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An Update on Randomized Clinical Trials in Metastatic Colorectal Carcinoma

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Keywords

Metastatic colorectal cancer; randomized control trial; chemotherapy; monoclonal antibody

Introduction

There have been remarkable advances in the treatment of metastatic colorectal cancer (mCRC) for the last 20 years. Metastasectomy has been associated with the significant survival advantage and indeed even the potential for cure. In some patients with initially unresectable metastases who respond well to systemic therapy, it may be possible to “convert to resectable” disease. However, in patients with unresectable metastatic disease, advances in therapies have directly resulted in an improvement of median overall survival from approximately 11–12 months in the 5-FU single agent era, to more than 24 months with sequential multi-agent regimens in the modern era (Figure 1). These advances have been a direct result of a number of landmark trials which have defined the current standard of care.

Current NCCN guidelines for advanced or mCRC recommends use of a doublet regimens (oxaliplatin-based: FOLFOX or CAPOX, irinotecan-based: FOLFIRI) with monoclonal antibody agent (anti-VEGF agent bevacizumab or anti-EGFR agents cetuximab or panitumumab [for RAS wild-type tumors]) as initial therapy. For appropriate patients a triplet cytotoxic backbone of 5-FU, oxaliplatin and irinotecan (FOFOXIRI) combined with bevacizumab may be used. Following this, patient should get similar alternative cytotoxic along with a biological agent. Anti-VEGF agents approved in this setting also include aflibercept and ramucirumab. Regorafenib or Trifluridine/tipiracil are options after progression with those therapies. Anti-PD1 immunotherapy drugs such as nivolumab and pembrolizumab can also be used in patients with MMR-deficient mCRC. This article will review the data from the randomized clinical trials which have contributed to our current

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The Authors have nothing to disclose

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treatment paradigms, mainly focusing on patients treated for initially inoperable metastatic disease.

Equivalence of 5-FU and Capecitabine

Capecitabine is an oral fluoropyrimidine which gets converted to 5-FU using enzymes such as thymidine phosphorylase which are present at higher levels in tumor compared to normal tissue. Two RCTs have demonstrated similar efficacy of capecitabine given daily for 14 of every 21 days cycle and IV FU/LV (Mayo regimen) for treatment of mCRC.^{1,2} The toxicity profile of these drugs is distinct. 5-FU is associated with more mucositis and neutropenic sepsis and capecitabine with more hyperbilirubinemia and hand-foot syndrome. In both RCTs stated above capecitabine was compared to bolus 5-FU regimen; and has not been compared in RCTs with infusional 5-FU, the more commonly used schedule. Notably, in at least one RCT (N = 448), infusional regimen was associated with less toxicity and a better response rate and PFS.³ However, in a large meta-analysis of individual data from 6,171 patients, oral capecitabine was found to be equivalent to IV 5-FU in terms of overall survival.⁴ These agents can be used interchangeably in combination with oxaliplatin. However caution is advised with use of capecitabine with irinotecan (XELIRI or CAPIRI) due to overlapping toxicity of diarrhea. In one RCT comparing CAPIRI plus bevacizumab to FOLFIRI plus bevacizumab in first-line treatment of patients with mCRC, no difference was observed in efficacy but patients on CAPIRI-Bev arm had significantly higher incidence of grade 3/4 diarrhea (16% vs. 9%), febrile neutropenia (5% vs. 0.6%) and hand-foot skin reactions (4.2% vs. 1.2%).⁵

Irinotecan-containing regimens - IFL/FOLFIRI/CAPIRI

Irinotecan, a topoisomerase I inhibitor, was approved by the US Food and Drug Administration (FDA) in 1996 as a second-line treatment for patients with progressive colorectal cancer. It is effective as a monotherapy, but it is more effective in combination with 5-FU as well as with the targeted agents such as bevacizumab and cetuximab. It is most commonly administered as FOLFIRI consisting of 5-fluorouracil (5-FU), leucovorin calcium (calcium folinate, LV), and irinotecan. An alternative schedule is IFL in which the fluorouracil is given as a bolus injection rather than as an infusion over 48 hours as in FOLFIRI. The survival benefit with the addition of irinotecan to conventional 5-FU/LV therapy in first line has been demonstrated by three RCTs.

Three-hundred eighty-seven patients in France were randomly assigned to receive irinotecan combined with 5-FU/LV (irinotecan group) versus 5-FU/LV alone (no-irinotecan group) as first-line treatment for mCRC. The objective response rate was significantly higher (49 vs. 31%; $p < 0.001$ for evaluable patients) and time to progression significantly longer (median 6.7 vs. 4.4 months; $p < 0.001$) with the addition of irinotecan. Overall survival was also improved (median 17.4 vs. 14.1 months; $p = 0.031$), and the increased frequency of treatment side effects associated with addition of irinotecan seemed manageable.⁶

The European Organization for Research and Treatment of Cancer (EORTC) 40986 randomized 430 previously untreated mCRC patients to FOLFIRI or 5-FU/LV alone.

Patients who were treated with FOLFIRI had a higher response rate (62.2 vs. 34.4%; $p<0.0001$) and longer median progression free survival (8.5 vs. 6.4 months; $p<0.0001$) than those treated with 5-FU/LV alone. They also had longer median overall survival (20.1 vs. 16.9 months; $p=0.28$), but this was not statistically significant likely due to the fact that two-thirds of the 5-FU/LV patients received irinotecan in the second line setting.⁷

The benefit of combination regimen of irinotecan and 5-FU/LV was also reported by Saltz et al. from North America. The multicenter randomized control study of 683 patients investigating first-line treatment for mCRC compared 3 arms: bolus 5-FU/LV, bolus 5-FU/LV with irinotecan (IFL), and irinotecan-alone (IRI). The combination of irinotecan with 5-FU/LV was associated with higher response rate (39 vs. 21 %; $p<0.001$), longer progression free survival (median, 7.0 vs 4.3 months; $p=0.004$), and longer overall survival (median, 14.8 vs. 12.6 months; $p=0.04$). The treatment outcomes were similar between 5-FU/LV group and irinotecan-alone group.⁸

These studies proved the effectiveness of the addition of irinotecan to a fluorouracil-based regimen, and established the basic concept of doublet therapy for mCRC. Drug sequencing and method of administration is associated with frequency of toxicity. Fuchs et al. reported a phase III study (BICC-C trial) that compared the safety and efficacy of different irinotecan-containing regimens in the first-line treatment. The three arms included 144 patients who received FOLFIRI, 141 patients who received modified IFL, and 145 patients who received CAPIRI. Median progression free survival was longer in the FOLFIRI group (7.6 months) as compared to modified IFL (5.9 months; $p=0.004$) or CAPIRI (5.8 months; $p=0.15$). CAPIRI was associated with higher rate of side effects, particularly with vomiting and diarrhea. This study showed superiority of the FOLFIRI regimen as compared to the other irinotecan-containing regimens.⁹ Higher rates of GI side effect associated with CAPIRI as compared to FOLFIRI were also reported by other prospective studies.^{5,10}

Oxaliplatin-containing regimens - FOLFOX/CAPOX/XELOX

Oxaliplatin, a platinum derivative agent effective for colorectal cancer, was approved by the FDA in 2002 for progressive colorectal cancer and in 2004 as an initial treatment of advanced colorectal cancer. Oxaliplatin has been shown in phase II trials to have some activity as monotherapy, but it is much more effective in combination with a fluorouracil-based regimen, likely due to synergetic effect with fluorouracil. In fact, in RCTs, single agent oxaliplatin was found to have no significant activity and therefore, unlike irinotecan, oxaliplatin should not be used as a single agent therapy in mCRC.¹¹ The combination of oxaliplatin and 5-FU/LV (FOLFOX) is now the standard regimen for mCRC. A variety of modifications of 5-FU/LV and oxaliplatin dosage have been used. Modified FOLFOX6 (mFOLFOX6) is the most commonly used, which administers 85mg/m² of oxaliplatin on day 1 and fluorouracil over 2 days (400 mg/m² bolus on day 1, followed by 2400–3000 mg/m² over 46 hours).

De Gramont et al. reported a randomized control study of 420 previously untreated mCRC patients, comparing 5-FU/LV either with or without oxaliplatin. The oxaliplatin containing regimen (FOLFOX) had a higher response rate (50.7 vs. 22.3%; $p=0.0001$) and longer

progression free survival (median 9.0 vs. 6.2 months; $p=0.0003$) than control. Overall survival was not statistically significantly different between the groups (median, 16.2 vs. 14.7 months; $p=0.12$), but this was likely because cross-over obscured the impact on survival.¹²

To replace intravenous 5-FU with the oral agent capecitabine, multiple randomized trials were conducted comparing CAPOX (or XELOX) and 5-FU with oxaliplatin as a first-line treatment, which showed comparable efficacies but different toxicity profiles. The German Arbeitsgemeinschaft Internistische Onkologie (AIO) study group compared CAPOX to high-dose infusional 5-FU/LV and oxaliplatin (FUFOX) in a randomized control study of 474 patients. There were no differences between CAPOX and FUFOX in the response rate (54 vs. 48%), progression free survival (hazard rate [HR] 1.17, 95% confidence interval [CI] 0.96–1.43; $p=0.117$), or overall survival (HR 1.12, 95% CI 0.92–1.38; $p=0.26$). Both regimens were generally well tolerated, but CAPOX was associated with higher rate of grade 2/3 hand-foot syndrome (10 vs. 4%; $p=0.028$).¹³ A recent meta-analysis of 8 randomized control trials including 4,363 patients, comparing CAPOX and FOLFOX, showed that there were no statistical differences between the regimens with respect to overall survival and response rates. However, CAPOX was associated with higher incidence of thrombocytopenia, hand-foot syndrome and diarrhea, while FOLFOX was associated with higher incidence of neutropenia.¹⁴

Oxaliplatin-containing regimens have been shown to be effective for second-line or third-line treatment after progression with irinotecan-containing regimens. Rothenberg et al. reported a randomized control trial of 463 mCRC patients from 120 sites in North America, who progressed after IFL therapy. This study compared 5-FU/LV, oxaliplatin monotherapy, and FOLFOX4. The objective response rate was higher in the FOLFOX4 group (9.9%) as compared to 5-FU/LV (0%; $p<0.001$), with longer time to progression (4.6 vs. 2.7 months; $p<0.001$). Oxaliplatin monotherapy had a similar efficacy as 5-FU/LV. Authors concluded that FOLFOX4 is superior treatment as a second-line regimen, than 5-FU/LV.¹¹

In a randomized trial of 214 patients with progressive mCRC after exactly two previous chemotherapy regimens that include irinotecan- but not oxaliplatin-containing regimens, patients were randomized either to receive bolus and infusional 5-FU/LV with or without oxaliplatin (FOLFOX4). In this salvage setting, the objective response rate was higher with FOLFOX4 than with 5-FU/LV (13 vs. 2%; $p=0.0027$) and median time to progression was longer with FOLFOX4 as well (4.8 vs. 2.4 months; $p<0.001$). There was no overall survival between groups (9.9 vs. 11.4 months; $p=0.20$). Grade 3 and 4 toxicities were notably higher in the FOLFOX4 patients; neutropenia (42 vs. 13%), diarrhea (16 vs. 6%), and neuropathy (6 vs. 0%).¹⁵ The noninferiority of CAPOX to FOLFOX as second-line therapy has also been shown. In a study of 627 patients with mCRC after progression with prior irinotecan-based chemotherapy, patients were randomized to CAPOX or FOLFOX4. There was no significant difference between CAPOX and FOLFOX in median progression free survival (4.7 vs. 4.8 months), or overall survival (median, 11.9 vs. 12.5 months, HR 1.02, 95% CI 0.86–1.21). Grade 3 and 4 adverse events were observed in 50% of CAPOX and 65% of FOLFOX4 patients. Authors concluded that CAPOX is noninferior to FOLFOX4 as second-line therapy after progression with irinotecan-based regimens.¹⁶

FOLFOX vs. FOLFIRI

The demonstrated efficacy of the combination regimens with irinotecan or oxaliplatin led to the obvious next question of the comparative efficacy of FOLFOX (or oxaliplatin-containing regimens) and FOLFIRI (or irinotecan-containing regimens). Several studies have shown that they are similarly effective as first-line therapy.

The GERCOR group compared patients with advanced colorectal cancer randomized to FOLFIRI followed by FOLFOX6 or the reverse sequence. A total of 230 patients were randomly assigned to either group. There were no significant differences between the FOLFIRI-first or FOLFOX-first groups in median overall survival (21.5 vs. 20.6 months, $p=0.99$) or median second progression free survival (14.2 vs. 10.9 months; $p=0.64$). Response rates as first-line therapy were similar between FOLFIRI-first and FOLFOX-first (56% vs. 54%; p -value was not significant). Metastasectomy was performed more frequently in the FOLFOX-first group (22% vs. 9%; $p=0.02$), and those patients who underwent metastasectomy achieved excellent survival. Response rates as second-line therapy were higher with FOLFOX than FOLFIRI (15 vs. 4%; $p=0.05$). Authors concluded that both sequences achieved a similarly prolonged survival.¹⁷

A multicenter study of the Gruppo Oncologico Dell'Italia Meridionale compared first-line FOLFIRI and FOLFOX in patients with mCRC. A total of 360 patients were randomized to either group. There was no statistically significant difference between FOLFIRI and FOLFOX groups in overall response rates (31 vs. 34%; $p=0.60$), in median time to progression (7 vs. 7 months; $p=0.64$), or overall survival (14 vs. 15 months; $p=0.28$). Grade 3 or 4 toxicities were uncommon in either group, but the toxicity profile was different between groups; FOLFIRI was more frequently associated with gastrointestinal symptoms and FOLFOX was more frequently associated with thrombocytopenia and neurosensorial symptoms. Authors concluded that either FOLFIRI or FOLFOX was similarly effective as first-line therapy for advanced colorectal cancer patients.¹⁸

Irinotecan and oxaliplatin were also compared in the setting of bevacizumab containing regimens in a recent randomized control study from Japan (WJOG4407G) which randomized patients with mCRC to bevacizumab plus FOLFIRI or bevacizumab plus mFOLFOX6 as first-line treatment. A total of 402 patients were enrolled and no difference between FOLFIRI and FOLFOX groups was observed in median progression free survival (12.1 vs. 10.7 months, HR 0.905, 95% CI 0.72–1.13; $p=0.003$ for noninferiority) or median overall survival (31.4 vs. 30.1 months, HR 0.99, 95% CI 0.79–1.25) demonstrating the equivalent efficacy of FOLFIRI and FOLFOX in combination with bevacizumab in first-line.¹⁹

FOLFOX and FOLFIRI were compared in combination with cetuximab, in a setting of unresectable liver-only metastases. The phase II CELIM trial included 111 patients with initially non-resectable liver metastases, who were randomly assigned to receive cetuximab with either FOLFOX6 or FOLFIRI. There was no difference in response rate (68% vs. 57%; $p=0.23$) between groups. Response rate in patients with KRAS wild-type tumor was 70% (47/67), which was higher than that of patients with KRAS mutated tumors (29%, 11/27;

p=0.008). R0 resection was achieved in 38% (20/53) in FOLFOX6 group, and 30% (16/53) in FOLFIRI group (p-value not provided).²⁰

Oxaliplatin and irinotecan-containing regimens – IROX/FOLFOXIRI

Regimens containing both oxaliplatin and irinotecan have been investigated. A regimen consisting of oxaliplatin and irinotecan is called IROX, and one with the addition of 5-FU/LV infusion is called FOLFOXIRI.

IROX

With the expansion of treatment options, the US Intergroup (INT) N9741 trial investigated the efficacy of IROX (oxaliplatin plus irinotecan) ^{21–23}. This study randomly assigned a total of 1691 patients into one of seven fluorouracil-, oxaliplatin-, and irinotecan-containing regimens between 1998 and 2002. Four out of those 7 arms were discontinued because of inefficacy or toxicity. Remaining three arms included: weekly bolus IFL, FOLFOX, and bolus IROX. The FOLFOX group had a better 5-year survival rate (9.8%) than IFL (3.7%; p=0.04) or IROX (5.1%; p=0.128). Median overall survival and time to progression were also longer in FOLFOX group (20.2 months and 8.9 months, respectively) than those of IFL (14.6 months and 6.1 months, respectively; p<0.001 for both) or those of IROX (17.3 months and 6.7 months, respectively; p<0.001).²³ IROX was associated with higher frequency of grade 3 or worse hematologic toxicity in patients over the age of 70 than FOLFOX.²² IROX regimen is an acceptable alternative in patients who cannot receive either capecitabine or 5-FU in combination with oxaliplatin and irinotecan.

FOLFOXIRI

FOLFOXIRI contains all three active cytotoxic agents. In two Italian randomized control trials, progression free survival was improved by FOLFOXIRI compared to FOLFIRI with and without bevacizumab. The first study randomized a total of 244 patients to receive FOLFOXIRI or FOLFIRI. FOLFOXIRI was associated with a longer median progression free survival (9.8 vs. 6.8 months; p<0.001) and longer median overall survival (23.4 vs. 16.7 months; p=0.026) with higher 5-year overall survival rate (15 vs. 8%) than FOLFIRI.²⁴ However, FOLFOXIRI was associated with higher rates of grade 2 to 3 peripheral neuropathy (19 vs. 0%; p<0.001) and grade 3 to 4 neutropenia (50 vs. 28%; p<0.001). The incidence of febrile neutropenia (5 vs. 3%) and grade 3 to 4 diarrhea was not different. But by achieving a higher response rate with FOLFOXIRI (66 vs. 41%; p=0.002), subsequent R0 metastasectomy was more frequently achieved in FOLFOXIRI treated patients than in the control (15 vs. 6%; p=0.033 among all patients, and 36 vs. 12%; p=0.017 among liver-only metastasis patients).²⁵

Based on the efficacy of the FOLFOXIRI triplet cytotoxic combination, The TRIBE phase III randomized control study compared FOLFIRINOX plus bevacizumab to FOLFIRI plus bevacizumab. A total of 508 patients with previously untreated mCRC were randomized. The overall response rate was higher (65 vs. 53%; p=0.006) and a median progression free survival was longer (12.1 vs. 9.7 months; p=0.003) with FOLFOXIRI and bevacizumab group. Overall survival was not statistically different between groups (31.0 vs. 25.8 months,

HR 0.79, 95% CI 0.63–1.00; $p=0.054$) and FOLFOXIRI was associated with a higher frequency of toxicity. In addition, this study did not confirm the benefit of FOLFOXIRI over FOLFIRI in terms of rate of successful metastasectomy; the rates of R0 resection of metastases were 15 % in FOLFOXIRI group and 12% in FOLFIRI group; $p=0.33$.²⁶

In contrast, a report from the Hellenic Oncology Research Group in the UK did not confirm benefit of FOLFOXIRI regimen over FOLFIRI. Souglakos et al. reported a multicenter randomized control study of 283 previously untreated mCRC patients, comparing FOLFOXIRI and FOLFIRI as first-line therapy. There was no difference in response rate (43 vs. 33.6%; $p=0.168$), median time to progression (8.4 vs. 6.9 months; $p=0.17$), or median overall survival (21.5 vs. 19.5 months; $p=0.34$). However, the 3-drug combination of FOLFOXIRI was associated with higher frequency of toxicity including alopecia, diarrhea, and neurosensory toxicity, as compared to FOLFIRI.²⁷

There is limited available data comparing FOLFOXIRI to FOLFOX. Gruenberger et al. reported a multinational randomized phase II trial comparing mFOLFOX6 plus bevacizumab and FOLFOXIRI plus bevacizumab as first-line treatment for colorectal cancer patients with unresectable liver metastases (OLIVIA trial). A total of 80 patients were enrolled. Bevacizumab plus FOLFOXIRI was associated higher response rate (81 vs. 62%) and R0 resection rate (49 vs. 23%), and longer median progression free survival (18.6 vs. 11.5 months) as compared to bevacizumab plus FOLFOX. The FOLFOXIRI arm was associated with higher rate of grade 3 and higher toxicities of neutropenia (50 vs. 35%) and diarrhea (30 vs. 14%) but due to the small sample size and type of study (phase II), statistical comparison was not made in the analysis.²⁸

The preliminary results of a phase II STEAM trial was presented at the 2016 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium.²⁹ This phase II trial randomized 280 unresectable previously untreated mCRC patients to 3 treatment arms: 1. bevacizumab plus concurrent FOLFOXIRI, 2. bevacizumab plus sequential FOLFOXIRI (alternating FOLFOX and FOLFIRI), or 3. bevacizumab plus FOLFOX. Concurrent FOLFOXIRI plus bevacizumab group had higher response rate (77% vs. 54%) and higher R0 resection rate (15 vs. 6%) as compared to FOLFOX plus bevacizumab group. Study is completed in March 2016, and results are pending.

In summary although triplet cytotoxic backbone has more activity than doublet, it comes at the cost of increased toxicity and therefore should be used in carefully selected patients, preferably, young and good PS patients.

Monoclonal antibody therapy

Bevacizumab

Bevacizumab (Avastin) is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), which inhibits angiogenesis. Bevacizumab has been shown to be effective to prolong survival when combined with a variety of first-line regimens for mCRC; however, the survival benefit of addition of Bevacizumab is modest at most, if it is used with modern doublet regimens such as FOLFIRI and FOLFOX. In the first phase III trial

comparing IFL plus bevacizumab and IFL plus placebo, 813 patients with previously untreated mCRC were randomized. Bevacizumab group had a higher response rate (44.8 vs. 34.8%; $p=0.004$) and longer median progression free survival (10.6 vs. 6.2 months; $p<0.001$) as compared to placebo group. The addition of bevacizumab resulted in prolonged median overall survival (20.3 vs. 15.6 months; $p<0.001$). Grade 3 hypertension was more commonly observed in bevacizumab group (11.0 vs. 2.3%) but it was easily manageable.³⁰

The addition of bevacizumab has also been reported in combination with bolus 5-FU/LV in patients who are not optimal candidates for first-line irinotecan-containing regimen. A randomized phase II trial compared 5-FU/LV and bevacizumab vs 5-FU/LV and placebo as first-line therapy in 209 mCRC patients who were not considered optimal for irinotecan-containing regimen. The addition of bevacizumab was associated with an improved response rate (26 vs. 15.2%; $p=0.055$) and longer progression free survival (9.2 vs. 5.5 months; $p<0.001$). Overall survival was also longer in bevacizumab group, albeit statistically not significant (16.6 vs. 12.9 months; $p=0.16$).³¹

Benefit of the addition of bevacizumab has been reported in combination with FOLFIRI. The BICC-C (described in more detail above) randomized phase III study compared irinotecan-containing regimens with or without bevacizumab in 430 previously untreated mCRC patients. FOLFIRI plus bevacizumab had a longer progression free survival than modified IFL plus bevacizumab, although the difference was not statistically significant (11.2 vs. 8.3 months; $p=0.28$).⁹ In a follow-up report, they reported superior median overall survival in FOLFIRI plus bevacizumab as compared to modified IFL plus bevacizumab (28.0 vs. 19.2 months, HR 1.79, 95% CI 1.12–2.88; $p=0.037$).

In contrast, a Greek randomized control trial failed to confirm a survival benefit with bevacizumab in combination with FOLFIRI in treatment naïve patients. A total of 222 patients were enrolled, and there was no statistically significant difference between the bevacizumab versus placebo groups in response rate (37 vs. 35%; p -value not provided) or median overall survival (22 vs. 25; $p=0.139$).³² But survival in the control arm with FOLFIRI was somewhat better than expected.

Bevacizumab was also studied in combination with oxaliplatin-based regimens. The TREE study, randomized previously untreated metastatic or recurrent colorectal cancer patients to receive mFOLFOX6, bolus FOL (bolus 5-FU/LV with oxaliplatin), or CAPOX at phase 1 ($n=150$), and subsequently modified such that patients in phase 2 were randomized to the same regimens plus bevacizumab ($n=223$). Overall response rates were improved from no-bevacizumab regimens (41%, 20%, and 27%, respectively) to bevacizumab-containing regimens (52%, 39%, and 46%, subsequently). In this study, first-line bevacizumab plus oxaliplatin-containing therapy achieved median overall survival of 23.7 months, while it was 18.2 months for no-bevacizumab regimens.³³

The Eastern Cooperative Oncology Group (ECOG) E3200 study compared FOLFOX4 with and without bevacizumab, as second-line therapy after progression with irinotecan-containing therapy. This study enrolled 829 patients for randomization. The addition of bevacizumab to FOLFOX4 resulted in higher response rate and 2.1 months longer median

overall survival (22.7% and 12.9 months in bevacizumab plus FOLFOX group vs. 8.6% and 10.8 months in FOLFOX group, respectively; HR 0.75; $p=0.001$). Progression free survival was also longer in bevacizumab plus FOLFOX group than FOLFOX group (7.3 vs. 4.7 months; $p<0.001$). The addition of bevacizumab with FOLFOX4 resulted in a 14% overall increase in grade 3 and 4 toxicity, including hypertension, bleeding, and vomiting (Table 2).³⁴

Results from another large randomized control trial of bevacizumab in addition to oxaliplatin-based therapy did not confirm survival benefit. Saltz et al. reported NO 16966 study which randomized a total of 1,401 patients in 2×2 factorial design, to CAPOX vs. FOLFOX4, and then to bevacizumab vs. placebo. Although addition of bevacizumab was associated with improved progression free survival (9.4 vs. 8.0 months; $p=0.0023$), there was no statistical difference between bevacizumab group and no-bevacizumab group in median overall survival (21.3 vs. 19.9 months; $p=0.077$), with similar response rates.³⁵

Continuation of bevacizumab in second-line after progression with first-line bevacizumab-containing regimens has also been studied and found beneficial. A European multicenter phase III TML trial compared bevacizumab plus chemotherapy and chemotherapy alone as second-line therapy, after progression with bevacizumab-containing first-line therapy. This study randomized a total of 820 patients with mCRC in such setting. Maintenance of bevacizumab in the second-line therapy was associated with longer median overall survival (11.2 vs. 9.8 months; $p=0.0062$).³⁶ The benefit of continuation of bevacizumab in second-line therapy was confirmed by the randomized BEBYP trial. This Italian study randomized a total of 185 patients with mCRC who progressed after first-line chemotherapy plus bevacizumab, to receive either mFOLFOX6 or FOLFIRI based on first-line regimen, with or without bevacizumab. Continuation of bevacizumab was associated with improved overall survival (HR 0.77, 95% CI 0.56–1.06; stratified log-rank $p=0.043$).³⁷

Other Anti-VEGF agents (Aflibercept and Ramucirumab)

There are two other anti-VEGF agents approved for mCRC: aflibercept and ramucirumab.

Van Custsem et al. reported a randomized control trial of 1,226 mCRC patients who had progressed on or after previous treatment with an oxaliplatin-based chemotherapy regimen. Patients were randomly assigned to receive aflibercept or placebo in combination with FOLFIRI. Addition of aflibercept was associated with an improved response rate (19.8% vs. 11.1%; $p<0.001$), improved progression-free survival (HR 0.76, 95% CI 0.66–0.87; $p<0.001$), and improved overall survival (HR 0.82, 95%CI 0.71–0.94; $p=0.003$).³⁸

An international multicenter randomized control trial showed effectiveness of ramucirumab. This trial randomly assigned 1,072 patients with mCRC after disease progression during or within 6 months of the last dose of first-line therapy to receive ramucirumab or placebo in combination with FOLFIRI. There was no difference in response rate (13.4% in ramucirumab group vs. 12.5% in placebo group; $p=0.63$), but progression-free survival (HR 0.79, 95% CI 0.70–0.90; $p<0.001$) and overall survival (HR 0.84, 95% CI 0.73–0.98; $p=0.022$) was better in ramucirumab group as compared to placebo group. The incidence of

grade 3 or worse adverse events was higher in the ramucirumab group than in the placebo group (79% vs. 62%; p-value not provided).³⁹

Since both these studies and the TML study demonstrated the value of continued VEGF inhibition after progression on bevacizumab based regimen in first-line, aflibercept, ramucirumab and bevacizumab, all are reasonable agents in this setting. The toxicity profile of bevacizumab appears to be favorable and has therefore been a more widely used agent.

Epidermal growth factor receptor (EGFR) inhibitors

Cetuximab (Erbix) and panitumumab (Vectibix) are monoclonal antibodies targeting EGFR and they have been proven to be effective against mCRC in patients whose tumors are associated with a mutation in KRAS. KRAS mutation status is the first predictive molecular marker for treatment response in patients with advanced disease and patient selection based on biomarker analysis is critical, since both cetuximab and panitumumab are known to be only effective on tumors with wild-type (not mutated) K-ras oncogenes, which is observed in approximately 60% of mCRC patients.⁴⁰

Cetuximab

Cetuximab is a mouse/human chimeric monoclonal antibody targeting EGFR. Cetuximab efficacy has been demonstrated as monotherapy or in combination with irinotecan for patients with K-ras wild-type tumors. A multicenter randomized control trial of cetuximab monotherapy vs. best supportive care for patients with progressive disease after fluorouracil, irinotecan, and oxaliplatin or had contraindications for those agents showed improved overall survival (median 6.1 vs. 4.6 months, HR 0.77, 95% CI 0.64–0.92; p=0.005), and longer progression free survival (HR 0.68, 95% CI 0.57–0.80; p<0.001).⁴¹ After further analysis, the benefit of cetuximab was found to be limited to patients with K-ras wild-type tumors. Of the tumors evaluated for K-ras mutations (n=394), 42.3% had at least one mutation in exon 2 of the K-ras gene. In patients with K-ras wild type tumors, cetuximab treatment was strongly associated with overall survival (median, 9.5 vs. 4.8 months, HR 0.55, 95% CI 0.41–0.74; p<0.001), while it was not in patients with K-ras mutated tumors (HR 0.98; p=0.89).⁴² Cetuximab monotherapy as compared to best supportive care was also associated with improved quality of life in mCRC patients.⁴³

The EPIC phase III study demonstrated the efficacy of cetuximab in combination with irinotecan in second-line. It compared cetuximab plus irinotecan and irinotecan alone as second-line therapy, after progression with fluorouracil and oxaliplatin treatment in mCRC patients. A total of 1,298 patients were enrolled. The combination with cetuximab had longer progression free survival than irinotecan alone (median, 4.0 vs. 2.6 months, HR 0.692, 95% CI 0.617–0.776; p<0.0001) and a higher response rate (16.4 vs. 4.2%; p=0.047). Overall survival was not different between groups (10.7 vs. 10.0 months; p=0.71), likely because 47% of the irinotecan alone group subsequently received cetuximab. Skin rash (76 vs. 5), grade 3/4 diarrhea (28 vs. 16%), and fatigue (8 vs 3%) were more frequently observed in combination therapy (76 vs. 5%), but quality of life was reported better in combination therapy group.⁴⁴

Cetuximab monotherapy and cetuximab plus irinotecan in patients who progressed with previous irinotecan-based chemotherapy was compared in a randomized study of 329 patients with metastatic K-ras WT colorectal cancer. The response rate was higher in the combination-therapy group than the cetuximab monotherapy group (22.9 vs. 10.8%; $p=0.007$) and the time to progression was longer in the combination group as well (4.1 vs. 1.5 months; $p<0.001$). However the difference in overall survival did not reach statistical significance (8.6 vs. 4.9 months; $p=0.48$).⁴⁵

Cetuximab has also been investigated in first-line treatment for mCRC. The CRYSTAL multicenter phase III trial compared first-line FOLFIRI with or without cetuximab in a total of 1,198 patients. The addition of cetuximab was associated with improved progression free survival (HR 0.85, 95% CI 0.72–0.99; $p=0.048$), although overall survival was not different between groups (HR 0.93, 0.81–1.07; $p=0.31$).⁴⁶ After further analysis of K-ras status (89% of patients were tested), K-ras wild-type patients were found to have improved response rate (57 vs. 40%; $p<0.001$), progression free survival (median, 9.9 vs. 8.7 months; $p=0.02$), and overall survival (median, 23.5 vs 20.0 months, HR 0.796; $p=0.009$). The rate of R0 resection was also higher with cetuximab and in subgroup analysis of K-ras wild-type tumor patients was 5.1 vs. 2.0%, odds ratio 2.65; $p=0.026$. Toxicity was more frequently observed in cetuximab group; grade 3 to 4 diarrhea, 16 vs. 11%, skin toxicity, 19.7 vs. 0.2%, and infusion reaction 2.5 vs. 0%.⁴⁷

Addition of cetuximab has also been tested with FOLFOX as first-line therapy. The OPUS phase II trial randomized previously untreated mCRC patients to receive either FOLFOX4 with or without cetuximab.⁴⁸ In subsequent analysis with more patients tested with biomarker status (including 179 patients with wild-type K-ras status), K-ras wild-type patients who were treated with cetuximab plus FOLFOX4 had a higher response rate (57 vs. 34%; $p=0.0027$) and prolonged progression free survival (median, 8.3 vs. 7.2 months; $p=0.0064$) than those who received FOLFOX4 alone, but the difference in overall survival did not reach statistical significance (median, 22.8 vs. 18.5 months; $p=0.39$).⁴⁹

A benefit of adding cetuximab to chemotherapy was also tested in a Chinese study of a total of 138 patients with synchronous unresectable liver-only metastases. Patients with KRAS wild-type tumors were randomized after resection of the primary tumors, to receive chemotherapy (FOLFOX6 or FOLFIRI) plus cetuximab or chemotherapy alone. R0 resection rate was significantly improved with addition of cetuximab (25.7% vs. 7.4%; $p<0.01$), and also 3-year overall survival was also improved (41% vs. 18%; $p=0.013$).⁵⁰

Other studies have examined the impact of adding cetuximab to oxaliplatin-based regimens. The phase III MRC COIN trial conducted in the UK randomized 1630 patients with mCRC to either chemotherapy (either FOLFOX or CAPOX) alone or chemotherapy with cetuximab. In subset analysis of K-ras wild-type tumors ($n=729$, 58%), the response rate was higher with cetuximab (64 vs. 57%; $p=0.049$), but there was no survival difference between groups (median overall survival 17.9 in chemotherapy alone group vs. 17.0 months in cetuximab group; $p=0.67$).⁵¹ Another study from the UK (EPOC) randomized a total of 257 patients with potentially resectable mCRC with K-ras wild-type tumors and showed even inferior survival outcomes with cetuximab plus oxaliplatin-based chemotherapy as compared

to chemotherapy alone (median progression free survival, 14.1 vs. 20.5 months; $p=0.03$).⁵² Thus the jury remains out with respect to first-line treatment with cetuximab and an oxaliplatin containing chemotherapy backbone (Table 1).

Bevacizumab versus Cetuximab

A number of randomized studies have attempted to compare bevacizumab and cetuximab. The FIRE-3 study is a multicenter randomized phase III trial that compared FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line therapy for patients with mCRC with K-ras wild-type tumors. This study enrolled a total of 592 patients and although response rates and progression free survival were not different between groups, overall survival was significantly longer in the cetuximab group as compared to the bevacizumab group (median, 28.7 vs. 25.0 months; $p=0.017$).⁵³ A criticism of this study is that details regarding treatment after progression with the first-line treatment have not been described. The protocol recommended for second-line treatment of FOLFOX plus bevacizumab for the cetuximab group or cetuximab second-line therapy for the bevacizumab group; however, investigators were free to vary from such recommendations.⁵⁴

In the US another randomized control study has compared bevacizumab and cetuximab in combination with FOLFOX or FOLFIRI in patients with K-ras wild-type metastatic colorectal metastasis (CALGB/SWOG 80405). In contrast to FIRE-3, 80405 did not demonstrate superiority of cetuximab over bevacizumab. This study randomized a total of 1,137 patients. In a preliminary report at the ASCO 2014 annual meeting, there were no difference between groups in either progression free survival (median, 10.8 months in bevacizumab group vs. 10.5 months in cetuximab group) or overall survival (median, 29.0 months in bevacizumab group vs. 29.9 months in cetuximab group).⁵⁵

Bevacizumab plus Cetuximab

Given the efficacy of bevacizumab and of cetuximab, there was interest in a potential role for dual antibody therapy with both bevacizumab and cetuximab. However, data from the CAIRO2 study, which randomly assigned 755 patients with previously untreated K-ras wild-type mCRC to CAPOX plus bevacizumab with or without cetuximab, shows that the addition of cetuximab was associated with shorter progression free survival (10.7 in no-cetuximab group vs. 9.4 months in cetuximab group; $p=0.01$), while there was no difference in overall survival and response rate.⁵⁶

Panitumumab

Panitumumab is a fully human monoclonal antibody specific for the extracellular domain of EGFR. Panitumumab was shown beneficial in K-ras wild-type tumors, either as monotherapy (vs. best supportive care),^{57–59} or in combination at first-line therapy.^{60,61} Panitumumab was associated with high incidence of skin toxicity (90%).⁶¹

The multicenter phase III PRIME trial randomized 1,183 previously untreated patients with mCRC to either to receive panitumumab plus FOLFOX4 or FOLFOX4 alone.⁶⁰ In analysis of K-ras wild-type patients ($n=656$), Panitumumab plus FOLFOX4 was associated with prolonged progression free survival (median, 10.0 vs. 8.6 months; $p=0.01$) without a

significant improvement in overall survival (median, 23.9 vs. 19.7 months; $p=0.17$). Survival analysis showed that panitumumab regimen was associated with improved overall survival (HR 0.83, 95% CI 0.70–0.98; $p=0.03$).⁶¹ The addition of panitumumab was associated with reduced progression free survival in K-ras mutant patients (HR 1.29; 95% CI 1.04–1.62; $p=0.02$).⁶⁰

Regorafenib

Regorafenib and Trifluridine/tipiracil are two recently approved agents for palliative therapy in patients with refractory mCRC. Regorafenib (BAY 73-4506), an orally active multikinase inhibitor that blocks several protein kinases, including receptors associated with angiogenesis (VEGFR1, VEGFR2, VEGFR3, and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF), and the tumor microenvironment (PDGFR and FGFR). Regorafenib was approved by US FDA in 2012, for patients with mCRC who progressed after fluorouracil, oxaliplatin, and irinotecan-based chemotherapy, and monoclonal antibodies including anti-VEGF and (if K-ras wild-type) anti-EGFR agents. Grothey et al. reported its efficacy for patients with progressive mCRC in the phase III multicenter CORRECT trial. This study randomized a total of 760 patients in a 2:1 ratio to receive oral regorafenib or placebo. Regorafenib treatment was associated with modest increase in median overall survival (6.4 vs. 5.0 months; $p=0.005$) but treatment associated adverse events were observed more frequently in regorafenib group (93 vs. 61%), most commonly with hand-foot skin reaction (17%), and fatigue (10%).⁶²

The benefit of regorafenib over best supportive care was confirmed in the Asian multicenter CONCUR phase III trial. This study randomized a total of 243 patients with progressive mCRC in a 2:1 ratio to receive regorafenib or placebo. Regorafenib treatment was associated with longer median overall survival (8.8 vs. 6.3 months; one-sided $p=0.00016$). Again, drug related adverse events were observed frequently (97%) in the regorafenib group, most frequently with hand-foot skin reaction (16%)⁶³.

Trifluridine/tipiracil

Trifluridine/tipiracil (TAS-102) is an orally active combination of trifluridine (a thymidine-based nucleic acid analogue) and tipiracil hydrochloride (a thymidine phosphorylase inhibitor). Trifluridine is the active cytotoxic component by being incorporated into DNA causing strand breaks, while tipiracil inhibits trifluridine metabolism. TAS-102 was approved by FDA in 2015 for the same indication as for regorafenib.

The RECURSE phase III trial proved the efficacy of TAS-102 monotherapy over placebo in refractory mCRC patients. This study randomly assigned a total of 800 patients with refractory colorectal cancer, who progressed with at least previous two standard chemotherapy regimens, in a 2:1 ratio, to receive either TAS-102 or placebo. TAS-102 treatment was associated with improved median overall survival (7.1 vs. 5.3 months; $p<0.001$) as compared to placebo. The most common adverse events observed in TAS-102 group were neutropenia (38%) and leukopenia (21%).⁶⁴

Immune checkpoint inhibitors

Immunotherapies have achieved remarkable discoveries for the last decade in cancer treatment, not limited to colorectal cancer. Of those recent discoveries, immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors, which were initially found to be effective against melanoma, were now reported to be potentially effective against mCRC as well, particularly in tumors with mutations in one of several DNA mismatch repair (MMR) genes.⁶⁵ Although pembrolizumab has received FDA breakthrough therapy designation for mCRC and is now included in NCCN guidelines, these immune checkpoint inhibitors have not been examined in randomized control studies.

Resectable liver metastases

With accumulation of case series that reported an excellent outcomes with 5-year overall survival averaging 40–50% after surgical resection of liver metastases,⁶⁶ surgical resection is believed to offer the best chance of cure for patients with resectable liver metastases (liver lesions 4). However, resectability of disease, and the optimal patient selection and timing for surgical resection of mCRC are not well defined.⁶⁷ A European Organisation for Research and Treatment of Cancer (EORTC) 40983 trial was conducted to answer the question whether perioperative chemotherapy improves survival after resection of liver metastasis. In this phase III study, a total of 364 patients with resectable metastatic liver disease of colorectal cancer recruited from 78 hospitals internationally, were randomly assigned to either perioperative FOLFOX4 or surgery alone. Perioperative therapy group received six cycles of chemotherapy before and after the surgery. Similar proportions of patients underwent successful resection of metastatic disease (83% in perioperative therapy group vs. 84% in surgery alone group). In the update at a median follow-up of 8.5 years, they found no difference in overall survival with the addition of perioperative chemotherapy; 5-year overall survival was 51.2% in perioperative therapy group and 47.8% in surgery alone group ($p = 0.34$). In a subset analysis only including eligible patients ($n = 342$), they found an improved progression free survival in perioperative therapy group (3-year progression free survival 39% vs. 30%; $p=0.035$).⁶⁸ Because of these mixed results from this randomized trial, the benefit of perioperative therapy for resectable liver metastasis remained unclear.

Conclusion

In this article, we reviewed the available data from randomized clinical trials in advanced, mCRC. Remarkable discoveries have been made over the last 20 years, which have dramatically improved survival and established the current treatment. Improved response rates to those systemic therapies have also increased the potential for identifying patients who are candidates for curative resection. Current evidence supports combination therapy such as FOLFOX plus bevacizumab as first-line therapy, but further studies are needed to define the optimal sequence of treatment regimens. Future discoveries are expected in molecularly directed monoclonal antibody therapies and for the use of immune checkpoint inhibitors, to improve the prognosis of mCRC patients.

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KEY POINTS

1. Combination cytotoxic chemotherapy regimens using 5-Fluorouracil backbone, such as FOLFOX (with oxaliplatin) and FOLFIRI (with irinotecan) have significantly improved survival of metastatic colorectal cancer patients.
2. The addition of monoclonal antibodies (bevacizumab, cetuximab/panitumumab, aflibercept, ramucirumab) with chemotherapy has further improved survival outcomes.
3. Novel therapies such as regorafenib and trifluridine/tipiracil have been also approved for management of refractory disease.
4. Immune checkpoint inhibitors have been reported to be effective for metastatic colorectal cancer patients with mismatch repair-deficient tumors, but have not examined by randomized control trials.

SYNOPSIS

There has been remarkable advances in the treatment of metastatic colorectal cancer over the past 20 years, chiefly achieved by development of new active drugs and establishment of effective systemic therapy regimens. Multidisciplinary care of resectable liver disease with use of peri-operative systemic therapy and superior liver resection has resulted in prolonged survival of select patients. Median overall survival has significantly improved from approximately 12 months in the 5-FU single agent era, to more than 2 years with the modern multi-agents regimens. This manuscript will review recent high-quality randomized clinical trials which were conducted to address optimal treatment for advanced and metastatic colorectal carcinoma, mainly focused on initially inoperable metastatic disease.

Figure 1.

Improved survival of metastatic colorectal cancer over time.

From Kopetz et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009;27:3678, with permission.

Table 1

Phase III clinical trials of chemotherapy regimens for metastatic colorectal cancer

Regimens	Indication	Author, year (Study name)	N	Treatment	Median survival (months)	p-value
Irinotecan regimens	1 st line	Douillard, 2000	287	Irinotecan + 5-FU/LV vs. 5-FU/LV	PFS: 6.7 vs. 4.4 OS: 17.4 vs. 14.1	<0.001 0.031
		Kohne, 2005 (EORTC 40986)	430	FOLFIRI vs. 5-FU/LV	PFS: 8.5 vs. 6.4 OS: 20.1 vs. 16.9	<0.001 0.28
		Fuchs, 2007 (BICC-C)	430	FOLFIRI vs. IFL vs. CAPIRI	PFS: 7.6 vs. 5.9 vs. 5.8 OS: 23.1 vs. 17.6 vs. 18.9	0.004* 0.09*
Oxaliplatin regimens	1 st line	De Gramont, 2000	420	FOLFOX vs. 5-FU/LV	PFS: 9.0 vs. 6.2 OS: 16.2 vs. 14.7	<0.001 0.12
		Ducreux, 2011 (FFCD 2005-5)	205	1 st /2 nd /3 rd line (1) 5-FU+LV/FOLFOX6/FOLFIRI (2) FOLFOX6/FOLFIRI	OS: 16.2 vs. 16.4	0.85
		Porschen, 2007	474	CAPOX vs. FUFOX	PFS: 7.1 vs. 8.0 OS: 16.8 vs. 18.8	0.12 0.26
	2 nd line	Rothenberg, 2003	463	FOLFOX4 vs. 5-FU/LV vs. oxaliplatin	PFS: 4.6 vs. 2.7 vs. 1.6	<0.001*
		Rothenberg, 2008	627	FOLFOX4 vs. CAPOX	PFS: 4.8 vs. 4.7 OS: 12.5 vs. 11.9	Non-inferior
	3 rd line	Kemeny, 2004	214	FOLFOX4 vs. 5-FU/LV	PFS: 4.8 vs. 2.4 OS: 9.9 vs. 11.4	<0.001 0.20
FOLFIRI vs. FOLFOX	1 st line	Tournigand, 2004 (GRECOR)	230	1 st /2 nd line (1) FOLFIRI/FOLFOX (2) FOLFOX/FOLFIRI	OS: 21.5 vs. 20.6 2 nd PFS: 14.2 vs. 10.9	0.99 0.64
		Colucci, 2005	360	FOLFIRI vs. FOLFOX	PFS: 7 vs. 7 OS: 14 vs. 15	0.64 0.28
		Yamazaki, 2016 (WJOG4407G)	402	Bev+FOLFIRI vs. Bev+mFOLFOX6	PFS: 12.1 vs. 10.7 OS: 31.4 vs. 30.4	Non-inferior
FOLFOXIRI	1 st line	Falcone, 2007	244	FOLFOXIRI vs. FOLFIRI	PFS: 9.8 vs. 6.8 OS: 23.4 vs. 16.7	<0.001 0.026
		Loupakis, 2014 (TRIBE)	508	Bev+FOLFOXIRI vs. Bev+FOLFIRI	PFS: 12.1 vs. 9.7 OS: 31.0 vs. 25.8	0.003 0.054
		Souglakos, 2006	283	FOLFOXIRI vs. FOLFIRI	PFS: 8.4 vs. 6.9 OS: 21.5 vs. 19.5	0.17 0.34

* comparing first two regimens

Table 2

Phase III clinical trials of monoclonal antibody therapies for metastatic colorectal cancer

Agents	Indication	Author, year (Study name)	N	Treatment	Median survival (months)	p-value
Bevacizumab	1 st line	Hurwitz, 2004	813	Bev+IFL vs. IFL	PFS: 10.6 vs. 6.2 OS: 20.3 vs. 15.6	<0.001 <0.001
		Stathopoulos, 2010	222	Bev+FOLFIRI vs. FOLFIRI	OS: 22 vs. 25	0.139
		Giantonio, 2007 (ECOG E3200)	829	Bev+FOLFOX vs. FOLFOX	PFS: 7.3 vs. 4.7 OS: 12.9 vs. 10.8	<0.001 0.001
		Saltz, 2008 (NO16966)	1,401	2×2 factorial design CAPOX vs. FOLFOX4, Bev vs. Placebo	(Bev vs. placebo) PFS: 9.4 vs. 8.0 OS: 21.3 vs. 19.9	0.002 0.077
	2 nd line	Bennouna, 2013 (ML18147)	820	Bev+chemo vs. chemo (oxaliplatin- or irinotecan-based)	OS: 11.2 vs. 9.8	0.006
		Masi, 2015 (BEBYP)	185	Bev+chemo vs. chemo (mFOLFOX or FOLFIRI)	OS: 6.8 vs. 5.0	0.043
Aflibercept	2 nd line	Van Cutsem, 2012	1,226	Aflibercept+FOLFIRI vs. FOLFIRI	PFS: 6.9 vs. 4.7 OS: 13.5 vs. 12.1	<0.001 0.003
Ramucirumab	2 nd line	Tabernero, 2015 (RAISE)	1,072	Ramucirumab+FOLFIRI vs. FOLFIRI	PFS: 5.7 vs. 4.5 OS: 13.3 vs. 11.7	<0.001 0.022
Cetuximab	Progressive disease	Jonker, 2007 Karapetis, 2008	572	Cet vs. placebo	OS: 9.5 vs. 4.8 (Analysis of K-ras WT pts, n=394)	(<0.001)
	2 nd line	Sobrero, 2008 (EPIC)	1,298	Cet+irinotecan vs. irinotecan	PFS: 4.0 vs. 2.6 OS: 10.7 vs. 10.0	<0.001 0.71
	2 nd line	Cunningham, 2004	329	Cet vs. Cet+irinotecan	PFS: 4.1 vs. 1.5 OS: 8.6 vs. 4.9	<0.001 0.48
	1 st line	Van Cutsem, 2009	1,198	Cet+FOLFIRI vs. FOLFIRI	PFS: 9.9 vs. 8.7 OS: 23.5 vs. 20.0 (Analysis of K-ras WT pts, n=348)	0.02 0.009
	1 st line	Maughan, 2011 (MRC COIN)	1,630	Cet+chemo vs. chemo (FOLFOX or CAPOX)	OS: 17.0 vs. 17.9 (Analysis of K-ras WT pts, n=729)	0.67
	1 st line	Primrose, 2014 (New EPOC)	257	Cet+chemo vs. chemo (oxaliplatin-based)	OS: 14.1 vs. 20.5	0.03
Bev vs. Cet	1 st line	Heinemann, 2014 (FIRE-3)	592	Bev+FOLFIRI vs. Cet+FOLFIRI	OS: 25.0 vs. 28.7	0.017
	1 st line	Venook, 2014 (CALGB/SWOG 80405, abstract)	1,137	FOLFIRI or mFOLFOX6, combined with Bev or Cet	(Bev group vs. Cet group) PFS: 10.8 vs. 10.5 OS: 29.0 vs. 29.9	Not reported 0.34
Panitumumab	1 st line	Douillard, 2010 (PRIME)	1,183	Pan+FOLFOX4 vs. FOLFOX4	PFS: 10.0 vs. 8.6 OS: 23.9 vs. 19.7 (Analysis of K-ras WT pts, n=656)	0.01 0.17

Chemo; chemotherapy, Bev; bevacizumab, Cet; cetuximab, Pan; panitumumab, WT; wild type

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