Published in final edited form as:
Gastroenterol Clin North Am. 2010 September ; 39(3): 601–613. doi:10.1016/j.gtc.2010.08.017.

Targeted Therapeutic Agents for Colorectal Cancer

Cheng E. Chee, MD[a] and **Frank A. Sinicrope, MD**[a,b,*]

[a]Division of Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[b]Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN, USA

Abstract

Colorectal cancer (CRC) is the third most incident cancer and cause of cancer-related deaths in the United States. In 2009, the number of new cases of CRC in the United States was estimated at 146,970 with 49,920 deaths expected from this malignancy.[1] The incidence and mortality rate of CRC have continued to decline largely owing to improved screening efforts that lead to early detection and removal of precancerous polyps and improvements in anticancer treatment. Despite current therapies, approximately 40% to 50% of patients with CRC who undergo potentially curative surgery ultimately relapse and die of metastatic disease.[2] In addition, approximately 20% of patients with CRC present with metastases (stage IV disease) at diagnosis, for which palliative systemic therapy is the primary treatment modality.[3] Although the medical management of CRC has steadily improved, the focus of this review is on the use of molecular targeted agents for the treatment of CRC. The objective of targeted anticancer therapeutics is to disrupt specific steps in the molecular pathway of tumorigenesis, with the goal of tumor regression while producing minimal systemic toxicity.

Keywords

Colorectal cancer; Targeted therapy; VEGF; EGFR

SYSTEMIC CHEMOTHERAPY FOR ADVANCED CRC

The backbone of systemic chemotherapy for metastatic CRC consists of 5-fluorouracil (5-FU) and folinic acid (FA, also known as leucovorin), a regimen used for many years that achieves response rates of approximately 20% and a median survival of 11 months compared with 5 months with best supportive care (BSC).[4] The platinum analogue oxaliplatin and irinotecan (CPT-11), a topoisomerase 1 inhibitor, were later added to the 5-FU/FA backbone, and it was observed that the combination chemotherapy produced higher response rates (35%–53%) and prolonged progression-free survival (PFS) (5–8 months) and overall survival (14–18 months).[5–8] The standard combination chemotherapy in the first-line setting includes 5-FU/FA and oxaliplatin (FOLFOX) or 5-FU/FA and irinotecan (FOLFIRI). FOLFOX and FOLFIRI have shown equivalent clinical activity but have different safety profiles, with peripheral sensory neuropathy occurring with oxaliplatin and gastrointestinal toxicity being more frequent with irinotecan.[9, 10] Substitution of 5-FU/FA with the oral fluoropyrimidine capecitabine (Xeloda) has been tested in combination with oxaliplatin (XELOX) or with irinotecan (XELIRI), and the capecitabine-based combinations have

*Corresponding author. Divisions of Oncology, Gastroenterology & Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. sinicrope.frank@mayo.edu.

The authors have nothing to disclose.

shown similar efficacy to their equivalent 5-FU–based combinations.[11–13] Capecitabine is an oral agent that is metabolized to 5-FU in vivo and has been shown to be at least as effective as intravenous 5-FU.[14–16] The side-effect profile of capecitabine differs from bolus 5-FU in that a lower incidence of myelosuppression, mucositis, and diarrhea is observed, but the incidence of hand-foot syndrome was higher in the capecitabine treatment arms.[14, 16]

TARGETED THERAPY IN CRC

The 2 signaling pathways important in the growth and metastatic potential of human CRCs include the vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways. Molecular targeted agents against VEGF and EGFR have been developed, and in clinical trials, they have shown to enhance the efficacy of cytotoxic chemotherapy in patients with advanced CRC. Based on these data, anti-VEGF (bevacizumab, Avastin) and anti-EGFR (cetuximab, Erbitux; panitumumab, Vectibix) monoclonal antibodies were approved by the US Food and Drug Administration (FDA) for the treatment of advanced CRC.

Angiogenesis Inhibitors

Angiogenesis results in the formation of new blood vessels, and in tumors, this process promotes tumor growth and metastasis. The VEGF family, composed of VEGFs and VEGF receptors (VEGFRs), regulates the process of angiogenesis, and various strategies have evolved to inhibit this signaling pathway.[17] Bevacizumab is a humanized monoclonal antibody that binds to VEGF-A, thereby preventing the binding of this growth factor to its associated VEGFRs.[17, 18] Besides inhibiting angiogenesis, it has been postulated that anti-VEGF therapy can transiently normalize tumor vasculature and improve drug and oxygen delivery to tumor cells, making them more chemosensitive and radiosensitive.[19] The potential role for bevacizumab in the treatment of CRC was initially shown in a phase 2 trial that compared 2 doses of bevacizumab in combination with 5-FU/FA with 5-FU/FA alone in patients with metastatic CRC. This study showed that the bevacizumab combinations produced improved response rates and extended median time to disease progression and median survival rates and favored the lower bevacizumab dose of 5 mg/kg.[20] This study led to the pivotal randomized phase 3 trial that gained the approval of bevacizumab in the United States in 2004 as the first-line agent in the treatment of metastatic CRC (Table 1).[21] When compared with the irinotecan and 5-FU/FA combination (coined IFL), the addition of bevacizumab to IFL showed improved median survival (20.3 vs 15.6 months, hazard ratio [HR] 0.66, $P<.001$), response rates (44.8% vs 34.8%, $P = .004$), and median duration of response (10.4 vs 7.1 months, HR 0.62, $P = .001$).[21] Grade 3 hypertension was more common in the bevacizumab group but was easily treated with antihypertensives.[21] Bevacizumab has also shown improved clinical efficacy with a comparable safety profile, when combined with the current standard oxaliplatin- and irinotecan-based regimens for advanced CRC.[21–23]

Bevacizumab is at present approved by the FDA for use in the first and second-line treatment of metastatic CRC. At present, in the United States, first-line therapy for patients with advanced CRC is combination chemotherapy of FOLFOX, XELOX or FOLFIRI, all given in combination with bevacizumab. The role of bevacizumab beyond the first progression was analyzed in the Bevacizumab Regimens: Investigation of Treatment Effects (BRiTE) study, which showed an improved overall survival with continued VEGF inhibition with bevacizumab beyond the initial progression of disease.[24] This study supports the hypothesis that continued suppression of the VEGF pathway may be important to maximize the clinical benefit of bevacizumab in metastatic CRC.[24] Further data supporting this hypothesis include observations of a rebound increase in VEGF concentration in human tumors and rapid tumor growth in mouse xenograft models after stopping the administration

of a VEGF inhibitor.[25] Bevacizumab was approved as a second-line agent in metastatic CRC treatment after the Eastern Cooperative Oncology Group (ECOG) 3200 trial demonstrated that the combination of FOLFOX with bevacizumab significantly improved PFS (7.3 vs 4.7 months) and median survival (12.9 vs 10.8 months) compared with FOLFOX alone.[26] The role of bevacizumab in addition to chemotherapy to increase the resectability of liver metastasis has been explored by several small studies.[27, 28] One study showed that the use of bevacizumab with chemotherapy in a preoperative setting can achieve a high objective tumor response rate of 73% and the treatment was also safe, whereby the incidence of wound and bleeding complications and liver dysfunction was not increased.[28] Confirmation of the ability of bevacizumab to enable more patients to undergo resection of hepatic metastases requires larger studies.

The most common side effects from bevacizumab are hypertension, which is seen in 11% to 24% of cases, and the potential for bleeding, gastrointestinal perforations (1.5%–2% of patients), arterial thrombotic events (approximately 4%–5%), and proteinuria.[29, 30] In clinical practice, bevacizumab can be given to patients with advanced CRC with intact primary tumors, and in circumstances in which surgery is planned, the drug administration is generally stopped 4 weeks before surgery so as not to increase bleeding or interfere with wound healing.[31] At present, there are no predictive biomarkers available to predict which patient cohorts may benefit most from bevacizumab therapy. Expression of VEGF protein in human CRC tissues has not correlated with the clinical outcome of bevacizumab therapy.[32]

A variety of novel molecules, which target the VEGF signaling pathway, are currently under investigation. Vatalanib and axitinib are tyrosine kinase inhibitors that block VEGFR-1, VEGFR-2, and VEGFR-3. Vatalanib was studied in the first and second-line setting in the Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases (CONFIRM) 1 and 2 trials, respectively, and no significant benefit was observed in the treatment of metastatic CRC when vatalanib was combined with FOLFOX.[33, 34] Targeted agents, which are currently being tested in the first-line setting for metastatic CRC, include a phase 1 or 2 trial of axitinib and bevacizumab, a phase 3 trial of cediranib (tyrosine kinase inhibitor to VEGFR-1, VEGFR-2, VEGFR-3, and c-kit) with FOLFOX,[35] a phase 2 trial of aflibercept (VEGF Trap) and FOLFOX,[35] and a phase 3 trial of sunitinib (oral multitarget tyrosine kinase inhibitor) with FOLFIRI.[35] In the second-line setting, ongoing clinical trials include a phase 3 trial of aflibercept and FOLFIRI,[35] a phase 3 trial of brivanib (dual kinase inhibitor of VEGFR-2 and fibroblast growth factor) with cetuximab,[35] a phase 2 trial of axitinib with FOLFOX or FOLFIRI,[35] and a phase 1b study of AMG 706 (tyrosine kinase inhibitor to VEGF, platelet-derived growth factor, and c-kit) with panitumumab in addition to FOLFOX or FOLFIRI.[36]

EGFR Inhibitors

EGFR expression in tumor cell membranes is detected in approximately two-thirds of human CRC and is an adverse prognostic marker in this malignancy.[37] Cetuximab is a chimeric IgG1 monoclonal antibody against EGFR.[38, 39] By binding to the extracellular domain of the human EGFR, cetuximab competitively inhibits the binding of epidermal growth factor (EGF) and other ligands to EGFR, blocking receptor phosphorylation and activation of receptor-associated kinases, thereby inhibiting downstream signal transduction and resulting in the inhibition of cell proliferation, induction of apoptosis, and reduction in angiogenesis.[38–40] EGFR is upregulated in 60% to 80% of CRC cases.[41, 42] Initial in vivo studies on human colon cancer cells xenografted into nude mice indicated that cetuximab enhanced antitumor activity when combined with irinotecan.[43] Subsequent clinical trials validated these findings. In a phase 2 clinical trial, single-agent cetuximab was used to treat patients with advanced and treatment-refractory CRC with prior exposure to irinotecan either alone or in a combination regimen. Partial response was achieved in 10.5% of 57

evaluable patients, and the median survival time was 6.4 months.[44] The activity of cetuximab in combination with irinotecan in refractory metastatic CRC was confirmed in the Bowel Oncology with Cetuximab Antibody (BOND) trial that showed a significantly higher response rate and median time to progression (TTP) in the combination arm compared with cetuximab alone (22.9% versus 10.8%, $P = .007$ and 4.1 versus 1.5 months, $P < .001$, respectively) (see Table 1).[41] In contrast to bevacizumab, cetuximab shows activity as monotherapy with an approximate 10% response rate in patients with advanced CRC.[26, 41] Cetuximab monotherapy was shown to be superior to BSC in patients who had been either previously treated with a fluoropyrimidine-, irinotecan-, and oxaliplatin-based regimen or had contraindications to treatment with these drugs.[45] In this study, cetuximab improved overall survival (HR 0.77; 95% confidence interval [CI], 0.64–0.92; $P = .005$) with a median survival of 6.1 months in the cetuximab group compared with 4.6 months in the BSC group and it also preserved quality-of-life measures.[45] The administration of anti-EGFR monoclonal antibodies can cause an acneiform rash in more than 80% of patients, with the incidence of grade 3 or 4 skin rash in less than 10% of patients.[25] Other side effects include hypomagnesemia, diarrhea, and hypersensitivity reactions, particularly with the chimeric antibody cetuximab.[30] Cetuximab is FDA approved as a single agent in metastatic CRC treatment after the failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. Cetuximab is also approved in combination with irinotecan in patients with metastatic CRC who are refractory to irinotecan-based chemotherapy.

Panitumumab is a high-affinity fully human IgG2 monoclonal antibody that also targets EGFR.[46] In a phase 2 trial of heavily pretreated patients with metastatic CRC, single-agent panitumumab had a median PFS of 14 weeks and median overall survival of 9 months.[47] The overall response rate of 9% was similar to single-agent cetuximab. Skin toxicities occurred in 95% of patients but were rarely severe, and there was a very low incidence of hypersensitivity reactions (1 of 148 patients) when compared with cetuximab.[47] This led to a pivotal phase 3 trial that led to the approval of panitumumab as a single-agent salvage therapy for patients with metastatic CRC in the United States (see Table 1).[48] In this study, patients previously exposed to fluoropyrimidine-, irinotecan-, or oxaliplatin-based treatment were randomized to panitumumab and BSC versus BSC alone. Results demonstrated that panitumumab, in a third-line setting, was superior to BSC alone with a response rate of 10% and PFS of 8 weeks versus 7.3 weeks (HR 0.54; 95% CI, 0.44–0.66; $P < .0001$). Overall survival was not significantly different because 76% of the patients crossed over from the BSC arm to the panitumumab arm.[48] Panitumumab monotherapy was approved in patients with metastatic CRC with progression on or after fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Predictive Biomarkers for Anti-EGFR Therapy

The use of biomarkers to predict the clinical outcomes of EGFR-targeted therapy in metastatic CRC has been highlighted recently. Several trials with cetuximab and panitumumab have noted an intriguing correlation between rash intensity and survival outcomes, whereby the higher the grade of skin rash, the better the clinical outcome.[41, 44, 48] This finding suggests that the intensity of the skin rash induced by anti-EGFR antibodies can serve as a predictive marker of therapeutic efficacy.

The most important recent development is the finding that the mutational status of *KRAS* oncogene is a predictive biomarker for the efficacy of anti-EGFR therapies.[49–53] *KRAS* encodes for the RAS protein, which functions as a GTPase that is involved in signal transduction events, and loss of RAS is associated with hyperproliferation.[54, 55] Mutation in the codons 12 and 13 of *KRAS* gene is present in approximately 40% of human CRCs and is an early event in tumorigenesis such that the frequency of mutation is not affected by the

tumor stage.[55] When *KRAS* status was determined on archived tissue from completed anti-EGFR clinical trials in CRC, improved clinical outcomes were observed in patients with wild-type *KRAS* tumors but not in those with mutant *KRAS* tumors.[49, 51, 56, 57] When cetuximab was compared with BSC, overall survival was nearly doubled in tumors with wild-type *KRAS* compared with CRCs with mutated *KRAS* (9.5 vs 4.8 months; HR 0.55; 95% CI, 0.41–0.74; $P<.001$).[51] Importantly, patients whose tumors had mutated *KRAS* showed no significant difference in outcomes between cetuximab therapy and BSC.[51] Similar observations have been noted with panitumumab. Using archived tissue from a phase 3 trial comparing panitumumab monotherapy with BSC, patients with wild-type *KRAS* tumors who were treated with panitumumab had a response rate of 17% and a median PFS of 12.3 weeks versus 7.3 weeks in patients with wild-type *KRAS* tumors who were in the BSC group (HR 0.45; 95% CI, 0.34–0.59; $P<.0001$).[49] In the patients with mutated *KRAS* tumors, the response rate was 0% and PFS was identical, that is, 7.4 weeks versus 7.3 weeks (HR 0.99; 95% CI, 0.73–1.36) in the panitumumab versus BSC study arms.[49]

The RAS/RAF/MAPK signaling pathway occurs downstream from EGFR pathway. Once RAS is activated, it recruits the oncogene *RAF* that phosphorylates MAP2K-1 and MAP2K-2, thus initiating MAPK signaling that ultimately leads to expression of proteins involved in cell proliferation, differentiation, and survival.[58–60] More recently, mutations in the *BRAF* oncogene have been shown to be another potential predictive marker for response to anti-EGFR therapy. Mutations in *BRAF* oncogene are detected in approximately 10% of sporadic CRCs.[61, 62] Tumors with mutations in the *BRAF* gene do not respond to EGFR inhibitors, and patients with mutant *BRAF* tumors have been shown to have significantly shorter PFS and overall survival rates compared with patients whose tumors carry wild-type *BRAF*.[61, 62] Although mutations in *BRAF* and loss of PTEN expression seem to be associated with resistance to EGFR-targeted monoclonal-antibody treatment, these markers require validation before they can be used in clinical practice.[63] At present, all patients with a new diagnosis of metastatic CRCshould be tested for *KRAS* mutation in the tumor sample, and the use of cetuximab or panitumumab should be restricted to patients with CRCs containing wild-type*KRAS*.

Based on the results outlined earlier, the idea of combining the agents targeting both VEGF and EGFR pathways has been tested. The use of combined targeted therapy in refractory CRC was an attractive concept, with the potential to eliminate the use of conventional cytotoxic drugs. This concept was first highlighted in the BOND-2 study, in which the combination of bevacizumab and cetuximab was used as a salvage therapy in heavily pretreated patients with metastatic CRC.[64] This study showed a modest response rate of 20% for combined targeted therapy with a 4.9-month median TTP when compared with an approximate 10% response rate and 1.5-month median TTP reported in previous studies.[41, 44] Two prospective randomized phase 3 trials, Capecitabine, Irinotecan, and Oxaliplatin in advanced colorectal cancer (CAIRO)-2 and Panitumumab Advanced Colorectal Cancer Evaluation (PACCE), were subsequently performed in an attempt to validate these findings but showed inferior outcomes and increased toxicities with the combination of anti-VEGF and anti-EGFR treatment and chemotherapy.[65, 66] Based on these results, anti-VEGF and anti-EGFR antibodies should not be used concurrently in patients with CRC in clinical practice outside a clinical trial. Other strategies under investigation include combining an anti-EGFR antibody with a small molecule such as a tyrosine kinase inhibitor against EGFR, such as erlotinib (Tarceva). In preclinical studies, this combination has shown synergistic effects compared with either drug alone, and phase 2 trials are currently ongoing to evaluate this strategy.[67–69]

ADJUVANT THERAPY

Patients with stage II and III (lymph node-positive) CRC, resected with curative intent, are candidates for adjuvant systemic chemotherapy. As 5-FU/FA was the standard treatment of advanced CRC, this regimen was later evaluated in the adjuvant setting and found to be effective, with 2 studies demonstrating an improvement in 3-year overall survival by 5%, when 5-FU/FA was compared with observation only.[70–73] In the late 1990s, when FOLFOX showed superiority over 5-FU/FA alone in the metastatic setting, the use of FOLFOX in the adjuvant setting was then evaluated in the Multicenter International Study of Oxaliplatin/5-fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial.[74] This was a European multi-institution trial that compared infusional 5-FU/FA with and without the addition of oxaliplatin in stage II and III disease.[74] The overall 5-year disease-free survival (DFS) was 73.3% versus 67.4%, with and without oxaliplatin, respectively, for stage II and III disease combined. For stage III disease, 6-year overall survival rates were 78.5% and 76% in the FOLFOX and 5-FU/FA groups, respectively (HR 0.84; 95% CI, 0.71–1.00; $P = .046$), with no significant difference in the stage II group.[75] Peripheral neuropathy, a known side effect of oxaliplatin, was well tolerated and generally reversible. The MOSAIC data were later confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial revealing a 6% benefit in 4-year DFS for the oxaliplatin-containing regimen in stage II and III disease.[76] A similar 20% reduction in recurrence was seen in both the stages. Based on these data, the US FDA approved the use of oxaliplatin in adjuvant therapy, and FOLFOX has now become the new standard of care for stage III disease. Besides stage III disease, considerations for adjuvant therapy should be made in the treatment of high-risk stage II disease. However, in rectal cancer, preoperative or neoadjuvant chemoradiation is a standard approach in the United States because of the potential advantages of increased radiosensitivity in the unoperated pelvis and enhanced sphincter preservation.[77]

Despite its enhanced efficacy with advanced CRC, bevacizumab has not been shown to be active in an adjuvant setting. The NSABP C-08 trial reported that the addition of bevacizumab to modified FOLFOX-6 in patients with stage II and III CRC did not significantly prolong DFS, although a transient benefit was seen during the 1-year interval when bevacizumab was used.[78] Furthermore, grade 31 toxicities such as hypertension, wound complications, pain, and proteinuria may not substantiate its use and tolerability in the long term in this patient population.[29] Although it is possible that a longer duration of bevacizumab therapy may be required to obtain potential benefit, it must be emphasized that this drug, given in combination with a standard adjuvant regimen, was ineffective in the adjuvant setting. The results of the AVANT study, another adjuvant trial using bevacizumab and chemotherapy in patients with high-risk stage II and III CRC, will be reported soon. The North Central Cancer Treatment Group conducted a phase 3 intergroup trial (N0147) assessing the potential benefit of adding the anti-EGFR antibody cetuximab to a modified FOLFOX-6 regimen as adjuvant therapy in patients with completely resected stage III colon cancer.[79] The recently reported results of this study showed that the addition of cetuximab to modified FOLFOX-6 was of no benefit for patients with resected stage III wild-type *KRAS* CRC.[80]

SUMMARY

The development of molecular targeted therapies has greatly affected the current treatment of patients with advanced CRC. Agents targeting the VEGF or EGFR pathways have been shown to increase the efficacy of cytotoxic chemotherapy resulting in the extension of survival and have led to newer regimens that are now the standard of care for the treatment of metastatic CRC. Although associated with some adverse effects, these agents are

considerably better tolerated than conventional cytotoxic agents. Regrettably, attempts to move targeted therapies to earlier stage disease have yet to show any clinical benefit. Another important advance is the identification of predictive biomarkers for anti-EGFR therapies. Specifically, clinical benefit of anti-EGFR antibody therapy is restricted to CRCs with wild-type *KRAS* oncogene, and *KRAS* testing should now be performed in tumor samples of all patients with metastatic CRC. These data, as well as emerging data for other predictive biomarkers, can enable individualized treatment decisions and more personalized therapeutic approaches. The continued development of molecular targeted therapies holds much promise for further improvement in patient outcomes and in quality of life for patients with CRC.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59(4):225–249. [PubMed: 19474385]
2. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum. 1997; 40(1):15–24. [PubMed: 9102255]
3. Wagner AD, Arnold D, Grothey AA, et al. Anti-angiogenic therapies for metastatic colorectal cancer. Cochrane Database Syst Rev. 2009; 3 CD005392.
4. Scheithauer W, Rosen H, Kornek GV, et al. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ. 1993; 306(6880):752–755. [PubMed: 7683942]
5. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000; 18(16):2938–2947. [PubMed: 10944126]
6. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000; 355(9209):1041–1047. [PubMed: 10744089]
7. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2000; 18(1):136–147. [PubMed: 10623704]
8. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. N Engl J Med. 2000; 343(13):905–914. [PubMed: 11006366]
9. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004; 22(2):229–237. [PubMed: 14657227]
10. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the gruppo oncologico dell'italia meridionale. J Clin Oncol. 2005; 23(22):4866–4875. [PubMed: 15939922]
11. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008; 26(12):2006–2012. [PubMed: 18421053]
12. Porschen R, Arkenau HT, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol. 2007; 25(27):4217–4223. [PubMed: 17548840]
13. Skof E, Rebersek M, Hlebanja Z, et al. Capecitabine plus Irinotecan (XELIRI regimen) compared to 5-FU/LV plus Irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. BMC Cancer. 2009; 9:120. [PubMed: 19386096]
14. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001; 19(21):4097–4106. [PubMed: 11689577]

15. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer. 2004; 90(6):1190–1197. [PubMed: 15026800]
16. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol. 2001; 19(8):2282–2292. [PubMed: 11304782]
17. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993; 362(6423):841–844. [PubMed: 7683111]
18. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol. 2001; 19(3):843–850. [PubMed: 11157038]
19. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005; 307(5706):58–62. [PubMed: 15637262]
20. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003; 21(1):60–65. [PubMed: 12506171]
21. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004; 350(23):2335–2342. [PubMed: 15175435]
22. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol. 2008; 26(21):3523–3529. [PubMed: 18640933]
23. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008; 26(12):2013–2019. [PubMed: 18421054]
24. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol. 2008; 26(33):5326–5334. [PubMed: 18854571]
25. Van Cutsem, E. First-line treatment: approaches with cytotoxic and biologic agents. In: Chu, E., editor. New treatment strategies for metastatic colorectal cancer. New York: CMPMedica; 2008. p. 21-46.
26. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated meta-static colorectal cancer: results from the eastern cooperative oncology group study E3200. J Clin Oncol. 2007; 25(12): 1539–1544. [PubMed: 17442997]
27. Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC Cancer. 2007; 7:91. [PubMed: 17537235]
28. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol. 2008; 26(11):1830–1835. [PubMed: 18398148]
29. Allegra CJ, Yothers G, O'Connell MJ, et al. Initial safety report of NSABP C-08: a randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol. 2009; 27(20):3385–3390. [PubMed: 19414665]
30. Grothey A. Recognizing and managing toxicities of molecular targeted therapies for colorectal cancer. Oncology (Williston Park). 2006; 20(14 Suppl 10):21–28. [PubMed: 17354514]
31. Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. J Clin Oncol. 2008; 26(32):5254–5260. [PubMed: 18854565]

32. Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. J Clin Oncol. 2006; 24(2):217–227. [PubMed: 16365183]
33. Hecht JR, Trarbach T, Jaeger E, et al. A randomized, double-blind, placebo-controlled, phase III study in patients (Pts) with metastatic adenocarcinoma of the colon or rectum receiving first-line chemotherapy with oxaliplatin/5-fluorouracil/leucovorin and PTK787/ZK 222584 or placebo (CONFIRM-1). J Clin Oncol. 2005; 23(16S) LBA3.
34. Kohne K, Bajetta E, Lin E, et al. Final results of CONFIRM 2: A multinational, randomized, double-blind, phase III study in 2nd line patients (pts) with meta-static colorectal cancer (mCRC) receiving FOLFOX4 and PTK787/ZK 222584 (PTK/ZK) or placebo. J Clin Oncol. 2007; 25(18S): 4033. [PubMed: 17827451]
35. US National Institute of Health. [Accessed March 11] 2010. Available at: www.clinicaltrials.gov.
36. Schwartzberg LS, Hurwitz H, Stephenson J, et al. Safety and pharmacokinetics (PK) of AMG 706 with panitumumab plus FOLFIRI or FOLFOX for the treatment of patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol. 2007; 25(18S):4081.
37. Rego RL, Foster NR, Smyrk TC, et al. Prognostic effect of activated EGFR expression in human colon carcinomas: comparison with EGFR status. Br J Cancer. 2010; 102(1):165–172. [PubMed: 19997103]
38. Baselga J. The EGFR as a target for anticancer therapy–focus on cetuximab. Eur J Cancer. 2001; 37(Suppl 4):S16–S22. [PubMed: 11597400]
39. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res. 1995; 1(11):1311–1318. [PubMed: 9815926]
40. Graham J, Muhsin M, Kirkpatrick P. Cetuximab. Nat Rev Drug Discov. 2004; 3(7):549–450. [PubMed: 15272498]
41. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004; 351(4):337–345. [PubMed: 15269313]
42. Messa C, Russo F, Caruso MG, et al. TGF-alpha, and EGF-R in human colorectal adenocarcinoma. Acta Oncol. 1998; 37(3):285–289. [PubMed: 9677101]
43. Prewett MC, Hooper AT, Bassi R, et al. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. Clin Cancer Res. 2002; 8(5):994–1003. [PubMed: 12006511]
44. Saltz LB, Meropol NJ, Loehrer PJ Sr, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol. 2004; 22(7): 1201–1208. [PubMed: 14993230]
45. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007; 357(20):2040–2048. [PubMed: 18003960]
46. Yang XD, Jia XC, Corvalan JR, et al. Development of ABX-EGF, a fully human anti-EGF receptor monoclonal antibody, for cancer therapy. Crit Rev Oncol Hematol. 2001; 38(1):17–23. [PubMed: 11255078]
47. Hecht JR, Patnaik A, Berlin J, et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. Cancer. 2007; 110(5):980–988. [PubMed: 17671985]
48. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007; 25(13):1658–1664. [PubMed: 17470858]
49. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008; 26(10):1626–1634. [PubMed: 18316791]
50. Lievre A, Bachet JB, Le Corre D, et al. KRASmutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006; 66(8):3992–3995. [PubMed: 16618717]
51. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359(17):1757–1765. [PubMed: 18946061]

52. Di Fiore F, Van Cutsem E, Laurent-Puig P, et al. Role of KRAS mutation in predicting response, progression-free survival, and overall survival in irinotecan-refractory patients treated with cetuximab plus irinotecan for a metastatic colorectal cancer: Analysis of 281 individual data from published series. J Clin Oncol. 2008; 26(Suppl 20):4035. [PubMed: 18711195]
53. Lievre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol. 2008; 26(3):374–379. [PubMed: 18202412]
54. Bos JL. Ras oncogenes in human cancer: a review. Cancer Res. 1989; 49(17):4682–4689. [PubMed: 2547513]
55. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61(5):759–767. [PubMed: 2188735]
56. Bokemeyer C, Bondarenko I, Hartmann JT, et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: the OPUS experience. J Clin Oncol. 2008; 26(15S):4000.
57. Van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. J Clin Oncol. 2008; 26(15S):2.
58. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001; 2(2):127–137. [PubMed: 11252954]
59. Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res. 2006; 12(18):5268–5272. [PubMed: 17000658]
60. McCubrey JA, Steelman LS, Abrams SL, et al. Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance. Adv Enzyme Regul. 2006; 46:249–279. [PubMed: 16854453]
61. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008; 26(35):5705–5712. [PubMed: 19001320]
62. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. N Engl J Med. 2009; 361(1):98–99. [PubMed: 19571295]
63. Siena S, Sartore-Bianchi A, Di Nicolantonio F, et al. Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer. J Natl Cancer Inst. 2009; 101(19):1308–1324. [PubMed: 19738166]
64. Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. J Clin Oncol. 2007; 25(29):4557–4561. [PubMed: 17876013]
65. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009; 360(6):563–572. [PubMed: 19196673]
66. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009; 27(5):672–680. [PubMed: 19114685]
67. Bos M, Mendelsohn J, Kim YM, et al. PD153035, a tyrosine kinase inhibitor, prevents epidermal growth factor receptor activation and inhibits growth of cancer cells in a receptor number-dependent manner. Clin Cancer Res. 1997; 3(11):2099–2106. [PubMed: 9815602]
68. Matar P, Rojo F, Cassia R, et al. Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting. Clin Cancer Res. 2004; 10(19):6487–6501. [PubMed: 15475436]
69. Huang S, Armstrong EA, Benavente S, et al. Dual-agent molecular targeting of the epidermal growth factor receptor (EGFR): combining anti-EGFR antibody with tyrosine kinase inhibitor. Cancer Res. 2004; 64(15):5355–5362. [PubMed: 15289342]
70. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol. 1993; 11(10):1879–1887. [PubMed: 8410113]

71. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995; 345(8955):939–944. [PubMed: 7715291]

72. O'Connell MJ, Mailliard JA, Kahn MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol. 1997; 15(1):246–250. [PubMed: 8996149]

73. Zaniboni A, Labianca R, Marsoni S, et al. GIVIO-SITAC 01: a randomized trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma–long term results and evaluation of the indicators of health-related quality of life. Gruppo Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adiuvante Colon. Cancer. 1998; 82(11):2135–2144. [PubMed: 9610692]

74. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004; 350(23):2343–2351. [PubMed: 15175436]

75. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009; 27(19):3109–3116. [PubMed: 19451431]

76. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007; 25(16):2198–2204. [PubMed: 17470851]

77. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004; 351(17):1731–1740. [PubMed: 15496622]

78. Wolmark N, Yothers G, O'Connell MJ, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2009; 27(18S) LBA4.

79. Alberts SR, Sinicrope FA, Grothey A. N0147: a randomized phase III trial of oxaliplatin plus 5-fluorouracil/leucovorin with or without cetuximab after curative resection of stage III colon cancer. Clin Colorectal Cancer. 2005; 5(3):211–213. [PubMed: 16197625]

80. Alberts SR, Sargent DJ, Smyrk TC, et al. Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (pts) with resected stage III colon cancer (CC): results from NCCTG Intergroup Phase III Trial N0147. J Clin Oncol. 2010; 28(Suppl 18) CRA3507.

Table 1

Targeted therapy in metastatic colorectal cancer

Study	No. of Patients	Study Type	Response Rate	Median TTP	Median PFS	Median OS	References
First-line Therapy							
5-FU/FA	36	Phase 2	17%	5.2 mo	—	13.8 mo	20
5-FU/FA and Bevacizumab[a]	35		40% (*P* = .029)	9.0 mo (*P* = .005)	—	21.5 mo	
IFL	411	Phase 3	34.8%	—	6.2 mo	15.6 mo	21
IFL/Bevacizumab	402		44.8% (*P* = .004)	—	10.6 mo (*P*<.001)	20.3 mo (*P*<.001)	
FOLFOX-4 or XELOX	701	Phase 3	49%	—	8.0 mo	19.9 mo	23
FOLFOX-4 or XELOX with Bevacizumab	699		47% (*P* = .31)	—	9.4 mo (*P* = .002)	21.3 mo (*P* = .08)	
Second-line Therapy							
FOLFOX-4	291	Phase 3	8.6%	—	4.7 mo	10.8 mo	26
FOLFOX-4/Bevacizumab	286		22.7% (*P*<.0001)	—	7.3 mo (*P*<.0001)	12.9 mo (*P* = .001)	
Cetuximab	111	Phase 2	10.8%	1.5	—	6.9 mo	41
Cetuximab/Irinotecan	218		22.9% (*P* = .007)	4.1 mo (*P*<.001)	—	8.6 mo	
BSC	285	Phase 2	0%	—	—	4.6 mo	45
Cetuximab/BSC	287		8% (*P*<.001)	—	—	6.1 mo (*P* = .005)	
BSC	232	Phase 3	0%	—	1.8 mo	—	48
Panitumumab/BSC	231		10% (*P*<.0001)	—	2.0 mo (*P*<.0001)	—	
Cetuximab/Bevacizumab	40	Phase 2	20%	4.9 mo	—	11.4 mo	64
Cetuximab/Bevacizumab/ Irinotecan	43		37%	7.3 mo	—	14.5 mo	

Abbreviations: BSC, best supportive care; IFL, irinotecan, bolus 5-fluorouracil and folinic acid; OS, overall survival; TTP, time to progression; PFS, progression free survival.

[a]Using bevacizumab at 5 mg/kg.