

# Targeting metastatic colorectal cancer – present and emerging treatment options

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**Abstract:** Metastatic colorectal cancer is a significant cause of morbidity and mortality in the US and around the world. While several novel cytotoxic and biologic therapies have been developed and proven efficacious in the past two decades, their optimal use in terms of patient selection, drug combinations, and regimen sequences has yet to be defined. Recent investigations regarding anti-epidermal growth factor receptor therapies include the comparison of single-agent panitumumab and cetuximab, the benefit of adding cetuximab to chemotherapy in the conversion therapy setting, the comparison of cetuximab and bevacizumab when added to first-line chemotherapy, and predictive biomarkers beyond *KRAS* exon 2 (codons 12 and 13) mutations. With respect to anti-vascular endothelial growth factor therapies, new data on continuing bevacizumab beyond disease progression on a bevacizumab-containing chemotherapy regimen, the addition of bevacizumab to triplet chemotherapy in the first-line setting, maintenance therapy with bevacizumab plus either capecitabine or erlotinib, the addition of aflibercept to chemotherapy, and regorafenib as monotherapy have emerged. Recent scientific and technologic advances in the field of metastatic colorectal cancer promise to elucidate the biological underpinnings of this disease and its therapies for the goal of improving personalized treatments for patients with metastatic colorectal cancer.

**Keywords:** cetuximab, panitumumab, bevacizumab, aflibercept, regorafenib, biomarker

## Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the US, and third in cancer prevalence in both men and women. An estimated 142,820 new cases and 50,830 deaths from CRC are expected in 2013 alone.<sup>1</sup> While important efforts in the prevention and early detection of CRC are ongoing, approximately one-fifth of patients diagnosed with CRC will have evidence of distant spread at diagnosis.<sup>1</sup> Advances in systemic chemotherapeutics have led to a remarkable improvement in overall survival (OS) for patients with metastatic CRC (mCRC) since the era of single-agent 5-fluorouracil (5-FU). Notably, the incorporation of oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib into treatment strategies for mCRC beyond 5-FU has easily doubled the median OS for this disease, with more patients enjoying long-term survival (Table 1). As we advance our knowledge of the underlying biology of mCRC, appropriate development and use of targeted therapies such as anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) agents and others promise to further improve our treatment of this prevalent disease.

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**Table 1** Selected Phase III trials employing targeted biologic therapies with or without chemotherapy in metastatic colorectal cancer

Trial	Biologic ± chemotherapy	Sample size	Endpoints	P-value
Price et al <sup>17</sup> ASPECCT	Cetuximab vs panitumumab in refractory mCRC	N=999	OS: 10.0 vs 10.4 mos PFS: 4.4 vs 4.1 mos ORR: 19.8% vs 22%	P=0.0007
Ye et al <sup>18</sup>	Chemotherapy (mFOLFOX6 or FOLFIRI) ± cetuximab in first-line mCRC therapy	N=138	R0 resection rate for liver mets: 25.7% vs 7.4% ORR: 57.1% vs 29.4% OS: 30.9 vs 21.0 mos	P<0.01  P<0.01 P=0.013
Heinemann et al <sup>19</sup> FIRE-3 (AIO KRK-0306)	FOLFIRI + cetuximab vs FOLFIRI + bevacizumab in first-line mCRC therapy	N=508	ORR: 62% vs 58% PFS: 10.0 vs 10.3 mos OS: 28.7 vs 25 mos	P=0.183 P=0.547 P=0.017
Bennouna et al <sup>32</sup> ML18147	Second-line chemotherapy ± bevacizumab	N=820	OS: 11.2 vs 9.8 mos	P=0.0062
Falcone et al <sup>36</sup> TRIBE	FOLFOXIRI + bevacizumab vs FOLFIRI + bevacizumab	N=508	PFS: 12.2 vs 9.7 mos ORR: 65% vs 53% R0 resection rate: 15% vs 12% OS: 31.0 vs 25.8 mos	P=0.0012 P=0.006 P=0.327 P=0.054
Punt et al <sup>39</sup> CAIRO-3	CAPOX-B followed by maintenance capecitabine + bevacizumab or observation	N=558	PFS1: 8.5 vs 4.1 mos PFS2: 11.5 vs 10.5 mos TTP2: 18.7 vs 14.1 mos OS: 21.7 vs 18.0 mos	P<0.0001 P=0.03 P<0.0001 P=0.16
Johnsson et al <sup>40</sup> Nordic ACT	First-line doublet chemotherapy + bevacizumab, followed by bevacizumab ± erlotinib	N=249	PFS: 5.7 vs 4.2 mos OS: 21.5 vs 22.8 mos	P=0.19 P=0.51
Van Cutsem et al <sup>42</sup> VELOUR	FOLFIRI + aflibercept vs FOLFIRI + placebo in previously oxaliplatin- treated mCRC	N=1,226	OS: 13.50 vs 12.06 mos ORR: 19.8% vs 11.1% PFS: 6.90 vs 4.67 mos	P=0.0032 P=0.0001 P<0.0001
Grothey et al <sup>45</sup> CORRECT	Regorafenib vs placebo in refractory mCRC	N=1,513	OS: 6.4 vs 5.0 mos PFS: 1.9 vs 1.7 mos ORR: 1.0% vs 0.4%	P=0.0052 P<0.0001 P=0.19

**Abbreviations:** mCRC, metastatic colorectal cancer; mets, metastases; mos, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS1, PFS at first progression; PFS2, PFS at second progression; TTP2, time to second progression; FOLFOX, chemotherapy regimen involving drugs folinic acid, fluorouracil, and oxaliplatin; FOLFIRI, chemotherapy regimen involving drugs folinic acid, fluorouracil, and irinotecan; FOLFOXIRI, chemotherapy regimen involving folinic acid, fluorouracil, oxaliplatin and irinotecan; CAPOX-B, chemotherapy regimen involving capecitabine, oxaliplatin and bevacizumab.

## CRC and its underlying biology: implications for therapy

The development of CRC occurs as a result of specific genetic alterations, many of which have been elucidated or further clarified with recent advances in molecular technologies. The well-known Vogelstein model has long hypothesized that germline or somatic mutations are required for malignant transformation, and the accumulation of multiple mutations determines the biological behavior of the tumor.<sup>2</sup> Furthermore, three molecular pathways have been implicated in colorectal tumorigenesis, and these include the chromosomal instability pathway,<sup>3</sup> the mutator-phenotype/DNA mismatch repair pathway,<sup>4</sup> and the hypermethylation phenotype, or hyperplastic/serrated polyp pathway.<sup>5</sup> While a detailed description of these pathways is outside the scope of this article, it is important to recognize that distinctive molecular characteristics of these pathways have implications for targeted therapies and their potential efficacy. For example,

mutator-phenotype tumors from patients with hereditary nonpolyposis CRC (HNPCC) only demonstrate *KRAS* mutations and not *BRAF* mutations, whereas *BRAF* mutations are seen almost entirely in hypermethylation pathway tumors that are *KRAS* wild-type.<sup>6,7</sup> Understanding the underlying biology of how colorectal tumors form is therefore critically important in developing effective personalized therapies for patients with this disease.

## Anti-EGFR treatment strategies: controversies regarding optimal sequence and use

The anti-EGFR monoclonal antibodies (mAb) cetuximab (an immunoglobulin [Ig]G1 chimeric mAb) and panitumumab (a fully human mAb) have proven efficacy in the treatment of *KRAS* wild-type mCRC, both as monotherapy and in combination with chemotherapy in various settings (Table 2).<sup>8–16</sup> However, their optimal use and sequence in therapy is not defined.

**Table 2** Summary of approved targeted therapies for metastatic colorectal cancer

Drug	Class	Method of administration	Target(s)	Pathway(s)
Cetuximab (Erbix <sup>®</sup> )	Monoclonal antibody (IgG1 chimeric)	Intravenous	EGFR	PI3K/Akt, MAPK
Panitumumab (Vectibix <sup>®</sup> )	Monoclonal antibody (fully human)	Intravenous	EGFR	PI3K/Akt, MAPK
Bevacizumab (Avastin <sup>®</sup> )	Monoclonal antibody	Intravenous	VEGF-A	Angiogenesis
Aflibercept (Zaltrap <sup>®</sup> )	Recombinant fusion protein	Intravenous	VEGF-A, VEGF-B, PIGF-1, PIGF-2	Angiogenesis
Regorafenib (Stivarga <sup>®</sup> )	Tyrosine kinase inhibitor	Oral	VEGFR1, VEGFR2, VEGFR3, PDGFR- $\beta$ , FGFR1, TIE2, KIT, RET, BRAF	Angiogenesis, oncogenesis, tumor microenvironment

**Notes:** Manufacturers are as follows: Erbitux: Bristol-Myers Squibb, New York, NY, USA; Vectibix: Amgen Inc., Thousand Oaks, CA, USA; Avastin: Genentech, Inc., South San Francisco, CA, USA; Zaltrap: Sanofi-Aventis, Bridgewater, NJ, USA; Stivarga: Bayer AG, Leverkusen, Germany.

**Abbreviations:** EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; Ig, immunoglobulin; MAPK, mitogen-activated protein kinase; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Important questions regarding their use that have been recently investigated include the comparable efficacy of cetuximab versus panitumumab, as well as anti-EGFR therapy versus other biologics, and potential biomarkers to more accurately predict for response to anti-EGFR therapy.

### Single-agent cetuximab versus panitumumab in the refractory mCRC setting

As single agents, both cetuximab and panitumumab have efficacy in the treatment of patients with *KRAS* wild-type mCRC. It was unclear, however, whether cetuximab had a survival advantage over panitumumab in the refractory setting. Therefore, the non-inferiority, Phase III ASPECCT trial sought to compare the efficacy and safety of cetuximab and panitumumab in chemorefractory mCRC (Table 1).<sup>17</sup> A total of 999 mCRC patients previously treated with irinotecan, oxaliplatin, and fluorouracil-based treatment were randomized 1:1 to either single-agent cetuximab (400 mg/m<sup>2</sup> intravenous [IV] loading dose, followed by 250 mg/m<sup>2</sup> IV weekly) or panitumumab (6 mg/kg IV every 2 weeks). Non-inferiority in this trial was defined as panitumumab preserving at least 50% of the cetuximab OS effect when compared to best supportive care. With a median OS of 10.4 versus 10.0 months for panitumumab and cetuximab, respectively, the non-inferiority endpoint was met (hazard ratio [HR]: 0.97, 95% confidence interval [CI]: 0.84–1.11,  $P=0.0007$ ). Additionally, median progression-free survival (PFS; 4.1 versus [vs] 4.4 months for panitumumab vs cetuximab, HR: 1.00, 95% CI: 0.88–1.14) and overall response rates (ORR) (22% vs 19.8% for panitumumab vs cetuximab) were similar. Given the similar results of the two agents in this trial, it was concluded that these therapies have equivalent efficacy as monotherapy for mCRC.

### Anti-EGFR therapy in combination with first-line chemotherapy as conversion therapy

Given the established efficacy of cetuximab in combination with chemotherapy in the first- and second-line settings, Chinese investigators sought to determine whether the addition of cetuximab to first-line chemotherapy could increase the rate of metastasectomy in patients with liver-limited, unresectable, *KRAS* wild-type mCRC (Table 1).<sup>18</sup> A total of 138 patients were randomly assigned to mFOLFOX6 (folinic acid, 5-FU, and oxaliplatin) or FOLFIRI (folinic acid, 5-FU, and irinotecan) plus cetuximab (loading dose of 400 mg/m<sup>2</sup> followed by 250 mg/m<sup>2</sup> weekly, or 500 mg/m<sup>2</sup> on day 1 and every 2 weeks thereafter) or chemotherapy alone. Patients on the cetuximab-containing arm were found to have improved R0 resection rates for liver metastases (25.7% vs 7.4%,  $P<0.01$ ), objective response rates (57.1% vs 29.4%,  $P<0.01$ ), and median survival time (30.9 vs 21.0 months,  $P=0.013$ ). These results add to those of prior studies suggesting that the addition of an anti-EGFR agent to chemotherapy may be important in improving outcomes, including OS, with conversion therapy.

### Anti-EGFR versus anti-VEGF therapy in combination with first-line chemotherapy

To investigate the potential superiority of anti-VEGF or anti-EGFR therapy in combination with first-line chemotherapy, the Phase III FIRE-3 (AIO KRK-0306) trial randomized patients with *KRAS* wild-type (exon 2) mCRC to treatment with FOLFIRI at standard doses plus cetuximab (400 mg/m<sup>2</sup> on day 1, followed by 250 mg/m<sup>2</sup> weekly) or bevacizumab (5 mg/kg every 2 weeks; Table 1).<sup>19</sup> This study did not meet its primary endpoint of improvement in ORR, as ORR was comparable between arms (62% vs 58% for the cetuximab- vs

bevacizumab-containing arms, respectively; odds ratio (OR): 1.18, 95% CI: 0.85–1.64,  $P=0.183$ ). PFS between the two arms was similar as well (10.0 vs 10.3 months, HR: 1.06, 95% CI: 0.88–1.26,  $P=0.547$ ). Interestingly, however, OS was significantly improved in the cetuximab-containing arm (28.7 vs 25 months, HR: 0.77, 95% CI: 0.62–0.96,  $P=0.017$ ). The presence of a benefit in OS but lack thereof in PFS and ORR for the cetuximab-containing arm is puzzling, but it may be at least partially explained by subsequent therapies that the study patients received. Results from a completed intergroup study comparing first-line treatment with either FOLFOX or FOLFIRI and cetuximab and/or bevacizumab, CALGB 80405, are expected in 2014 and should shed additional light on this subject.<sup>20,21</sup> In the meantime, however, the FIRE-3 results underscore the need for predictive biomarkers to more accurately select patients appropriate for anti-EGFR and/or anti-VEGF therapies.

### Exon 2 *KRAS* wild-type status as a predictive biomarker for anti-EGFR therapy: necessary but not sufficient

While it is known that patients with *KRAS* mutations in codons 12 and 13 (exon 2) do not benefit from the anti-EGFR agents cetuximab and panitumumab, it was unclear whether other *RAS* mutations were negative predictive biomarkers for anti-EGFR therapy as well. A mutational analysis of the Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) study, in which mCRC patients were randomized to FOLFOX4 with or without panitumumab 6 mg/kg IV every 2 weeks, was therefore performed.<sup>22</sup> Tumor tissue samples were analyzed for mutations in *KRAS* exons 3 (codon 61) and 4 (codons 117, 146); *NRAS* exons 2 (codons 12, 13), 3 (codon 61), and 4 (codons 117, 146); and *BRAF* exon 15 (codon 600). Patients without any *RAS* mutations had improved PFS (10.1 vs 7.9 months, HR: 0.72, 95% CI: 0.58–0.90,  $P=0.0004$ ) and OS (26.0 vs 20.2 months, HR: 0.78, 95% CI: 0.62–0.99,  $P=0.04$ ) when panitumumab was added to FOLFOX4 chemotherapy. Additionally, the presence of any *RAS* mutation was associated with inferior PFS and OS with panitumumab–FOLFOX4 treatment.

Similar to the PRIME study, mutational status beyond exon 2 of *KRAS* was found to be important in the FIRE-3 trial as well. When the FIRE-3 patients' tumors were tested for *KRAS* exons 3 (codons 59, 61) and 4 (codons 117, 146); *NRAS* exons 2 (codons 12, 13), 3 (codons 59, 61), and 4 (codons 117, 146); and *BRAF* (V600E), the wild-type *RAS* group demonstrated an increased ORR when treated with FOLFIRI/cetuximab

(76.0% vs 65.2%, Fisher's two-sided  $P=0.044$ ).<sup>23</sup> PFS was comparable in the wild-type *RAS* group treated with cetuximab versus bevacizumab (10.5 vs 10.4 months, HR: 0.94, 95% CI: 0.75–1.19,  $P=0.63$ ), but OS was significantly prolonged with cetuximab (33.1 vs 25.9 months, HR: 0.69, 95% CI: 0.52–0.92,  $P=0.01$ ). Though retrospective, the PRIME and FIRE-3 data emphasize the importance of continued predictive biomarker investigation and discovery based on underlying biologic mechanisms of mCRC.

### Anti-VEGF treatment strategies: controversies regarding optimal choice of agent and sequence

Anti-VEGF therapy in the form of bevacizumab (Avastin<sup>®</sup>; Genentech, Inc., South San Francisco, CA, USA), a monoclonal antibody that targets VEGF-A, has been an important adjunct in the treatment of mCRC for almost a decade (Table 2). Investigations regarding its use, particularly in the second-line setting after progression with bevacizumab-containing chemotherapy, and in combination with capecitabine or erlotinib in the maintenance setting, have been undertaken and recently published.<sup>32,38–40</sup> Additionally, agents with antiangiogenic effects such as aflibercept (Zaltrap<sup>®</sup>; Sanofi-Aventis, Bridgewater, NJ, USA) and regorafenib (Stivarga<sup>®</sup>; Bayer AG, Leverkusen, Germany) have been developed in attempts to maximize anti-VEGF targeting (Table 2). Questions remain regarding optimal treatment settings in which to employ these agents, as well as biomarkers to more accurately predict response to therapy.

### Bevacizumab beyond progression

Bevacizumab has proven clinical efficacy when used in combination with first- or second-line fluorouracil-based chemotherapy.<sup>24–29</sup> Given this efficacy, it was wondered whether bevacizumab was beneficial when continued beyond disease progression on first-line, bevacizumab-containing chemotherapy. Observational studies had previously hypothesized a benefit to bevacizumab beyond progression,<sup>30,31</sup> but recent prospective data confirmed the benefit. In the Phase III ML18147 trial, 820 patients with mCRC with progressive disease after first-line bevacizumab plus chemotherapy were randomized to second-line chemotherapy with or without bevacizumab (2.5 mg/kg IV per week equivalent; Table 1).<sup>32</sup> There was an OS benefit to continuing bevacizumab with chemotherapy in the second-line setting when compared to chemotherapy alone (median OS: 11.2 vs 9.8 months, HR: 0.81, 95% CI: 0.69–0.94, unstratified log-rank tested  $P=0.0062$ ). As a result, maintaining angiogenesis inhibition



through the continued use of bevacizumab while switching chemotherapies after disease progression on first-line regimens has become a standard in the treatment of mCRC patients.

### Bevacizumab plus triplet chemotherapy

Given the efficacy of doublet fluorouracil-based regimens for mCRC (ie, FOLFOX, FOLFIRI), it was wondered whether the combination of 5-FU, irinotecan, and oxaliplatin in the first-line setting would be more efficacious than doublet therapy. The triplet regimen FOLFOXIRI (folinic acid, 5-FU, oxaliplatin and irinotecan) has been studied in two Phase III trials with encouraging results, although sample sizes were small and chemotherapy doses not consistent.<sup>33–35</sup> Given that bevacizumab is relatively well-tolerated in patients without contraindications to its therapy and that it is a standard in combination with doublet chemotherapy, investigators hypothesized that the addition of bevacizumab to triplet chemotherapy may further increase its benefit. The Phase III TRIBE trial randomized 508 untreated mCRC patients to either FOLFOXIRI/bevacizumab (irinotecan 165 mg/m<sup>2</sup>, oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 200 mg/m<sup>2</sup>, 5-FU infusion of 3,200 mg/m<sup>2</sup> over 48 hours, and bevacizumab 5 mg/kg) or FOLFIRI/bevacizumab (irinotecan 180 mg/m<sup>2</sup>, leucovorin 200 mg/m<sup>2</sup>, 5-FU bolus 400 mg/m<sup>2</sup>, followed by 5-FU infusion of 2,400 mg/m<sup>2</sup> over 48 hours, and bevacizumab 5 mg/kg) in order to answer this question (Table 1).<sup>36,37</sup> Of note, therapy was continued for up to 12 cycles and then followed by 5-FU/bevacizumab until disease progression. In this study, treatment with FOLFOXIRI/bevacizumab led to improved median PFS (12.2 vs 9.7 months, HR: 0.73, 95% CI: 0.60–0.88, *P*=0.0012) and response rate (65% vs 53%, *P*=0.006) when compared to FOLFIRI/bevacizumab, but did not increase the R0 secondary resection rate (15% vs 12%, *P*=0.327) or median OS (31.0 vs 25.8 months, HR: 0.79, *P*=0.054). Not unexpectedly, toxicities were greater in the FOLFOXIRI/bevacizumab arm. While these data are not encouraging enough to adopt FOLFOXIRI/bevacizumab as the standard of care in first-line chemotherapy, it can be considered for selected patients.

### Maintenance anti-VEGF and anti-EGFR therapy in mCRC

Another key question with respect to biologic therapy in mCRC involves the use of maintenance anti-VEGF therapy with or without anti-EGFR therapy. The CAIRO-3 study from the Dutch Colorectal Cancer Group (DCCG) sought to investigate the efficacy of maintenance bevacizumab in

mCRC patients who had not progressed after six cycles of induction treatment with capecitabine, oxaliplatin, and bevacizumab (CAPOX-B; Table 1).<sup>38,39</sup> A total of 558 patients were randomized to either observation or maintenance treatment with lower dose, continuous capecitabine 625 mg/m<sup>2</sup> orally twice daily, and bevacizumab 7.5 mg/kg IV every 3 weeks. At first progression (PFS1), patients in both arms were treated with CAPOX-B until second progression (PFS2). Recent updated analysis of this trial demonstrated an improvement in median PFS1 with capecitabine/bevacizumab treatment (8.5 vs 4.1 months, HR: 0.44, 95% CI: 0.37–0.53, *P*<0.0001) and a small but statistically significant improvement in median PFS2 (11.5 vs 10.5 months, HR: 0.81, 95% CI: 0.67–0.98, *P*=0.03), despite a smaller percentage of the maintenance therapy arm receiving CAPOX-B at PFS1 (47% vs 75%).<sup>39</sup> Median time to second progression (TTP2) was improved with maintenance capecitabine/bevacizumab (18.7 vs 14.1 months, HR: 0.67, 95% CI: 0.56–0.82, *P*<0.0001), but OS was not (21.7 vs 18.0 months, HR: 0.87, 95% CI: 0.71–1.06, *P*=0.16). Overall quality of life was not different between the two arms.

To test the hypothesis that combined anti-VEGF and anti-EGFR therapy would be superior to single-agent biologic maintenance therapy, the Phase III Nordic ACT trial was performed (Table 1). In this study, 249 mCRC patients received first-line doublet chemotherapy (XELOX, XELIRI, FOLFOX, or FOLFIRI) and bevacizumab for 18 weeks.<sup>40</sup> Those with at least stable disease at the completion of induction therapy were then randomized to bevacizumab 7.5 mg/kg IV every 3 weeks with or without erlotinib 150 mg daily, an anti-EGFR tyrosine kinase inhibitor. Median PFS was similar between arms (5.7 months for the combination arm vs 4.2 months for bevacizumab alone, HR: 0.79, 95% CI: 0.55–1.12, *P*=0.19), as was median OS from the start of maintenance treatment (21.5 vs 22.8 months, HR: 0.88, 95% CI: 0.61–1.27, *P*=0.51). As expected, higher rates of grades 3 and 4 adverse events were seen with the combination arm (53% vs 13%). As a result, combined anti-VEGF and anti-EGFR maintenance therapy is not a standard at this time.

### Aflibercept: a decoy VEGF receptor

While bevacizumab has proven efficacy in the treatment of mCRC, other agents with antiangiogenic properties have been investigated with the goal of more complete antiangiogenic inhibition. Aflibercept, a recombinant fusion protein containing VEGF-binding portions from the extracellular domains of human VEGF receptors 1 and 2, fused to the Fc portion of human IgG1, is an example of one such agent.<sup>41</sup> Aflibercept

acts as a decoy VEGF receptor, preventing ligands such as VEGF-A, VEGF-B, and placental growth factor (PlGF)-1 and PlGF-2 from binding to their endogenous receptors. After promising early phase clinical trials with aflibercept, the Phase III VELOUR trial randomized 1,226 mCRC patients previously treated with oxaliplatin-based chemotherapy to FOLFIRI plus placebo or FOLFIRI plus aflibercept 4 mg/kg IV every 2 weeks (Table 1).<sup>42</sup> The addition of aflibercept to FOLFIRI improved OS when compared to the addition of placebo to FOLFIRI (median OS 13.50 vs 12.06 months, HR: 0.817, 95% CI: 0.713–0.937,  $P=0.0032$ ). ORR was significantly increased with aflibercept (19.8% vs 11.1%, 95% CI: 8.5%–13.8%,  $P=0.0001$ ), as was PFS (median PFS 6.90 vs 4.67 months, HR: 0.758, 95% CI: 0.661–0.869,  $P<0.0001$ ).

Interestingly, this survival benefit was seen even in the 30% of patients who had previously received bevacizumab. This suggests either that aflibercept's benefit is mechanistically different from bevacizumab, or that the benefit to agents with antiangiogenic properties beyond disease progression in the first-line setting is perhaps not limited to bevacizumab. In any case, the survival benefit of aflibercept is small, and similar benefit has not been seen in other mCRC treatment settings, either as monotherapy or in combination with other chemotherapeutic agents. Furthermore, predictive biomarkers for aflibercept have not yet been discovered, though there is a suggestion that patients with liver-only metastases may benefit from aflibercept more than other patients.<sup>43</sup>

### Regorafenib: an oral multikinase inhibitor for the refractory mCRC setting

Regorafenib, an oral multikinase inhibitor, is an agent recently demonstrated to have efficacy as a single agent in the treatment of refractory mCRC. It inhibits a variety of angiogenic, stromal, and oncogenic kinases, including VEGF receptors (VEGFR)1-3, platelet-derived growth factor receptor- $\beta$  (PDGFR- $\beta$ ), fibroblast growth factor receptor 1 (FGFR1), TIE2, *KIT*, *RET*, and *BRAF*,<sup>44</sup> thereby distinguishing it from bevacizumab and aflibercept. The Phase III CORRECT trial treated a total of 1,513 mCRC patients refractory to therapy to either placebo or regorafenib 160 mg daily for the first 3 weeks out of every 4-week cycle (Table 1).<sup>45</sup> The primary endpoint of OS was met at the second interim analysis. Median OS was improved with regorafenib when compared to placebo (6.4 vs 5.0 months, HR: 0.77, 95% CI: 0.64–0.94, one-sided  $P=0.0052$ ). Median PFS for regorafenib versus placebo was also improved (1.9 vs 1.7 months, HR: 0.49, 95% CI: 0.42–0.58,  $P<0.0001$ ), but ORR were similarly small (1.0%

vs 0.4%,  $P=0.19$ ). Despite the small survival benefit, however, regorafenib treatment led to significant toxicities, with 93% of patients receiving regorafenib experiencing treatment-related adverse events when compared with 61% of patients receiving placebo. Like aflibercept, predictive biomarkers to predict which patients would most benefit from regorafenib have not yet been discovered.

### Future directions for personalized therapy in mCRC

Despite promising data regarding the use of biologic therapy in mCRC, more knowledge is needed to optimize and refine their use in the appropriate patient settings. Recent advances in the molecular characterization of CRC are building a foundation for further refinement of existing drugs and development of new targeted therapies. For example, in 2012, The Cancer Genome Atlas (TCGA) Network published results from multidimensional genomic analyses of 276 human colorectal carcinomas, the first comprehensive study of its kind.<sup>46</sup> These analyses provided insights into pathways dysregulated in CRC, and perhaps more importantly, those amenable to therapeutic targeting. As a result, potential targets under preclinical and clinical investigation for the treatment of CRC include those in the Wnt/beta-catenin pathway, the PI3K/Akt/mTOR pathway, and the TGF- $\beta$  pathway. Analyses such as these from TCGA and others will provide necessary biological infrastructure for the development of more novel and effective therapies for mCRC.

In addition to understanding the biological underpinnings of this complex and often heterogeneous disease, improved knowledge regarding the mechanisms of action of the targeted therapies is needed to employ these most effectively. Once these mechanisms of initial response and intrinsic and acquired resistance are elucidated, development of accurate predictive biomarkers should be possible. As the FIRE-3 and PRIME data demonstrate, even currently established predictive biomarkers such as *KRAS* exon 2 mutations are not the definitive answer for anti-EGFR therapy selection; furthermore, biomarkers for the anti-VEGF agents are lacking. Availability of robust markers of response based on biological mechanisms of disease and therapy will not only minimize ineffective treatments for mCRC patients, but also improve response rates and survival benefits of established and novel drugs through accurate patient selection and therapy matching.

### Conclusion

mCRC remains a significant cause of cancer-related death worldwide. While advances in drug development over the last

two decades have expanded the number of therapies at our disposal for this disease, several significant challenges regarding the optimization of these therapies remain. Better understanding of the mechanisms of action of our targeted therapies such as cetuximab, panitumumab, bevacizumab, aflibercept, and regorafenib is needed to determine the most appropriate patients to treat with these agents. Insight into the effects of combining targeted therapies with cytotoxic chemotherapy, as well as the best sequence of agents to employ, is vital. Knowledge of potential resistance mechanisms of targeted agents, both intrinsic and acquired, will also play a key role in the treatment of this complex disease. Finally, development of new agents, predictive biomarkers, and more effective combinatorial therapy will be possible through scientific knowledge gleaned through emerging molecular technologies.

## Disclosure

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