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Emerging Treatments in Recurrent and Metastatic Colorectal Cancer

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Abstract

Metastatic colorectal cancer (mCRC) is a prevalent disease for which many new therapies have been developed over the past decade. Currently, standard of care chemotherapeutic regimens for mCRC include doublet cytotoxic chemotherapy with or without the anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, anti–epidermal growth factor receptor (EGFR) monoclonal antibodies such as cetuximab and panitumumab with or without chemotherapy, and single-agent cytotoxic chemotherapy or targeted therapy for patients intolerant of combination regimens. Recent studies have investigated the efficacy of triplet cytotoxic chemotherapeutic regimens, bevacizumab in combination with chemotherapy beyond first-line therapy disease progression, dual anti-VEGF and anti-EGFR antibody therapy, and the more novel agents ziv-aflibercept and regorafenib for treatment of mCRC. Furthermore, molecular profiling of CRC has identified several genetic alterations for which targeted therapies are currently being developed. Optimal drug combinations and treatment sequences have yet to be defined, but an expanding armamentarium of therapies with which to treat CRC offers a promising future.

Colorectal cancer (CRC) is both the third most prevalent and third most fatal tumor type in the United States, with an estimated 143,460 new cases and 51,690 deaths in 2012 alone.[1]

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Although surgical resection with or without adjuvant chemotherapy can be a curative strategy for localized disease, a substantial number of patients with CRC will experience disease recurrence. Furthermore, a significant proportion of patients with newly diagnosed CRC have advanced disease. As a result, effective therapies for metastatic CRC (mCRC), whether recurrent or newly diagnosed, are greatly needed. Several new drugs have recently been approved for the treatment of CRC or are currently under development for this indication, and novel combinations of available drugs are also under investigation. This article reviews current standard therapies, novel drugs, emerging new therapeutic strategies, and unanswered questions regarding the treatment of mCRC.

Current Standards of Care in mCRC

For many years, fluoropyrimidines in combination with leucovorin were the sole efficacious agents for the treatment of mCRC.[2,3] With the advent of oxaliplatin[4] and irinotecan,[5,6] however, treatment of mCRC with various combinations of these agents in addition to fluoropyrimidines led to significant improvement in overall survival. In general, doublet cytotoxic chemotherapy regimens have been effective and tolerable as palliative therapy for mCRC, and many standard options exist, including FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI (5-FU, leucovorin, irinotecan), XELOX (capecitabine, oxaliplatin), and others.[7–9] For patients unable to tolerate doublet chemotherapy, infusional 5-FU and leucovorin or oral capecitabine, or single-agent irinotecan are still reasonable treatment options.[6,9–11] In addition, first-line capecitabine plus bevacizumab was recently shown to improve both progression-free survival and response rate compared with capecitabine alone in elderly patients with mCRC in the open-label phase III AVEX trial.[12] Targeted therapies against vascular endothelial growth factor (VEGF), such as bevacizumab and ziv-aflibercept (Tables 1 and 2); epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab (Tables 2 and 3); or multiple tyrosine kinases, such as regorafenib,[13,14] have also improved the efficacy of mCRC treatment in selected patients, both in combination with cytotoxic chemotherapy and as single agents in some cases. In addition to systemic chemotherapy, surgical resection of limited metastatic disease can play an important, and sometimes curative, role in the treatment of select patients with mCRC.[15,16] Despite the efficacy of these agents and techniques, optimal drug combinations and treatment sequences remain unclear, and this is currently an intense area of research in mCRC.

Triplet Cytotoxic Chemotherapy Regimens

In addition to standard doublet cytotoxic chemotherapy regimens, regimens containing all 3 active cytotoxic chemotherapeutic agents in the first-line setting have also been explored in the hope of significantly increasing response rates and overall survival for patients with mCRC. An Italian phase III trial randomized 244 patients with mCRC to either FOLFOXIRI (irinotecan, 165 mg/m^2 day 1; oxaliplatin, 85 mg/m^2 day 1; leucovorin, 200 mg/m^2 day 1; and 5-FU, 3200 mg/m^2 48-hour continuous infusion starting on day 1, every 2 weeks) or the Douillard FOLFIRI regimen (irinotecan, 180 mg/m^2 day 1; leucovorin, 200 mg/m^2 days 1 and 2; and 5-FU, 400 mg/m^2 bolus then 600 mg/m^2 over 22 hours days 1 and 2, every 2 weeks) for 6 months as induction chemotherapy in the first-line metastatic setting.[17,18] With a primary end point of response rate (RR), the FOLFOXIRI group was significantly superior

to FOLFIRI (66% vs 41%; *P*=.0002). With a median follow-up of 60.6 months, patients in the FOLFOXIRI arm had statistically significant improvements in median progression-free survival (9.8 vs 6.8 months; hazard ratio [HR], 0.59; 95% CI, 0.45–0.76; *P*<.001) and median overall survival (23.4 vs 16.7 months; HR, 0.74; 95% CI, 0.56–0.96; *P*=.026). This survival advantage was partly from the patients who were able to undergo metastasectomy, because the survival benefit of FOLFOXIRI was no longer statistically significant compared with FOLFIRI when postmetastasectomy patients were excluded from the analysis. The 5-year survival rate of patients receiving FOLFOXIRI treatment was improved compared with those who received FOLFIRI, with a 7% absolute survival benefit over this period (15% vs 8%).

A similarly sized phase III study of first-line FOLFOXIRI (irinotecan, 150 mg/m^2 day 1; oxaliplatin, 65 mg/m^2 day 2; leucovorin, 200 mg/m^2 days 2 and 3; and 5-FU, 400 mg/m^2 intravenous bolus and 600 mg/m^2 as a 22-hour continuous infusion on days 2 and 3) versus FOLFIRI (irinotecan, 180 mg/m^2 day 1; leucovorin, 200 mg/m^2 days 2 and 3; and 5-FU, 400 mg/m^2 intravenous bolus and 600 mg/m^2 as a 22-hour continuous infusion on days 2 and 3) every 2 weeks was also completed.[19] In contrast to the Italian study, however, no overall survival advantage was seen for the FOLFOXIRI cohort (median overall survival, 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; *P*=.337), although this group did have statistically significant higher rates of toxicity. Lower cytotoxic chemotherapy doses and possible selection bias leading to superior median overall survival in this trial have been cited as possible reasons for this intertrial discordance.

Before triplet cytotoxic chemotherapy regimens such as FOLFOXIRI can be considered standard of care in the first-line mCRC setting, however, their survival advantage and tolerable toxicity profile must be confirmed in larger, multinational studies. In the meantime, given the improved response rates and complete metastasectomy rates with FOLFOXIRI versus FOLFIRI, a possible role for this regimen is in patients with initially unresectable disease who might become surgical candidates with a robust response to chemotherapy, as suggested by Masi et al.[20] Other active questions under investigation include the safety and efficacy of adding either anti-EGFR or anti-VEGF therapies to triplet cytotoxic regimens; preliminary results of these trials appear promising.[21–24]

Bevacizumab Beyond Progression

Prior studies have investigated whether bevacizumab, the monoclonal antibody targeting VEGF-A, affords a survival advantage when combined with cytotoxic chemotherapy either in the first- or second-line treatment of CRC.[25,26] Until recently, however, whether the addition of bevacizumab to chemotherapy improved survival if started in the first-line setting and continued with chemotherapy beyond initial disease progression was unclear. In addition to registry-based retrospective analyses that attempted to answer this question, a European phase III trial prospectively randomized 820 patients to continuing bevacizumab or not with second-line chemotherapy after disease progression while on first-line bevacizumab-containing chemotherapy ("bevacizumab beyond progression").[27] Median overall survival for the bevacizumab plus chemotherapy group was significantly prolonged compared with the chemotherapy alone group (11.2 vs 9.8 months; *P*=.0062), as was progression-free

survival (5.7 vs 4.1 months; $P<.0001$). Achievement of confirmed disease response was not statistically different between the groups, and no statistically significant increase was seen in bevacizumab-related adverse events.

Despite this small overall survival benefit for patients with mCRC receiving bevacizumab, significant risks are associated with the therapy, including arterial thromboembolic events, hemorrhage, and bowel perforation, and the cost for this therapy remains high. Whether particular subgroups of patients would benefit more from the addition of bevacizumab to chemotherapy is currently unclear, because validated predictive markers of response to bevacizumab have not yet been developed. In the United States, however, bevacizumab in combination with chemotherapy remains a standard of care for patients with mCRC who have no contraindication to this therapy.

VEGF and/or EGFR Antibody Therapy

Given the survival advantage conferred when targeting either VEGF or the EGFR in mCRC, the combination of these therapies was hypothesized to be additive to or synergistic with chemotherapy. The phase II BOND2 trial randomized 83 bevacizumab- and cetuximab-naïve patients with chemorefractory mCRC to cetuximab and bevacizumab with or without irinotecan.[28] Time to progression (TTP), RR, and overall survival were all improved for the cetuximab/bevacizumab/irinotecan (CBI) arm compared with the cetuximab/bevacizumab (CB) arm, and toxicity profiles were similar. However, 2 subsequent larger phase III trials that combined chemotherapy with bevacizumab and either cetuximab or panitumumab in the first-line setting failed to demonstrate a similar survival advantage with the 3-pronged therapeutic approach.[29,30] Patients in the PACCE trial were randomized to chemotherapy and bevacizumab with or without panitumumab, 6 mg/kd every 2 weeks. After early discontinuation of the trial because of futility, both median progression-free survival (10.0 vs 11.4 months; HR, 1.27; 95% CI, 1.06–1.52) and median overall survival (19.4 vs 24.5 months; HR, 1.43; 95% CI, 1.11–1.83) were found to be worse in the panitumumab-containing arm of the oxaliplatin-receiving patient cohort, even in patients with *KRAS* wild-type tumors. Toxicities were also much more significant in the panitumumab-containing arm. In CAIRO2, patients with mCRC were randomized to capecitabine, oxaliplatin, and bevacizumab with or without weekly cetuximab. Similar to the PACCE trial, median progression-free survival in the cetuximab-containing arm of CAIRO2 was only 9.4 months, in contrast to a median progression-free survival of 10.7 months in the non–cetuximab-containing arm ($P=.01$).[30] Patients in the cetuximab-containing arm also had a worse quality of life in this trial because of increased toxicities associated with therapy. Based on these results, chemotherapy combined with anti-VEGF and anti-EGFR therapy is not recommended in the first-line setting, although whether this combination is also detrimental in later lines of therapy is unclear and is an ongoing area of research.

Furthermore, investigation is ongoing with regard to superiority of either anti-EGFR or anti-VEGF therapy in combination with FOLFIRI chemotherapy in the first-line setting, with results from the AIO KRK-0306 (FIRE-3) study recently reported.[31] In this trial, although the primary end point of overall response rate was comparable between arms in the intent-to-treat analysis, superior overall survival was seen in patients with *KRAS* wild-type tumors

receiving cetuximab plus FOLFIRI compared with those receiving bevacizumab plus FOLFIRI (28.8 vs 25.0 months; HR, 0.77; *P*=.0164; 95% CI, 0.620–0.953). From these trials and others, it is clear that the optimal sequences and/or combinations of biologics with or without chemotherapy have yet to be determined in mCRC.

Ziv-Aflibercept

In 2012, the anti-VEGF and anti–placental growth factor (anti-PlGF) agent ziv-aflibercept was approved by the FDA in combination with FOLFIRI for the treatment of patients with mCRC who had previously received an oxaliplatin-containing chemotherapeutic regimen. Ziv-aflibercept, a functional decoy VEGF receptor with a propensity to bind VEGF-A, VEGF-B, PlGF-1, and PlGF-2, was shown to improve progression-free and overall survivals in combination with FOLFIRI in the prospective, randomized, placebo-controlled phase III VELOUR trial.[32] Patients in this study received FOLFIRI plus either ziv-aflibercept, 4 mg/kg intravenously, or placebo every 2 weeks until unacceptable toxicity or disease progression. Efficacy analysis of the 1226 randomized patients showed a small overall survival advantage for the ziv-aflibercept group compared with the placebo group (median overall survival, 13.50 vs 12.06 months; *P*=.0032) and improved progression-free survival (median progression-free survival, 6.90 vs 4.67 months; *P*<.001). Response rates of 19.8% and 11.1%, respectively, were seen (*P*<.001), with 30.4% of the patients overall having received prior bevacizumab. Grade 3 and 4 adverse events, both those associated with antiangiogenic agents and those typically associated with FOLFIRI, were seen more frequently in the ziv-aflibercept arm (83.5% vs 62.5%). Interestingly, efficacy of ziv-aflibercept was maintained even in prespecified subgroup analysis of patients having previously received bevacizumab. It is currently unclear, however, how significant a role ziv-aflibercept will play in the mCRC treatment landscape given its cost and the availability of other antiangiogenic agents, as well as negative studies of ziv-aflibercept both as a single agent and in preliminary studies in combination with oxaliplatin-containing regimens in the first-line setting.[33,34] Importantly, studies are ongoing to define predictive biomarkers for response to ziv-aflibercept.

Regorafenib

Regorafenib, a multikinase inhibitor, was approved by the FDA in 2012 for the treatment of patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and with an anti-EGFR therapy, if *KRAS* wild-type. Regorafenib is an oral inhibitor of such tyrosine kinases as VEGFR1, VEGFR2, VEGFR3 and TIE2, among others. A preplanned interim analysis of the placebo-controlled phase III CORRECT study demonstrated an overall survival advantage for the regorafenib arm over placebo (6.4 vs 5.0 months; one-sided *P*=.0052), and progression-free survival advantage (1.9 vs 1.7 months; one-sided *P*<.000001).[13] Notably, grade 3 or 4 treatment-related adverse events occurred in 54% of patients in the regorafenib arm compared with 14% of patients in the placebo arm; these regorafenib-related adverse events included hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation. Like ziv-aflibercept, predictive biomarkers have not yet been defined for regorafenib. However, unlike ziv-aflibercept or bevacizumab, regorafenib monotherapy seems to play a role in the

treatment of refractory mCRC distinct from other therapies, provided the patients for whom it is prescribed have an adequate performance status.

Genomics-Driven Therapy of mCRC

Advances in the field of genomics, as recently exemplified by The Cancer Genome Atlas Network and others, have led to an increasing understanding of the genetic alterations underlying particular tumors such as CRC.[35] Knowledge of these genetic alterations has led to initial efforts in CRC to personalize therapy for patients according to the biology of their tumors. Two proven examples of this approach are the selective treatment of *KRAS* wild-type tumors with anti-EGFR therapies, such as cetuximab or panitumumab,[36–38] and the decision to forego adjuvant fluoropyrimidine monotherapy for patients with stage II CRC whose tumors have features of microsatellite instability.[39–41]

As more genetic alterations in CRC are discovered, however, efforts both to determine appropriate subgroups of patients for known therapies and to develop and test novel targeted agents for these tumors have escalated. For example, the PICCOLO study showed improved progression-free survival and response rate, although not overall survival, for patients with all-wild-type (*KRAS* codons 12, 13, 61, 146; *BRAF* codon 600; *NRAS* codons 12, 13, 61; *PIK3CA* codons 542, 545, 546 [exon 9] and 1047 [exon 20]) CRC treated with irinotecan and panitumumab compared with those treated with irinotecan alone.[42] However, in patients with any of these mutations, panitumumab had no effect on progression-free survival or response rate, and an adverse effect on overall survival. These data emphasize the need for more comprehensive CRC genotyping and studies of tumor mutational effects on treatment efficacy.

In terms of developing novel therapies against these tumor subtypes, treatment of *BRAF*-mutated CRC with *BRAF* inhibitor monotherapy has not been as effective as was hoped,[43] for example, partly because of upregulation of compensatory pathways.[44,45] However, efforts are underway to develop rationally designed combinations of targeted therapies (eg, *BRAF*/*MEK* inhibition[46] and others) for increased efficacy against these tumors. In addition, a recent observation that the regular use of aspirin correlates with improved survival among patients with *PIK3CA*-mutated CRC compared with *PIK3CA* wild-type CRC[47] confirms the need for improved mechanistic understanding of tumor response to agents, both novel and approved. As underlying mechanisms of these novel drugs are elucidated, CRC clinical trials will need to become increasingly biomarker- and genomics-driven, as exemplified by the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial in lung cancer[48] and the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis (I-SPY 1) trial in breast cancer.[49]

Conclusions

The treatment landscape of mCRC has changed considerably over the past decade with the development of efficacious new agents and novel strategies with which to administer them. Many unanswered questions remain, however, including the best combinations and

sequences in which to use these therapies. Interestingly, unlike in other tumor types, such as melanoma, immunotherapies do not seem to be effective in CRC, and investigational targets in CRC have primarily focused on signal transduction pathways. In this realm, better prognostic and predictive biomarkers are greatly needed. As the biologic underpinnings of these tumors are increasingly discovered and understood, molecular profiling and the selection of therapies according to an individual's specific tumor biology will become more important. Understanding the genetic heterogeneity of tumors, optimizing treatment tolerability for patients, maximizing cost-effectiveness of these agents, and developing strategies to overcome both intrinsic and acquired resistance to these therapies will dominate the efforts to improve patient quality of life and survival in this disease.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Differentiate the various treatment options for mCRC
- Appraise the recent clinical trial results of anti-EGFR and anti-VEGF therapies for determining optimal drug combinations and treatment sequences for mCRC
- Describe the 2 proven examples of genetic alterations leading to personalized therapy for patients with mCRC

Table 1

Phase III Trials of Anti-VEGF Therapies in Metastatic Colorectal Cancer

Trial and Associated Chemotherapy ± Anti-VEGF Therapy Regimens	Trial Size	Efficacy Outcomes (Chemotherapy vs Chemotherapy + Biologic)
AVF2107[50]	N=411 vs 402	OS: 15.6 vs 20.3 mo; *P*<.001
IFL (bolus) ± bevacizumab[a]		PFS: 6.2 vs 10.6 mo; *P*<.001
First-line		ORR: 34.8% vs 44.8%; *P*=.004
NO16966[51]	N=701 (350 CAPOX, 351 FOLFOX4) vs 699 (350 CAPOX, 349 FOLFOX4)	OS: 19.9 vs 21.3 mo; *P*=.769
CAPOX/FOLFOX4 ± bevacizumab[b]		PFS: 7.9 vs 10.4 mo; *P*=.0023
First-line		ORR: 38% vs 38%; *P*=.99
Stathopoulos et al[52]	N=108 vs 114	OS: 25.0 vs 22.0 mo; *P*=.1391
FOLFIRI/FOLFOX ± bevacizumab[c]		RR: 35.19% vs 36.84%
First-line		
E3200[26]	N=291 vs 286	OS: 10.8 vs 12.9 mo; *P*=.011
FOLFOX4 ± bevacizumab[d]		PFS: 4.7 vs 7.3 mo; *P*<.0001
Second-line		ORR: 8.6% vs 22.7%; *P*<.0001
ML18147[27]	N=411 vs 409	OS: 9.8 vs 11.2 mo; *P*=.0062
Crossover chemotherapy ± bevacizumab (beyond progression)[e]		PFS: 4.1 vs 5.7 mo; *P*<.0001
Second-line		ORR: 3.9% vs 5.4%; *P*=.3113
BEBYP[53]	N=92 vs 92	OS: not yet mature
Chemotherapy ± bevacizumab (beyond progression)[f]		FS: 4.97 vs 6.77 mo; *P*=.0062
Second-line		ORR: 18% vs 21%; *P*=.71
VELOUR[32]	N=614 vs 612	OS: 12.05 vs 13.50 mo; *P*=.0032
FOLFIRI ± ziv-aflibercept[g]		FS: 4.67 vs 6.90 mo; *P*<.0001
Second-line		ORR: 11.1% vs 19.8%; *P*<.001

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

[a]Irinotecan, 125 mg/m^2; 5-FU, 500 mg/m^2 bolus; leucovorin, 20 mg/m^2 once weekly for 4 weeks followed by 2 weeks rest ± bevacizumab, 5 mg/kg every 2 weeks.

[b] CAPOX (oxaliplatin, 130 mg/m^2 on day 1; capecitabine, 1000 mg/m^2 twice a day on days 1–14 of a 21-day cycle) ± bevacizumab, 7.5 mg/kg on day 1. FOLFOX4 (oxaliplatin, 85 mg/m^2 on day 1 + leucovorin, 200 mg/m^2/d and 5-FU bolus, 400 mg/m^2 followed by a 22-hour 5-FU infusion of 600 mg/m^2/d on days 1 and 2 every 2 weeks) ± bevacizumab, 5 mg/kg on day 1.

[c] Dosing schedule not detailed in abstract.

[d] FOLFOX4 (oxaliplatin, 85 mg/m^2 on day 1 + leucovorin, 200 mg/m^2 on days 1 and 2 + 5-FU, 400 mg/m^2 bolus followed by 600 mg/m^2 continuous infusion on days 1 and 2) ± bevacizumab, 10 mg/kg on day 1.

[e] Chemotherapy regimen was designed as a crossover on the patient's first-line regimen (ie, patients receiving fluoropyrimidine/oxaliplatin in the first line would be switched to fluoropyrimidine/irinotecan, and vice versa). Eligible fluoropyrimidine regimens included both bolus and infusional 5-FU, and capecitabine. Bevacizumab was given at 2.5 mg/kg/wk.

[f] Chemotherapy regimen was either FOLFOX or FOLFIRI and depended on first-line chemotherapy received. Bevacizumab was given at 5 mg/kg every 2 weeks.

[g] Irinotecan, 180 mg/m^2 + leucovorin, 400 mg/m^2 and 5-FU, 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 continuous infusion administered over 26 hours ± 4 mg/kg of ziv-aflibercept every 2 weeks.

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Table 2

Phase III Trials of Anti-VEGF and Anti-EGFR Therapies in Metastatic Colorectal Cancer

Trial and Associated Chemotherapy ± Anti-VEGF ± Anti-EGFR Therapy Regimens	Trial Size	Efficacy Outcomes (Chemotherapy vs Chemotherapy + Biologic)
CAIRO2[30]	N=378 (156 *KRAS* WT, 108 *KRAS* MT) vs 377 (158 *KRAS* WT, 98 *KRAS* MT)	Overall
Bevacizumab/CAPOX ± cetuximab[a]		OS: 20.3 vs 19.4 mo; *P*=.16
First-line		PFS: 10.7 vs 9.4 mo; *P*=.01
		ORR: 50.0% vs 52.7%; *P*=.49
		KRAS WT
		OS: 22.4 vs 21.8 mo; *P*=.64
		PFS: 10.6 vs 10.5 mo; *P*=.30
		ORR: 50.0% vs 61.4%; *P*=.06
PACCE[29]	N=410 vs 413	Overall
Bevacizumab/ox-CT ± panitumumab[b]		OS: 24.5 vs 19.4 mo
First-line		PFS: 11.4 vs 10.0 mo
		ORR: 48% vs 46%
		KRAS WT
		OS: 24.5 vs 20.7 mo
		PFS: 11.5 vs 9.8 mo
		ORR: 56% vs 50%
PACCE[29]	N=115 vs 115	Overall
Bevacizumab/iri-CT ± panitumumab[c]		OS: 20.5 vs 20.7 mo
First-line		PFS: 11.7 vs 10.1 mo
		ORR: 40% vs 43%
		KRAS WT
		OS: 19.8 vs not estimable
		PFS: 12.5 vs 10.0 mo
		ORR: 48% vs 54%

Abbreviations: CT, chemotherapy; EGFR, epidermal growth factor receptor; iri, irinotecan; MT, mutant; ORR, overall response rate; OS, overall survival; ox, oxaliplatin; PFS, progression-free survival; VEGF, vascular endothelial growth factor; WT, wild-type.

[a] Capecitabine, 1000 mg/m^2 twice daily on days 1–14; oxaliplatin, 130 mg/m^2 on day 1; bevacizumab, 7.5 mg/kg on day 1 ± cetuximab at loading dose of 400 mg/m^2 and weekly dose of 250 mg/m^2.

[b] Any infusional or bolus 5-FU regimen allowed per investigator's choice. Capecitabine regimens not permitted. Bevacizumab was given every 2 weeks at doses per investigators choice ± panitumumab dosed at 6 mg/kg every 2 weeks.

[c] Oxaliplatin, 85 mg/m^2 day 1; leucovorin, 200 mg/m^2 and 5-FU, 400 mg/m^2 bolus followed by 5-FU, 600 mg/m^2 infusion over 22 hours on days 1 and 2 every 2 weeks ± bevacizumab, 10 mg/kg on day 1 every 2 weeks.

Table 3

Phase III Trials of Anti-EGFR Therapies in Metastatic Colorectal Cancer

Trial and Associated Chemotherapy ± Anti-EGFR Therapy Regimens	Trial Size	Efficacy Outcomes (Chemotherapy vs Chemotherapy + Biologic)
CRYSTAL[54,55]	N=599 (350 *KRAS* WT, 183 *KRAS* MT) vs 599 (316 *KRAS* WT, 218 *KRAS* MT)	Overall (ITT)
FOLFIRI ± cetuximab[a]		OS: 18.6 vs 19.9 mo; *P*=.31
First-line		PFS: 8.0 vs 8.9 mo; *P*=.048
		ORR: 38.7% vs 46.9%; *P*=.004
		KRAS WT
		OS: 20.0 vs 23.5 mo; *P*=.0093
		PFS: 8.4 vs 9.9 mo; *P*=.0012
		ORR: 39.7% vs 57.3%; *P*<.001
Nordic VII[56]	N=76 (46 *KRAS* WT, 43 *KRAS* MT) vs 94 (45 *KRAS* WT, 35 *KRAS* MT)	Overall (ITT)
Nordic FLOX (bolus) ± cetuximab[b]		OS: 20.4 vs 19.7 mo; *P*=.67
First-line		PFS: 7.9 vs 8.3 mo; *P*=.31
		ORR: 41% vs 49%; *P*= 15
		KRAS WT
		OS: 22.0 vs 20.1 mo; *P*=.48
		PFS: 8.7 vs 7.9 mo; *P*=.66
		ORR: 47% vs 46%; *P*=.89
COIN[57]	N=815 (367 *KRAS* WT, 268 *KRAS* MT) vs 815 (362 *KRAS* WT, 297 *KRAS* MT)	*KRAS* WT
CAPOX/FOLFOX ± cetuximab[c]		OS: 17.9 vs 17.0 mo; *P*=.67
First-line		PFS: 8.6 vs 8.6 mo; *P*=.60
		ORR: 57% vs 64%; *P*=.049
PRIME[58]	N=332 vs 546	*KRAS* WT
FOLFOX4 ± panitumumab[d]		OS: 19.7 vs 23.9 mo; *P*=.072
First-line		PFS: 8.0 vs 9.6 mo; *P*=.02
		ORR: 48% vs 55%; *P*=.068
Study 181[59]	N=595 (294 *KRAS* WT, 248 *KRAS* MT) vs 591 (303 *KRAS* WT, 238 *KRAS* MT)	*KRAS* WT

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Trial and Associated Chemotherapy ± Anti-EGFR Therapy Regimens	Trial Size	Efficacy Outcomes (Chemotherapy vs Chemotherapy + Biologic)
FOLFIRI ± panitumumab[e]		OS: 12.5 vs 14.5 mo; *P*=.12
Second-line		PFS: 3.9 vs 5.9 mo; *P*=.004
		ORR: 10% vs 35%; *P*<.0001

Abbreviations: EGFR, epidermal growth factor receptor; ITT, intent-to-treat; MT, mutant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; WT, wild-type.

[a]Irinotecan, 180 mg/m^2 + racemic leucovorin or levo-leucovorin at a dose of 400 or 200 mg, respectively, and 5-FU, 400 mg/m^2 bolus on day 1 followed by 46-hour infusion of 5-FU, 2400 mg/m^2 every 2 weeks ± cetuximab, 400 mg/m^2 loading dose and 200 mg/m^2 weekly.

[b]Oxaliplatin, 85 mg/m^2 on day 1 + bolus 5-FU, 500 mg/m^2 and leucovorin, 60 mg/m^2 on days 1 and 2 ± cetuximab at 400 mg/m^2 loading dose and 200 mg/m^2 weekly dose.

[c]CAPOX (oxaliplatin, 130 mg/m^2 on day 1 followed by capecitabine, 1000 mg/m^2 twice a day [dose reduced to 850 mg/m^2] for 2 weeks in a 3-week cycle) ± cetuximab at loading dose of 400 mg/m^2 and weekly dose of 250 mg/m^2. FOLFOX [oxaliplatin, 85 mg/m^2 on day 1 + levo-leucovorin, 175 mg or racemic leucovorin, 350 mg and bolus 5-FU, 400 mg/m^2 followed by 5-FU, 2400 mg/m^2 infused over 46 hours] ± cetuximab at loading dose of 400 mg/m^2 and weekly dose of 250 mg/m^2.

[d]Oxaliplatin, 85 mg/m^2 on day 1 and leucovorin, 200 mg/m^2 (or equivalent) and 5-FU, 400 mg/m^2 bolus followed by 600 mg/m^2 22-hour continuous infusion on days 1 and 2 ± panitumumab, 6 mg/kg every 2 weeks on day 1.

[e]Irinotecan, 180 mg/m^2 + racemic leucovorin, 400 mg/m^2 (or levo-leucovorin, 200 mg/m^2) and 5-FU, 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 continuous infusion administered over days 1 and 2 ± panitumumab, 6 mg/kg every 2 weeks.