKI inhibitor, sunitinib, which inhibits PDGFR, VEGFR1-3, KIT, FLT3 and RET, also failed to show activity in treating mCRC while in combination with mFOLFOX6 or FOLFIRI as first-line therapy. A Phase 2b study demonstrated that the addition of sunitinib to mFOLFOX6 led to shorter median PFS when compared to mFOLFOX6/BV (9.1 vs. 11.2 months, p = 0.96), and a Phase 3 trial showed that treatment with FOLFIRI/sunitinib was associated with a shorter median PFS than that of FOLFIRI/placebo (7.8 vs. 8.4, p = 0.807), as well as a poorer safety profile.

Many 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 assessed for activity in this disease and in various treatment settings.

Nintedanib (BIBF 1120) is a novel kinase inhibitor that simultaneously interferes with the activity of three families of growth factor receptors, VEGFR (-1, -2, -3), PDGFR (-α and -β), and FGFR (-1, -2, -3). Because of this, this agent may be able to overcome resistance to other anti-VEGF agents. This kinase inhibitor was evaluated in combination with mFOLFOX6 and compared with BV plus mFOLFOX6 as a first-line treatment in 126 patients with mCRC. The interim results from this randomized, open-label Phase 2 trial displayed a median PFS of 10.6 months for both treatment arms. The PFS rate was 63% for the BIBF arm compared with 69% for the BV arm, while the ORR at 9 months was 61.2% for the BIBF arm and 53.7% for the BV. The frequency of serious adverse events in the BIBF 1120 arm was lower than that of the BV (34.1% vs. 53.7%).

Tas-102, which is a novel formulation of the fluorinated pyrimidine analogue triflurouridine and an inhibitor of the angiogenic enzyme thymidine phosphorylase, has been found to stabilize disease in patients with refractory solid tumors after heavy pretreatment with 5-FU. Although the study found that the maximum tolerable dose was 13 mg/kg, the PK clearance appeared saturated at 8 mg/kg. Consequently, the 8 mg/kg dose was selected for ensuing clinical trials.

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were reported for 19% of patients treated with Tas-102, compared to 9% in the placebo group. No treatment-related deaths were noted for either group. The results from a Phase 3 placebo-controlled trial of Tas-102 in patients with refractory mCRC, RECURSE, were recently reported. The researchers found that Tas-102 significantly improved overall survival, the primary endpoint, compared to placebo. Tas-102 prolonged the median OS compared to placebo (7.1 vs. 5.3 months; HR = 0.68) and also improved PFS compared to placebo (2.0 vs. 1.7 months; HR = 0.48). The most common grade 3 or higher adverse events associated with Tas-102 were neutropenia (34.9%), leukopenia (12.8%), and anemia (16.5%); febrile neutropenia also occurred in 3.8% in patients treated with Tas-102.

Another human monoclonal antibody, IMC-18F1, which targets VEGFR-1, is a potential therapy for mCRC patients, having shown an ability to inhibit tumor growth in breast cancer xenograft models concomitant with the suppression of Akt activation. The results of a Phase 1 dose-finding study of IMC-18F1 in patients with advanced melanoma showed that dovitinib 400 mg/day inhibited FGFR and VEGFR signaling and had an acceptable toxicity profile. Two Phase 2 trials of dovitinib are underway for the treatment of advanced CRC: (1) a pilot study of FGFR biomarkers to evaluate the activity in CRC and non-small cell lung cancer patients who had already been treated with anti-VEGF therapy, and (2) a study of dovitinib as maintenance and adjuvant therapy in patients with colon and pancreatic cancers who had stable disease post-initial treatment. The primary endpoint for the maintenance dovitinib trial is biomarker discovery, with secondary endpoints of PFS and safety.

MEGF0444A is a human monoclonal antibody and novel targeting agent that binds to and inhibits the epidermal growth factor-like domain 7 (EGF7) extracellular matrix protein that promotes endothelial cell differentiation, proliferation and migration in proliferating, but not mature, tissue. A Phase 1a open-label, dose-escalation study of single agent MEGF0444A, which evaluated its tolerability in patients with advanced solid tumors, found a low rate of transfusion reactions; however, there were no tumor responses nor dose-limiting toxicities that were associated with the investigational drug up to the highest planned dose, 15 mg/kg. Interestingly, dynamically contrast enhanced magnetic resonance imaging (DCE-MRI) showed a decrease in circulating progenitor cells (CPCs), which suggests potential vascular targeting. CONGO, a randomized, double-blind Phase 2 trial comparing MEGF0444A and placebo in combination with BV and FOLFOX as second-line therapy in patients with mCRC after failure on an irinotecan-containing regimen was recently completed; results for this study are pending.

Biomarkers for Antiangiogenic Therapy in Colorectal Cancer

An important finding in the majority of clinical studies for antiangiogenic agents has been the discovery of potential prognostic rather than predictive biomarkers. Numerous biomarkers related to angiogenesis have been correlated with patient outcome in mCRC clinical trials. Elevated serum VEGF levels have been associated with tumor size, tumor volume, and poorer prognosis. In another trial, researchers determined that microvessel density as measured with CD31 or CD34 immunohistochemistry was associated with poor prognosis in CRC.

One example of the use of biomarkers in treatment selection is KRAS mutational status. KRAS status is currently used as a biomarker to help predict potential response to EGFR-targeted agents, such as cetuximab and erlotinib. This is a powerful example of a predictive biomarker; patients with activating mutations in KRAS do not receive any benefit from treatment with EGFR-targeted agents. KRAS, and its signaling partner, BRAF, which is located downstream of receptor tyrosine kinase activation, are associated with poor prognosis; however, they play no role in predicting any benefit from antiangiogenic nor other types of agents. In fact, studies have shown that patients with wild-type and mutant KRAS benefit from treatment with BV (HR = 0.44 and 0.41) and regorafenib (HR = 0.48 and 0.53).

As outlined, while BV/chemotherapy is the standard clinical practice for first-line therapy for mCRC, identifying patients who would benefit most, or not at all, from antiangiogenic agents would be an important development in the management of this disease. The search for predictive biomarkers is currently underway in clinical trials of antiangiogenic agents in the treatment of CRC, but predictive markers have yet to be clinically confirmed. Serum levels of VEGF have been studied at length across tumor types since high levels of serum VEGF were correlated with metastasis and the dissemination of disease. Plasma levels of VEGF are often markedly elevated after exposure to anti-VEGF therapy and drop once the therapy has been discontinued. This finding has also been observed with BV; a meta-analysis assessed the value of circulating VEGF levels as a prognostic biomarker for outcome and as a predictive biomarker of benefit from BV-containing treatment across five randomized trials, including four Phase 3 studies. To assess VEGF levels, the analysis included the archived baseline plasma samples of VEGF ELISA from 1,816 patients with metastatic colorectal cancer, NSCLC, and renal cell carcinoma. The investigators found that higher baseline levels of circulating VEGF were associated with shortened PFS and OS in all tumor types regardless of exposure to BV. This suggested that VEGF levels were 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 the tumor expression of VEGF. Hypertension has also been proposed as a noninvasive biomarker of non-physiological secretion of HGF-associated proteins, such as VEGF-A, into the tumor microenvironment. A Phase 1 study that evaluated ornatuzumab in combination with BV in patients who had advanced solid malignancies found that both single-agent ornatuzumab and ornatuzumab/BV were well tolerated; the researchers also found that in the patients treated with combination therapy, there was no pharmacokinetic interaction between the two agents. A placebo-controlled Phase 2 trial is currently underway to assess the addition of ornatuzumab to first-line FOLFOX/BV therapy in patients with mCRC. The primary endpoint for this trial is PFS with secondary endpoints including RR, time to treatment failure (TTF), OS, and safety.
response to antiangiogenic therapy. A principal hypothesis for this effect is that VEGF inhibition by these agents reduces the synthesis of nitric oxide in capillary walls, and leads to increased vasoconstriction and higher blood pressure. Numerous clinical trials in breast, colorectal, pancreatic, lung, and kidney cancers have found that patients who had higher levels of hypertension showed improved response rates and increased PFS and OS. However, a recent meta-analysis that included approximately 5,900 patients across six studies of metastatic cancer treated with BV did not confirm a correlation in most of the studies between higher blood pressure and PFS or OS. Only one study in patients with colorectal cancer has shown that hypertension that occurred in the first 60 days of treatment predicted superior PFS and OS in the BV 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.

Changes in baseline serum cytokine levels after the start of treatment with antiangiogenic therapy have been comprehensively studied. A Phase 2 study with 43 patients followed variations in serum levels of 37 circulating angiogenic factors (CAFs), from baseline, after the initiation of first-line therapy with FOLFIRI/BV in patients with mCRC. 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 was correlated with increased tumor volume (Spearman r = 0.62; p < .001). Another study reported that baseline CA19.9 levels were independently associated with PFS in patients treated with FOLFIRI/BV as first-line therapy for mCRC. Patients with abnormal CA19.9 levels benefited significantly from BV while the patients with normal levels did not.

Various studies have approached identifying potential predictive biomarkers for antiangiogenic therapy from the genetic perspective and have focused on differences in the DNA sequences of candidate biomarker genes. A retrospective analysis conducted with data from 119 patients treated between 2004 and 2009 with BV/FOLFOX or BV/XELOX as first-line therapy for mCRC in multiple institutions assessed the association with PFS and RR and SNPs in 26 candidate genes of VEGF-dependent and -independent angiogenesis pathways. This study identified the CXCRI1 rs2234671 SNP as a potential predictive marker for response to BV. However, a subsequent international, prospective study of SNPs in patients treated with BV/FOLFIRI failed to validate any previously recognized variants, leading the investigators to conclude that future studies of angiogenic biomarkers should be assessed using various approaches rather than focusing on differences in genetic sequences.

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 ascribed to the induction of alternate hypoxia-dependent proangiogenic factors and signaling pathways among other physiological mechanisms. Alternate angiogenic factors that cause this re-establishment of angiogenesis have not been conclusively identified, but several studies have suggested the association of several proangiogenic cytokines with acquired resistance to BV. Notably, results from a prospective Phase 2 study of FOLFIRI/BV showed that circulating factors that play a role in angiogenesis and myeloid recruitment increased prior to radiologic progression of disease. Serum levels of FGF (p = 0.046), HGF (hepatocyte growth factor) (p = 0.046), PIGF, 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. Accumulating evidence supports a role for members of the FGF signaling pathway in providing mechanisms for escape from VEGF inhibition. Although terminating anti-VEGF therapy during progression has been shown to start even more rapid tumor growth in some preclinical studies, this has not been replicated in recent meta-analysis from randomized BV clinical studies, and may be confined to murine models. Clinical research that can identify the mechanisms of escape from antiangiogenic therapy, and the successive formulation of treatment strategies that prevent tumor re-vascularization and growth, is ongoing and remains a goal of prospective trial design for many researchers across fields.

**Antiangiogenic Combination Strategies for Colorectal Cancer**

Pairing antiangiogenic agents, sequentially or in series, with other targeted biologics in order to disrupt multiple pathways necessary for tumor growth and survival is an enduring strategy for treating metastatic disease and overcoming escape from antiangiogenic suppression. In mCRC treatment, 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 are not currently being pursued as a potential therapeutic strategy for mCRC patients. A small Phase 2 study evaluated the efficacy and tolerability of capecitabine, OX, and BV, each in combination with cetuximab as first-line therapy for advanced CRC. The mutational status of KRAS, BRAF and PI3K was also evaluated in these patients. One patient had a CR and 12 patients had a PR, which led to an ORR of 43%. Fifteen patients had stable disease. The median time to progression was 10.3 months and the median overall survival was 18.8 months. The researchers found that the addition of cetuximab did not improve the activity of the capecitabine, OX, and BV and, moreover, was associated with significant adverse events. In addition, despite initially promising results from the BOND-2 Phase 2 trial, which found that this dual biologic regimen produced responses in both patients with and without irinotecan (37% vs. 20%), these findings did not translate to Phase 3 clinical trials. The PACCE Phase 3 trial that evaluated 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 EGFR, was stopped after a planned interim assessment. This assessment revealed that the addition of panitumumab to Ox/BV and Iri/BV was associated with shorter median PFS (HR = 1.27 and 1.19, respectively) and median OS (HR = 1.43 and 1.42, respectively). A second Phase 3 trial of dual biologics as first-line therapy for mCRC, CAIRO-2, comparing CAPOX/BV with and without cetuximab, yielded results comparable to PACCE. The researchers found that the median PFS and OS were shorter in patients treated with CAPOX/BV+cetuximab than in those patients treated with CAPOX/BV (HR = 1.22). Grade 3 or 4 serious events were amplified in the anti-EGFR/BV combination arms in both studies.

To extend this strategy of paired antiangiogenic agents and other targeted biologics to more combinations, a different approach to therapy with dual VEGF/EGFR blockade was undertaken in a French Phase 3 trial, GERCOR DREAM, which evaluated the efficacy and tolerability of BV plus erlotinib, a small molecule inhibitor of EGFR, vs. BV alone as maintenance therapy for mCRC patients who did not progress on standard first-line BV-based induction therapy (FOLFOX/
Antiangiogenic treatments are generally well tolerated relative to cytotoxic chemotherapy, and their length of use is not typically limited by toxicities. However, agents that function by blocking VEGF-related signaling have been associated with a number of distinct adverse events 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 who were treated with first-line BV plus chemotherapy developed grade 3 hypertension requiring aggressive medical therapy. The true incidence of hypertension, however, may be considerably higher depending on the chemotherapy regimen paired with BV and the specific hypertension criteria used.

There has been some evidence that the onset of hypertension during anti-VEGF therapy may be prognostic of clinical response. Two small retrospective analyses found better outcomes in mCRC patients who developed hypertension while on BV. In one of these studies, the researchers determined that patients who developed arterial hypertension during treatment had a significant increase in PFS compared with those who did not (15.1 vs. 8.3 months; p = 0.04). 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 of the disease course for either BV or control treatment arms. However, in the one study that had found a positive connection—a Phase 3 trial in mCRC (AVF2107g)—hypertension predicted a longer PFS and OS in the BV arm, and shorter OS in the control arm. Overall, the authors noted that these findings suggest the limits of using blood pressure as a marker of anti-VEGF activity and that individualizing BV therapy based on blood pressure should be avoided.

Other serious but less frequent adverse events documented in patients on BV include thromboembolic (primarily arterial) and bleeding events, delayed wound healing, gastrointestinal perforation, and nasal septum perforation. A large meta-analysis of randomized clinical trials of BV as therapy for advanced solid tumors found that the addition of BV was associated with an increased risk (relative risk 1.33) of FAEs (fatal adverse events) compared to chemotherapy alone. The correlations between BV use and dose or tumor type were not statistically significant. However, the associated risk of FAEs and the type of chemotherapy partners was statistically significant; treatment with BV in combination with taxanes or platinum agents was associated with a much higher relative risk than when BV was prescribed 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 meta-analysis from the 2012 Annual Meeting of the American Society of Clinical Oncology evaluated the incidence of adverse events in data from 2,662 patients across three double-blind, placebo-controlled Phase 3 trials who had metastatic colorectal, lung, and pancreatic cancers, and had been treated with ziv-aflibercept in combination with chemotherapy. Compared to placebo, treatment with ziv-aflibercept was associated with a statistically significant increased risk of grade 3 hypertension (RR = 9.21; p < 0.05), proteinuria (RR = 8.37; p < 0.05), and hemorrhage (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.

The adverse event profile may be somewhat different with regorafenib than with BV and includes asthenia, hypertension, diarrhea, and hand-foot skin reaction (HFSR). A 2013 meta-analysis evaluated the incidence and risk of HFSR in patients treated with regorafenib. This evaluation included a total of 1078 patients who had received regorafenib to treat mCRC, gastrointestinal stromal tumors (GIST), renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC). The incidence of all-grade and high-grade HFSR were 60.5% and 20.4%, respectively. The research also determined that the incidence of HFSR varied depending on the specific tumor type, at 71.4% for RCC to 46.6% for mCRC. Understanding the incidence of this adverse event and the risk according to tumor type would be beneficial to clinicians and further research is needed to assess the incidence and risk of HFSR in regorafenib-treated patients.
Future Directions

Antiangiogenic agents play an important part of the available therapeutic regimens spanning across all lines of treatment for mCRC. At this time, the standard first-line therapy for mCRC includes BV and the FDA has recently approved ziv-aflibercept in combination with FOLFIRI as a second-line therapy option, and single-agent regorafenib as a choice for salvage therapy for refractory patients. In contrast, it is remarkable that several studies have demonstrated that antiangiogenic therapy has no role in the adjuvant treatment setting of CRC. While many facts are known about these agents and their relationship to mCRC, there are ongoing questions regarding their use. These questions include: 1) can we determine 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 therapies; and 3) how do we identify and target pathways involved in resistance to therapy using these agents? To find the answers to these questions, researchers are undertaking numerous clinical and laboratory investigations; these findings will hopefully improve the medical care of all patient populations with mCRC.

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CME REQUIREMENTS

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RELEASE AND EXPIRATION

Date of original release: October 1, 2014
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CME Course Code: 2014CRC

TARGET AUDIENCE

Practicing oncologists, gastroenterologists, and primary care physicians in the U.S., researchers and medical students.

HEALTHCARE GAP

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women.

Three critical needs have been identified by The Angiogenesis Foundation in regards to colorectal cancer. There is a large amount of information emerging on colorectal cancer therapies and clinicians do not have enough time to adequately review all of this important information in this rapidly expanding field. Clinicians are not educating patients about the side effects of antiangiogenic therapy and are referring patients to specialists to optimize management of side effects and improving patient outcomes. There are many ongoing clinical trials 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. One promising strategy that has 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 investigational therapy targets.

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 read, in order, 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 (https://www.cmeonlinex.org) by selecting the name of the program (registration required). Course Code: 2014CRC

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COURSE FACULTY

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DISCUSSION OF UNLABELLED USE

This CME activity contains discussion of published and/or investigational use of: aflibercept (Zaltrap®), bevacizumab (Avastin®), brivanib, cediranib, cedoximab, dovitinib (TKI258), IMC-18F1, MEGF0444A, MK-2206, nintedanib, ramucirumab, regorafenib (Stivarga®), sunitinib (Sutent®), and Tas-102.

TOPICS AND EDUCATIONAL CONTENT

Update on Antiangiogenic Therapy for Metastatic Colorectal Cancer:

- VEGF Suppression: FDA Approved Antiangiogenic Agents for CRC
- Antiangiogenic Agents in Clinical Development for CRC
- Biomarkers for Antiangiogenic Therapy in Colorectal Cancer
- Antiangiogenic Escape Mechanisms and Clinical Management
- Antiangiogenic Combination Strategies for Colorectal Cancer
- Side Effects of Antiangiogenic Therapy in Colorectal Cancer
- Future Directions

SYSTEM REQUIREMENTS

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For questions about this program, please contact The Angiogenesis Foundation at 617-401-2779 or outreach@angio.org.