A Paradigm Shift From One-Size-Fits-All to Tailor-Made Therapy for Metastatic Colorectal Cancer

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Abstract: Colorectal cancer is the second leading cause of cancer death in the United States. At least 50% of patients develop metastases, and most of these patients have unresectable tumors. Treatment options for metastatic colorectal cancer (mCRC) include several lines of chemotherapy, salvage surgery, maintenance therapy, and local therapy. For decades, 5-fluorouracil (5-FU) was the only chemotherapy option for patients with mCRC. This changed markedly over the last decade with the approval of irinotecan, oxaliplatin, capecitabine, humanized monoclonal antibodies that target either vascular endothelial growth factor (bevacizumab, aflibercept, and ramucirumab) or the epidermal growth factor receptor (cetuximab and panitumumab), and, most recently, regorafenib and trifluridine/tipiracil. In this review, we focus on first-line treatments for mCRC. We discuss how results from multiple clinical trials over the last 10 to 20 years confirmed the benefit of adding oxaliplatin and irinotecan to the established 5-FU chemotherapy backbone, and then further defined benefit in certain patient subgroups with the addition of mAbs. Ongoing investigations attempt to illustrate the role of newer molecular and immune therapies in the fight against mCRC. We acknowledge the tremendous advances made in first-line mCRC treatment, admit that we still have a long way to go, and highlight exciting lines of research for patients with mCRC in the burgeoning fields of precision medicine and immunotherapy.

Introduction

In 2013, colorectal cancer (CRC) affected almost 1.6 million people worldwide.[1] In 2015, there were an estimated 132,700 new cases of CRC and 49,700 deaths from this disease in the United States alone, making it the fourth most prevalent cancer and the second most common cause of cancer-related death in this country.[2]

Approximately 20% of patients with CRC have metastatic disease at diagnosis, and these patients have a 5-year overall survival (OS) rate of only 13.1%.[2] The treatment of metastatic colorectal

Table. Selected Trials in Metastatic Colorectal Cancer

Trial	Year	Patients, n	Group 1	Group 2	PFS, mo, median	*P* value	OS, median	*P* value
OxMdG[4]	2000	420	5-FU bolus & infusion/LV d 1-2	Group 1 + oxaliplatin	6.2 vs 9.0	.0003	14.7 vs 16.2	.12
NO16966[11]	2008	2034	XELOX + bev vs placebo	FOLFOX4 + bev vs placebo	8.0 vs 8.5	NS	19.8 vs 19.6	NS
TRIBE[23] (update)	2015	508	FOLFIRI + bev	FOLFOXIRI + bev	9.7 vs 12.3	.006	25.8 vs 29.8	.03
IFL/bev[28]	2004	813	IFL + bev	IFL + placebo	10.6 vs 6.2	<.001	20.3 vs 15.6	<.001
CRYSTAL[40]	2009	599	FOLFIRI	FOLFIRI + cetuximab	8.0 vs 8.9 (all)	.048	18.6 vs 19.9 (all)	.31
CRYSTAL[44] (update)	2015				8.4 vs 9.9 (WT)	.0012	20.0 vs 23.5 (WT)	.0093
PRIME[38] (final results)	2014	1183	FOLFOX4	FOLFOX4 + panitumumab	8.6 vs 10.0 (WT)	.01	19.7 vs 23.9 (WT)	.17
					9.2 vs 7.4 (MT)	.02	19.2 vs 15.5 (MT)	.14
CALGB/SWOG 80405[54]	2014	1137	FOLFIRI/ mFOLFOX6 + bev	FOLFIRI/ mFOLFOX6 + cetuximab	10.8 vs 10.5 (WT only)	NS	29.0 vs 29.9 (WT only)	.34

bev, bevacizumab; CALGB/SWOG, Cancer and Leukemia Group B/Southwest Oncology Group; CRYSTAL, Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer; d, day(s); FOLFIRI, 5-FU/leucovorin/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; FOLFOXIRI, 5-FU/leucovorin/oxaliplatin/irinotecan; IFL, irinotecan/5-FU/leucovorin; LV, leucovorin; MT, *KRAS* mutant; NS, not significant (reported as "non-inferior"; no *P* value given); OS, overall survival; OxMdG, oxaliplatin and modified de Gramont; PFS, progression-free survival; PRIME, Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; TRIBE, Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer; WT, *KRAS* wild type; XELOX, capecitabine/oxaliplatin.

cancer (mCRC) frequently involves a multimodality approach comprising chemotherapy, surgery, radiation, and liver-directed therapy. Recent advances include the addition of biologics: monoclonal antibodies directed against specific tumor signaling pathways; immunotherapy, which unleashes the body's natural defenses against tumor cells; and molecular profiling, such as next-generation sequencing, to determine molecular drivers of tumor growth and treatment resistance. We review the current standard of care for mCRC, as well as novel approaches being developed for the first-line treatment of this disease.

First-Line Treatment Options

Chemotherapy

Chemotherapy remains the mainstay of first-line treatment in mCRC, and a plethora of trials have been published in this arena. In this review, we discuss results from the more definitive trials carried out over the last 10 to 20 years (Table).

Building upon earlier work in pretreated patients with mCRC,[3] de Gramont and colleagues demonstrated in their phase 3 study that the addition of oxaliplatin to first-line infusional 5-fluorouracil (5-FU) and leucovorin resulted in prolonged median progression-free survival (mPFS). The mPFS was 9.0 months following oxaliplatin/5-FU/leucovorin compared with 6.2 months following 5-FU/leucovorin (*P*=.0003) (Table).[4] Complete or partial responses were seen in 50% of 210 patients treated with the oxaliplatin regimen (95% CI, 42%-58%).[4,5] The investigators administered daily intravenous (IV) leucovorin (200 mg/m^2/d) and 5-FU (IV bolus, 400 mg/m^2/d; 22-hour infusion, 600 mg/m^2/d) for 2 consecutive days, with or without IV oxaliplatin (85 mg/m^2 given on day 1), every 2 weeks.[4] This group's basic 5-FU/leucovorin regimen is known as the standard de Gramont (dG) regimen. Following the inclusion of oxaliplatin, the dG regimen became the oxaliplatin and modified de Gramont (OxMdG) regimen, also known as FOLFOX (the regimen in this particular phase 3 trial is known as FOLFOX4).

Subsequently, in 2002, the team behind the dG regimen reported clinical results in both previously treated and treatment-naive patients following modification of the original dG and OxMdG regimens. Most significantly, the team increased the continuous 5-FU infusion time and dose with the aim of achieving greater efficacy, a more convenient treatment regimen, and reduced cost.[5] A flat dose of leucovorin (instead of a dose calculated per body surface area) was also incorporated. It is worth

noting that leucovorin (folinic acid) is a diastereomeric compound that naturally exists as a mixture of dextro (D)- and levo (L)-rotatory forms. Chemical separation of these enantiomers yields the pharmacologically active L-folinic acid (D-folinic acid is inactive).[6,7] Thus, Cheeseman and colleagues studied the use of one 46-hour IV infusion of 5-FU (as opposed to two 22-hour infusions) along with dosing of leucovorin (350 mg [dextro-levogyre] or 175 mg [levogyre]) on day 1, with or without oxaliplatin on day 1, every 2 weeks. An initial dose escalation phase set the 46-hour 5-FU infusion at 2800 mg/m^2 for patients who did not additionally receive oxaliplatin and at 2400 mg/m^2 for those who did receive oxaliplatin. The efficacy of this modified dosing regimen in treatment-naive patients was positive; mPFS was 10.6 months with oxaliplatin (OxMdG or modified [m] FOLFOX) and 9.3 months without oxaliplatin (modified [M] dG).[5] Partial or complete responses following OxMdG treatment were seen in 72% of 25 patients (95% CI, 50%-88%)[5], which is consistent with OxMdG (FOLFOX4) results.[4]

FOLFOX6 was subsequently established and reported by the de Gramont team in 2004.[8] The FOLFOX6 regimen is well known in the oncology world today. In standard 2-week cycles, IV leucovorin (dosed according to body surface area) is administered concurrently on day 1 with IV oxaliplatin, followed by bolus 5-FU and a 46-hour infusion of 5-FU (2400 mg/m^2, increased to 3000 mg/m^2 in cycle 3 onward in the absence of greater than grade 1 toxicity during the first 2 cycles).[8] In the 2004 study of patients with advanced CRC, a complete or partial response following FOLFOX6 treatment was seen in 56% of 109 treatment-naive patients (95% CI, 46%-66%).[8]

Currently, 5-FU remains the backbone of modern mCRC chemotherapy regimens, and many investigators have studied the addition of agents other than oxaliplatin to this backbone, with the aim of improving patient survival. Capecitabine is an oral prodrug that is enzymatically converted to 5-FU in vivo.[9] When compared in the first-line setting with an IV bolus 5-FU regimen (leucovorin 20 mg/m^2 and 5-FU 425 mg/m^2 on days 1-5 of a 4-week cycle), capecitabine (1250 mg/m^2 twice daily for 2 weeks of a 3-week cycle) was noninferior in terms of median OS (mOS; 12.5 vs 13.3 months, P=.974), caused less grade 3 or 4 stomatitis and neutropenia (P<.0001), and had the advantage of the convenience of an oral medication.[10] The main side effects of capecitabine were hand-foot syndrome, diarrhea, and hyperbilirubinemia.

NO16966 was a phase 3, first-line study that randomly assigned patients with mCRC 1:1 to receive either FOLFOX4 or a combination of capecitabine and oxaliplatin (XELOX).[11] At first, 634 patients were randomly assigned to receive either XELOX (capecitabine at a dose of 1000 mg/m^2 twice daily on days 1-15 every 3 weeks and oxaliplatin at a dose of 130 mg/m^2 on day 1 every 3 weeks) or FOLFOX4. However, within the first year of trial initiation, a protocol amendment allowed another 1401 patients to be enrolled and randomly assigned, in a 2 × 2 factorial design, to receive XELOX or FOLFOX4 followed by either the monoclonal antibody bevacizumab (Avastin, Genentech) or placebo. A total of 2034 patients were enrolled in this study. Regardless of bevacizumab treatment, the mPFS times following XELOX vs FOLFOX4 treatment were comparable (8.0 vs 8.5 months), as were the mOS times (19.8 vs 19.6 months) (Table).[11] As seen previously with IV 5-FU,[10] FOLFOX4 resulted in more grade 3 or 4 neutropenia (44% vs 7%) and febrile neutropenia (4.8% vs 0.9%), whereas XELOX resulted in a greater incidence of grade 3 diarrhea (19% vs 11%) and hand-foot syndrome (6% vs 1%).[11] These results suggested that capecitabine is an appropriate alternative to IV 5-FU in standard regimens, with or without oxaliplatin, for the first-line treatment of mCRC.

When irinotecan, a topoisomerase 1 inhibitor, was added to mCRC chemotherapy regimens, notable improvements in survival were reported. In a phase 3 trial, Saltz and colleagues randomly assigned 430 patients to 1 of 3 arms: single-agent irinotecan (125 mg/m^2 [IV over 90 minutes] weekly for 4 of 6 weeks), bolus 5-FU/leucovorin (4-week cycle), or irinotecan/bolus 5-FU/leucovorin (6-week cycle). The 3-drug regimen (irinotecan/5-FU/leucovorin) was superior to the 2-drug regimen (leucovorin/5-FU) in terms of mOS (14.8 vs 12.6 months, P=.04). Treatment with irinotecan alone resulted in mOS similar to that of the 2-drug regimen (12.0 vs 12.6 months).[12] In a further comparison of the 3-drug with the 2-drug regimen, patients who received the 3-drug regimen had more grade 3 or 4 diarrhea (22.7% vs 13.2%) and vomiting (9.7% vs 4.1%), but less mucositis (2.2% vs 16.9%), neutropenia (53.8% vs 66.2%), and febrile neutropenia (7.1% vs 14.6%). Thus, the addition of irinotecan to bolus 5-FU/leucovorin (IFL) resulted in survival benefit at the cost of increased rates of diarrhea and vomiting. The serious gastrointestinal toxicity related to the IFL regimen prompted an alteration of American Society of Clinical Oncology (ASCO) guidelines to incorporate a treatment algorithm addressing diarrhea induced by cancer treatment.[13,14]

The combination of irinotecan with infusional 5-FU (as opposed to IV bolus alone) was initially devised by Douillard and colleagues.[15] This combination was further evaluated in the phase 3 BICC-C (Randomized, Controlled Trial of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer) study, which randomly assigned 430 patients to first-line treatment with 1 of 3 regimens:

(1) irinotecan (IV, 180 mg/m^2 on day 1) plus leucovorin (IV, 400 mg/m^2 on day 1) plus 5-FU (400-mg/m^2 IV bolus on day 1 and 2400-mg/m^2 continuous infusion over the first 46 hours) on a 2-week cycle (FOLFIRI);

(2) irinotecan (IV, 125 mg/m^2) with 5-FU (IV bolus, 500 mg/m^2) and leucovorin (IV, 20 mg/m^2) on days 1 and 8 of a 3-week cycle (mIFL); or

(3) irinotecan (250 mg/m^2 on day 1) with capecitabine (oral, 1000 mg/m^2 twice daily on days 1-14) on a 3-week cycle (capeIRI).[16]

Based on the US Food and Drug Administration (FDA) approval of bevacizumab, this protocol was also amended to randomly assign an additional 117 patients to receive either FOLFIRI plus bevacizumab (5 mg/kg on day 1 of each cycle; 57 patients) or mIFL plus bevacizumab (7.5 mg/kg on day 1 of each cycle; 60 patients). The capeIRI arm was discontinued owing to toxicity, in addition to inferior efficacy.[16]

Comparison of the original 430 patients enrolled showed a trend toward superior mOS in the FOLFIRI arm (23.1 months for FOLFIRI vs 17.6 months for mIFL, *P*=.09; 23.1 months for FOLFIRI vs 18.9 months for capeIRI, *P*=.27). Regarding the additional 117 patients, mOS for those in the FOLFIRI-plus-bevacizumab arm could not be calculated at the time of publication, but a study update published a few months later reported that FOLFIRI plus bevacizumab yielded an mOS of 28.0 months, compared with 19.2 months for mIFL plus bevacizumab (*P*=.037). In addition, 87% of the patients on FOLFIRI/bevacizumab were alive at the 1-year mark, compared with 61% of those on mIFL/bevacizumab.[17] Unfortunately, owing to the trial amendment to include bevacizumab, the study was deemed underpowered to detect a survival benefit.

FOLFIRI plus bevacizumab was generally well tolerated, and although the incidences of neutropenia (53.6% vs 28.8%), febrile neutropenia (5.4% vs 1.7%), and hypertension (12.5% vs 1.7%) were higher with FOLFIRI plus bevacizumab than with mIFL plus bevacizumab, the greatly increased efficacy of FOLFIRI plus bevacizumab meant that this regimen represented an effective first-line treatment option for mCRC.[16]

Some phase 2 studies of first-line capeIRI suggested acceptable patient response rates and tolerability.[18-20] However, the intolerable capeIRI toxicities observed in the BICC-C phase 3 study and a European Organisation for Research and Treatment of Cancer (EORTC) phase 3 study led to the minimal use of this combination seen today.[16,17,21]

In a phase 3 trial of first-line mCRC treatment by the Gruppo Oncologico Nord Ovest (GONO), Falcone and colleagues randomly assigned 244 patients 1:1 to receive either FOLFIRI or 5-FU/leucovorin/oxaliplatin/irinotecan (FOLFOXIRI).[18] FOLFOXIRI was associated with greater tumor shrinkage and a higher likelihood of achieving an R0 resection at metastasectomy (*P*=.018; hazard ratio [HR], 3.1). The mOS was also improved following FOLFOXIRI compared with FOLFIRI in this study (22.6 vs 16.7 months, *P*=.032), with comparable toxicities except for grade 2 or 3 peripheral neuropathy (19% vs 0%, *P*<.0001) and grade 3 or 4 neutropenia (50% vs 28%, *P*=.0006).[18]

A similar phase 3 first-line study by the Hellenic Oncology Research Group (HORG) involved 288 patients with mCRC who were randomly assigned to receive either FOLFOXIRI or FOLFIRI. However, in this study, no significant difference was observed in mOS (21.5 months with FOLFOXIRI vs 19.5 months with FOLFIRI, *P*=.337). In addition, significantly more grade 3 or 4 alopecia (32% vs 12%, *P*=.0001), diarrhea (27.7% vs 10.9%, *P*=.001), and neurotoxicity (5.8% vs 0%, *P*=.001) were observed in the FOLFOXIRI arm.[20]

In the more recently published multicenter TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) phase 3 study, Loupakis and colleagues randomly assigned 508 patients with mCRC 1:1 to receive either 12 cycles of FOLFOXIRI plus bevacizumab or 12 cycles of FOLFIRI plus bevacizumab, followed by maintenance therapy with 5-FU/leucovorin and bevacizumab until disease progression.[19] Prior adjuvant oxaliplatin-based therapy was allowed only if it had been completed at least 12 months prior to relapse. After completion, the study demonstrated an improvement in mPFS in the FOLFOXIRI arm compared with the FOLFIRI arm (12.1 vs 9.7 months, *P*=.003) and a trend toward improved mOS (31.0 vs 25.8 months, *P*=.054).[19] In the recently published update of TRIBE study survival data, the OS and PFS benefit following treatment with FOLFOXIRI/bevacizumab compared with FOLFIRI/bevacizumab was confirmed: at a median follow-up time of 48.1 months, mOS was 29.8 months in the FOLFOXIRI/bevacizumab arm compared with 25.8 months in the FOLFIRI/bevacizumab arm (*P*=.03), and the mPFS was 12.3 vs 9.7 months, respectively (*P*=.006) (Table). The estimated 5-year OS rates were 24.9% vs 12.4%.[22,23] However, higher rates grade 3 or 4 neuropathy (5.2% vs 0%, *P*<001), stomatitis (8.8% vs 4.3%, *P*=.048), diarrhea (18.8% vs 10.6%, *P*=.01), and neutropenia (50.0% vs 20.5%, *P*<.001) were observed in the FOLFOXIRI arm compared with the FOLFIRI arm.[19]

The jury is still out regarding the benefit of adding oxaliplatin to a FOLFIRI regimen. The majority of studies report a significant increase in toxicity with this oxaliplatin-containing arsenal (especially grade 3 myelosuppression), and many oncologists use it only in special circumstances. These instances include the need

to convert unresectable liver-only metastases to resectable ones and the need to obtain a rapid reduction in tumor size to protect organ function in patients with excellent performance status.

A phase 3, first-line trial by the Hellenic Cooperative Oncology Group compared a FOLFIRI plus bevacizumab combination with a XELIRI (capecitabine [1000 mg/m^2 on days 1-14] and irinotecan [240 mg/m^2 on day 1] on a 21-day cycle) plus bevacizumab combination.[24] The investigators randomly assigned 285 patients to 1 of these 2 treatments. At the end of the study, the 2 groups had similar mPFS (10.2 months for XELIRI vs 10.8 months for FOLFIRI, *P*=.74) and mOS (20.0 for XELIRI vs 25.3 months for FOLFIRI, *P*=.099).[24] Grade 3 or 4 toxicities were also comparable between the 2 arms, with the exception of vomiting, which was more common in the XELIRI/bevacizumab treatment arm (5% vs 0%, *P*=.014).

Biologics

Biologics—in the form of humanized antibodies against targets of tumorigenesis—are an exciting addition to standard chemotherapy regimens.

Vascular Endothelial Growth Factor Inhibitors. The cancer therapeutic potential of targeting tumor angiogenesis was first suggested in the early 1970s.[25] Members of the vascular endothelial growth factor (VEGF) family of proteins were found to modulate angiogenesis and so became appealing targets for anticancer therapy.[26,27] As discussed earlier, bevacizumab (the first clinically approved anti-vascular endothelial growth factor A [VEGF-A] antibody) is used in the treatment of mCRC with some success. Trials were carried out primarily to investigate the benefit of adding bevacizumab to standard first-line chemotherapy. One remarkable phase 3 study randomly assigned 813 patients to receive IFL (irinotecan [125 mg/m^2], bolus 5-FU [500 mg/m^2], and leucovorin [20 mg/m^2]) weekly for 4 of 6 weeks, plus either bevacizumab (5 mg/kg once every 2 weeks) or placebo. The mOS was significantly longer in the bevacizumab arm than in the placebo arm (20.3 vs 15.6 months, *P*<.001) (Table), but the addition of bevacizumab comparatively increased the incidence of hypertension (22.4% vs 8.3%, *P*<.01) and gastrointestinal perforation (1.5% vs 0%, *P*<.01).[28]

In light of the NO16966 phase 3 trial, which was originally designed to compare FOLFOX4 with XELOX but was amended to a randomized 2 × 2 factorial design to also compare bevacizumab with placebo, 1400 patients were randomly assigned to receive oxaliplatin-based chemotherapy (FOLFOX4 or XELOX) and then bevacizumab or placebo.[11] The mPFS was longer in the bevacizumab arms than in the placebo arms (9.4 vs 8.0 months, *P*=.0023). There also was a trend toward longer mOS, which was not significant (21.3 months [bevacizumab/chemotherapy] vs 19.9 months [placebo/chemotherapy], *P*=.0769).[29] Grade 3 or 4 adverse events that were more common with bevacizumab included diarrhea and vomiting (32% vs 27%), cardiac disorders (4% vs <1%), and hand-foot syndrome (7% vs 3%).[29] Many patients (71% of those on bevacizumab and 53% of those on placebo) discontinued study treatment before progression of disease, possibly diluting the survival benefit of these studied bevacizumab regimens. That said, the lack of significant OS benefit gained from the addition of bevacizumab to FOLFOX or XELOX was disappointing.

In the phase 3 AVEX (Avastin in the Elderly With Xeloda) study, Cunningham and colleagues examined the addition of bevacizumab to capecitabine for survival benefit in elderly patients with previously untreated, unresectable mCRC.[30] A total of 280 patients were randomly assigned 1:1 to receive capecitabine alone (1000 mg/m^2 by mouth twice daily for 2 of every 3 weeks) or capecitabine (1000 mg/m^2 by mouth twice daily for 2 of every 3 weeks) plus bevacizumab (7.5 mg/kg on day 1 every 3 weeks). Treatment was given until disease progression unless a patient withdrew from the study before that time owing to toxicity or until withdrawal of consent.[30] The mPFS was significantly longer when bevacizumab was added to capecitabine (9.1 months [bevacizumab/capecitabine] vs 5.1 months [capecitabine alone], *P*<.0001). Grade 3 or 4 treatment-related adverse events occurred in 40% of patients in the bevacizumab/capecitabine treatment arm, compared with 22% of patients in the capecitabine-only arm. Common grade 3 or 4 adverse events were hand-foot syndrome (16% vs 7%), diarrhea (7% vs 7%), and venous thromboembolic events (8% vs 4%).[30]

These studies describe a positive effect of adding bevacizumab to the first-line treatment of mCRC, and this biologic agent was approved by the FDA for combination use in treatment-naive patients with mCRC.

Epidermal Growth Factor Receptor Inhibitors. The epidermal growth factor receptor (EGFR) protein is a member of the ERBB family of receptor tyrosine kinases. It has been shown to be overexpressed and play a significant role in the promotion and progression of CRC. Initially, it was theorized that blocking EGFR activity could be fundamental in the treatment of CRC, and monoclonal antibodies were devised to do just that.[31,32] However, results from early studies did not show a relationship between EGFR expression and response to these monoclonal antibodies.[33] After further investigation of downstream signal transduction pathways, an oncogene called *KRAS* was found to play a part in the response to this therapy. Researchers discovered that when *KRAS* was mutated to become constitutionally active (in exon 2, codons 12 and 13), which was found to be the case

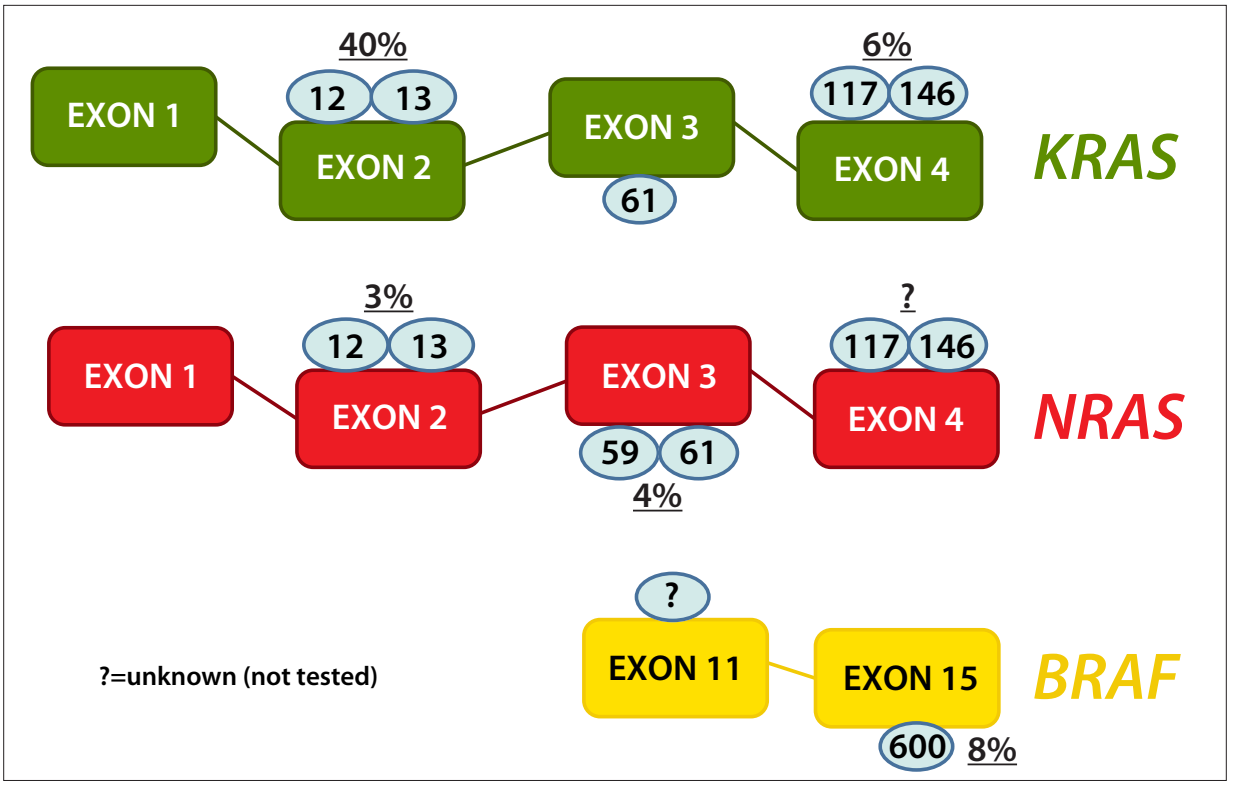

Figure 1. Extended *RAS* genetic mutation profile based on information from Douillard and colleagues.[47] Mutations other than *KRAS* mutations have been detected at a rate of 17% and these also impact patient treatment with EGFR inhibitors. *BRAF* mutations appear to affect patient response to chemotherapy.

in 40% of CRCs, downstream signaling pathways were activated that could bypass EGFR, leading to ineffective anti-EGFR therapy.[34,35] During these earlier stages of *KRAS* investigation, routine *KRAS* testing was not common practice. Testing had to be validated, and eventually *KRAS* assays that were compliant with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) were established.

Validated *KRAS* testing subsequently was used to select only patients with the wild-type (WT) gene for anti-EGFR therapy. However, it was soon discovered that a response to these monoclonal antibodies was not guaranteed in all patients with WT disease, suggesting that other molecular determinants existed that could dictate resistance to monoclonal antibodies against EGFR.[32,36,37] Douillard and colleagues hypothesized that *RAS* mutations other than those known for *KRAS* might lead to anti-EGFR therapy failure. The use of bidirectional Sanger sequencing and high-performance liquid chromatography techniques enabled Douillard and colleagues to realize that 17% of the patients in their PRIME (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) study, who had originally been defined as having *KRAS* WT (in exon 2), had additional *RAS* mutations (in *KRAS* exons 3 and 4 and in *NRAS* exons 2, 3, and 4).[38] Thus, clinical practice has evolved to adopt extended *RAS* testing, which now includes *KRAS* and *NRAS* codons 12 and 13 (exon 2), 59 and 61 (exon 3), and 117 and 146 (exon 4)[39] (Figure 1). Monoclonal antibody therapy against EGFR is currently restricted to patients with this extended *RAS* WT status.

EGFR-directed therapy was shown to improve survival when added to traditional 5-FU–based chemotherapy. Cetuximab (Erbitux, Lilly) is a chimeric mouse/human monoclonal antibody against EGFR. In the phase 3 CRYSTAL (Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer) trial, Van Cutsem and colleagues were the first to demonstrate that cetuximab added to FOLFIRI improved PFS compared with FOLFIRI alone. A total of 599 patients (unselected for *RAS* status) were randomly assigned to FOLFIRI plus cetuximab or FOLFIRI alone. Patients in the combination arm had longer mPFS (8.9 vs 8.0 months, P=.048) and a statistically nonsignificant trend toward longer mOS (19.9 vs 18.6 months, P=.31) (Table).[40] At the time of this study, *KRAS* had not been established as a reliable biomarker for predicting response to cetuximab, but it did show promise. When patients in the study of Van Cutsem and colleagues were selected according to *KRAS* status, 172 patients in the combination arm and 176 patients in the FOLFIRI arm had *KRAS*

WT mCRC. The mPFS was improved when only the patients with *KRAS* WT were taken into account (9.9 vs 8.7 months, *P*=.02), and the mOS showed a greater trend toward improvement (24.9 vs 21.0 months, not statistically significant). Thus, the benefit of adding cetuximab was predominantly observed in patients with *KRAS* WT (PFS HR, 0.68; 95% CI, 0.50-0.94 for *KRAS* WT vs PFS HR, 1.07; 95% CI, 0.71-1.61 for *KRAS* mutant). Cetuximab plus FOLFIRI led to more grade 3 or 4 adverse events compared with FOLFIRI alone, including diarrhea (15.7% vs 10.5%, *P*=.008), rash (8.2% vs 0%, *P*<.001), and dermatitis acneiform (5.3% vs 0%, *P*<.001).[40]

The phase 3 COIN (Combination Chemotherapy With or Without Cetuximab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) trial was initiated to study an oxaliplatin-based fluoropyrimidine chemotherapy backbone plus or minus cetuximab. For this study, 1630 patients were randomly assigned 1:1 to cetuximab or no cetuximab.[41] Oncologists could choose between 2 chemotherapy regimens: oxaliplatin plus capecitabine or oxaliplatin plus fluorouracil (bolus and infusional) and leucovorin. The primary study endpoint was OS in patients with *KRAS* WT tumors (43% of evaluable patients). OS did not differ between the treatment groups (median survival was 17.9 months in the control group vs 17.0 months in the cetuximab group). Similarly, there was no effect of cetuximab on PFS (8.6 vs 8.6 months). These negative data appeared to be in contrast with the positive data yielded from the CRYSTAL trial. This discrepancy brought up the question of whether the use of irinotecan in place of oxaliplatin was of importance. Is there a "preferred chemotherapy partner for EGFR antibodies"?[42]

In the randomized phase 2 OPUS (Oxaliplatin and Cetuximab in First-line Treatment of Metastatic Colorectal Cancer) trial, Bokemeyer and colleagues showed that a combination of FOLFOX4 plus cetuximab was superior to FOLFOX4 alone in the first-line treatment of patients with mCRC. A total of 344 patients received FOLFOX with or without cetuximab; 134 of these patients had *KRAS* WT tumors and 99 had *KRAS* mutant tumors. The addition of cetuximab increased mPFS only in the WT group (7.7 vs 7.2 months, *P*=.0163). In the mutant group, mPFS was decreased (5.5 vs 8.6 months, *P*=.0192).[43] These findings confirmed that *KRAS* mutation status is vital to predicting outcomes with cetuximab.

More recently, in 2015, Van Cutsem and colleagues reported extended *RAS* mutation testing of tumor samples from patients who had been in the CRYSTAL trial. Sixty-three patients with previously established *KRAS* WT (exon 2, codons 12 and 13) tumors (32 patients in the FOLFIRI-plus-cetuximab arm and 31 in the FOLFIRI-alone arm) were reclassified as having *RAS* mutant disease. When these patients were excluded from new survival analyses and only patients with extended *RAS* WT tumors were included, patients in the combination treatment arm had significantly better mOS (28.4 vs 20.2 months, *P*=.0024) and mPFS (11.4 vs 8.4 months, *P*<001) than those in the FOLFIRI-alone arm, supporting the benefit of adding cetuximab to standard chemotherapy regimens in patients with *RAS* WT tumors (Table).[44]

In 2015, Bokemeyer and colleagues reported a reanalysis of 118 evaluable *KRAS* exon 2 WT tumor samples from the OPUS study for "other" *RAS* mutations in 4 additional *KRAS* codons (exons 3 and 4) and 6 additional *NRAS* codons (exons 2-4).[45] Of the 118 *KRAS* exon 2 WT tumor samples, 87 were found to be of extended *RAS* WT status (as previously defined), and 31 harbored "other" *RAS* mutations. The objective response rate was shown to be significantly better in patients with extended *RAS* WT receiving cetuximab/FOLFOX4 than in those receiving FOLFOX4 alone (58% vs 29%; odds ratio, 3.33 [95% CI, 1.36-8.17]; *P*=.0084), and there appeared to be a similar trend for PFS and OS. However, patients with "other" *RAS* mutations did not appear to benefit from cetuximab, although the sample size was too small to carry out a sound statistical comparison. In the combined population of patients with any *RAS* mutation (*KRAS* exon 2 or other *RAS*), a clear detrimental effect was associated with the addition of cetuximab to FOLFOX4.[45] The conclusion was made that cetuximab should be administered to patients with extended *RAS* WT tumors only if the full benefit of tailored therapy with cetuximab is to be realized.[45]

Panitumumab (Vectibix, Amgen) is a fully humanized monoclonal antibody against EGFR. The phase 3 PRIME study compared panitumumab (6 mg/kg every 2 weeks) added to FOLFOX4 (patient group 1) vs FOLFOX4 alone (patient group 2) in the first-line treatment of mCRC. A total of 1183 patients were randomized into 1 of the 2 arms. *KRAS* profiling results were available for 93% of the patients; 60% had *KRAS* WT tumors and 40% had *KRAS* mutant tumors. The effect of the addition of panitumumab to chemotherapy on mPFS differed according to tumor *KRAS* status. Thus, in patients with *KRAS* WT tumors, mPFS was longer in the panitumumab/FOLFOX4 arm than in the FOLFOX4-alone arm (9.6 vs 8.0 months, *P*=.02), whereas in patients with *KRAS* mutant tumors, mPFS was comparatively shorter in the panitumumab/FOLFOX4 arm (7.3 vs 8.8 months, *P*=.02).[46] Similarly, the addition of panitumumab to FOLFOX4 was associated with a trend toward prolonged mOS in the WT group (23.9 vs 19.7 months, *P*=.072) but shortened mOS in the mutant group (15.5 vs 19.3 months, *P*=.068). These findings are comparable with those of Bokemeyer and colleagues.[43] for cetuximab and are further supported by subsequent studies, including a

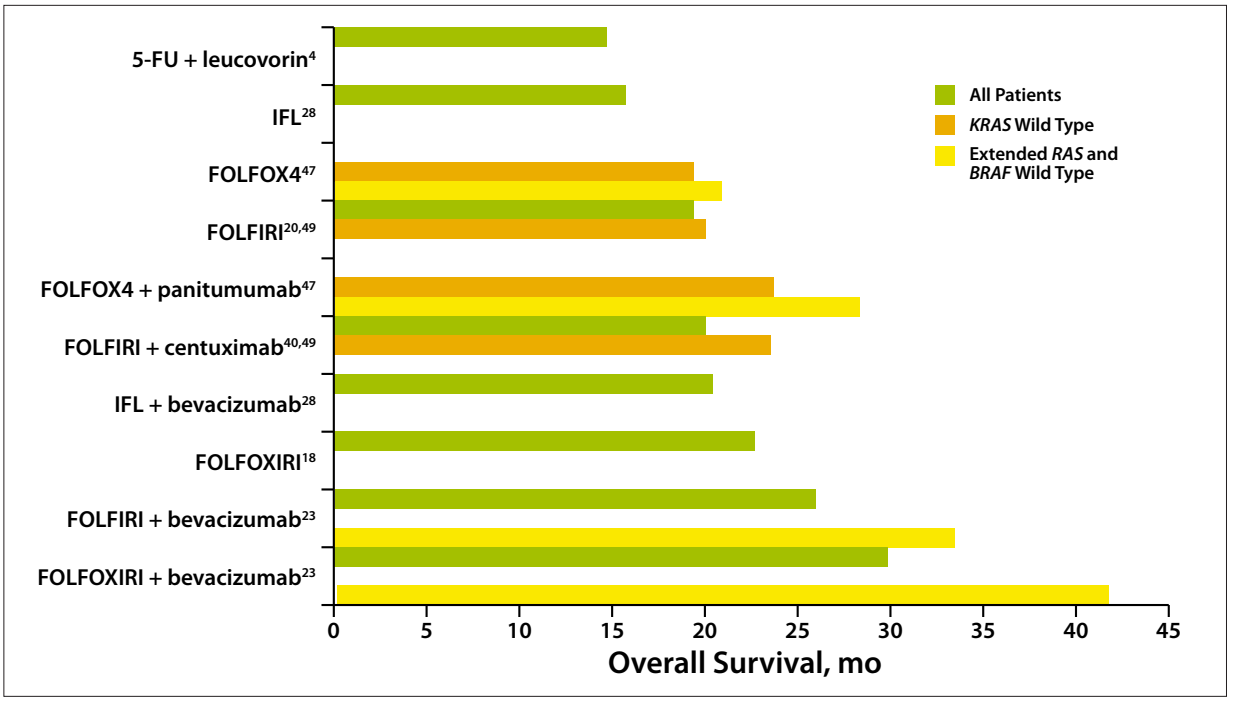

Figure 2. Overall survival of patients with metastatic colorectal cancer according to genetic predetermination and treatment choice. 5-FU, 5-fluorouracil; FOLFIRI, 5-FU/leucovorin/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; FOLFOXIRI, 5-FU/leucovorin/oxaliplatin/irinotecan; IFL, irinotecan/5-FU/leucovorin.

30-month update of the PRIME study results (Table).[38] This update indicated that treatment with anti-EGFR antibodies in general should be restricted to patients with *RAS* WT tumors (see Figure 1 for *RAS* mutation details and prevalence).[46,47] There is additional evidence to suggest that the treatment of patients with *BRAF* as well as *RAS* mutations should be avoided.[36,48,49] Approximately 10% of patients with CRC possess a mutation in BRAF, a protein kinase that acts downstream of RAS.[50,51]

Mutational analyses now frequently guide treatment decisions in the first-line management of mCRC (Figure 2). It has become obvious that EGFR inhibitors should be avoided in patients with extended *RAS* mutational status. However, oncologists now have to decide whether patients with *RAS* WT mCRC are best treated in the first-line setting with chemotherapy plus an EGFR inhibitor (cetuximab or panitumumab) or with chemotherapy plus a VEGF inhibitor (bevacizumab).

The phase 3 German Arbeitsgemeinschaft Internistische Onkologie (AIO) study, the FIRE-3 trial (FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-line Treatment of *KRAS* Wild-Type Metastatic Colorectal Cancer), was initially designed to compare the relative benefit of cetuximab or bevacizumab in combination with FOLFIRI in the front-line treatment of mCRC. Patients were initially recruited regardless of their tumor *KRAS* mutation status, but the evidence published by Bokemeyer and Van Cutsem[40,43] that cetuximab was of no benefit in patients with *KRAS* exon 2 mutations (codon 12 or 13) led to an AIO study protocol amendment; patients with these particular *KRAS* mutations were to be excluded from the study. At this decision point, a previously unplanned subgroup analysis (KRK-0306) was carried out, which demonstrated no significant difference in mPFS or in mOS between the cetuximab/FOLFIRI and bevacizumab/FOLFIRI treatment arms in a *KRAS* mutant population, providing further evidence to support the exclusion of patients with *KRAS* mutations from cetuximab therapy.[52] The multicenter FIRE-3 trial continued to compare FOLFIRI plus cetuximab (400 mg/m^2 during the first week of a 2-week cycle, then 250 mg/m^2 weekly during every 2-week cycle thereafter) with FOLFIRI plus bevacizumab (5 mg/kg during every 2-week cycle) in the first-line treatment of 592 patients with exon 2 WT mCRC. This phase 3 trial took approximately 5½ years to complete, and mPFS turned out to be similar in the 2 arms (10.0 months in the cetuximab arm vs 10.3 months in the bevacizumab arm, *P*=.55), although mOS was significantly longer in the cetuximab arm (28.7 vs 25.0 months, *P*=.017).[53] Likewise, in an extended *RAS* WT population, mPFS was similar (10.4 months in the cetuximab arm vs 10.2 months in the bevacizumab arm, *P*=.54), but mOS was markedly longer in the cetuximab arm (33.1 vs 25.6 months, *P*=.011).[53]

In the phase 3 Cancer and Leukemia Group B/Southwest Oncology Group (CALGB/SWOG) 80405 trial of

FOLFIRI or mFOLFOX6 (oncologist's choice), between November 2005 and March 2012, 3058 patients with mCRC were randomly assigned to also receive cetuximab (400 mg/m^2 during the first week and then 250 mg/m^2 weekly thereafter) or bevacizumab (5 mg/kg every 2 weeks). Upon trial initiation, the plan was to enroll patients unselected for their *KRAS* status. However, after 4 years of ever-increasing knowledge, the inclusion criteria were altered to allow only patients with *KRAS* WT tumors into the study. Patients were accrued over a period of more than 6 years and treated until progression, death, unacceptable toxicity, or curative surgery (or patient withdrawal of consent). Median follow-up was 24 months. Thus, in 2334 patients with *KRAS* WT (exon 2, codons 12 and 13) randomly assigned to receive chemotherapy plus cetuximab or chemotherapy plus bevacizumab, the mOS was found to be equivalent in the 2 treatment arms—29.93 (range, 27.56-31.21) months in the cetuximab group vs 29.04 (range, 25.66-31.21) months in the bevacizumab group (Table).[54]

Newer sequencing studies suggest that germline single-nucleotide polymorphisms in genes that regulate EGFR turnover may confer sensitivity to cetuximab.[55]

Based on the inference derived from earlier studies that simultaneously blocking VEGF and EGFR pathways might increase antitumor activity, Hecht and colleagues decided to study the effects of adding panitumumab (6 mg/kg IV every 2 weeks) to bevacizumab plus chemotherapy (oxaliplatin- or irinotecan-based) in the first-line treatment of mCRC.[56] In this phase 3B trial, 823 patients were randomly assigned 1:1 to receive oxaliplatin-containing chemotherapy/bevacizumab with or without panitumumab, and 230 patients were randomly assigned 1:1 to receive irinotecan-containing chemotherapy/bevacizumab with or without panitumumab. A preplanned interim analysis showed decreased efficacy in the patients receiving oxaliplatin together with panitumumab; therefore, panitumumab was discontinued (812 of the planned 823 patients had been treated with oxaliplatin-containing chemotherapy/bevacizumab [with or without panitumumab] at this point). In the final analysis, mPFS was 10.0 months (with panitumumab) vs 11.4 months (without panitumumab). The mOS was 19.4 months (panitumumab) vs 24.5 months (without panitumumab). Increased toxicity without evidence of improved efficacy was also observed in the panitumumab arm of the cohort receiving irinotecan-containing chemotherapy.

Skin-related toxicities were the most common grade 3 toxicities observed in the patients receiving panitumumab in both the oxaliplatin and irinotecan cohorts. Significant grade 3 or 4 toxicities in the oxaliplatin cohort (panitumumab arm vs non-panitumumab arm) were skin toxicity (36% vs 1%), diarrhea (24% vs 13%), infections (19% vs 10%), and pulmonary embolism (6% vs 4%). These toxicities were also observed in the panitumumab arm of the irinotecan cohort, along with a higher incidence of deep venous thrombosis. Approximately 19% of the patients receiving panitumumab had a panitumumab-related serious adverse event. Adverse outcomes were observed in patients in the panitumumab arm regardless of *KRAS* status.

The coadministration of cetuximab and bevacizumab with chemotherapy in the front-line setting had been anticipated, and in preparation for this, the novel BOND-2 (Molecular Predictors of Combination Targeted Therapies [Cetuximab, Bevacizumab] in Irinotecan-Refractory Colorectal Cancer) study combined cetuximab and bevacizumab with irinotecan (CBI) in patients previously treated with chemotherapy but naive to treatment with both monoclonal antibodies.[57] Results indicated that CBI treatment was favorable in comparison with historical controls (treated with cetuximab alone or cetuximab plus irinotecan), and this study paved the way for the phase 3 trial by Tol and colleagues that compared capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in the front-line setting.[58] Thus, 775 patients were randomly assigned to capecitabine (1000 mg/m^2 twice daily on days 1-14), oxaliplatin (130 mg/m^2 on day 1), and bevacizumab (7.5 mg/kg on day 1) vs the same regimen plus cetuximab (400 mg/m^2, then 250 mg/m^2 weekly) every 3 weeks. This study demonstrated that patients actually did better without cetuximab (mPFS 10.7 vs 9.4 months, P=.01; mOS 20.3 vs 19.4 months, P=.16), especially if they had a *KRAS* mutation (mPFS 12.5 vs 8.1 months, P=.003).[58]

In conclusion, it appears that combining VEGF inhibition with EGFR inhibition in first-line chemotherapy for mCRC does not provide greater benefit than treatment with either alone, regardless of the patient's *KRAS* status.

Local Therapy

Surgical Resection

Despite the presence of metastases at diagnosis, the disease of patients with mCRC and synchronous lung, liver, or other organ metastases may be resectable; in these cases, surgical resection is often performed in an attempt to render patients disease-free. This has been most widely studied in patients with synchronous liver metastases. In 2007, Reddy and colleagues first demonstrated, in a retrospective analysis of 610 patients, that the simultaneous resection of a colorectal primary and minor hepatectomy are safe and preferred when compared with staged resections.[59] The addition of perioperative chemotherapy was evaluated in the phase 3 EORTC 40983 trial, which randomly assigned 364 patients with mCRC and up to 4 liver metastases to 6 cycles of FOLFOX4 followed by surgery or to surgery alone. The mOS did not vary significantly between the groups (61.3 months in the chemotherapy-plus-surgery arm vs 54.3

months in the surgery-alone arm, *P*=.34).[60] However, mPFS was significantly longer in the chemotherapy-plus-surgery arm (20.9 vs 12.5 months, *P*=.035).

Of note, the use of perioperative cetuximab with chemotherapy in patients who had resectable liver metastases of CRC was evaluated by Primrose and colleagues in the phase 3 New EPOC study.[61] A total of 272 patients with *KRAS* exon 2 WT mCRC were randomly assigned 1:1 to receive chemotherapy with FOLFOX, XELOX, or FOLFIRI with or without cetuximab for 12 weeks before resection and for 12 weeks after surgery. The patients randomly assigned to cetuximab actually had worse outcomes; the mPFS for all chemotherapy groups was 14.1 months with added cetuximab and 20.5 months without (*P*=.03). The mOS was 39.1 months in the cetuximab arms but was not reached in the chemotherapy-alone arms (lower limit 32.0 months, *P*=.16). The study was closed prematurely because predefined futility criteria had been met. Thus, perioperative cetuximab is contraindicated in the setting of resectable liver metastases.

The clinical decision regarding the resection of an asymptomatic primary tumor in the setting of unresectable metastatic disease remains mired in controversy. To further evaluate the clinical question of whether to resect an asymptomatic primary tumor in the setting of unresectable metastatic disease, the phase 3 CAIRO4 (The Role of Surgery of the Primary Tumour in Patients With Synchronous Unresectable Metastases) study, which is ongoing, is randomizing patients with unresectable CRC metastases—and few or no symptoms—to primary tumor resection followed by systemic chemotherapy (fluoropyrimidine-based plus bevacizumab, local oncologist's preference) or systemic chemotherapy alone.[62] It is anticipated that results from this study will help alleviate some of the controversy.

The selection of adjuvant therapy after complete resection of a primary tumor and liver resection is also frequently debated. In their phase 3 study, Ychou and colleagues randomly assigned 321 patients who had just undergone R0 resection to 12 cycles of infusional 5-FU with leucovorin or FOLFIRI. The primary endpoint was disease-free survival, which was similar in the 2 groups (21.6 months for 5-FU/leucovorin vs 24.7 months for FOLFIRI, *P*=0.47, mOS not reached).[63] Based on these data, adjuvant FOLFIRI does not improve survival following the resection of liver metastases. The ongoing EORTC BOS2 (Efficacy of FOLFOX Alone, FOLFOX Plus Bevacizumab and FOLFOX Plus Panitumumab in Patients With Resectable Liver Metastases) study will evaluate the preferred perioperative chemotherapy regimen in this setting, randomly assigning patients with *KRAS* WT tumors 1:1:1 to mFOLFOX6, mFOLFOX6 plus bevacizumab, or mFOLFOX6 plus panitumumab for 6 cycles before and 6 cycles after surgery (NCT01508000).

Transarterial Radioembolization

Transarterial radioembolization (TARE) with yttrium 90 (^{90}Y) microspheres is a burgeoning therapeutic option for patients with mCRC and significant liver metastases. The phase 3 SIRFLOX (FOLFOX Plus SIR-SPHERES Microspheres Versus FOLFOX Alone in Patients With Liver Metastases From Primary Colorectal Cancer) trial randomly assigned 530 patients with unresectable liver-only or liver-dominant metastases to mFOLFOX6 with or without bevacizumab or to mFOLFOX6 with or without bevacizumab plus ^{90}Y TARE,[64] once with cycle 1. Interim analyses showed no improvement in mPFS (10.2 vs 10.7 months with added TARE, *P*=.428) but did show prolonged liver mPFS (12.6 vs 20.5 months, *P*=.002) and a higher hepatic response rate (68.8% vs 78.7%, *P*=.042). The OS rate was 68.0% without TARE vs 76.4% with TARE (*P*=.113). With regard to safety, grade 3 or higher adverse events occurred in 73.4% vs 85.4% of patients. The most common toxicities in both groups were hematologic and gastrointestinal. The principal investigator stated that "the addition of SIRT, using ^{90}Y resin microspheres, to FOLFOX-based first-line chemotherapy in patients with liver-dominant metastases did not improve overall progression-free survival."[64] Final results from the SIRFLOX trial are pending.

New Directions

Additional strategies that remain unapproved are showing promise in the treatment of mCRC. These include BRAF-, human epidermal growth factor receptor 2 (HER2)-, and immune-related therapies.

BRAF

BRAF is a protein kinase downstream of RAS in the RAS/RAF/MEK/ERK kinase pathway. Mutations in *BRAF* are present in approximately 7% to 10% of patients with mCRC.[65,66] Assessing *BRAF* mutation status has the potential to be an important task before EGFR-directed therapy is initiated. The presence of the predominant *BRAF* mutation—*BRAF* V600E—was shown to decrease tumor cell response to cetuximab and panitumumab, although this inhibition could be counteracted by the addition of BRAF inhibitors, thereby restoring anti-EGFR activity.[48] Vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) is an experimental BRAF inhibitor. In a recently published phase 2 trial, single-agent vemurafenib was found to be clinically ineffective in 21 pretreated patients with *BRAF* V600E mCRC.[67] However, it is believed that a combined-modality EGFR/BRAF therapy should be further evaluated in the small but significant group of patients with *BRAF* mutant mCRC.[48] Next-generation sequencing platforms will enable treating oncologists to

access information regarding *BRAF* mutations and other, less common mutations, which might reveal other novel drug targets.

BRAF mutations have other implications. An update of the TRIBE study—in which 508 patients with mCRC were enrolled over approximately 3 years and randomly assigned to receive FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab—reported that at a median follow-up time of 48.1 months, mOS was 37.1 months in the *RAS* and *BRAF* WT subgroups, compared with 25.6 months in the subgroup assessed as *RAS* mutant and 13.4 months in the subgroup assessed as *BRAF* mutant.[23] The *BRAF* mutation was thus shown to be associated with significantly shorter OS (HR, 2.24; 95% CI, 1.32-3.81; *P*=.003) and PFS (HR, 1.88; 95% CI, 1.14-3.09; *P*=.013). No significant effect of *RAS* mutation status on survival was noted. The PRIME study also noted a relatively poor mOS (9-10 months) for patients with mCRC that was *BRAF* mutant, regardless of treatment provided.

When all these data are considered, it may be concluded that the *BRAF* mutational status confers a poor prognosis, regardless of the chemotherapy regimen used. Thus, until there is an alternative, all stops should be pulled out and the full FOLFOXIRI regimen given to patients with tumors that are *BRAF* mutant, or they should be encouraged to enroll in a clinical trial.

HER2

HER2, like EGFR, is a member of the ERBB family of tyrosine kinase receptors. However, it is the only member whose extracellular domain is capable of assuming a stable, pseudo-ligand activated conformation, which allows it to dimerize regardless of the presence of ligand; dimerization is induced by overexpression or mutation.[68,69] Once HER2 is dimerized and activated, its receptor signal transduction cascade causes cell proliferation, which occurs through the RAS/MAPK pathway.[70] Trastuzumab (Herceptin, Genentech) is a humanized monoclonal antibody consisting of 2 antigen-specific sites that bind to the extracellular domain of HER2 and prevent the activation of its pathway.[71]

Breast and gastric cancers overexpress HER2 (gene amplification), and these HER2-positive cancers are sensitive to trastuzumab.[72] Trastuzumab currently is clinically approved as single and combination therapy in all lines of breast cancer treatment, as long as the cancer overexpresses HER2 and the patient has no cardiac complications.[73] HER2 appears to be overexpressed in 5% of mCRCs that are *KRAS* WT (in exon 2). In a small study by Siena and colleagues,[74] trastuzumab and lapatinib (Tykerb, Novartis), which is a dual inhibitor of HER2 and EGFR, were administered to patients with disease resistant to standard therapies. This study demonstrated an objective response rate of 35% (the primary endpoint) and suggests that dual anti-HER2 therapies warrant further evaluation, possibly in the first-line treatment of mCRC.

Microsatellite Instability and Immunotherapy

The American Gastroenterological Association and the National Comprehensive Cancer Network (NCCN) recommend that all patients with mCRC be tested for microsatellite instability (MSI).[75,76] This testing can identify potential cases of Lynch syndrome. It also can identify patients with MSI-high tumors, who may benefit from immunotherapy approaches.

Immunotherapy holds significant promise throughout the oncology landscape, yet gastrointestinal malignancies have been slow to benefit from the advent of this novel form of therapy. CRC is thought to be less immunogenic than metastatic melanoma, renal cell carcinoma, or squamous cell lung carcinoma, and its lower average mutational burden is thought to confer lower response rates to checkpoint inhibitors. A higher level of infiltrating T lymphocytes is shown to be a positive prognostic factor in mCRC.[77] Le and colleagues hypothesized that patients with MSI-high (mismatch repair [MMR]–deficient) CRC might benefit from checkpoint inhibitors, given the higher mutational burden of these tumors through impaired DNA repair mechanisms. In a phase 2 study of patients with pretreated mCRC, 18 patients with MMR-proficient (MSI-low) mCRC and 9 patients with MMR-deficient (MSI-high) mCRC were treated with pembrolizumab (Keytruda, Merck). Pembrolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) kappa antibody against the programmed death 1 (PD-1) receptor that blocks the interaction of this receptor with ligands PD-L1 and PD-L2. This suppressive action results in a cytotoxic response; it allows the release of T cells against tumor cells, which causes tumor cell death. The mPFS of patients with MMR-proficient cancers was only 2.2 months, the mOS was 5.0 months, and no objective responses were observed. Stable disease was observed in only 11% of patients. However, the median survival endpoints for patients with MMR-deficient/MSI-high cancers were much longer (many had still not been reached by the end of the study); 40% of patients had a partial response, and 50% had stable disease at 12 weeks.[78] Although immunotherapy does not currently hold a place in the front-line treatment of mCRC, it holds promise for future effectiveness.

Conclusion

The first-line treatment of mCRC remains something of a conundrum, and we have not definitively answered all of the questions that have been raised in this review. It is still unclear why *BRAF* mutations confer worse outcomes and how to deal with this issue satisfactorily; why some *RAS* mutations may not necessarily lead to a bad prognosis;

and whether asymptomatic primary tumors in the setting of unresectable metastatic disease should be resected or merely managed with systemic therapy. It is certainly clear that a paradigm shift is occurring from the practice of one-size-fits-all therapy to that of individually tailored therapy. Many promising treatments for mCRC are on the horizon, and this malignancy is beginning to look less like a chronic illness and more like a curable disease.

Large comparative trials are necessary and, as speed is of primary importance, global multicenter trials are key. Strides in molecular profiling are being taken, but the learning curve is steep. Based on next-generation sequencing analyses, it is evident that mCRC is not one but many diseases with different molecular drivers and different mechanisms of resistance. The identification of genetic mutations and phenotypic differences and their significance is crucial to our understanding of mCRC.

To summarize, tremendous advances have been made in the treatment of mCRC in recent years, yet there is still a long way to go to make significant improvements in the treatment of this devastating disease. Advances in chemotherapy, biologic therapy, and liver-directed therapy, as well as (more importantly) a better understanding of the genetic drivers of CRC, have added many weapons to oncologists' arsenal that can be used against mCRC. The burgeoning fields of precision medicine and immunotherapy are in the vanguard and hold much future promise in the treatment of mCRC.

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