An Update on Randomized Clinical Trials in Metastatic Colorectal Carcinoma

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KEYWORDS

• Metastatic colorectal cancer • Randomized controlled trial • Chemotherapy • Monoclonal antibody

KEY POINTS

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

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 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 to 12 months in the 5-fluorouracil (5-FU) single-agent era, to more than 24 months with sequential multiagent regimens in the modern era (**Fig. 1**). These advances have been a direct result of several landmark trials that have defined the current standard of care.

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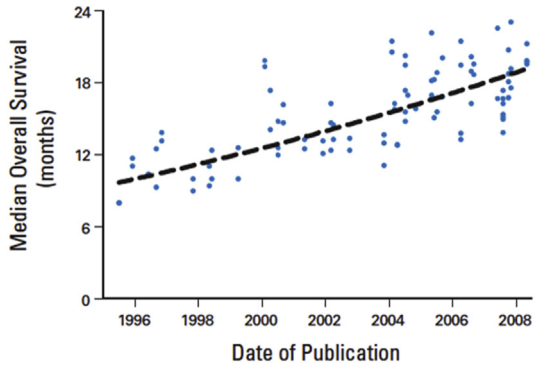

Fig. 1. Improved survival of metastatic colorectal cancer over time. (*From* Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3678; with permission.)

Current National Comprehensive Cancer Network (NCCN) guidelines for advanced colorectal cancer or mCRC recommend use of a doublet regimen (oxaliplatin based, FOLFOX [folinic acid, fluorouracil, oxaliplatin] or CAPOX [capecitabine, oxaliplatin]; irinotecan based, FOLFIRI [folinic acid, fluorouracil, irinotecan]) with monoclonal antibody agent (anti–vascular endothelial growth factor [VEGF] agent bevacizumab or anti–epidermal growth factor receptor [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, the patient should get a similar alternative cytotoxic agent along with a biologic 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-programmed cell death-1 (Anti-PD1) immunotherapy drugs such as nivolumab and pembrolizumab can also be used in patients with mismatch repair (MMR)-deficient mCRC. This article reviews the data from the randomized clinical trials that have contributed to the current treatment paradigms, mainly focusing on patients treated for initially inoperable metastatic disease.

Equivalence of 5-Fluorouracil and Capecitabine

Capecitabine is an oral fluoropyrimidine that gets converted to 5-FU using enzymes such as thymidine phosphorylase that are present at higher levels in tumor compared with normal tissue. Two randomized controlled trials (RCTs) have shown similar efficacy of capecitabine given daily for 14 days in every 21-day cycle and intravenous (IV) FU/leucovorin (LV) (Mayo regimen) for treatment of mCRC.[1,2] The toxicity profiles of these drugs are distinct. 5-FU is associated with more mucositis and neutropenic sepsis and capecitabine with more hyperbilirubinemia and hand-foot syndrome. In both RCTs mentioned earlier, capecitabine was compared with a bolus 5-FU regimen; it has not been compared in RCTs with infusional 5-FU, which is the more commonly used schedule. Notably, in at least 1 RCT (N = 448), an infusional regimen was associated with less toxicity and a better response rate and progression-free survival.[3] However, in a large meta-analysis of individual data from 6171 patients, oral capecitabine was 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 the use of capecitabine with irinotecan (XELIRI or CAPIRI) because of overlapping

toxicity of diarrhea. In one RCT comparing CAPIRI plus bevacizumab with FOLFIRI plus bevacizumab in first-line treatment of patients with mCRC, no difference was observed in efficacy but patients in the CAPIRI-bevacizumab arm had significantly higher incidence of grade 3 or 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: 5-Flourouracil/LV with Irinotecan/Folinic Acid, Fluorouracil, Irinotecan/Capecitabine, Irinotecan

Irinotecan, a topoisomerase I inhibitor, was approved by the US Food and Drug Administration (FDA) in 1996 as a second-line treatment of 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-FU, leucovorin calcium (calcium folinate, LV), and irinotecan. An alternative schedule is 5-FU/LV with irinotecan (IFL), in which the FU 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 shown by 3 RCTs.

In France, 387 patients 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 of mCRC. The objective response rate was significantly higher (49% vs 31%; $P<.001$ for evaluable patients) and time to progression significantly longer (median 6.7 vs 4.4 months; $P<.001$) with the addition of irinotecan. Overall survival was also improved (median 17.4 vs 14.1 months; $P = .031$), and the increased frequency of treatment side effects associated with addition of irinotecan seemed manageable.[6]

The European Organisation for Research and Treatment of Cancer (EORTC) 40986 randomized 430 previously untreated patients with mCRC to FOLFIRI or 5-FU/LV alone. Patients who were treated with FOLFIRI had a higher response rate (62.2% vs 34.4%; $P<.0001$) and longer median progression-free survival (8.5 vs 6.4 months; $P<.0001$) than those treated with 5-FU/LV alone. They also had longer median overall survival (20.1 vs 16.9 months; $P = .28$), but this was not statistically significant, likely because two-thirds of the 5-FU/LV patients received irinotecan in the second-line setting.[7]

The benefit of a combination regimen of irinotecan and 5-FU/LV was also reported by Saltz and colleagues[8] from North America. The multicenter randomized controlled study of 683 patients investigating first-line treatment of mCRC compared 3 arms: bolus 5-FU/LV, bolus IFL, and irinotecan alone. The combination of irinotecan with 5-FU/LV was associated with higher response rate (39% vs 21%; $P<.001$), longer progression-free survival (median, 7.0 vs 4.3 months; $P = .004$), and longer overall survival (median, 14.8 vs 12.6 months; $P = .04$). The treatment outcomes were similar between the 5-FU/LV group and the irinotecan-alone group.

These studies proved the effectiveness of the addition of irinotecan to an FU-based regimen, and established the basic concept of doublet therapy for mCRC. Drug sequencing and method of administration are associated with frequency of toxicity. Fuchs and colleagues[9] reported a phase III study (BICC-C trial) that compared the safety and efficacy of different irinotecan-containing regimens in first-line treatment. The 3 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) compared with modified IFL (5.9 months; $P = .004$) or CAPIRI (5.8 months; $P = .15$). CAPIRI was associated with a higher rate of side effects, particularly with vomiting and diarrhea. This study showed the superiority of the FOLFIRI regimen compared with the other irinotecan-containing regimens.

Higher rates of gastrointestinal side effects associated with CAPIRI compared with FOLFIRI were also reported by other prospective studies.[5,10]

Oxaliplatin-Containing Regimens: Folinic Acid, Fluorouracil, Oxaliplatin/Capecitabine, Oxaliplatin/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 an FU-based regimen, likely because of a synergetic effect with FU. In RCTs, single-agent oxaliplatin had no significant activity and therefore, unlike irinotecan, oxaliplatin should not be used as a single-agent therapy in mCRC.[11] 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 85 mg/m^2 of oxaliplatin on day 1 and FU over 2 days (400 mg/m^2 bolus on day 1, followed by 2400–3000 mg/m^2 over 46 hours).

De Gramont and colleagues[12] reported a randomized controlled study of 420 previously untreated patients with mCRC, comparing 5-FU/LV either with or without oxaliplatin. The oxaliplatin-containing regimen (FOLFOX) had a higher response rate (50.7% vs 22.3%; $P = .0001$) and longer progression-free survival (median 9.0 vs 6.2 months; $P = .0003$) than the control. Overall survival was not statistically significantly different between the groups (median, 16.2 vs 14.7 months; $P = .12$), but this was likely because crossover obscured the impact on survival.

To replace IV 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 with high-dose infusional 5-FU/LV and oxaliplatin (FUFOX) in a randomized controlled study of 474 patients. There were no differences between CAPOX and FUFOX in the response rate (54% vs 48%), progression-free survival (hazard ratio [HR], 1.17; 95% confidence interval [CI], 0.96–1.43; $P = .117$), or overall survival (HR, 1.12; 95% CI, 0.92–1.38; $P = .26$). Both regimens were generally well tolerated, but CAPOX was associated with a higher rate of grade 2 or 3 hand-foot syndrome (10% vs 4%; $P = .028$).[13] A recent meta-analysis of 8 RCTs including 4363 patients, comparing CAPOX and FOLFOX, showed that there were no statistically significant differences between the regimens with respect to overall survival and response rates. However, CAPOX was associated with a higher incidence of thrombocytopenia, hand-foot syndrome, and diarrhea, whereas FOLFOX was associated with a 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 and colleagues[11] reported an RCT of 463 patients with mCRC 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%) compared with 5-FU/LV (0%; $P<.001$), with longer time to progression (4.6 vs 2.7 months; $P<.001$). Oxaliplatin monotherapy had a similar efficacy to 5-FU/LV. The investigators concluded that FOLFOX4 is superior treatment to 5-FU/LV as a second-line regimen.

In a randomized trial of 214 patients with progressive mCRC after 2 previous chemotherapy regimens that include irinotecan-containing but not oxaliplatin-containing regimens, patients were randomized 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%; $P = .0027$) and median time to progression was longer with FOLFOX4 as well (4.8 vs 2.4 months; $P<.001$). There was no overall survival difference between groups (9.9 vs 11.4 months; $P = .20$). 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. The investigators concluded that CAPOX is noninferior to FOLFOX4 as second-line therapy after progression with irinotecan-based regimens.[16]

Folinic Acid, Fluorouracil, Oxaliplatin Versus Folinic Acid, Fluorouracil, Irinotecan

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 have similarly efficacy to 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; $P = .99$) or median second progression-free survival (14.2 vs 10.9 months; $P = .64$). Response rates as first-line therapy were similar between FOLFIRI-first and FOLFOX-first groups (56% vs 54%; P-value was not significant). Metastasectomy was performed more frequently in the FOLFOX-first group (22% vs 9%; $P = .02$), and those patients who underwent metastasectomy achieved excellent survival. Response rates as second-line therapy were higher with FOLFOX than FOLFIRI (15% vs 4%; $P = .05$). The investigators 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%; $P = .60$), in median time to progression (7 vs 7 months; $P = .64$), or overall survival (14 vs 15 months; $P = .28$). Grade 3 or 4 toxicities were uncommon in either group, but the toxicity profiles were different between groups; FOLFIRI was more frequently associated with gastrointestinal symptoms and FOLFOX was more frequently associated with thrombocytopenia and neurosensorial symptoms. The investigators concluded that either FOLFIRI or FOLFOX was similarly effective as first-line therapy for patients with advanced colorectal cancer.[18]

Irinotecan and oxaliplatin were also compared in the setting of bevacizumab-containing regimens in a recent randomized controlled study from Japan (WJOG4407G) that 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; $P = .003$ for noninferiority) or median overall survival (31.4 vs 30.1 months; HR, 0.99; 95% CI, 0.79–1.25), showing

the equivalent efficacy of FOLFIRI and FOLFOX in combination with bevacizumab in first-line treatment.[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 nonresectable liver metastases, who were randomly assigned to receive cetuximab with either FOLFOX6 or FOLFIRI. There was no difference in response rate (68% vs 57%; $P = .23$) between groups. Response rate in patients with KRAS wild-type tumor was 70% (47 out of 67), which was higher than that of patients with KRAS mutated tumors (29%; 11 out of 27; $P = .008$). R0 resection was achieved in 38% (20 out of 53) in the FOLFOX6 group, and 30% (16 out of 53) in the FOLFIRI group (*P*-value not provided).[20]

Oxaliplatin-Containing and Irinotecan-Containing Regimens: Oxaliplatin and Irinotecan/FOLFOXIRI

Regimens containing both oxaliplatin and irinotecan (IROX) have been investigated. IROX with the addition of a 5-FU/LV infusion is called FOLFOXIRI.

Oxaliplatin and irinotecan

With the expansion of treatment options, the US Intergroup (INT) N9741 trial investigated the efficacy of IROX.[21–23] This study randomly assigned a total of 1691 patients into one of 7 regimens containing FU, oxaliplatin, and irinotecan between 1998 and 2002. Four out of those 7 arms were discontinued because of inefficacy or toxicity. The remaining 3 arms were weekly bolus IFL, FOLFOX, and bolus IROX. The FOLFOX group had a better 5-year survival rate (9.8%) than IFL (3.7%; $P = .04$) or IROX (5.1%; $P = .128$). Median overall survival and time to progression were also longer in the FOLFOX group (20.2 months and 8.9 months, respectively) than for IFL (14.6 months and 6.1 months, respectively; $P<.001$ for both) or IROX (17.3 months and 6.7 months, respectively; $P<.001$).[23] IROX was associated with higher frequency of grade 3 or worse hematologic toxicity in patients more than 70 years of age than FOLFOX.[22] The 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 3 active cytotoxic agents. In 2 Italian RCTs, progression-free survival was improved by FOLFOXIRI compared with 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; $P<.001$) and longer median overall survival (23.4 vs 16.7 months; $P = .026$) 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%; $P<.001$) and grade 3 to 4 neutropenia (50% vs 28%; $P<.001$). The incidences of febrile neutropenia (5% vs 3%) and grade 3 to 4 diarrhea were not different. However, by achieving a higher response rate with FOLFOXIRI (66% vs 41%; $P = .002$), subsequent R0 metastasectomy was more frequently achieved in FOLFOXIRI-treated patients than in the control patients (15% vs 6% [$P = .033$] among all patients, and 36% vs 12% [$P = .017$] among patients with liver-only metastasis).[25]

Based on the efficacy of the FOLFOXIRI triplet cytotoxic combination, the TRIBE phase III randomized controlled study compared FOLFIRINOX plus bevacizumab with FOLFIRI plus bevacizumab. A total of 508 patients with previously untreated mCRC were randomized. The overall response rate was higher (65% vs 53%; $P = .006$) and median progression-free survival was longer (12.1 vs 9.7 months; $P = .003$) with the

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; $P = .054$) and FOLFOXIRI was associated with a higher frequency of toxicity. In addition, this study did not confirm the benefit of FOLFOXIRI compared with 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 ($P = .33$).[26]

In contrast, a report from the Hellenic Oncology Research Group in the United Kingdom did not confirm the benefit of the FOLFOXIRI regimen compared with FOLFIRI. Souglakos and colleagues[27] reported a multicenter randomized controlled study of 283 previously untreated patients with mCRC, comparing FOLFOXIRI and FOLFIRI as first-line therapy. There was no difference in response rate (43% vs 33.6%; $P = .168$), median time to progression (8.4 vs 6.9 months; $P = .17$), or median overall survival (21.5 vs 19.5 months; $P = .34$). However, the 3-drug combination of FOLFOXIRI was associated with higher frequency of toxicity, including alopecia, diarrhea, and neurosensory toxicity, compared with FOLFIRI.

There are limited available data comparing FOLFOXIRI with FOLFOX. Gruenberger and colleagues[28] reported a multinational randomized phase II trial comparing mFOLFOX6 plus bevacizumab and FOLFOXIRI plus bevacizumab as first-line treatment of patients with colorectal cancer with unresectable liver metastases (OLIVIA trial). A total of 80 patients were enrolled. Bevacizumab plus FOLFOXIRI was associated with 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) compared with 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, because of the small sample size and type of study (phase II), statistical comparison was not made in the analysis.

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

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

Monoclonal Antibody Therapy

Bevacizumab

Bevacizumab (Avastin) is a humanized monoclonal antibody targeting VEGF that 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 the 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. The bevacizumab group had a higher response rate (44.8% vs 34.8%; $P = .004$) and longer median progression-free survival (10.6 vs 6.2 months; $P<.001$) compared with the placebo group. The addition of bevacizumab resulted in prolonged median overall survival (20.3 vs 15.6 months; $P<.001$).

Grade 3 hypertension was more commonly observed in the 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 a first-line irinotecan-containing regimen. A randomized phase II trial compared 5-FU/LV and bevacizumab versus 5-FU/LV and placebo as first-line therapy in 209 patients with mCRC who were not considered optimal for an irinotecan-containing regimen. The addition of bevacizumab was associated with an improved response rate (26% vs 15.2%; $P = .055$) and longer progression-free survival (9.2 vs 5.5 months; $P<.001$). Overall survival was also longer in bevacizumab group, albeit statistically not significant (16.6 vs 12.9 months; $P = .16$).[31]

Benefit of the addition of bevacizumab has been reported in combination with FOLFIRI. The BICC-C randomized phase III study (described in more detail earlier) compared irinotecan-containing regimens with or without bevacizumab in 430 previously untreated patients with mCRC. 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; $P = .28$).[9] In a follow-up report, there was superior median overall survival for FOLFIRI plus bevacizumab compared with modified IFL plus bevacizumab (28.0 vs 19.2 months; HR, 1.79; 95% CI, 1.12–2.88; $P = .037$).

In contrast, a Greek RCT failed to confirm a survival benefit with bevacizumab in combination with FOLFIRI in treatment-naive 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 months; $P = .139$).[32] However, survival in the control arm with FOLFIRI was better than expected.

Bevacizumab was also studied in combination with oxaliplatin-based regimens. The TREE study randomized patients with previously untreated metastatic or recurrent colorectal cancer 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). First-line bevacizumab plus oxaliplatin-containing therapy achieved median overall survival of 23.7 months, whereas 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 a 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; $P = .001$). Progression-free survival was also longer in the bevacizumab plus FOLFOX group than in the FOLFOX group (7.3 vs 4.7 months; $P<.001$). The addition of bevacizumab with FOLFOX4 resulted in a 14% overall increase in grade 3 and 4 toxicity, including hypertension, bleeding, and vomiting (**Table 1**).[34]

Results from another large RCT of bevacizumab in addition to oxaliplatin-based therapy did not confirm survival benefit. Saltz and colleagues[35] reported the NO16966 study, which randomized a total of 1401 patients in 2 by 2 factorial design, to CAPOX versus FOLFOX4, and then to bevacizumab versus placebo. Although the addition of bevacizumab was associated with improved progression-free survival

Table 1
Phase III clinical trials of monoclonal antibody therapies for metastatic colorectal cancer

Agents	Indication	Author, Year (Study Name)	N	Treatment	Median Survival (mo)	*P*-Value
Bev	First line	Hurwitz et al,[30] 2004	813	Bev + IFL vs IFL	PFS: 10.6 vs 6.2	<.001
					OS: 20.3 vs 15.6	<.001
		Stathopoulos et al,[32] 2010	222	Bev + FOLFIRI vs FOLFIRI	OS: 22 vs 25	.139
		Giantonio et al,[34] 2007 (ECOG E3200)	829	Bev + FOLFOX vs FOLFOX	PFS: 7.3 vs 4.7	<.001
					OS: 12.9 vs 10.8	.001
		Saltz et al,[35] 2008 (NO16966)	1401	2 × 2 factorial design	(Bev vs placebo)	
				CAPOX vs FOLFOX4, Bev vs placebo	PFS: 9.4 vs 8.0	.002
					OS: 21.3 vs 19.9	.077
	Second line	Bennouna et al,[36] 2013 (ML18147)	820	Bev + chemo vs chemo (oxaliplatin or irinotecan based)	OS: 11.2 vs 9.8	.006
		Masi et al,[37] 2015 (BEBYP)	185	Bev + chemo vs chemo (mFOLFOX or FOLFIRI)	OS: 6.8 vs 5.0	.043
Aflibercept	Second line	Van Cutsem et al,[38] 2012	1226	Aflibercept + FOLFIRI vs FOLFIRI	PFS: 6.9 vs 4.7	<.001
					OS: 13.5 vs 12.1	.003
Ramucirumab	Second line	Tabernero et al,[39] 2015 (RAISE)	1072	Ramucirumab + FOLFIRI vs FOLFIRI	PFS: 5.7 vs 4.5	<.001
					OS: 13.3 vs 11.7	.022

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Table 1
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Agents	Indication	Author, Year (Study Name)	N	Treatment	Median Survival (mo)	*P*-Value
Cet	Progressive disease	Jonker et al,[41] 2007; Karapetis et al,[42] 2008	572	Cet vs placebo	OS: 9.5 vs 4.8 Analysis of K-ras WT pts, n = 394	<.001
	Second line	Sobrero et al,[44] 2008 (EPIC)	1298	Cet + irinotecan vs irinotecan	PFS: 4.0 vs 2.6 OS: 10.7 vs 10.0	<.001 .71
	Second line	Cunningham et al,[45] 2004	329	Cet vs Cet + irinotecan	PFS: 4.1 vs 1.5 OS: 8.6 vs 4.9	<.001 .48
	First line	Van Cutsem et al,[46] 2009	1198	Cet + FOLFIRI vs FOLFIRI	PFS: 9.9 vs 8.7 OS: 23.5 vs 20.0 Analysis of K-ras WT pts, n = 348	.02 .009
	First line	Maughan et al,[51] 2011 (MRC COIN)	1630	Cet + chemo vs chemo (FOLFOX or CAPOX)	OS: 17.0 vs 17.9 Analysis of K-ras WT pts, n = 729	.67
	First line	Primrose et al,[52] 2014 (New EPOC)	257	Cet + chemo vs chemo (oxaliplatin based)	OS: 14.1 vs 20.5	.03
Bev vs Cet	First line	Heinemann et al,[53] 2014 (FIRE-3)	592	Bev + FOLFIRI vs Cet + FOLFIRI	OS: 25.0 vs 28.7	.017
	First line	Venook et al,[55] 2014 (CALGB/SWOG 80405, abstract)	1137	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 .34
Panitumumab	First line	Douillard et al,[60] 2010 (PRIME)	1183	Pan + FOLFOX4 vs FOLFOX4	PFS: 10.0 vs 8.6 OS: 23.9 vs 19.7 Analysis of K-ras WT pts, n = 656	.01 .17

Abbreviations: Bev, bevacizumab; Cet, cetuximab; Chemo, chemotherapy; OS, overall survival; Pan, panitumumab; PFS, progression-free survival; pts, patients; WT, wild type.

(9.4 vs 8.0 months; $P = .0023$), there was no statistically significant difference between the bevacizumab group and the no-bevacizumab group in median overall survival (21.3 vs 19.9 months; $P = .077$), with similar response rates.

Continuation of bevacizumab in second-line regimens 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 this setting. Maintenance of bevacizumab in the second-line therapy was associated with longer median overall survival (11.2 vs 9.8 months; $P = .0062$).[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 as the 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, $P = .043$).[37]

Other anti–vascular endothelial growth factor agents (aflibercept and ramucirumab)

There are 2 other anti-VEGF agents approved for mCRC: aflibercept and ramucirumab.

Van Custsem and colleagues[38] reported an RCT of 1226 patients with mCRC 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%; $P<.001$), improved progression-free survival (HR, 0.76; 95% CI, 0.66–0.87; $P<.001$), and improved overall survival (HR, 0.82; 95% CI, 0.71–0.94; $P = .003$).

An international multicenter RCT showed effectiveness of ramucirumab. This trial randomly assigned 1072 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; $P = .63$), but progression-free survival (HR, 0.79; 95% CI, 0.70–0.90; $P<.001$) and overall survival (HR, 0.84; 95% CI, 0.73–0.98; $P = .022$) were better in the ramucirumab group compared with the 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]

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

Epidermal growth factor receptor inhibitors

Cetuximab (Erbitux) and panitumumab (Vectibix) are monoclonal antibodies targeting EGFR and they been proved 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 because both cetuximab and panitumumab are known to be effective only on tumors with wild-type (not mutated) K-ras oncogenes, which is observed in approximately 60% of patients with mCRC.[40]

Cetuximab

Cetuximab is a mouse/human chimeric monoclonal antibody targeting EGFR. Cetuximab efficacy has been shown as monotherapy or in combination with irinotecan for

patients with K-ras wild-type tumors. A multicenter RCT of cetuximab monotherapy versus best supportive care for patients with progressive disease after FU, irinotecan, and oxaliplatin or patients with contraindications for those agents showed improved overall survival (median, 6.1 vs 4.6 months; HR, 0.77; 95% CI, 0.64–0.92; $P = .005$) and longer progression-free survival (HR, 0.68; 95% CI, 0.57–0.80; $P<.001$).[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 1 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; $P<.001$), whereas it was not in patients with K-ras–mutated tumors (HR, 0.98; $P = .89$).[42] Cetuximab monotherapy compared with best supportive care was also associated with improved quality of life in patients with mCRC.[43]

The EPIC phase III study showed the efficacy of cetuximab in combination with irinotecan in second-line therapy. It compared cetuximab plus irinotecan and irinotecan alone as second-line therapy, after progression with FU and oxaliplatin treatment in patients with mCRC. A total of 1298 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; $P<.0001$) and a higher response rate (16.4 vs 4.2%; $P = .047$). Overall survival was not different between groups (10.7 vs 10.0 months; $P = .71$), likely because 47% of the irinotecan-alone group subsequently received cetuximab. Skin rash (76 vs 5%), grade 3 to 4 diarrhea (28 vs 16%), and fatigue (8 vs 3%) were more frequently observed with combination therapy, but quality of life was reported to be better in the combination therapy group.[44]

Cetuximab monotherapy and cetuximab plus irinotecan in patients who progressed with previous irinotecan-based chemotherapy were compared in a randomized study of 329 patients with metastatic K-ras wild type colorectal cancer. The response rate was higher in the combination therapy group than the cetuximab monotherapy group (22.9% vs 10.8%; $P = .007$) and the time to progression was longer in the combination group as well (4.1 vs 1.5 months; $P<.001$). However, the difference in overall survival did not reach statistical significance (8.6 vs 4.9 months; $P = .48$).[45]

Cetuximab has also been investigated in first-line treatment of mCRC. The CRYSTAL multicenter phase III trial compared first-line FOLFIRI with or without cetuximab in a total of 1198 patients. The addition of cetuximab was associated with improved progression-free survival (HR, 0.85; 95% CI, 0.72–0.99; $P = .048$), although overall survival was not different between groups (HR, 0.93; 95% CI, 0.81–1.07; $P = .31$).[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%; $P<.001$), progression-free survival (median, 9.9 vs 8.7 months; $P = .02$), and overall survival (median, 23.5 vs 20.0 months; HR, 0.796; $P = .009$). The rate of R0 resection was also higher with cetuximab and in subgroup analysis of patients with K-ras wild-type tumors was 5.1% versus 2.0% (odds ratio, 2.65; $P = .026$). Toxicity was more frequently observed in the cetuximab group; grade 3 to 4 diarrhea, 16% versus 11%; skin toxicity, 19.7% versus 0.2%; and infusion reaction, 2.5% versus 0%.[47]

Addition of cetuximab has also been tested with FOLFOX as first-line therapy. The OPUS phase II trial randomized previously untreated patients with mCRC to receive 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%; $P = .0027$) and prolonged progression-free survival (median, 8.3 vs 7.2 months; $P = .0064$) than those who received FOLFOX4

alone, but the difference in overall survival did not reach statistical significance (median, 22.8 vs 18.5 months; $P = .39$).[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. The R0 resection rate was significantly improved with addition of cetuximab (25.7% vs 7.4%; $P<.01$), and 3-year overall survival was also improved (41% vs 18%; $P = .013$).[50]

Other studies have examined the impact of adding cetuximab to oxaliplatin-based regimens. The phase III MRC COIN trial conducted in the United Kingdom 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%; $P = .049$) but there was no survival difference between groups (median overall survival, 17.9 months in the chemotherapy-alone group vs 17.0 months in the cetuximab group; $P = .67$).[51] Another study from the United Kingdom (EPOC) randomized a total of 257 patients with potentially resectable mCRC with K-ras wild-type tumors and showed inferior survival outcomes with cetuximab plus oxaliplatin-based chemotherapy compared with chemotherapy alone (median progression-free survival, 14.1 vs 20.5 months; $P = .03$).[52] Thus the results are inconclusive with respect to first-line treatment with cetuximab and an oxaliplatin-containing chemotherapy backbone (**Table 2**).

Bevacizumab versus cetuximab

Several 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 compared with the bevacizumab group (median, 28.7 vs 25.0 months; $P = .017$).[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 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 these recommendations.[54]

In the United States, another randomized controlled study 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 with FIRE-3, 80405 did not show the superiority of cetuximab compared with bevacizumab. This study randomized a total of 1137 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

Table 2
Phase III clinical trials of chemotherapy regimens for metastatic colorectal cancer

Regimens	Indication	Author, Year (Study Name)	N	Treatment	Median Survival (mo)	*P*-Value
Irinotecan regimens	First line	Douillard et al,[6] 2000	287	Irinotecan + 5-FU/LV vs 5-FU/LV	PFS: 6.7 vs 4.4 OS: 17.4 vs 14.1	<.001 .031
		Kohne et al,[7] 2005 (EORTC 40986)	430	FOLFIRI vs 5-FU/LV	PFS: 8.5 vs 6.4 OS: 20.1 vs 16.9	<.001 .28
		Fuchs et al,[9] 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	.004[a] .09[a]
Oxaliplatin regimens	First line	De Gramont et al,[12] 2000	420	FOLFOX vs 5-FU/LV	PFS: 9.0 vs 6.2 OS: 16.2 vs 14.7	<.001 .12
		Ducreux et al,[69] 2011 (FFCD 2000-05)	205	First/second/third line 1. 5-FU + LV/FOLFOX6/FOLFIRI 2. FOLFOX6/FOLFIRI	OS: 16.2 vs 16.4	.85
		Porschen et al,[13] 2007	474	CAPOX vs FUFOX	PFS: 7.1 vs 8.0 OS: 16.8 vs 18.8	.12 .26
	Second line	Rothenberg et al,[11] 2003	463	FOLFOX4 vs 5-FU/LV vs oxaliplatin	PFS: 4.6 vs 2.7 vs 1.6	<.001[a]
		Rothenberg et al,[16] 2008	627	FOLFOX4 vs CAPOX	PFS: 4.8 vs 4.7 OS: 12.5 vs 11.9	Noninferior
	Third line	Kemeny et al,[15] 2004	214	FOLFOX4 vs 5-FU/LV	PFS: 4.8 vs 2.4 OS: 9.9 vs 11.4	<.001 .20
FOLFIRI vs FOLFOX	First line	Tournigand et al,[17] 2004 (GRECOR)	230	First/second line 1. FOLFIRI/FOLFOX 2. FOLFOX/FOLFIRI	OS: 21.5 vs 20.6 Second PFS: 14.2 vs 10.9	.99 .64
		Colucci et al,[18] 2005	360	FOLFIRI vs FOLFOX	PFS: 7 vs 7 OS: 14 vs 15	.64 .28
		Yamazaki et al,[19] 2016 (WJOG4407G)	402	Bev + FOLFIRI vs Bev + mFOLFOX6	PFS: 12.1 vs 10.7 OS: 31.4 vs 30.4	Noninferior
FOLFOXIRI	First line	Falcone et al,[25] 2007	244	FOLFOXIRI vs FOLFIRI	PFS: 9.8 vs 6.8 OS: 23.4 vs 16.7	<.001 .026
		Loupakis et al,[26] 2014 (TRIBE)	508	Bev + FOLFOXIRI vs Bev + FOLFIRI	PFS: 12.1 vs 9.7 OS: 31.0 vs 25.8	.003 .054
		Souglakos et al,[27] 2006	283	FOLFOXIRI vs FOLFIRI	PFS: 8.4 vs 6.9 OS: 21.5 vs 19.5	.17 .34

[a] Comparing first 2 regimens.

cetuximab, show that the addition of cetuximab was associated with shorter progression-free survival (10.7 months in no-cetuximab group vs 9.4 months in cetuximab group; $P = .01$), whereas 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 to be beneficial in K-ras wild-type tumors, either as monotherapy (vs best supportive care)[57–59] or in combination as first-line therapy.[60,61] Panitumumab was associated with a high incidence of skin toxicity (90%).[61]

The multicenter phase III PRIME trial randomized 1183 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; $P = .01$) without a significant improvement in overall survival (median, 23.9 vs 19.7 months; $P = .17$). Survival analysis showed that the panitumumab regimen was associated with improved overall survival (HR, 0.83; 95% CI, 0.70–0.98; $P = .03$).[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; $P = .02$).[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 (VEGF receptor [VEGFR] 1, VEGFR2, VFGFR3, and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF), and the tumor microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor). Regorafenib was approved by the FDA in 2012 for patients with mCRC who progressed after FU, oxaliplatin, and irinotecan chemotherapy, and monoclonal antibodies including anti-VEGF and (if K-ras wild type) anti-EGFR agents. Grothey and colleagues[62] 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 a modest increase in median overall survival (6.4 vs 5.0 months; $P = .005$) but treatment-associated adverse events were observed more frequently in the regorafenib group (93% vs 61%), most commonly with hand-foot skin reaction (17%) and fatigue (10%).

The benefit of regorafenib compared with 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; 1-sided $P = .00016$). 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, whereas tipiracil inhibits trifluridine metabolism. TAS-102 was approved by FDA in 2015 for the same indication as for regorafenib.

The RECOURSE phase III trial proved the efficacy of TAS-102 monotherapy compared with placebo in patients with refractory mCRC. This study randomly assigned a total of 800 patients with refractory colorectal cancer, who progressed with at least previous 2 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; $P<.001$) compared with placebo. The most common adverse events observed in the 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 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 controlled studies.

Resectable Liver Metastases

With the accumulation of case series that reported excellent outcomes, with 5-year overall survival averaging 40% to 50% after surgical resection of liver metastases,[66] surgical resection is thought to offer the best chance of cure for patients with resectable liver metastases ($\leq$4 liver lesions). However, resectability of disease and the optimal patient selection and timing for surgical resection of mCRC are not well defined.[67] The EORTC 40,983 trial was conducted to establish whether perioperative chemotherapy improves survival after resection of liver metastasis. In this phase III study, a total of 364 patients with resectable metastatic liver disease of colorectal cancer recruited from 78 hospitals internationally were randomly assigned to either perioperative FOLFOX4 or surgery alone. The perioperative therapy group received 6 cycles of chemotherapy before and after the surgery. Similar proportions of patients underwent successful resection of metastatic disease (83% in perioperative therapy group vs 84% in surgery-alone group). In the update at a median follow-up of 8.5 years, there was no difference in overall survival with the addition of perioperative chemotherapy; 5-year overall survival was 51.2% in the perioperative therapy group and 47.8% in the surgery-alone group ($P = .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%; $P = .035$).[68] Because of these mixed results from this randomized trial, the benefit of perioperative therapy for resectable liver metastasis remains unclear.

SUMMARY

This article reviews the available data from randomized clinical trials in advanced mCRC. Remarkable discoveries have been made over the last 20 years that 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 patients with mCRC.

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