# Frontline Strategies for Metastatic Colorectal Cancer: New Sides to the Story

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## Abstract

The plethora of available new agents and multidisciplinary management have improved the prognosis of metastatic colorectal cancer and have correspondingly made first-line treatment decisions variable and complex. Predictive biomarkers such as RAS, and to an extent, BRAF have aided greatly in selecting patients who are likely to benefit from anti-EGFR therapy in the first-line setting. More recently, retrospective analyses of large randomized trials of chemotherapy and biologicals in the first-line setting have shown that sidedness of the primary tumor, whether left or right, is a surrogate of tumor biology and has significant prognostic and predictive value. Data show that in a cohort of RAS wild-type metastatic colorectal cancer, patients with left sided primaries have better prognosis and response to anti-EGFR therapy than those with right-sided primaries. Mismatch repair deficiency has also recently been shown to predict response to immune-checkpoint blockade and will likely be available in the near future for use in the first-line treatment of this subset. In patients without predictive biomarkers, chemotherapy remains the standard and addressing goals of care accurately with the patient guides selection of either single-agent or combination cytotoxic therapy. In a small minority of patients with oligometastatic disease, long term survival and potential cure is possible with multimodal management and resection. Borderline resectable disease can be converted into a resectable situation with active combination chemotherapy with high response rates. This review highlights various approaches in the first-line treatment of mCRC, as well as recent discoveries in tumor biology that may impact selection of the appropriate strategy.


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## Introduction

The prognosis for metastatic colorectal cancer (mCRC) remains poor, with a5-year survival of approximately 13%.1 Recent years have brought a plethora of new agents, with 11 drugs currently approved.2 Most patients with mCRC will receive many of these drugs, making treatment strategies variable and complex. This review highlights various approaches in the first-line treatment of mCRC, as well as recent discoveries in tumor biology that may impact selection of the appropriate strategy.

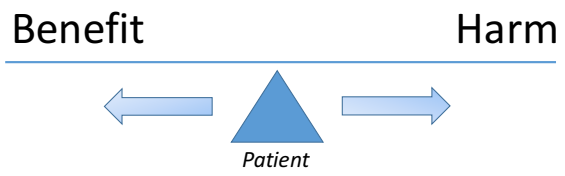
## Goals of Therapy

A majority of patients with mCRC cannot be cured with surgical resection. In these situations, the goal of treatment is twofold: palliation of symptoms and extension of quality of life. Symptomatic disease is likely to benefit from therapy with high response rates (RRs) that promptly decreases tumor burden. In contrast, some patients will be asymptomatic, and extension of this state is the goal. In these cases, RR may be irrelevant, and well-tolerated regimens with overall survival (OS) benefit are preferred. A minority of patients with borderline-resectable, oligometastatic CRC may be cured through multidisciplinary management, with conversion to resectable disease if target lesions achieve significant shrinkage.3 The potential for cure is thus contingent on response, and combination cytotoxic regimens with high RR are preferred in selected patients, even at the cost of higher toxicity. In all situations, the potential for benefit must always be weighed against potential for harm. Eliciting a patient's fulcrum along a "therapeutic lever" is a useful tool in determining the appropriate strategy to achieve the goal of therapy **(Figure 1)**.

## Predictive Biomarkers

The development of predictive biomarkers in mCRC over the past 10 years has greatly aided the clinician in subdividing patients into treatment groups and appropriate designation of first-line therapy. Mutations in *RAS* oncogenes (*KRAS, NRAS*) are present in approximately half of mCRCs, which results in constitutive activation of the RAS-RAF-ERK pathway and resistance to anti-EGFR therapy.[4,5] Activating mutations in *RAF*, particularly *BRAF* $^{V600E}$, are present in 5% to 10% of colon cancers and portend a poor prognosis. Although not as robust, evidence suggests

**FIGURE 1.** Eliciting a patient's fulcrum along a therapeutic lever to weigh potential benefit versus potential harm.




that response to anti-EGFR therapy is unlikely in patients who harbor a *BRAF* $^{V600E}$ mutation.[6,7] In the subset of patients with *RAS* wild-type (WT) disease, recent data show primary tumor location to predict benefit from anti-EGFR therapy, with left-sided primaries having significant survival advantage over right-sided primaries.[8,9] Lastly, approximately 4% to 9% of mCRCs display microsatellite instability (MSI) caused by a genotype with mismatch repair deficiency (dMMR).[10,11] Although not yet approved for first-line use, PD-1 blockade has demonstrated robust and prolonged responses in mCRC, with dMMR characterized by an MSI-high (MSI-H) status.[12]

### *RAS* Wild-Type and *BRAF* Wild-Type mCRC

Patients who do not harbor activating mutations in *RAS* and *BRAF* derive the most benefit from first-line combination treatment with chemotherapy and anti-EGFR therapy. Cetuximab and panitumumab are the 2 anti-EGFR monoclonal antibodies (mAbs) currently approved in this setting. The CRYSTAL trial investigated the combination of cetuximab plus FOLFIRI chemotherapy in patients with *KRAS* exon 2 WT tumors, and found significant improvements in RR, progression-free survival (PFS), and median OS (23.5 vs 20 months; HR, 0.0796; *P* =.0093).[13,14] This study, however, did not test for other mutations in *KRAS* or *NRAS*, and may have led to about 10% to 25% of patients being misassigned to the *RAS* WT population.

The importance of determining other *RAS* mutations was further underscored in the PRIME trial, which investigated the addition of panitumumab to FOLFOX in a *RAS* WT cohort (no mutations in exons 2,3, and 4 of both *KRAS* and *NRAS*). The trial not only demonstrated superior PFS and OS in patients with *RAS* WT disease who received panitumumab, but also showed poor outcomes, with significant decreases in PFS (HR, 1.31; *P* =.008) and OS (HR, 1.21; *P* =.04), when patients with *RAS* mutations received anti-EGFR therapy.[15] Although the number of patients with *BRAF* $^{V600E}$ mutations in these trials was small, a meta-analysis including both of these studies suggests lack of benefit of anti-EGFR therapy in this subset.[6]

In contrast, studies combining chemotherapy with the anti-VEGF-A mAb bevacizumab versus anti-EGFR agents did not show *RAS* and *BRAF* mutations to confer resistance to antiangiogenic therapy.[16,17] Bevacizumab is the only antiangiogenic agent approved and recommended for use in the first-line setting in combination with chemotherapy.7 Notable toxicities include hypertension, proteinuria, delayed wound healing, bleeding, and more seriously, rare thromboembolic events and intestinal perforation. The timing of administration with chemotherapy may hence be variable, pending resolution of issues such as surgical wounds and intestinal obstruction. The incidence and severity of toxicities, however, does not appear to be significantly affected by choice of chemotherapy backbone, as demonstrated in the STEAM and MAVERICC trials.[18,19]

The question of which biologic therapy is superior in the first line has been investigated in 3 large trials. FIRE-3 (N=592) and CALGB/SWOG 80405 (N=1137) are phase III trials that evaluated cetuximab versus bevacizumab, and the phase II PEAK trial (N=278) evaluated panitumumab and bevacizumab. The primary endpoint of FIRE-3 was RR, with PFS and OS as secondary endpoints. FIRE-3 failed to show improvements in RR or PFS but revealed a significant increase in OS in favor of cetuximab plus FOLFIRI (28.7 vs 25 months; HR, 0.77; *P* =.017).[20] A post-hoc analysis showed a more marked improvement in OS in favor of cetuximab when analysis was limited to all patients with *RAS* WT disease. Similarly, PEAK showed significant improvements in OS as a secondary endpoint in patients with *KRAS* WT disease receiving panitumumab.[21] These 2 studies suggested superiority of anti-EGFR therapy over bevacizumab, though conclusions could not firmly be made, as both trials were not powered to detect an OS advantage of one over the other.

Conversely, the CALGB/SWOG 80405 trial was powered to detect a 5.5-month improvement in OS.[22] The amended study included 1137 patients with previously untreated *KRAS* exon 2 WT mCRC randomized to either cetuximab or bevacizumab with either FOLFOX or FOLFIRI. The study did not detect a significant difference in either PFS or OS. Subgroup analysis also did not show any benefit of either biological when combined with either FOLFOX or FOLFIRI.[17] Based on the initial presentation of this data, both biologic agents appeared to have similar efficacy in the first-line treatment of *RAS* WT mCRC. However, a retrospective analysis by sidedness showed a significant prognostic and predictive impact of primary tumor location (see section below). Combination of both EGFR- and VEGF-targeted therapies in the treatment of mCRC has clearly been shown to increase toxicity and shorten PFS, as demonstrated by the PACCE and CAIRO2-trials.[23,24]

### Primary Tumor Location of *RAS* Wild-Type mCRC: Left vs Right

The biological and clinical significance of primary tumor location is not a new concept. The embryologic origin of the colon is dichotomous, with the proximal right side being derived from the midgut and the distal left side from the hindgut. Differing

clinical outcomes based on sidedness also have been implicated in prior trials. The E2290 trial, which investigated leucovorin modulation of 5-fluorouracil (5-FU), found that patients with mCRC with left-sided primaries had longer median OS than patients with right-sided primaries (15.8 vs 10.9 months; *P* <.001).25 Moreover, analysis of the NCIC CO.17, AVF2107g, PROVETTA, and NO16966 trials also show a significant survival advantage for mCRC with left-sided primaries **(Table)**.[26,27] None of these trials, however, compared one biological against another.

Potentially practice-changing data have emerged from retrospective analyses of primary tumor location in the cohorts of CALGB/SWOG 80405, FIRE-3, and CRYSTAL trials. These studies defined left-sided primaries as those arising from the rectum to the splenic flexure and right-sided primaries as arising from the cecum to the hepatic flexure. In the *RAS* WT cohort of CALGB/SWOG 80405, investigators found that patients with left-sided primaries had longer median OS versus right-sided primaries (33.3 vs 19.4 months; HR, 1.55; *P* <.0001).[8] They also found primary tumor location to be predictive of response to biologic therapy, with a marked 19.3-month increase in OS in cetuximab-treated patients with left-sided primaries versus right-sided primaries (36 vs 16.7 months; HR, 1.87; *P* <.0001). A similar but less pronounced survival advantage was also seen in patients receiving bevacizumab in favor of left-sided versus right-sided primaries (31.4 vs 24.2 months; HR, 1.32; *P* <.01). A side-by-biologic interaction was detected (*P* interaction = .003), with superiority of cetuximab in left-sided primaries (log rank *P* =.04) and bevacizumab in right-sided primaries (*P* =.03).[8]

A recent nonpooled analysis of patients with *RAS* WT mCRC from the CRYSTAL and FIRE-3 trials also found a prognostic and predictive impact of primary sidedness. Similar to CALGB/SWOG 80405, patients with left-sided primaries had superior outcomes in RR, PFS, and OS, especially if they received anti-EGFR therapy.[28] These results bolster the argument that anti-EGFR therapy may be the preferred biologic in patients with mCRC with left-sided primaries, and bevacizumab for right-sided primaries in first-line treatment. An interesting finding in the multivariate analysis was that *BRAF* mutational status was an independent prognostic

**TABLE.** Outcomes in Relation to Primary Tumor Location in Randomized Trials

| Study | Patients | Molecular Selection | Treatment | Outcome | Right (months) | Left (months) |
|---|---|---|---|---|---|---|
| O'Dwyer et al. *J Clin Oncol.* 2001 (E2290) | N = 1120 | None | 5-FU-based regimens | Median OS | 10.9 | 15.8 |
| Brule et al. *Eur J Can.* 2015 (CO.17) | n = 399 | *KRAS* WT | Arm A: best supportive care<br>Arm B: best supportive care + cetuximab | Median PFS | 1.9<br>1.8 | 1.9<br>5.4 |
| Loupakis et al. *J Natl Canc Inst.* 2015 | N = 2053 | None | FOLFIRI + bevacizumab (PROVETTA)<br>XELOX/FOLFOX4 + bevacizumab (NO16966)<br>IFL + bevacizumab (AVF2107g) | Median OS | 24.8<br>18.0<br>14.6 | 42.0<br>23.0<br>24.0 |
| Venook et al. ASCO 2016 (CALGB/SWOG 80405) | n = 1025<br>n = 213 | *KRAS* WT<br>*KRAS*-mutant | Arm A: FOLFOX/FOLFIRI + cetuximab<br>Arm B: FOLFOX/FOLFIRI + bevacizumab<br>Both arms | Median OS | 16.4<br>24.2<br>23.1 | 36<br>31.4<br>30.3 |
| Lenz et al. GI Symposium ASCO (MAVERICC) | n = 376 | None | Arm A: FOLFOX + bevacizumab<br>Arm B: FOLFIRI + bevacizumab | Median OS | 22.7<br>27.4 | 24.1<br>27.5 |
| Tejpar et al. *JAMA Oncol.* 2016 | N = 758 | *RAS* WT | FOLFIRI + cetuximab (CRYSTAL)<br>FOLFIRI + cetuximab (FIRE-3)<br>FOLFIRI + bevacizumab (FIRE-3) | Median OS | 18.5<br>18.3<br>23.0 | 28.7<br>38.3<br>28.0 |

5-FU = 5-fluorouracil; ASCO = American Society of Clinical Oncology; GI = gastrointestinal; IFL = irinotecan/fluorouracil/levoleucovorin; OS = overall survival; PFS = progression-free survival; WT = wild type.

variable. This suggests that the poor prognosis of patients with right-sided disease cannot be attributed only to the presence of a *BRAF* mutation.[9,29]

The consistent findings across all of these trials suggest that primary tumor location is a surrogate for tumor biology, and renders significant prognostic and predictive value. It confirms that right- and left-sided mCRC are clinically and biologically distinct, as further suggested by recent insights into the distribution of several molecular variables by side **(Figure 2)**.[30]

### *RAS*-Mutated and *BRAF*-Mutated mCRC

RAS and RAF are downstream effectors of EGFR-ligand activated signaling. Mutations in *RAS* and *RAF* result in constitutive activation of downstream effectors, resulting in the bypass of EGFR-driven signaling and resistance to anti-EGFR therapy.[31] Unfortunately, direct targeting of mutant *RAS* and *RAF* has not translated into effective clinical outcomes.[32] Targeting downstream effector pathways such as MAPK/ERK with MEK inhibitors has generated active therapeutic interest, but resistance mechanisms have made translation into effective clinical outcomes elusive.[33] Early trials to overcome resistance with combination MEK, BRAF, and EGFR show promise, and others are ongoing.[34,35] Targeting the PI3K/AKT/mTOR pathway, which can be activated by cross-talk with the RAS-RAF pathway, has also generated interest, but has not yet translated into significant clinical efficacy. As such, chemotherapy with or without bevacizumab remains the standard therapy for this patient population.

Multiple trials have established the superior activity of cytotoxic doublets incorporating oxaliplatin and irinotecan versus 5-FU monotherapy.[36] Leucovorin, 5-FU, and oxaliplatin (FOLFOX) and fluorouracil, leucovorin, and Irinotecan (FOLFIRI) are the 2 most commonly used and well-tolerated regimens. Phase III trials have demonstrated equivalence with no significant difference in RR, time to progression, or OS between the 2 regimens.[37,38] Optimal sequencing of these regimens has also been studied, and using either FOLFOX or FOLFIRI as initial therapy followed by the alternate sequence after first progression did not result in a significant difference in OS.[38] Moreover, data suggest that receipt of all 3 active first-line cytotoxic agents is correlated with an increase in survival, and may be more important than the sequence of administration.[39] As such, the National Comprehensive Cancer Network (NCCN) recommends FOLFOX or FOLFIRI as equivalent first-line regimens.[7]

Peripheral neuropathy is the limiting toxicity of oxaliplatin, and often results in dose reductions or abbreviations of FOLFOX treatment. The OPTIMOX trials demonstrated that OS was not affected by a "stop-and-go" approach using oxaliplatin-free intervals during continuous sLV5FU2.[40,41] This reduced neurotoxicity and did not compromise sensitivity to oxaliplatin if reintroduced. The complete cessation of chemotherapy, however, had a negative impact on duration of disease control and PFS.[41] On the other hand, neurotoxicity is not a common side effect of irinotecan, and patients are able to continue on it for longer intervals, which in the MAVERICC trial resulted in a trend toward increased OS with FOLFIRI versus FOLFOX, though this was not statistically significant (27.5 vs 23.9 months; HR, 0.76; $P$ =.0861).[19]

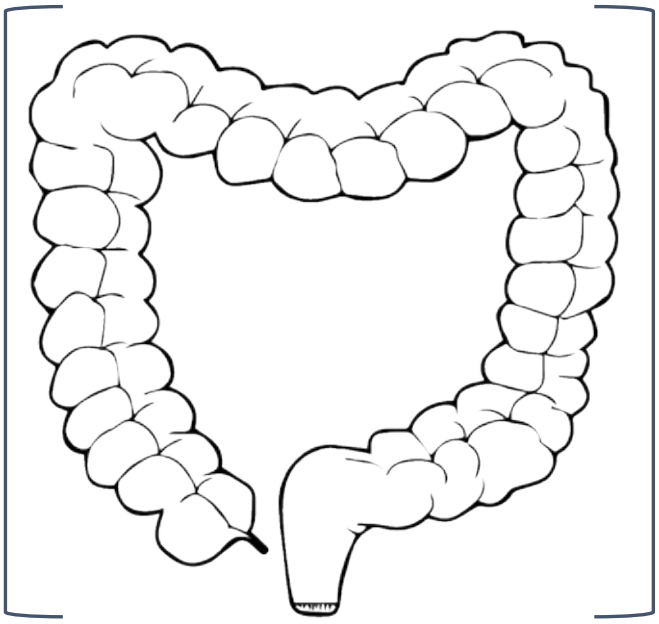
Incorporating bevacizumab with first-line chemotherapy is an effective first-line strategy in this population resistant to anti-EGFR agents. In the pivotal AVF2107g trial, bevacizumab in combination with irinotecan, fluorouracil, and leucovorin (IFL) demonstrated a significant improvement in median OS compared with IFL plus placebo (20.3 vs 15.6 months; HR, 0.66; $P$ <.001).[42] Interestingly, the gain in PFS and OS was more pronounced than gains in RR, suggesting survival benefit even in the absence of objective response to therapy. Subsequently, several chemotherapy regimens (FOLFOX, FOLFIRI, CapeOx) have been studied in combination with bevacizumab and have demonstrated modest clinical benefit.[22] The advantage of maintenance bevacizumab with chemotherapy was demonstrated in the CAIRO-3 trial, where increase in PFS was seen in patients who continued bevacizumab and capecitabine after first progression from completing 6 cycles of CapeOx.[43] Continuing bevacizumab as monotherapy, however, has no significant therapeutic value over observation, as shown in the SAKK 41/06 trial.[44]

In medically fit patients with highly symptomatic disease, intensification of therapy using a triplet combining 5-FU/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) is also an option. The GONO group investigated FOLFOXIRI versus FOLFIRI, and showed an approximate doubling of RR (60% vs 35%; $P$ <.0001), but at the cost of increased grade 3 or 4 neurotoxicity, stomatitis, diarrhea, and neutropenia.[45] Similar results were confirmed in GONO's larger TRIBE trial, where bevacizumab was added to FOLFOXIRI, with an updated intention-to-treat analysis showing a significant increase in median OS in favor of FOLFOXIRI plus bevacizumab (29.8 vs 25.8 months; HR, 0.8; $P$ =.03)[46] Preliminary results indicate that the BRAF-mutated subset especially may derive benefit from FOLFOXIRI plus bevacizumab (HR, 0.54; CI, 0.24-1.2), although confirmatory studies are needed.[47]

### Mismatch Repair–Deficient mCRC

Updated data from a phase II trial evaluating the anti-PD-1 immune checkpoint antibody pembrolizumab in a cohort of patients with progressive and treatment-refractory mCRC showed striking responses in patients with dMMR mCRC. Patients with dMMR mCRC had RR of 57% versus 0% in patients with mismatch repair–proficient (pMMR) mCRC. Moreover, the disease control rate was 89% in dMMR mCRC versus only 16% in pMMR CRC. By the time of presentation, median PFS and OS had not been reached for dMMR mCRC, and 50% of responders had a durable response indicating disease stability over time.[48] It is postulated that PD-1 inhibition enables the immune system to recognize neoantigens from the high mutational burden of dMMR tumors, marked by an MSI-H phenotype.[12,49,50] Break-

**FIGURE 2.** Differences in clinical factors, molecular markers, and gene expression profile of right- versus left-sided CRCs.




5-FU = 5-fluorouracil; ASCO = American Society of Clinical Oncology; GI = gastrointestinal; IFL = irinotecan/fluorouracil/levoleucovorin; OS = overall survival; PFS = progression-free survival; WT = wild type.

through therapy designation has been granted to pembrolizumab, and clinical trials of immune checkpoint inhibitors with and without chemotherapy in the treatment of first-line MSI-H mCRC are ongoing and in development.[51]

## Oligometastatic Disease

Studies of selected patients with mCRC undergoing surgical Studies of selected patients with mCRC undergoing surgical resection of liver metastases has shown that cure is possible with multidisciplinary management of oligometastatic disease. A meta-analysis of 60 studies showed 5-year and 10-year survival rates ranging from 16% to 75% (median 38%) and 9% to 69% (median 26%), respectively.[52] There is limited evidence of benefit for extrahepatic oligometastatic disease other than pulmonary metastasis, where surgical resection with 5-year survival rate of 50.3% has been reported.[53] In patients who are not candidates for surgical resection, there are some data to support long-term benefit from directed therapy with stereotactic body radiation, arterial-directed embolic therapy, or ablative techniques such as radiofrequency ablation, though this is classified as a category 3 recommendation by the NCCN.[7,54-56] As such, evaluation and coordination of treatment can be complex, and upfront consultation with a multidisciplinary team is recommended.[7]

Some patients with oligometastatic disease may have critical organ or vessel involvement precluding upfront surgery. In highly selected cases, these lesions can be converted into resectable lesions with preoperative, combination cytotoxic chemotherapy with high RRs. Several large trials have demonstrated a significant association of the likelihood of an R0 resection with response to combination chemotherapy with FOLFOX, FOLFIRI, and FOLFOXIRI.[57] It also appears that more chemotherapy upfront increases the rates of conversion, as demonstrated in the TRIBE trial, where liver-only R0 resection rates were significantly higher in patients who received FOLFOXIRI versus FOLFIRI (36% vs 12%; $P$ <.017).[46] In addition, anti-EGFR in patients with RAS WT disease increased RR and R0 resection rates, as suggested in the CRYSTAL, CELIM, OPUS, MetaPan, and, more recently, the METHEP-2 trial.[58-60] Data on increasing R0 resection rates by adding bevacizumab to chemotherapy are sparse, though RRs do increase compared with chemotherapy alone.[36,58]

Preoperative chemotherapy is not without its disadvantages, which include possible disease progression, decrease in performance status, and hepatotoxicity. Sinusoidal obstruction syndrome has been described with oxaliplatin, and irinotecan can induce nonalcoholic steatohepatitis.[58] As such, frequent evaluations are necessary, and a neoadjuvant period of 2 to 3 months is recommended.[7]

## Conclusions

The development of new drugs and interdisciplinary management have resulted in a meaningful increase in survival for patients with mCRC. As the number of therapeutic options increases and improves, considering goals of therapy and weighing potential benefit

with potential harm remain important tools in determining the appropriate first-line strategy. Insight into recent data reveals that right- and left-sided CRCs are clinically and biologically different. Sidedness conveys significant prognostic and predictive value that will shape the conduct of future trials and management of mCRC.

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