First-Line Therapeutic Strategies in Metastatic Colorectal Cancer

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Colorectal cancer is the third most common cancer in the United States.[1] In 2008, an estimated 148,810 new cases of colorectal cancer will be diagnosed and nearly 50,000 people will die of the disease.[1] In the past 20 years, great advances have been made in the treatment of advanced colorectal cancer, increasing survival from 6 months to over 2 years. However, among patients diagnosed with metastatic colorectal cancer (mCRC), the 5-year survival rate is, on average, only 8%.[2] This paper will outline the progression of treatment advances in mCRC, including single and combination chemotherapeutic agents and the addition of targeted agents.

Evolution of Combination Chemotherapy
Single vs Combination Chemotherapy
• Fluorouracil/Leucovorin—Prior to the integration of fluoropyrimidines in the management of mCRC, the median survival with best supportive care alone was a mere 6 months.[3] This improved to 10 to 12 months with the use of fluorouracil (5-FU) with or without leucovorin (LV).[3,4] 5-FU is thought to inhibit thymidylate synthase which then blocks DNA synthesis. Introduced more than 50 years ago, it was the first major breakthrough in the treatment of mCRC. The addition of LV, a reduced folate, was found preclinically to increase the intracellular concentration of reduced folates, resulting in increased binding of 5-FU to thymidylate synthase and therefore producing increased inhibition of DNA synthesis and enhanced antitumor effects.[3]

Numerous phase II and III trials assessing the dose, schedule, and method of administration of 5-FU-based chemotherapy were completed by the Groupe Coopérative Multidisciplinaire en Oncologie (GERCOR) trials group. The GERCOR trials culminated in the French Intergroup Study comparing monthly bolus 5-FU/ LV (North Central Cancer Treatment Group [NCCTG]-Mayo regimen) with bimonthly bolus and continuous-infusion 5-FU/LV (modified LV5FU2 regimen).[5] The dose of chemotherapy given with the LV5FU2 regimen was twice that of the Mayo regimen. While there was no statistically significant difference in overall survival (OS), both response rate and progression-free survival (PFS) were improved with the modified LV5FU2 regimen. The LV5FU2 regimen also was associated with fewer grade 3/4 toxicities than were seen with the monthly regimen.[5]

Both regimens had inconveniences related to delivery. The Mayo regimen required daily bolus administration of 5-FU for 5 consecutive days on a monthly basis. By comparison, the LV5FU2 regimen consisted of a 5-FU bolus followed by a continuous infusion of 5-FU for 48 hours every 2 weeks, which involved the need for long-term venous access and an administration pump.

Subsequently, two key meta-analyses assessed the impact of the modes of delivery of 5-FU/LV on survival[6] and the relative contribution of LV to 5-FU–based chemotherapy,[7] respectively. First, a meta-analysis was performed that compared infusional vs bolus 5-FU/LV from seven phase III clinical trials, representing 1,219 patients.[6] The meta-analysis showed that infusional 5-FU was associated with an improved tumor response (22% vs 14%, P = .0002) but without a corresponding improvement in median survival (12.1 vs 11.3 months, P = .039).[6] A companion paper described the toxicity profiles and showed that bolus 5-FU was associated with increased grade 3/4 hematologic toxicity, particularly neutropenia (4% vs 31%) and mucositis, whereas higher rates of hand-foot syndrome (34% vs 13%) were observed with infusional 5-FU.[8]

Another meta-analysis assessed the impact of modulation of 5-FU by LV.[7] The tumor response rate improved from 11% to 21% with the use of 5-FU/LV vs 5-FU alone (P < .0001). Median OS improved from 10.5 to 11.7 months (P = .004). The 1-year survival rate was 43% vs 49%, but 2-year survival was identical in both groups at 17%. Prognostic factors of a good tumor response included good performance status, metastases confined to the liver, and treatment with 5-FU/LV. One-year survival
was clearly worse with increasing performance status (63% vs 45% vs 20% for PS 0, 1, and 2, respectively) and was influenced by the site of metastatic disease (liver only, 50%; lung only, 57%; and other sites, 44%).[7] Overall, this analysis demonstrated a small but discernable benefit for the addition of LV to bolus 5-FU.

- **Irinotecan**—Irinotecan (CPT-11) was then added to the armamentarium, receiving US Food and Drug Administration (FDA) approval in 2002. Irinotecan inhibits the topoisomerase 1 enzyme. Normally, topoisomerase 1 catalyzes DNA breakage, repair, and rejoining of DNA strands, all necessary for DNA replication. Irinotecan-induced inhibition stabilizes these breaks, leaving fragmented DNA and resulting in cell death.[3]

Douillard et al[9] authored the first phase III study in which irinotecan was added to infusional 5-FU/calcium folinate compared to 5-FU/calcium folinate alone. This study demonstrated a benefit in response rate (35% vs 22%, P = .005) and median time to progression (7 vs 4 months, P = .001). The survival benefit was 3 months (17 vs 14 months, P = .031), with a 1-year survival of 69% vs 59%. Grade 3/4 toxicities were mostly limited to the irinotecan group, and consisted of diarrhea (44% vs 26%), vomiting, and leukopenia. Grade 3/4 neutropenia affected 29% of patients on irinotecan, but only 2% of all patients developed infection.[9]

At the same time, Saltz et al[10] compared three regimens: (1) weekly bolus irinotecan and 5-FU/LV (IFL); (2) 5-FU/LV (Mayo protocol); and (3) weekly single-agent irinotecan. The IFL regimen demonstrated a superior PFS compared to 5-FU/LV, increasing PFS from 4.3 to 7.0 months (P = .004) and enhanced survival from 12.6 to 14.8 months (P = .04). Survival and PFS for weekly irinotecan were similar to the 5-FU/LV regimen. However, additional toxicities of IFL included grade 3/4 diarrhea, vomiting, and infection. Mucositis was substantially increased (16.9% vs 2.2%) in the 5-FU/LV group and higher than expected by the meta-analysis data.[8]

- **Oxaliplatin**—Oxaliplatin (Eloxatin), a third-generation platinum derivative, demonstrated activity in mCRC in synergy with 5-FU/LV.[3] Oxaliplatin induces apoptosis by forming DNA adducts.[3] The first major study demonstrating the effectiveness of oxaliplatin when compared with the Mayo protocol (FOLFOX4 [leucovorin (folinic acid), 5-FU, oxaliplatin]) found a significant improvement in PFS from 6.2 to 9 months (P = .0001) and response rate over 5-FU/LV alone.[11] Overall survival improved from 14.7 to 16.2 months but was not statistically different between the two treatment arms, although this may have been obscured by crossover for salvage chemotherapy. Toxicity of oxaliplatin was predominantly neurosensory, overall affecting 68% of patients with grade 1 to 3 toxicity, including pharyngolaryngeal dysesthesia in almost one-quarter of the patients.[11]

- **Capecitabine**—Another advance in the management of mCRC was the demonstration of equivalence of 5-FU/LV and capecitabine (Xeloda). Capecitabine is an oral fluoropyrimidine that is converted enzymatically to fluorouracil, with a toxicity profile similar to infusional 5-FU.[3] Two simultaneous and identical phase III clinical trials were performed to compare the 5-FU/LV Mayo protocol with capecitabine.[12,13] One study demonstrated at least equivalence,[13] and the other demonstrated superiority of capecitabine[12] in terms of response rate. Otherwise, secondary endpoints were equivalent, including a median survival of 12 to 13 months. The toxicity profile of capecitabine demonstrated expected rates of diarrhea but more frequent hand-foot syndrome. Alopecia was less frequent and stomatitis was both less frequent and less severe with capecitabine than 5-FU.[12,13] These studies confirmed the interchangeability of 5-FU/LV and capecitabine.

Combination Comparisons and the Role of Sequential Therapies

By 2000, the optimal use of the available agents in first-line therapy, 5-FU/LV, irinotecan, and oxaliplatin, had not been determined, and capecitabine would shortly become a treatment option. Evidence was mounting for combination treatment to improve the objective response rate and time to disease progression. Irinotecan in combination with 5-FU/LV had demonstrated a benefit over 5-FU/LV or irinotecan alone,[9,10] as had oxaliplatin.[11] Second-line options were emerging, although not prespecified in trials, and the treatment options outside a clinical trial were limited. At this point, the combinations of treatments and sequencing of these agents became the focus of attention.

- **N9741 Trial**—In the phase III N9741 trial comparing IFL to FOLFOX and IROX (irinotecan/oxaliplatin), the superiority of FOLFOX was demonstrated in terms of improved time to progression and response rates, and an OS of 19.5 months compared to 15 months for IFL and 17.4 months for IROX (P = .0001).[14] Aside from sensory neuropathy (grade 3/4 in 18% vs 3%, P = .001), fewer and less severe toxicities were observed with FOLFOX compared to the toxicities seen with the IFL regimen. More severe vomiting and paresthesias, however, were observed with IROX as compared to IFL.[14] Based on response and survival rates, and toxicity profiles, FOLFOX was judged to be the superior regimen for mCRC, and in 2004, the FDA approved the use of FOLFOX for previously untreated...
mCRC.  
• BICC-C Trial—The Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib (BICC-C) trial was developed as a 3×2 factorial design comparing three chemotherapy options (FOLFIRI [leucovorin, 5-FU, irinotecan], modified [m]IFL, and CapeIRI [capecitabine, irinotecan]). A second randomization was performed to compare the use of celecoxib (Celebrex) or placebo with each of the chemotherapeutic regimens evaluated.[15] Due to the excessive number and severity of toxicities, the CapeIRI arm was subsequently dropped. As data emerged regarding its efficacy in CRC, bevacizumab (Avastin) was included in the trial. Patients in both the FOLFIRI and mIFL arms were subsequently randomized to receive chemotherapy plus bevacizumab or chemotherapy only. The final study design involved FOLFIRI vs mIFL with or without celecoxib, and with or without bevacizumab.

First, celecoxib did not influence therapeutic outcomes, and the randomization of celecoxib was not considered relevant to the analysis of the chemotherapeutic regimens administered either alone or in combination with bevacizumab.

Second, FOLFIRI was found to be superior to mIFL in PFS (7.6 vs 5.9 months, P = .004). Overall survival was similarly improved (23.1 vs 17.6 months, P = .09), with 1-year survival rates of 75% and 65%, respectively. CapeIRI and mIFL produced similar results for OS and PFS, but excessive toxicity was observed from CapeIRI compared to either FOLFIRI or mIFL. FOLFIRI still maintained a superior PFS over CapeIRI, even when the analysis excluded patients on the CapeIRI arm who discontinued treatment early due to significant toxicity.[15]

• XELOX vs FOLFOX—Subsequently, the NO16966 (XELOX-1) trial was designed to combine oxaliplatin with either capecitabine or 5-FU/LV.[16] Later in the trial, patients were randomized to receive XELOX and FOLFOX4 alone or with bevacizumab. The first objective of the amended protocol was to show the noninferiority of XELOX and FOLFOX4 for PFS, with or without bevacizumab. The investigators found no difference in PFS in the eligible patient population (7.9 vs 8.5 months; hazard ratio [HR] = 1.05; 97.5% confidence interval [CI] = 0.94–1.18, the upper limit being below the predefined 1.23 noninferiority margin). The median OS was also similar at 19.8 and 19.6 months, respectively. Toxicities were also similar aside from increased grade 3/4 diarrhea in the XELOX group and the increased rate of neutropenia in the FOLFOX group.[16] The interchangeability of XELOX and FOLFOX was then established.

• FOLFIRI vs FOLFOX—Colucci et al [17] reported a direct comparison of an irinotecan 5-FU combination (Douillard regimen) with FOLFOX4 (de Gramont regimen). The authors found no differences in response rate, time to progression, or survival. Almost two-thirds of patients had previously received second-line chemotherapy, mostly oxaliplatin in the FOLFIRI group and irinotecan in the FOLFOX4 group. The analysis of those patients previously treated with second-line chemotherapy demonstrated a median survival of 17 months, compared to a median survival of 10 months among patients who did not get second-line chemotherapy.[17] This confirmed the similarity in activity between the FOLFOX and the Douillard 5-FU plus irinotecan regimens in first-line chemotherapy for mCRC. The choice of an initial regimen for mCRC then became a matter of patient and physician preference and toxicity profiles rather than differential efficacy. FOLFOX caused more neutropenia and sensory neuropathy, whereas the Douillard regimen was associated with hair loss and more gastrointestinal (GI) toxicity.

• Refining the Regimens—With no new chemotherapeutic agents on the horizon, the next issue was to determine the most appropriate delivery of the agents. This was done retrospectively by Grothey et al[18] and prospectively in the FOCUS (Fluorouracil, Oxaliplatin, and CPT-11 [irinotecan] Use and Sequencing) and CAIRO (CApecitabine, IRinotecan, Oxaliplatin) trials. The variation in median survival in studies using combination chemotherapy, which ranged from 14.8 to 21.5 months, was thought to be influenced more by the choice of salvage therapies following first-line treatment, rather than explained on the basis of patient selection or other factors unrelated to the treatments. Grothey et al[18] analyzed the impact of receiving all three active treatments (5-FU, irinotecan, and oxaliplatin) during the course of disease in a pooled analysis. Median survival was strongly correlated with the percentage of patients who received all three drugs (P = .0008). No correlation was found, however, with survival and percentage of patients who received second-line treatment (P = .19). Administration of all three drugs (combination therapy) was associated with a 3.5-month increase in median survival compared to the initial administration of only one of the three agents (monotherapy, P = .01).

This analysis brought up two important points. First, in these studies between 58% and 77% of the patients who initially received monotherapy later received second-line chemotherapy on progression. This would make a case for the early initiation of combination therapy, although the
potential influence of performance status at the time of progression affecting the second-line treatment choice cannot be excluded. These patients likely had a poorer performance status at the time of initial therapy and at the time of progression that affected the administration of second-line chemotherapy. Second, because of the survival benefit gained from second-line chemotherapy, other endpoints, such as PFS and time to treatment failure, might better assess the benefit of the initial chemotherapy regimen.[18]

Subsequently, Grothey and Sargent[19] presented an updated analysis with patients from four additional trials that validated this concept. They found that the median survival correlated with the percentage of patients receiving all three chemotherapy regimens. In multivariate analyses, only first-line exposure to all three treatments was correlated with survival.[19]

- **FOCUS and CAIRO Studies**—The FOCUS and CAIRO trials investigated whether combination treatment was indeed required to improve overall survival, as opposed to a sequential approach that used single agents. One obvious advantage of the sequential approach would be to minimize side effects. The Medical Research Council’s FOCUS trial compared three treatment options: 5-FU/LV followed by irinotecan at treatment failure, single-agent 5-FU/LV followed by combination chemotherapy, and combination chemotherapy at the outset.[20] In the combination chemotherapy arms, patients were further randomized to 5-FU/irinotecan or 5-FU/oxaliplatin. After second-line chemotherapy, salvage chemotherapy or supportive care was instituted. Initially, salvage with 5-FU and mitomycin was the treatment of choice, but with evidence supporting the sequential use of irinotecan and oxaliplatin, these agents were later recommended (although only received by 23% of patients).[20]

Compared with single-agent 5-FU/LV, only the initial combination arm with irinotecan demonstrated an improved overall survival by 2.6 months (P = .02, adjusting for multiple comparisons). However, no differences were reported between the three groups in 2-year OS (22% vs 25% vs 28%, respectively, adjusted for multiple comparisons). A further analysis found noninferiority between the two combination strategies. Additionally, no differences in quality of life or by performance status were noted.[20] The advantage of such a study is that it demonstrates that toxicities can be balanced with the treatment options, and that treatment can be individualized without compromising survival in patients for whom curative options are not available.

A similarly aimed study, CAIRO, was published simultaneously by the Dutch Colorectal Cancer Group.[21] It used a simple two-arm study design, comparing sequential treatment (capecitabine followed by irinotecan on progression followed by CapeOX [capecitabine, oxaliplatin]) with combination treatment (CapeRI followed by CapeOX on progression). Overall survival was not statistically different between the sequential and combination therapy groups (16.3 and 17.4 months, respectively). The 1-year survival rates were 64% and 67%, respectively (P = .38). However, multivariate analyses showed that worse survival was associated with a performance status of 2 and an abnormal lactate dehydrogenase (LDH).

Adverse effects were generally similar in the sequential and combination treatment arms except for grade 3 hand-foot syndrome, which was worse in the sequential group. Of note, both treatments were associated with grade 3/4 diarrhea (25%), nausea, vomiting, and febrile neutropenia. Quality of life was not significantly different in the two groups, aside from the incidence of diarrhea, which was worse in the combination group.[21] The diarrhea from CapeRI, however, was less severe in this trial than in either the BICC-C or the European Organisation for Research and Treatment of Cancer (EORTC) 40015 trial, where toxicities resulted in the closure of the BICC-C trial’s CapeRI arm and the premature closure of the EORTC 40015 trial. While possible explanations have been offered, these differences have yet to be explained.

While neither the FOCUS nor CAIRO studies used monoclonal antibody treatments, these studies were the first to determine that sequential treatment could produce similar survival as combination therapy among patients with unresectable or only potentially resectable disease. The increased median survival in the CAIRO study may be attributed to the use of all available treatments (5-FU, irinotecan, and oxaliplatin) in 36% of the sequential and 53% of the combination patients. By comparison, only 25% of the patients in the FOCUS trial received all three treatments. Clearly toxicity increased with combination treatment.

An accompanying editorial suggested that combination therapy may be most important for patients with potentially resectable disease to give the best possible chance of resection as well as for those with aggressive disease who have or are anticipated to have tumor-related symptoms or poor performance status related to disease.[22] Otherwise, the results of the FOCUS and CAIRO studies may be most appropriate for patients who do not fit into either of these two groups.[22]

- **Timing**—Another question relates to the sequencing of FOLFOX and FOLFIRI regimens. The C97 trials, for example, used single-agent 5-FU/LV followed by irinotecan on progression and demonstrated that irinotecan, in combination with oxaliplatin, may be more effective than irinotecan alone. The increased toxicity increased with combination treatment.
study by the GERCOR group compared FOLFIRI followed by FOLFOX6 at progression with the reverse sequence of regimens.[23] Performance status improved with both sequences, and the sequence of therapy had no impact on either PFS or OS. However, the sequence did influence toxicities. Grade 3/4 nausea, vomiting, and mucositis were more common with FOLFIRI, whereas neurotoxicity and neutropenia were more common with FOLFOX. Only grade 3 neurotoxicity with FOLFOX was increased when FOLFOX was used as second-line chemotherapy. Elderly patients did not experience more toxicities than younger patients.[23]

• Lower-Intensity Regimens—A previous pooled analysis in mCRC demonstrated that survival correlated with the proportion of patients receiving all three chemotherapy agents, yet did not correlate with the proportion of patients who receive second-line chemotherapy.[18] This prior analysis formed the basis of trials conducted separately by Falcone et al[24] and Souglakos et al.[25] who examined the efficacy of a modified, lower-intensity variation of the FOLFIRI regimen vs FOLFOXIRI (leucovorin, 5-FU, oxaliplatin, irinotecan) as first-line therapy. Previously, a phase II study reported a median survival of 28.4 months and a response rate of 72% with administration of FOLFOXIRI.[26]

The study by Souglakos et al[25] found that survival was not different between the groups (19.5 vs 21.5 months, P = .337), nor was time to progression (6.9 vs 8.4 months, P = .17). The dose intensity, which was only marginally higher in the mFOLFIRI group, did not explain the lack of difference. FOLFOXIRI was associated with increased diarrhea, neurosensory disorders, and severe alopecia. In contrast, the study by Falcone et al[24] was positive. The primary endpoint was response rate, which the authors justified by the strong correlations in meta-analyses between response rate and survival, and between response rate and rate of secondary surgery on metastases. When compared with mFOLFOX, FOLFOXIRI produced an impressive response rate (66% vs 41%, P = .002), for which treatment with FOLFOXIRI was the only independent predictor in multivariate analyses. PFS improved and overall survival increased from 16.7 to 22.5 months (P = .032). As expected, FOLFOXIRI was more toxic with regard to neurotoxicity and neutropenia, although the rates of febrile neutropenia were not different. The data were insufficient for quality-of-life analyses.[24]

So how do we evaluate these discrepant results? The study by Souglakos et al used a bolus 5-FU/LV regimen, which by virtue of its side-effect profile, may have limited the dosing of irinotecan and oxaliplatin. However, both studies demonstrated significant rates of grade 3/4 diarrhea. Additionally, the patients in the Souglakos study were older and had a higher performance status. Regardless, the FOLFOXIRI regimen is not a commonly used treatment option given the alternate available regimens that include monoclonal antibodies.

• ‘Stop and Go’ Strategies—The benefits of irinotecan and oxaliplatin in overall survival for patients with mCRC have been accompanied by added toxicity. The dose-limiting factor with oxaliplatin is the neurotoxicity. Tournigand et al[27] evaluated the concept of treatment breaks (“stop and go”) by comparing continuous FOLFOX4 until progression with a regimen of higher-dose oxaliplatin (FOLFOX7) for 6 cycles, followed by 5-FU/LV for 12 cycles, followed by FOLFOX7 for 6 cycles, in the OPTIMOX1 study. With this design, duration of disease control was the primary endpoint. This was defined as PFS for the continuous group, and for the stop-and-go arm, it combined the first PFS interval with the second PFS interval if a response or stable disease was achieved with the second regimen. Both regimens produced a similar duration of disease control (9 vs 10.6 months, P = .89), as well as overall survival (19.3 vs 21.2 months, P = .49) and PFS. In both groups, approximately 15% of patients underwent metastectomy with no difference in survival. The benefit of the stop-and-go arm was the reduced oxaliplatin-related neurotoxicity. The absolute benefit of oxaliplatin reintroduction on PFS and OS was ultimately difficult to discern because of the number of patients who never had reintroduction of oxaliplatin upon progression and the diverse reasons that the protocol-designated treatment plan was not followed.[27] For patients who experience toxicity or require breaks for various reasons, this information will help to guide clinicians in “real world” situations.

The OPTIMOX2 randomized phase II exploratory study assessed the stop-and-go strategy with oxaliplatin-based regimens, introducing the concept of chemotherapy-free intervals.[28] Randomization between the OPTIMOX1 regimen (mFOLFOX7 until progression, with adjusted oxaliplatin and 5-FU doses) vs mFOLFOX7 for six cycles and then no maintenance until progression, at which time FOLFOX7 was reintroduced. The duration of disease control was 12 and 9 months (P = .39), and PFS was 8.3 and 6.7 months in the two groups, respectively (P = .08), favoring the no-break arm. Response rates were similar in both arms. OS was 26 and 19 months (P = .0549) in favor of the no-break arm. The median chemotherapy-free interval was 17 weeks. The stop-and-go arm was better tolerated than the control arm. Although this study was underpowered to find...
statistically significant differences in survival unless such differences were large in magnitude, the data suggest that the OPTIMOX1 strategy (with 5-FU maintenance) is better than incorporating a chemotherapy-free interval.[28]

Role of Targeted Agents

Single-Agent Therapy: Which Target to Inhibit and for Which Subpopulations?

Next on the market were the targeted therapies that—based on preclinical data—brought the promise of inhibition of intra- and extracellular processes, resulting in tumor suppression and cell death. While the benefits of these therapies have been realized, the gains have not been as significant as initially anticipated. To date, bevacizumab, cetuximab (Erbitux), and panitumumab (Vectibix) have demonstrated a clinical benefit in mCRC. Cetuximab is the first antibody used in mCRC for which a defined pathologic subgroup—that with K-ras wild-type (WT) as opposed to K-ras mutant tumors—derived benefit from the treatment (at least in retrospective assessments). To date, panitumumab has only demonstrated benefit in treatment refractory mCRC.

• Bevacizumab—Bevacizumab is a humanized vascular endothelial growth factor (VEGF) antibody that binds the VEGF ligand.[3] The end result is reduced angiogenesis. The serious although uncommon side effects associated with bevacizumab include gastrointestinal perforation, arterial thromboembolic events, and wound healing problems. More commonly, bevacizumab is associated with reversible proteinuria and hypertension.

The pivotal trial of bevacizumab was a phase III placebo-controlled study conducted by Hurwitz et al, who combined IFL with or without bevacizumab. No crossover was permitted in the IFL group. IFL with bevacizumab increased survival from 15.6 to 20.3 months (HR = 0.66; P < .001).[29] The 1-year survival rates were 63.4% and 74.3%, in favor of the bevacizumab arm. Similarly, PFS, response rate, and duration of response were all improved. Grade 3/4 adverse events were common, occurring in 74% of patients in the IFL arm and 84.9% of those in the bevacizumab arm, mostly attributed to leukopenia, diarrhea, and hypertension. Only hypertension was more common in the bevacizumab group. Venous thromboembolic disease occurred in over 10% of patients. Bleeding was uncommon in both groups (2.5% and 3.1%, respectively). Unexpectedly, gastrointestinal perforation was seen in 1.5% of the bevacizumab patients.[29]

The impressive survival benefit seen in the Hurwitz trial was not unanimously accepted because of a perception on the part of some oncologists that bevacizumab paired with an inferior regimen (IFL) may have benefited patients more than if it had been paired with a more effective and less toxic regimen such as FOLFIRI. As oxaliplatin was not widely available at the time the Hurwitz trial was conducted, the effect of serial irinotecan- and oxaliplatin-based programs could not be assessed. The previously described BICC-C study comparing FOLFIRI and mIFL was later amended to include bevacizumab in both arms, and 117 patients were randomized.[15] While FOLFIRI was the clear choice over mIFL in the initial evaluation, the results were mixed when bevacizumab was added. While the primary endpoint of PFS increased from 8.3 to 11.2 months with FOLFIRI, the differences were not statistically significant, nor was there a difference in the objective response rate. However, overall survival increased from 19.2 months with mIFL/bevacizumab to 28.0 months with FOLFIRI/bevacizumab (P = .037).[30] Side effects including grade 3/4 nausea and vomiting (approximately 5% vs 10%) and febrile neutropenia (1.7% vs 5.4%) were more pronounced in the FOLFIRI/bevacizumab arm. The most striking difference was a 12.5% risk of grade 3/4 hypertension with FOLFIRI/bevacizumab compared to 1.7% in the mIFL/bevacizumab arm.[15] While differences in PFS and response rate were not positive, there was a clear survival benefit that is in fact the longest survival reported in the mCRC literature.

The NO16966 (XELOX-1) trial comparison of XELOX and FOLFOX4 became a 2×2 factorial design to incorporate bevacizumab or placebo once available data supported an improvement in PFS in the first-line setting with the addition of bevacizumab to IFL.[31] In this analysis, superiority of bevacizumab over chemotherapy alone would be concluded if PFS demonstrated significance at the P ≤ .025 level. In fact, bevacizumab improved PFS from 8.0 to 9.4 months (P = .0023). There was no improvement in response rate. The survival benefit was a modest 1.4 months and not statistically significant, increasing OS from 19.9 to 21.3 months. Adverse events attributed to bevacizumab were 16% in the bevacizumab arm and 8% in the placebo arm. Of these, only venous thromboembolism and hypertension were more common in the bevacizumab-treated patients.

In exploratory analyses of NO16966, reasons for the low PFS were considered. A prespecified analysis of “on treatment PFS” was done, comparing progressive disease or death from any cause (the usual PFS definition) to that analysis adjusted so that patients in whom progressive disease or death occurred longer than 28 days from the last dose of study treatment were censored from the time of the last scan showing no progressive disease. This was intended to assess the true effect of
the study drugs by censoring patients who went off treatment without progression. On treatment PFS was statistically better than for the “usual” PFS group (HR = 0.63; P = .0001), suggesting that continuation of bevacizumab may further improve PFS. Another hypothesized reason for the negative primary outcome was related to the discontinuation of bevacizumab at the time of development of side effects. Although the study allowed continuation of both 5-FU and bevacizumab when treatment was discontinued due to oxaliplatin side effects, this rarely occurred.[31] Further information about bevacizumab has been collected in two prospective observational cohorts of patients from Genentech-sponsored registries. In these populations, patients were treated with chemotherapy at the physician’s discretion (irinotecan-, oxaliplatin-, 5-FU-, or capecitabine-based) in combination with bevacizumab, in order to monitor the safety profile of bevacizumab. Each study registered over 1,900 patients starting in 2004, with multinational (First BEAT [Bevacizumab Expanded Access Trial]) and US-based (BriTE [Bevacizumab Regimens: Investigation of Treatment Effects and Safety]) populations.[32,33] To date, follow-up for the overall safety analyses has been 21.2 months for First BEAT and 12.9 months for BriTE. Reported toxicities for the First BEAT study were as expected based on phase III trials, including less than 6% grade 3 or higher toxicities (eg, hypertension and bleeding).[32] The BriTE cohort reported 16.4% hypertension requiring medication, as well as less than 3% GI perforation and hemorrhage.[33] Additionally, the long-term safety results of bevacizumab (continuous therapy for 12 months or more) from the BriTE study found no new serious adverse events compared to patients on shorter courses.[34] This provides some security for patients on long-term treatment. The First BEAT investigators reported an OS of 22.7 months and PFS of 10.8 months[32] whereas the BriTE study demonstrated an OS of 27.1 months and PFS of 10.1 months.[35] Additionally, Grothey et al.[36] performed a further multivariate analysis of the BriTE study, showing that patients who continued bevacizumab beyond the first disease progression may have had a longer survival than those who did not, but this finding is only hypothesis-generating at this point as it derives from registry rather than randomized patients. The overall efficacy results of both studies need to be considered cautiously, given their nonrandomized populations and therefore potentially biased results, in addition to the data having been presented in abstract form only, and the possibility of selective reporting. However, some investigators feel that the patients may reflect the general patient population, which may not have been represented in clinical trials. At the same time, three small studies of bevacizumab plus 5-FU/LV were all negative but with trends showing improvements in PFS and OS. No study to date has been adequately powered. An individual data meta-analysis of these trials was undertaken to determine the efficacy of these regimens.[37] Median OS increased from 14.6 to 17.9 months (P = .0081), while PFS increased from 5.6 to 8.8 months (P = .0001). Grade 3/4 adverse events were common but were as expected.[37] This was a particularly important study to assess any potential benefit of bevacizumab for patients who are not suitable for irinotecan or oxaliplatin treatment, demonstrating a role for bevacizumab without adding significant toxicity. • Cetuximab—Epidermal growth factor receptor (EGFR) is a receptor to which ligands bind, triggering an intracellular cascade of events affecting cellular growth, differentiation, proliferation, and apoptosis.[3] EGFR is overexpressed in up to 70% of CRCs and is associated with more advanced disease than tumors that do not overexpress EGFR.[38] Cetuximab is a chimeric IgG1 EGFR monoclonal antibody that binds the extracellular binding domain of EGFR, preventing its downstream effects and inducing antibody-dependent cell-mediated cytotoxicity.[38,39] The side effects are generally well tolerated and include an acne-like rash, dry skin, and rare hypersensitivity reactions.[3] To date, this agent has been used only in phase III trials for patients with EGFR-expressing tumors.[38] Recent studies have demonstrated that downstream proteins also affect the activity of the pathways, including the K-Ras protein. With the K-ras WT gene, the pathway is blocked by EGFR antibodies.[40] However with the K-ras gene mutation, the K-ras pathway is constitutively “on” or active, therefore bypassing the EGFR blockade. K-ras mutations are found in approximately 40% of patients. In early studies, patients with K-ras WT tumors had tumor responses, whereas those with K-ras mutant tumors did not.[40] The OPUS randomized phase II clinical trial assessed FOLFOX4 with and without cetuximab for patients with EGFR-expressing tumors.[41] Patients were treated until progression, symptomatic deterioration, or unacceptable toxicity. Response rates were modestly but not statistically significantly improved with cetuximab (35.7 vs 45.6%, P = .063). However, response rates were
positively correlated with increasing skin reactions, with up to 67% of responses seen among patients with a grade 3 rash. Infusion-related reactions were rare (4.1%) and no cetuximab-attributed treatment deaths occurred.[41]

At the 2008 annual meeting of the American Society of Clinical Oncology (ASCO), Bokemeyer et al reported the retrospective K-ras status and efficacy results of the OPUS trial. Quantitative polymerase chain reaction (PCR)-based K-ras mutation status was determined. Validation that the subset for whom this assessment was performed represented the overall study population was demonstrated by finding a similar PFS between the total study population and the K-ras–analyzed population.

In patients with K-ras WT tumors treated with cetuximab and FOLFOX, the response rate was improved. However, in patients with K-ras mutant gene status, response rates were in fact worse with cetuximab, but this finding was not statistically significant. Patients with K-ras WT had an improved PFS with cetuximab (7.7 vs 7.2 months, P = .016), whereas PFS was worse in the K-ras mutant group who received cetuximab (5.5 vs 8.6 months, P = .0192). Overall, patients on cetuximab with K-ras WT status had an improved PFS over K-ras mutant status. Among patients who received FOLFOX, there was no difference in PFS by K-ras gene status.

This study demonstrated that cetuximab with FOLFOX chemotherapy benefited patients with K-ras WT tumors, but had no beneficial effect—and may in fact be detrimental—in those with K-ras mutant tumors.[42] While this was a phase II clinical trial, it obligates researchers to consider K-ras status in future trials.

In a similar fashion, the CRYSTAL trial was a phase III clinical trial of FOLFIRI with and without cetuximab in patients with EGFR-expressing mCRC by immunohistochemistry.[39] PFS improved by 15% in favor of the cetuximab arm (8.0 vs 8.9 months, P = .0479). Response rates were also improved, and more patients were able to undergo metastasectomy with curative intent. Cetuximab resulted in increased grade 3/4 diarrhea, skin reactions (no grade 4), and infusion-related reactions. In a subgroup analysis, the severity of rash correlated with PFS, linking a PFS of 5.4 months with a grade 0 or 1 rash, 9.4 months for grade 2 rash, and 11.3 months for grade 3 rash.[39]

As with the OPUS trial, the retrospective K-ras status data for the CRYSTAL trial were presented.[40] Again, the PFS for the intent-to-treat and the K-ras–evaluable populations were similar, validating the K-ras evaluation. PFS for K-ras WT treated with cetuximab was 9.9 months, compared with 8.7 months in the chemotherapy-alone arm (P = .017). This translated into a 1-year PFS of 43 vs 25%. The K-ras mutant gene population showed no difference in PFS with cetuximab treatment. For patients treated with cetuximab, K-ras WT predicted for response compared to K-ras mutant status (PFS 9.9 vs 7.6 months, P = .007), with a corresponding improvement in response rate. However, there was no difference in PFS or response rate by K-ras status among patients treated with FOLFIRI alone (P = .87). Overall survival has not yet been reported.[40]

These two studies demonstrate retrospectively the PFS benefit of cetuximab with chemotherapy in patients with K-ras WT tumors and the absence of benefit and possible harm with cetuximab for patients with K-ras mutant tumors. Therefore, prospective assessment of K-ras status should be evaluated, restricting the use of cetuximab to patients who have K-ras WT tumors, and further studies should randomize patients with K-ras WT tumors to cetuximab vs another treatment or placebo. Survival data will also need to be followed, given the potential effects of subsequent therapies.

• Panitumumab—The third EGFR antibody, panitumumab, is a fully humanized IgG2 EGFR blocker that has shown efficacy in treatment-refractory mCRC.[38] Panitumumab is currently being evaluated in the first-line setting with FOLFOX in the PRIME phase III clinical trial. EGFR status is not required for entry. To date, only safety data have been presented, but no concerns have been reported.[43]

Targeted Therapy Combinations: Is There a Role for Dual Inhibition?

In light of the results of VEGF and EGFR inhibition and the modest associated improvements in PFS and OS, consideration was then given to dual inhibition. These mechanisms share common downstream signaling pathways and have demonstrated preclinical feasibility and efficacy in the irinotecan-resistant mCRC setting, as seen in the BOND2 study.[44]

The CAIRO2 phase III clinical trial randomized patients to CapeOX/bevacizumab with or without cetuximab.[45] Oxaliplatin was discontinued at cycle 7 to prevent severe neurotoxicity and reintroduced at the time of disease progression; the capecitabine dose was increased at cycle 7. Median PFS was 9.6 vs 10.7 months in favor of the arm that did not receive cetuximab (P = .018). However, median survival was not different in the two groups, at 20.3 and 20.4 months, respectively. Response rate and disease control rate were similarly unremarkable. These results were confirmed
in the EGFR-positive subgroup. As with previous assessments, PFS was significantly improved in patients treated with cetuximab who developed grade 2 or 3 skin toxicity, vs those with grade 0 or 1 toxicity (P ≤ .01). However, among patients who were not treated with cetuximab, PFS was no different in those with grade 2 or 3 skin toxicity but significantly worse in those with grade 0 or 1. When PFS was assessed by K-ras status, patients with WT tumors did not benefit from the addition of cetuximab. However, among patients with tumors manifesting the K-ras mutation, PFS was longer in those treated without cetuximab than in those treated with cetuximab (12.5 vs 8.6 months, P = .043). This finding was not associated with a worsening in OS. In terms of overall survival, no difference was seen with the addition of cetuximab or by K-ras gene mutation. The researchers hypothesized that there may be a deleterious interaction between VEGF and EGFR antibodies.[45] Similarly, Tournigand et al[46] reported the feasibility results of the four-arm DREAM-OPTIMOX3 study comparing mFOLFOX7/bevacizumab or mXELOX/bevacizumab, with or without erlotinib (Tarceva). Erlotinib is an oral tyrosine kinase inhibitor. However, the toxicities of this combined regimen were significant, so the DREAM study will proceed with bevacizumab and erlotinib following six cycles of chemotherapy with bevacizumab.[46] In an assessment in first-line treatment, the Panitumumab Advanced Colorectal Cancer Evaluation, or PACCE trial, randomized patients to bevacizumab or bevacizumab with panitumumab, in conjunction with oxaliplatin- or irinotecan-based chemotherapy at the investigator’s choice.[47] EGFR testing was not an entry criterion. The main analyses are intended for the oxaliplatin cohort. Only interim analyses have been presented to date, but these favored the bevacizumab-alone arm, resulting in discontinuation of the panitumumab arms due to inferior PFS and increased toxicities in the panitumumab arms.[47,48] Exploratory K-ras analysis of the irinotecan cohort suggested an improved response rate in the WT K-ras arm,[48] but this assessment has not been reported for the oxaliplatin cohort. Overall, the combination of targeted therapies in mCRC has been disappointing, but further assessment of subgroups that may benefit from combination therapy is warranted. Challenges and Issues in mCRC The treatment of metastatic colorectal cancer has changed dramatically from the 1980s, when only 5-FU was available for treatment and the median survival was at best 12 months, to a time when mCRC is a more chronic disease in which the median survival is now reported in excess of 2 years. In addition to the need for more and better agents to further extend survival and improve the quality of life of our patients, many questions remain regarding the administration of the drug regimens currently available. These questions concern the duration of treatment, the combination of agents, and the further delineation of patient subpopulations that may derive benefit from these therapies. Cost-effectiveness of targeted therapies and the societal implications are key concepts that also must be kept in mind with these therapies. When developing clinical trials, consideration must be given to the resectability of the disease and to specific populations, especially the elderly, and those with poorer performance status. The treatment of metastatic colorectal cancer will continue to be challenging in the years ahead.

References: References
First-Line Therapeutic Strategies in Metastatic Colorectal Cancer
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48. Hecht JR, Mitchell E, Chidiac T, et al: Interim results from PACCE: irinotecan (Iri)/bevacizumab (bev) ± panitumumab (pmab) as first-line treatment (tx) for metastatic colorectal cancer (mCRC)
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