Biologic Therapies in Colorectal Cancer: Indications and Contraindications

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OVERVIEW

The role of antiangiogenic and anti-epidermal growth factor receptor (EGFR) agents has been investigated extensively in colorectal cancer in the palliative, adjuvant, and neoadjuvant settings. Although the role of biologic agents has become well-defined in the first, second, and subsequent lines of treatment of metastatic colorectal cancer (mCRC), considerable debate continues around the optimal sequencing and around optimal patient selection. The benefits from integrating bevacizumab or cetuximab in the adjuvant setting have been investigated in several randomized phase III clinical trials in stage II/III disease, all with disappointing results. Neoadjuvant approaches incorporating biologic therapy in patients with liver metastatic disease have led to mixed results. Although the current evidence does suggest increased down-staging and increased resectability with the addition of cetuximab in patients with initially unresectable or borderline resectable liver metastases, a positive effect of anti-EGFR therapy on the overall survival (OS) in this setting is not conclusive. Patients with resectable liver metastases derive no benefit and may experience potential harm from the addition of cetuximab to neoadjuvant chemotherapy. Similarly, there is neither rationale nor adequate data to support the addition of bevacizumab to neoadjuvant chemotherapy in patients with resectable liver metastases. In this review, we examine the role of antiangiogenesis and anti-EGFR therapies across the spectrum of adjuvant, neoadjuvant, and metastatic disease.

Significant progress has been made in the last decade in the management of mCRC, with median OS of patients with mCRC now at or exceeding 30 months.1,2 The improvements in outcome are at least partially credited to the integration of biologic therapies, whether antiangiogenic or anti-EGFR, in the mainstream treatment of metastatic disease. Although significant progress has been made with the addition of these classes in advanced noncurable disease, their role has been disappointing in the adjuvant setting and continues to evolve in the neoadjuvant setting. In this review, we will summarize the current clinical data for biologic and targeted agents in adjuvant CRC, neoadjuvant, and nonresectable mCRC.

BILOGIC THERAPY IN THE ADJUVANT TREATMENT OF COLORECTAL CANCER

Bevacizumab in Stage II and III Colon Cancer

Several randomized phase III clinical trials have evaluated bevacizumab in combination with systemic chemotherapy in the adjuvant treatment of colorectal cancer. The NSABP C-08 clinical trial randomized 2,710 patients with stage II or III colon cancer to receive 6 months (12 cycles) of modified FOLFOX6 regimen with or without 1 year of bevacizumab.3,4 No significant effect on disease-free survival (DFS) or OS was noted in the study population or within the stage II or stage III subgroups. Interestingly, the effect of bevacizumab on DFS was different before and after the 15-month time point from study treatment. The hazard ratio (HR) for recurrence within 15 months from start of study treatment was 0.61 (95% CI, 0.48 to 0.78) in favor of bevacizumab. In contrast, a trend toward increased recurrence rate was noted after 15 months on the bevacizumab arm. A post hoc analysis of the NSABP-C08 population by mismatch repair status suggested a benefit from bevacizumab in the mismatch deficient cohort (HR 0.52; 95% CI, 0.29 to 0.94).5 The AVANT phase III clinical trial randomized patients with stage II or III colon cancer to receive 6 months of oxaliplatin plus a fluoropyrimidine with or without bevacizumab.6 Patients were randomly assigned in a 1:1:1 ratio to three arms of treatment: FOLFOX4, FOLFOX4 plus 1 year of bevacizumab, XELOX plus 1 year of bevacizumab. No benefits in DFS were noted with the addition of bevacizumab to chemotherapy. The HR for DFS for bevacizumab/FOLFOX4 and bevacizumab/XELOX compared with FOLFOX4 were 1.17 (95% CI, 0.98 to 1.39) and 1.07 (95% CI, 0.9 to 1.28), respectively. Similar to the NSABP-C08 study, bevacizumab was associated with an improved DFS in the initial period of follow-up. In the first year of the study, the HR for DFS was 0.63 and 0.61 on the bevacizumab/FOLFOX4 and bevacizumab/XELOX arms in comparison with FOLFOX4. This initial improvement in DFS...
was offset by a detrimental effect of bevacizumab in DFS in years 2 and 3, leading to an overall trend to increased recurrences on the bevacizumab arms. This rebound increase in recurrences in the bevacizumab arms translated into a trend toward a detriment in OS in both the bevacizumab/FOLFOX4 and bevacizumab/XELOX arms when compared with FOLFOX4. Finally, the QUASAR2 study randomized 1,941 patients with stage III or high-risk stage II colorectal cancer to receive eight cycles of capecitabine (24 weeks) with or without 16 cycles of every 3-week bevacizumab (48 weeks). An initial trend in improvement in DFS was noted in the bevacizumab arm in the first 2 years of follow-up. However, further follow-up after 2 years was associated with an increased recurrence rate in the bevacizumab arm, leading to a final HR for DFS of 1.06 in the bevacizumab arm compared with the control arm. Subgroup analysis in the microsatellite stable (MSS) and microsatellite instability (MSI) groups showed a significant detriment with bevacizumab in the MSS group (HR 1.43, p = 0.0005), whereas no significant difference in outcomes was noted in the MSI group (HR 0.74, p = 0.42).

No benefit is expected from the addition of bevacizumab to adjuvant cytotoxic chemotherapy in patients with stage II or III disease. To the contrary, worrisome trends toward increased recurrence rate after completion of bevacizumab therapy have been noted and have translated in a trend toward a worsened OS. The favorable trends noted with bevacizumab in tumors with MSI are hypothesis generating and may warrant further investigation in this subgroup of patients.

Cetuximab in the Adjuvant Treatment of Colorectal Cancer

The role of anti-EGFR therapy in the adjuvant treatment setting has been investigated through the N0147 and PETACC-8 clinical trials.8,9 The initial design of the N0147 included a randomization to 6 months of FOLFOX, FOLFIRI, or sequential FOLFOX followed by FOLFIRI, with or without cetuximab in patients with stage III colon cancer. Subsequent protocol amendments resulted in the closure of the FOLFIRI and sequential FOLFOX/FOLFIRI arms, as well as the limitation of enrollment to patients with KRAS-wild type (WT) tumors.8 The study accrued 2,070 patients with KRAS-WT tumors. No benefit in 3-year DFS in the cetuximab/FOLFOX compared with the FOLFOX arm was noted in the KRAS-WT (HR 1.21; 95% CI, 0.98 to 1.49) or KRAS/BRAF-WT populations. No advantage to the addition of cetuximab was noted in any of the subgroup analyses. Of note, no definitive conclusions could be deduced from the FOLFIRI cohorts on N0147 because of the small sample size. However, a trend toward improved DFS and OS was noted in the cetuximab/FOLFIRI compared with FOLFIRI in an exploratory analysis.10 The PETACC-8 clinical trial randomized patients with stage III colon cancer to 6 months of FOLFOX4 chemotherapy with or without cetuximab.8 Similar to N0147, the study was subsequently amended to include only patients with KRAS-WT tumors. No benefit from cetuximab was noted in terms of DFS in the KRAS-WT (HR 1.05; 95% CI, 0.85 to 1.29; p = 0.66) or in the KRAS/BRAF-WT (HR 0.99; 95% CI, 0.76 to 1.28; p = 0.92) populations. Interestingly, and in a preplanned subgroup analysis, patients with T4N2 tumors derived a significant benefit from the addition of cetuximab, whereas, women and patients with right colonic tumors experienced a significant improvement in DFS in the chemotherapy only arm.

Based on the N0147 and PETACC-8 studies, there is no current role for cetuximab in the adjuvant treatment of colon cancer. Although subgroup analyses of PETACC-8 suggest a benefit in more advanced T4N2 disease, this can be considered, at best, hypothesis generating. Clearly, a more predictive signature of response beyond RAS and BRAF mutations will be needed to revisit the role of anti-EGFR in the adjuvant treatment of mCRC. The reason for disconnect in benefits from anti-EGFR therapy between adjuvant and metastatic disease studies is not clear but could be explained by a failure to induce complete pathologic sterilization despite an increased antitumor down-staging in metastatic settings.

KEY POINTS

- There is no role for biologic therapy in the adjuvant treatment of colorectal cancer.
- In the setting of resectable metastatic disease to the liver, there is no evidence to suggest a benefit from adding either antiangiogenic or anti-epidermal growth factor receptor (EGFR) therapy. The addition of anti-EGFR therapy to chemotherapy in the neoadjuvant treatment of KRAS-wild type (WT) resectable liver metastases has been associated with a detrimental effect on disease-free survival.
- In patients with unresectable but potentially resectable disease, consideration for neoadjuvant FOLFOXIRI/bevacizumab (good performance status) or combination chemotherapy plus anti-EGFR agents (RAS-WT) should be made to increase the chances of curative-intent surgery.
- In RAS-mutant type or BRAF-MT metastatic colorectal cancer (mCRC), the continuum of angiogenesis targeting during the first two lines of treatment is recommended.
- Bevacizumab or anti-EGFR therapy in the first-line therapy of RAS-WT and BRAF-WT mCRC is acceptable with no clear evidence of superiority of one approach compared with another.

BIOLOGIC THERAPIES IN THE NEOADJUVANT TREATMENT OF MCRC

Biologic Therapies in the Neoadjuvant Treatment of Resectable mCRC

When considering neoadjuvant treatment in the management of metastatic colorectal cancer, one has to define the goal of therapy. The main indications for neoadjuvant treatment for metastatic colorectal cancer are: (1) decrease in the risk for recurrence of disease in the setting of resectable liver...
metastases and (2) down-staging for resection in patients with potentially resectable disease. The EORTC 40983 study randomized patients with four or less hepatic colorectal metastases to perioperative FOLFOX chemotherapy or observation. This study met its primary endpoint of 3-year DFS improvement in favor of FOLFOX. No significant improvement in OS was confirmed. Since the EORTC control arm did not include postoperative chemotherapy, the benefits of perioperative chemotherapy compared with adjuvant postoperative chemotherapy are currently not substantiated.

Bevacizumab addition to neoadjuvant CAPOX, FOLFOX, FOLFIRI, and FOLFOXIRI has been shown to be feasible in patients with resectable liver mCRC. Retroactively analyzes suggest an increased likelihood of complete pathologic responses of liver metastases and a lower incidence of sinusoidal damage with the integration of bevacizumab in the neoadjuvant chemotherapy treatment of liver mCRC. However, there is no strong evidence to date to support an improvement in DFS or OS with the addition of bevacizumab to perioperative chemotherapy in these settings. Given the discouraging DFS and OS data with bevacizumab in stage III colorectal clinical trials, there is no strong rationale to incorporate bevacizumab in the neoadjuvant or postoperative therapy in patients with resectable mCRC. Indeed, a recent retrospective analysis of patients undergoing hepatectomy with adjuvant chemotherapy with or without bevacizumab failed to show any additional benefit in the bevacizumab arm.

The role of cetuximab as part of a neoadjuvant chemotherapy regimen in resectable mCRC to the liver was investigated through the New EPOC trial. In this randomized phase III clinical trial, patients with resectable or suboptimally resectable KRAS-WT metastatic colorectal cancer to the liver were randomly assigned to perioperative chemotherapy with or without cetuximab. The progression-free survival (PFS) was significantly shorter in the chemotherapy/cetuximab compared with the chemotherapy arm (14.1 vs. 20.5 months; HR 1.48; 95% CI, 1.04 to 2.12; p = 0.03). Chemotherapy consisted predominantly of oxaliplatin-based therapy (FOLFOX or XELOX), although, 11% of the patient population received FOLFIRI. Given the small number of patients on the irinotecan arm, no definitive conclusions can be extrapolated from this subgroup. This study was criticized for lack of adequate surgical quality control, imbalance in patient characteristics, variations in chemotherapy backbones, and increased rate of early death without clear attribution.

The detrimental effect of cetuximab on the New EPOC trial and the lack of benefit from adjuvant cetuximab treatment in stage III disease suggest that the addition of cetuximab to chemotherapy in KRAS-WT tumors does not improve the rate of microscopic disease eradication and, hence, does not decrease the risk for disease relapse. This strategy should be avoided in patients with resectable liver metastases.

**Biologic Therapy in the Management of Potentially Resectable mCRC**

Down-staging for resection in the setting of metastatic disease that is deemed unresectable at the time of presentation but potentially resectable after a major clinical response should be considered a standard approach. Patients who are converted to resectable disease with chemotherapy achieve a 5-year OS of 30% to 50%, far exceeding any 5-year survival reported with palliative chemotherapy. Therefore, it is imperative that the most effective combination chemotherapy is considered in patients with advanced, potentially resectable, mCRC.

Since no randomized studies have evaluated the combination cytotoxic chemotherapy compared with cytotoxic chemotherapy/bevacizumab in such settings, one cannot conclusively determine the role of angiogenesis inhibition in down-staging for resection. However, since many of the patients with potentially-resectable disease do not achieve resectability, and given the positive effect of bevacizumab on PFS and OS, the routine implementation of bevacizumab in this setting is considered an acceptable practice, particularly when anti-EGFR therapy is not considered or advisable. Additional considerations for the addition of bevacizumab in this setting include retrospective analyses suggesting increased complete pathologic responses and decreased sinusoidal damage to the liver with the addition of bevacizumab to chemotherapy. When considering bevacizumab in the management of potentially resectable mCRC, it is important to consider the most effective chemotherapy backbones. To that end, the OLIVIA clinical trial randomized patients with initially unresectable colorectal liver metastases to FOLFOX plus bevacizumab or FOLFOXIRI plus bevacizumab. The FOLFOXIRI arm was associated with an improved response rate, a higher resection rate, higher R0 resection rate, and improved PFS (Table 1).

Although the addition of cetuximab to chemotherapy in the setting of resectable hepatic metastatic disease has resulted in disappointing results, the value of cetuximab in unresectable-potentially resectable hepatic metastatic disease has been supported by several studies. A phase III clinical trial randomized patients with KRAS-WT tumors with unresectable hepatic mCRC to receive first-line FOLFOX or FOLFOX/cetuximab. Patients assigned cetuximab achieved a higher response rate, R0 hepatic resection rates, and OS (Table 1). Additional support to this strategy comes from several other phase II clinical trials describing a high response rate and resection rates with cetuximab-based combinations. In addition, a recent update from CALGB 80405 reported that 15.7% of 1,137 patients with KRAS-WT tumors underwent resection after 1:1 randomization to chemotherapy with bevacizumab or chemotherapy plus cetuximab. A higher percentage of patients underwent resection (with no evidence of disease) in the cetuximab arm in comparison with bevacizumab (62% vs. 38%). No OS difference in outcome was noted between arms after resection, suggesting that preoperative cetuximab does not worsen postoperative outlook when compared with a bevacizumab backbone (Table 1).

Both bevacizumab and cetuximab are justified in the setting of unresectable, potentially-resectable mCRC. Since the majority of these patients do not attain resectability, the integration of biologic therapy in the first-line setting is recom-
mended in view of its positive effect on PFS and OS. In the setting of RAS-mutant type (MT) or BRAF-MT tumors, one would favor the use of FOLFOXIRI/bevacizumab in younger good performance status (PS) cases. In the setting where a doublet chemotherapy is chosen (more limited PS, older, etc.), an anti-EGFR addition is a reasonable choice in RAS-WT tumors given its more pronounced effect on downstaging compared with bevacizumab.

**BIOLOGIC THERAPY IN NON-RESECTABLE MCRC**

The choice of biologic therapies in mCRC is often considered in view of the genetic profile of the tumor. In this review, we will consider the pros and cons for angiogenesis targeting or EGFR targeting based on RAS and BRAF status.

**Biologic Therapies in RAS-MT and BRAF-MT Tumors**

Tumors with RAS mutations (exon 2, 3, and 4 of KRAS and NRAS) constitute approximately 50% of tumors; whereas, patients with BRAF mutations constitute 5% to 10% of patients with colorectal cancer. Patients with RAS-MT tumors derive no benefit from the addition of anti-EGFR therapy to chemotherapy. To the contrary, the addition of cetuximab to oxaliplatin-based chemotherapy has been associated with worsening in multiple outcome parameters. The benefits of bevacizumab in mCRC have been shown to transcend RAS or BRAF mutational status and, therefore, the benefits reported on from phase III clinical trials from molecularly unselected patients with mCRC can be extrapolated to both RAS-WT and RAS-MT tumors.

**Targeted Therapy in the First-Line Treatment**

The only angiogenesis-targeting agent to show improvement in PFS and OS in the first-line treatment of mCRC is bevacizumab. These studies were performed in RAS and BRAF unselected patients but can be extrapolated to the RAS-MT population. The only phase III study to report a significant improvement in OS was the AVF2107 study. AVF2107 randomized patients to irinotecan and 5-FU/leucovorin with or without bevacizumab. Subsequent first-line phase III studies have consistently confirmed an advantage to the addition of bevacizumab to several fluoropyrimidine-based backbones, albeit with a PFS primary endpoint. The advantage of the incorporation of bevacizumab in first-line treatment of mCRC has been particularly notable in the setting of fluoropyrimidine monotherapy. The addition of bevacizumab to FOLFOX or XELOX has resulted in a clinically modest improvement in PFS and insignificant improvement in OS. Given the favorable toxicity profile of bevacizumab and its reproducible positive effect on PFS, it is recommended that this agent is considered in the first-line treatment of patients with RAS-MT or BRAF-MT cancer (and as an option for RAS-WT as discussed below). Since anti-EGFR therapy is not an option in this setting, this is considered the only viable option for targeted therapy in this population. The reader is directed to our recent review on targeted therapy for further details on this topic.

There is no convincing evidence that patients with BRAF-MT mCRC derive a clinically significant benefit from anti-EGFR therapy. Significant progress is being made through the concurrent targeting of EGFR and BRAF (with or without MEK) in this population. However, such strategies are still considered investigational. Therefore, consideration of front-line addition of bevacizumab should be made in this subgroup of patients. However, the outlook of these patients continues to be dismal. Recent subgroup analysis from the TRIBE clinical trial has suggested a benefit from FOLFOXIRI/bevacizumab in comparison with FOLFIRI in patients with BRAF-MT disease. Given the aggressive biology of BRAF-MT cancers, consideration for up-front FOLFOXIRI/bevacizumab should be considered in the younger fit individuals.

**Targeted Therapy in the Second-Line Treatment**

The value of bevacizumab in the second-line treatment of patients with previously bevacizumab-naive disease who progressed on a first-line therapy of irinotecan plus 5-FU has been confirmed through the ECOG 3200 clinical trial. In this study, patients receiving FOLFOX/bevacizumab experienced a superior response rate, PFS, and OS than the
FOLFOX control arm (Table 2). However, in clinical practice, most patients who proceed to second-line treatment have had prior bevacizumab exposure. Three randomized phase III clinical trials have now reported on angiogenesis targeting post-bevacizumab progression.\(^{41-43}\) The results of these studies are summarized in Table 2. Both the ML18147 and RAISE clinical trials mandated prior progression on a bevacizumab-based therapy and resulted in significant improvements in PFS and OS in favor of bevacizumab and ramucirumab.\(^{44}\) The VELOUR clinical trial included both patients with bevacizumab-naive and bevacizumab pre-treated disease and resulted in significant improvement in PFS and OS in the overall population. None of the three trials showed an improvement in response rate in the patients who were bevacizumab-pretreated. The three agents investigated are different biologically with bevacizumab being directed toward VEGF-A, aflibercept toward VEGF-A, VEGF-B and PIGF, and ramucirumab toward VEGF-R-2. Although no head-to-head comparison among these agents have been performed to date, bevacizumab has been associated with the most favorable safety profile, whereas, concerns have been raised regarding the increased toxicity of aflibercept when combined with chemotherapy.\(^{45}\) All three antiangiogenic agents are considered acceptable options for second-line treatment, with a preference toward bevacizumab given its more established safety profile. Although bevacizumab can be considered across different backbones in the second-line treatment, aflibercept and ramucirumab should only be considered with FOLFIRI. No clinical or biologic biomarkers have been identified to direct treatment toward any of these three biologicals in the setting of second-line FOLFIRI.

### Targeted Therapy in Chemotherapy-Refractory or Resistant Colorectal Cancer

The CORRECT clinical trial\(^{45}\) enrolled patients with mCRC who progressed after or were intolerant of fluoropyrimidines, oxaliplatin, irinotecan, and anti-EGFR therapy (in KRAS-WT). All patients had received prior bevacizumab. The study showed a significant clinically modest improvement in OS (median OS 6.4 vs. 5 months; HR 0.77; 95% CI, 0.64 to 0.94; one-sided \(p = 0.0052\)). Consideration for single-agent regorafenib can therefore be made after progression on all standard chemotherapy.

### Biologic and Targeted Therapies in RAS-WT Tumors

It is important to note that the recommendations regarding antiangiogenesis therapies reported above for the RAS or BRAF-MT populations apply equally to the RAS/BRAF-WT population. On the other hand, the management of the RAS/BRAF-WT population is complicated by the proven effectiveness of anti-EGFR therapy across all lines of treatment. Therefore, treatment decisions in patients with RAS/BRAF-WT disease have to factor in efficacy and toxicity data with both classes of targeted agents. In this section we address the effect of anti-EGFR agents in this group of patients, and when feasible, put it in context of antiangiogenic therapies.

### Targeted Therapies in the First-Line Treatment of RAS-WT mCRC

The CRYSTAL clinical trial evaluated the combination of FOLFIRI with cetuximab compared with FOLFIRI alone in the first-line treatment of mCRC.\(^{46}\) No benefit was noted in the KRAS-MT (exon-2) population, whereas, a significant

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**TABLE 2. Angiogenesis Targeting in the Second-Line Treatment of mCRC**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
<th>Efficacy Objectives</th>
<th>Primary Efficacy Endpoint</th>
<th>Other Efficacy Endpoints</th>
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<tbody>
<tr>
<td>Gention et al(^{40}) ECOG 3200 Study</td>
<td>Second-line randomized phase III clinical trial in BV-naive disease</td>
<td>FOLFIRI4</td>
<td>Primary: OS</td>
<td>OS: 12.9 (FOLFIRI/BV) vs. 10.8 months (FOLFIRI) (HR 0.75, (p = 0.001))</td>
<td>PFS: 7.3 (FOLFIRI/BV) vs. 4.7 months (FOLFIRI) (HR 0.61, (p &lt; 0.0001)) RR: 22.7% (FOLFIRI/BV) vs. 8% (FOLFIRI) ((p &lt; 0.0001))</td>
</tr>
<tr>
<td>Bennouna et al(^{44}) ML18147 Study</td>
<td>Second-line randomized phase III clinical trial in patients post-BV first-line progression</td>
<td>Chemotherapy/BV</td>
<td>Primary: OS</td>
<td>OS: 11.2 (chemotherapy/BV) vs. 9.8 months (chemotherapy) (HR 0.81, (p = 0.0062))</td>
<td>PFS: 5.7 (chemotherapy/BV) vs. 4.1 months (chemotherapy) (HR 0.68, (p &lt; 0.0001)) No difference in RR</td>
</tr>
<tr>
<td>Van Cutsem et al(^{45}) VELOUR Study</td>
<td>Second-line randomized phase III clinical trial</td>
<td>FOLFIRI</td>
<td>Primary: OS</td>
<td>OS: 13.5 (FOLFIRI/aflibercept) vs. 12.06 months (FOLFIRI) (HR 0.817, (p = 0.0032))</td>
<td>PFS: 6.9 (FOLFIRI/aflibercept) vs. 4.7 months (FOLFIRI) (HR 0.758, (p &lt; 0.0001)) RR: 19.8% (FOLFIRI/aflibercept) vs. 11.1% (FOLFIRI) ((p &lt; 0.001)) No difference in RR in patients with prior BV</td>
</tr>
<tr>
<td>Tabernero et al(^{42}) RAISE Study</td>
<td>Second-line randomized phase III clinical trial in patients post-BV first-line progression</td>
<td>FOLFIRI/RAM</td>
<td>Primary: OS</td>
<td>OS: 13.3 (chemotherapy/RAM) vs. 11.7 months (chemotherapy) (HR 0.84, (p = 0.0029))</td>
<td>PFS: 5.7 (chemotherapy/RAM) vs. 4.5 months (chemotherapy) (HR 0.79, (p &lt; 0.0005)) No difference in RR</td>
</tr>
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</table>

Abbreviations: OS, overall survival; RR, response rate; PFS, progression-free survival; HR, hazard ratio; BV, bevacizumab; RAM, ramucirumab.
improvement in response rate, PFS, and OS was noted in the KRAS-WT subgroup. Subsequent analysis based on RAS-WT (no KRAS or NRAS exon 2–4 mutations) showed even more robust improvements in PFS and OS than the KRAS-WT population (Table 3). Similar benefits were noted with panitumumab with a FOLFOX backbone on the chemotherapy backbone, which was associated with increased toxicities when combined with cetuximab and, therefore, potentially confounding cetuximab efficacy. In addition, the lack of benefit on the NORDIC trial may have been confounded by a detrimental effect for cetuximab in the patients with KRAS (exon 3 and 4) and NRAS mutations who were included in the study analysis.

Three randomized first-line studies investigated bevacizumab compared with anti-EGFR therapy in the first-line treatment of KRAS-WT tumors (Table 4). All three studies have reported efficacy data based on RAS-MT. The FIRE-3 and CALGB 80405 studies confirmed an improved response rate in favor of anti-EGFR therapy, no difference in PFS among arms, but diverted in the OS results. The FIRE-3 clinical trial showed an improvement in OS in RAS-WT tumors favoring cetuximab, whereas, no difference was noted in the CALGB 80405 study (Table 4). The reason behind this difference in OS is unclear. A difference in postprogression salvage rate with anti-EGFR therapy in the bevacizumab arms could very well have contributed to these variations in outcome. Other contributing factors could be variations in treatment compliance, dose intensity, and early treatment discontinuation because of toxicity, all of which are yet to be reported on CAALGB 80405. The PEAK clinical trial is a smaller randomized phase II clinical trial of FOLFOX/panitumumab compared with FOLFOX/bevacizumab. The results from this study were somewhat consistent with the FIRE-3 clinical trial (Table 4). For further review, please refer to our recent review on this topic.

Both bevacizumab and anti-EGFR therapy are considered appropriate options in the first-line treatment of metastatic cancer. Given the increased down-staging potential of anti-EGFR therapy in the first-line setting compared with bevacizumab, this may be the more preferable biologic agent in the potentially resectable cases, especially when FOLFOXIRI (with or without bevacizumab) is contraindicated. In addition, anti-EGFR therapy is preferred in patients with higher risk for perforation (bulky primary, significant carcinomatosis) or with known risk factors for arterial thrombotic events. Bevacizumab is more preferable in patients who want to avoid skin toxicity.

### Targeted Therapies in the Second-Line Treatment of RAS-WT mCRC

Although anti-EGFR therapy clearly increases the response rate and PFS in patients with RAS-WT mCRC, no studies have reported an improvement in OS in this setting (Table 5). Two studies

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**Table 3. EGFR Targeting in the First-Line Treatment of mCRC**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Control Arm</th>
<th>Experimental Arm(s)</th>
<th>Efficacy Objectives</th>
<th>Primary Efficacy Endpoint</th>
<th>Other Efficacy Endpoints</th>
</tr>
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<tbody>
<tr>
<td><strong>Maughan et al</strong>&lt;sup&gt;28&lt;/sup&gt; <strong>COIN Study</strong></td>
<td>Randomized phase III clinical trial (KRAS-WT for codons 12, 13, and 61) 815 patients per arm</td>
<td>Arm A: oxaliplatin/fluoropyrimidine (FOLFOX or XELOX)</td>
<td>Primary: OS</td>
<td>OS: 17 (Arm B) vs. 17.9 months (Arm A) (HR 0.96, p = 0.6) in the KRAS-WT population</td>
<td>PFS: 8.6 months (Arms A and B) (HR 0.9, p = 0.037)</td>
</tr>
<tr>
<td><strong>Tweit et al</strong>&lt;sup&gt;29&lt;/sup&gt; <strong>NORDIC VII Study</strong></td>
<td>Randomized phase III clinical trial 566 patients</td>
<td>FLOX (bolus 5-FU, leucovorin, and oxaliplatin) (Arm A)</td>
<td>Primary: PFS</td>
<td>KRAS-WT population: PFS: 7.9 months (Arm A) vs. 8.6 months (Arm A) (HR 0.86, p = 0.66)</td>
<td>KRAS-WT population: RR: 49% (Arm B) vs. 41% (Arm A) (p = 0.15)</td>
</tr>
<tr>
<td><strong>Douillard et al</strong>&lt;sup&gt;30&lt;/sup&gt; <strong>PRIME study</strong></td>
<td>Randomized phase III clinical trial 1,883 patients</td>
<td>FOLFIRI</td>
<td>Primary: PFS</td>
<td>KRAS exon 2 WT: PFS: 9.6 months (FOLFIRI/Cmab) vs. 8 months (FOLFIRI) (HR 0.77, p = 0.004)</td>
<td>No difference in OS (Arm A vs. 22 months, Arm B vs. 20.1 months)</td>
</tr>
<tr>
<td><strong>Van Cutsem et al</strong>&lt;sup&gt;31,32&lt;/sup&gt; <strong>CRYSTAL Study</strong></td>
<td>Randomized phase III clinical trial 1,998 patients</td>
<td>FOLFIRI</td>
<td>Primary: PFS</td>
<td>KRAS exon 2 WT: PFS: 9.9 months (FOLFIRI/Cmab) vs. 8.4 months (FOLFIRI) (HR 0.9, p = 0.002)</td>
<td>KRAS exon 2 WT: OS: 23.5 months (FOLFIRI/Cmab) vs. 20.2 months (FOLFIRI) (HR 0.77, p = 0.009)</td>
</tr>
</tbody>
</table>

**Abbreviations:** mCRC, metastatic colorectal cancer; OS, overall survival; Cmab, cetuximab; Pmab, panitumumab; RR, response rate; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; OR, odds ratio; WT, wild type.
evaluated cetuximab and panitumumab in the setting of single-agent irinotecan. The EPIC trial did not select patients based on RAS status but reported improvements in response rate and PFS. The PICCOLO study excluded patients with KRAS codon 12, 13, and 61 mutations and codon 12, 13, and 61 mutations and KRAS exon 2 WT disease. A significant improvement in response rate and PFS was noted on the panitumumab arm. A recent update on this study showed further accentuation of benefit in favor of panitumumab in the RAS-WT population (Table 5).

It is unclear at this time what the best strategy is for a biologic therapy in the second-line setting of RAS-WT tumors after progression on first-line bevacizumab-based combinations. The continuation of bevacizumab or a switch to anti-EGFR–based therapy (in the setting of irinotecan-based backbone) is acceptable. However, in the setting where down-staging is important, anti-EGFR therapy is more appropriate.

### Targeted Therapies in the Third-Line Treatment of RAS-WT mCRC

There is no current data to support the continuation of bevacizumab in the third-line treatment in mCRC. In patients who have progressed on all cytotoxic chemotherapies, the combination of anti-EGFR plus irinotecan is considered the most appropriate choice in patients with good PS who are irinotecan tolerant. The use of cetuximab or panitumumab monotherapy in this setting is also considered appropriate based on the CO17 and the ASPECTCT trials (Table 6). Regorafenib should only be considered after failure (or intolerant).


<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Study Design</th>
<th>Control Arm</th>
<th>Experimental Arm(s)</th>
<th>Efficacy Objectives</th>
<th>Primary Efficacy Endpoint</th>
<th>Other Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartzberg et al&lt;sup&gt;38&lt;/sup&gt; PEAK Study</td>
<td>Randomized phase II clinical trial in KRAS-WT (exon 2) 285 patients</td>
<td>FOLFOX/BV</td>
<td>FOLFOX/Pmab</td>
<td>Primary: KRAS-WT PFS: 10.9 (Pmab) vs. 10.1 months (BV) (HR 0.81, p = 0.353)</td>
<td>RR: 57.8% (Pmab) vs. 53.5% (BV)</td>
<td>OS: 41.3 (Pmab) vs. 28.9 months (BV) (HR 0.62, p = 0.009)</td>
</tr>
<tr>
<td>Heinemann et al&lt;sup&gt;49&lt;/sup&gt; Stintzing et al&lt;sup&gt;50&lt;/sup&gt; FIRE-3 Study</td>
<td>Randomized phase III clinical trial in KRAS-WT WT (exon-2) 592 patients</td>
<td>FOLFIRI/BV</td>
<td>FOLFIRI/Cmab</td>
<td>Primary: KRAS-WT (independent review): RR: 65.5% (Cmab) vs. 55.6% (BV) (OR 1.58, p = 0.003)</td>
<td>KRAS-WT: OS: 28.7 (Cmab) vs. 25 months (BV) (HR 0.77, p = 0.007)</td>
<td>KRAS-WT: RR: 68.8% (cetuximab) vs. 56% (BV)</td>
</tr>
<tr>
<td>Veenook et al&lt;sup&gt;17&lt;/sup&gt; Lenz et al&lt;sup&gt;27&lt;/sup&gt; CALGB 80405</td>
<td>Randomized phase III clinical trial in KRAS-WT WT (exon 2) 526 patients</td>
<td>(FOLFOX or FOLFIRI)/BV</td>
<td>(FOLFOX or FOLFIRI)/ Cmab</td>
<td>Primary: KRAS-WT OS: 29.9 (Cmab) vs. 29 months (BV) (HR 1.01, p = 0.3)</td>
<td>KRAS-WT: RR: 67.5% (Cmab) vs. 56% (BV) (OR 1.58, p = 0.029)</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 5. EGFR Targeting in the Second-Line Treatment in KRAS-WT Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Control Arm</th>
<th>Experimental Arm(s)</th>
<th>Efficacy Objectives</th>
<th>Primary Efficacy Endpoint</th>
<th>Other Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeters et al&lt;sup&gt;32&lt;/sup&gt; 20050181 Study</td>
<td>Second-line randomized phase III clinical trial KRAS exon 2 WT: 597 patients</td>
<td>FOLFIRI</td>
<td>FOLFIRI + Pmab</td>
<td>Primary: PFS OS: 7.9 (FOLFIRI + Pmab) vs. 3.9 (FOLFIRI) (HR 0.73, p = 0.004)</td>
<td>OS: 14.5 (FOLFIRI + Pmab) vs. 12.5 months (BV) (HR 0.85, p = 0.12)</td>
</tr>
<tr>
<td>Seymour et al&lt;sup&gt;49&lt;/sup&gt; PICOLO Study</td>
<td>Second-line randomized phase III clinical trial KRAS WT (codon 12, 13, 61) 460 allocated to irinotecan with or without panitumumab</td>
<td>Irinotecan 300 mg/m&lt;sup&gt;2&lt;/sup&gt; to 350 mg/m&lt;sup&gt;2&lt;/sup&gt; every 3 weeks</td>
<td>Irinotecan/panitumumab (9 mg/kg every 3 weeks)</td>
<td>Primary: OS: 10.4 (irinotecan/Pmab) vs. 10.9 months (irinotecan) (HR 1.01, p = 0.91)</td>
<td>Pmab/irinotecan arm was superior to irinotecan (HR 0.78, p = 0.015)</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR, epidermal growth factor receptor; Pmab, panitumumab; Cmab, cetuximab; BV, bevacizumab; PFS, progression-free survival; OS, overall survival; RR, response rate; HR, hazard ratio; OR, odds ratio; WT, wild type.
TABLE 6. EGFR Targeting in Chemotherapy Resistant KRAS-WT mCRC

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Research Arm(s)</th>
<th>Efficacy Objectives</th>
<th>Primary Efficacy Endpoint</th>
<th>Other Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karapetis et al\textsuperscript{55} NCI-C017 Study</td>
<td>Randomized phase III clinical trial KRAST-WT (exon 2), 230 patients</td>
<td>Cmab</td>
<td>OS: 9.5 (Cmab) vs. 4.8 months (BSC) (HR 0.55, p &lt; 0.001)</td>
<td>PFS: 3.7 (Cmab) vs. 19 months (BSC) (HR 1.14, p &lt; 0.001)</td>
</tr>
<tr>
<td>Price et al\textsuperscript{55} ASPECTCT Study</td>
<td>Randomized phase III non-inferiority clinical trial in patients with KRAS-WT 1,010 patients</td>
<td>Cmab</td>
<td>OS: 10.4 (Pmab) vs. 10 months (BSC)</td>
<td>PFS: 4.1 (Pmab) vs. 4.4 months (Cmab) (HR 1.0; 85% CI, 0.88 to 1.34)</td>
</tr>
</tbody>
</table>

Abbreviations: mCRC, metastatic colorectal cancer; OS, overall survival; RR, response rate; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; Cmab, cetuximab; Pmab, panitumumab; OR, odds ratio; BSC, best supportive care; WT, wild type.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Institutional relationships are marked “Inst.” Relationships marked “U” are uncompensated.


References

2. Vennik A, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol. 2014;32:5s (suppl; abstr LBA4).
11. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver me-


42. Tabernero J, Cohn A, Obermannova R, et al. RAISE: a randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and
5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp). J Clin Oncol. 2015;33:3s (suppl; abstr 512).


