Options for Second-Line Treatment in Metastatic Colorectal Cancer

James J. Lee, MD, PhD, and Weijing Sun, MD

The authors are affiliated with the Division of Hematology/Oncology in the Department of Medicine at the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania. Dr Lee is an assistant professor of medicine and Dr Sun is a professor of medicine, director of the GI Cancers Section of Hematology-Oncology, and codirector of the University of Pittsburgh Medical Center GI Cancer Center of Excellence.

Corresponding author:
Weijing Sun, MD
Professor of Medicine
University of Pittsburgh
UPMC Cancer Pavilion
5150 Centre Avenue, Fifth Floor
Pittsburgh, PA 15232
Tel: (412) 864-7764
Fax: (412) 648-6579
E-mail: sunw@upmc.edu

Abstract: Colorectal cancer (CRC) remains a major public health problem in the United States and worldwide. The majority of patients who have CRC eventually present with metastatic disease. The overall therapeutic goals for most patients with metastatic CRC (mCRC) are to control the disease, prolong life span, and maximize quality of life. Therefore, the ratio of efficacy to toxicity is one of the most important factors in choosing among treatment options and sequencing regimens. In addition, the choice of first-line systemic therapy will affect the options for second-line treatment. Several newer cytotoxic agents for the treatment of mCRC have been approved during the past 2 decades by the US Food and Drug Administration (FDA), including irinotecan, oxaliplatin, and capecitabine. The combination of a fluoropyrimidine (5-fluorouracil or capecitabine) with either oxaliplatin or irinotecan has been widely accepted as standard cytotoxic chemotherapy for either the first- or second-line treatment of mCRC. The FDA has approved several pathway-targeting agents for the treatment of mCRC; these include agents that target the vascular endothelial growth factor receptor pathway (bevacizumab, ziv-aflibercept, and ramucirumab) and those that target the epidermal growth factor receptor pathway (cetuximab and panitumumab). Here, we review the current clinical options for the second-line treatment of mCRC and the rationales for their use.

Introduction

Colorectal cancer (CRC) remains a major public health problem in the United States, with an estimated 133,000 new cases[1] in 2015. In about 20% of patients, newly diagnosed CRC is metastatic at the time of initial presentation, and more than 50% of patients with early-stage CRC at initial diagnosis eventually develop metastatic disease. Despite significant progress in the treatment of metastatic CRC (mCRC) during the past 2 decades, the prognosis of patients

with mCRC remains disappointing. Systemic chemotherapy continues to be the main treatment modality for patients with mCRC.

Considerable advances in the treatment of mCRC have been made since the mid-1990s. The US Food and Drug Administration (FDA) has approved several cytotoxic agents and targeted agents for mCRC, including irinotecan, oxaliplatin, and capecitabine (S-1 has been approved in Japan and several other countries, but not in the United States). The combination of a fluoropyrimidine (5-fluorouracil [5-FU] or oral capecitabine) with either oxaliplatin or irinotecan has been widely accepted as standard cytotoxic chemotherapy for mCRC, as either first- or second-line therapy.[2-6] These regimens consist of folinic acid/5-FU/oxaliplatin (FOLFOX), capecitabine/oxaliplatin (XELOX), folinic acid/5-FU/irinotecan (FOLFIRI), and capecitabine/irinotecan (XELIRI). More recently, in September of 2015, the FDA approved a combination of trifluridine and tipiracil (Lonsurf, Taiho Oncology) for use in refractory mCRC.

Two major growth factor pathways have been targeted in mCRC: the vascular endothelial growth factor receptor (VEGFR) pathway and the epidermal growth factor receptor (EGFR) pathway, and several agents targeting these pathways have been approved for the treatment of mCRC. Bevacizumab (Avastin, Genentech), an anti-VEGF antibody, was approved in 2004, as was cetuximab (Erbitux, Lilly), a chimeric anti-EGFR antibody. In 2006, panitumumab (Vectibix, Amgen), a fully human anti-EGFR antibody, was approved for the treatment of chemotherapy-refractory mCRC. In 2012, ziv-aflibercept (Zaltrap, Sanofi/Regeneron), an anti-VEGF recombinant fusion protein, and regorafenib (Stivarga, Bayer Health-Care), a multikinase small-molecule inhibitor, were approved in the second- and third-line settings, respectively.[7] Most recently, in 2015, ramucirumab (Cyramza, Lilly)—a human monoclonal antibody targeting the extracellular domain of VEGFR-2—was approved for the second-line treatment of mCRC.

Because the treatment goals for most patients with metastatic disease are to control the disease, prolong life span, and maintain quality of life, rather than to cure, the ratio of efficacy to toxicity is the most important factor in choosing and sequencing systemic chemotherapy regimens. Second-line treatment options for patients with mCRC will be based on the treatment received in the first-line setting, or on previous adjuvant treatment in some patients. In the current practice setting, most patients with mCRC who have received a fluoropyrimidine-based combination regimen with either oxaliplatin (FOLFOX/XELOX) or irinotecan (FOLFIRI/XELIRI; XELIRI is used less commonly in clinical practice because of its toxicity profile) as first-line treatment will have

the other regimen as second-line treatment. However, because of new developments in antiangiogenic and anti-EGFR therapy for mCRC, combined with the concept of maintenance therapy as part of first-line treatment, there may be a need to discuss other options for second-line treatment. Herein, we review current clinical recommendations for the second-line treatment of mCRC.

Cytotoxic Chemotherapy

The choice of chemotherapy regimen in the second-line treatment of mCRC depends on the systemic therapies previously administered in the first-line setting. Most of the patients with mCRC receive combination chemotherapy consisting of a fluoropyrimidine (5-FU or oral capecitabine) plus oxaliplatin (FOLFOX/XELOX) or irinotecan (FOLFIRI/XELIRI) as either first- or second-line therapy. Based on the choice for first-line therapy, the other option generally will be accepted as second-line therapy.[2] However, a chronological review of the development of these drugs may help to increase our understanding of the principles and rationale underlying our choice when we treat our patients.

Irinotecan
In 1996, Rothenberg and colleagues reported the results of a phase 2 trial that evaluated irinotecan in patients who had mCRC with disease recurrence or progression on 5-FU therapy in the first-line setting.[8] A total of 48 patients received irinotecan at a dosage of 125 to 150 mg/m^2 intravenously (IV) weekly for 4 weeks, followed by a 2-week rest. The overall response rate (ORR) was 23%, median progression-free survival (PFS) was 6 months, and median overall survival (OS) was 10.4 months. Grade 4 diarrhea was most the common severe toxicity, affecting 44% of participants at the 150-mg/m^2 dose and 23% of participants at the 125-mg/m^2 dose.

In a later study, Cunningham and colleagues evaluated the role of irinotecan in 189 patients whose disease had progressed within 6 months of 5-FU therapy. Patients were randomly assigned in a ratio of 2:1 either to irinotecan (300-350 mg/m^2 once every 3 weeks) plus best supportive care or to best supportive care alone.[9] There was a significant OS benefit with irinotecan (median OS, 9.2 vs 6.2 months; P=.0001).

In another study, Rougier and colleagues randomly assigned patients who did not respond to 5-FU therapy in the first-line setting either to irinotecan (300-350 mg/m^2 once every 3 weeks, 133 patients) or to a continuous infusion of 5-FU (134 patients).[10] OS was significantly better in the irinotecan arm than in the 5-FU arm (median OS, 10.8 vs 8.5 months; P=.035). Median PFS also was better in the irinotecan arm (4.2 vs 2.9 months; P=.030).

These results spurred the further evaluation of irinotecan in combination with a different type of fluoropyrimidine infusion in patients with mCRC. In DA VINCI (DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA;BAY86-5321)]), patients with mCRC who had progressed on fluoropyrimidine chemotherapy were randomly assigned either to FOLFIRI (irinotecan 180 mg/m² IV on day 1, bolus 5-FU 400 mg/m² IV followed by a 46-hour continuous infusion of 5-FU 2400 mg/m² on days 1-2, and bolus folinic acid 20 mg/m² IV on day 1, every 2 weeks; 44 patients) or to irinotecan alone (350 mg/m² IV every 3 weeks, 45 patients).[11] There was no significant difference between the groups in overall quality of life, ORR, PFS, or OS.

FIRIS was a randomized phase 2/3 study to compare IRIS (irinotecan 125 mg/m² on days 1 and 15, S-1 40-60 mg [according to body surface area] twice daily for 2 weeks, every 4 weeks) with FOLFIRI (folinic acid 200 mg/m², irinotecan 150 mg/m², bolus 5-FU 400 mg/m² on day 1 followed by a continuous infusion of 5-FU 2400 mg/m² over 46 hours, every 2 weeks) as second-line therapy for mCRC in 426 Japanese patients.[12] The primary endpoint was PFS, with a noninferiority margin of 1.333. Approximately 60% of the enrolled patients received oxaliplatin-based therapy in the first-line setting. The median PFS was 5.1 months in the FOLFIRI arm and 5.8 months in the IRIS arm (hazard ratio [HR], 1.077 [95% CI, 0.879-1.319]; noninferiority test, P=.039). Grade 3/4 neutropenia was significantly higher in the FOLFIRI arm (52.1% vs 36.2%; P=.0012), whereas severe diarrhea was significantly higher in the IRIS arm (4.7% vs 20.5%; P<.0001). PFS with IRIS was not inferior to that with FOLFIRI in the patients undergoing second-line chemotherapy for mCRC. Because S-1 is not approved in the United States, this study result may not be relevant to current practice in this country. However, it supports the concept of the combination of a fluoropyrimidine plus irinotecan.

Oxaliplatin

At the time that irinotecan was being evaluated in clinical studies, oxaliplatin was being analyzed as well. Machover and colleagues reported a phase 2 study of oxaliplatin monotherapy in the second-line setting in 1996. A total of 106 patients with mCRC that had progressed on treatment containing 5-FU received oxaliplatin 130 mg/m² every 21 days.[13] The ORR was 10%. Peripheral neuropathy was the most common severe toxicity, with 23% of patients experiencing grade 3 peripheral neuropathy and 8% of patients experiencing grade 4.

De Gramont and colleagues evaluated the activity of oxaliplatin in combination with infusional 5-FU in the second-line setting.[14] A total of 46 patients with mCRC that had progressed with 5-FU plus leucovorin (LV) or

relapsed less than 6 months after the end of adjuvant therapy received FOLFOX2 (oxaliplatin 100 mg/m² on day 1, LV 500 mg/m² followed by a 24-hour infusion of 5-FU 1500-2000 mg/m² for 2 consecutive days) every 2 weeks. The ORR was 46%, median PFS was 7 months, and median OS was 17 months.

Andre and colleagues evaluated the efficacy of FOLFOX3 and FOLFOX4 in the second-line setting.[15] A total of 100 patients with mCRC that had progressed with 5-FU chemotherapy in the first-line setting received FOLFOX3 (oxaliplatin 85 mg/m² on day 1, LV 500 mg/m², and a continuous infusion of 5-FU 1500-2000 mg/m² over 22 hours, days 1-2, every 2 weeks) or FOLFOX4 (oxaliplatin 85 mg/m² on day 1, LV 200 mg/m², bolus 5-FU 400 mg/m², and a continuous infusion of 5-FU 600 mg/m² over 22 hours, days 1-2, every 2 weeks [LV5FU2]). The ORR was 18.4% for FOLFOX3 and 23.5% for FOLFOX4. Median PFS was 4.6 months for FOLFOX3 and 5.1 months for FOLFOX4. Median OS was 10.6 months for FOLFOX3 and 11.1 months for FOLFOX4. Grade 3/4 toxicities were peripheral neuropathy in 20.6% of patients and neutropenia in 27.8%.

In a phase 2 study, Maindrault-Goebel and colleagues investigated the efficacy and safety of FOLFOX6 in the second-line treatment of mCRC.[16] A total of 60 patients with mCRC that had progressed on a bimonthly regimen of LV plus infusional 5-FU received FOLFOX6 (oxaliplatin 100 mg/m² in combination with LV 400 mg/m² on day 1, followed by bolus 5-FU 400 mg/m² and a 46-hour infusion of 5-FU 2400-3000 mg/m²) every 2 weeks. ORR was 27%, median PFS was 5.3 months, and median OS was 10.8 months. Grade 3/4 toxicities were peripheral neuropathy in 16% of patients, nausea in 7%, diarrhea in 7%, mucositis in 5%, neutropenia in 24%, and thrombocytopenia in 2%. Of special interest, the regimen of FOLFOX7 (oxaliplatin 130 mg/m², LV 400 mg/m² on day 1, followed by bolus 5-FU 400 mg/m² and a 46-hour infusion of 5-FU 2400 mg/m² every 2 weeks) was evaluated as well. The ORR with this regimen was 42%, the median PFS was 6 months, and the median OS was 16.1 months. Grade 3/4 toxicities were peripheral neuropathy in 15% of patients, nausea in 8%, diarrhea in 11%, neutropenia in 9%, and thrombocytopenia in 11%.[17] This series of FOLFOX regimens showed consistently high ORRs (>40%) in the second-line treatment of mCRC that had progressed on 5-FU/LV therapy.

The combination of oxaliplatin with different forms of fluoropyrimidine has also been studied. Pfeiffer and colleagues reported a phase 2 study of XELOX (capecitabine 1000 mg/m² orally twice daily on days 1-14 and oxaliplatin 130 mg/m² on day 1) in 70 patients with mCRC that had progressed after irinotecan as the first-line treatment.[18] The ORR was 17%, the median time to

progression (TTP) was 5.4 months, and the median OS was 9.5 months. Grade 3/4 toxicities were neurotoxicity in 6% of patients, nausea/vomiting in 9%, diarrhea in 14%, and hand-foot syndrome in 8%.

Rothenberg and colleagues reported a pivotal phase 3 trial in which 463 patients with mCRC that had progressed on or relapsed within 6 months of first-line therapy with irinotecan, bolus 5-FU, and LV (IFL) were randomly assigned to (1) bolus and infusional 5-FU and LV (LV5FU2), (2) single-agent oxaliplatin, or (3) the combination (FOLFOX4).[19] FOLFOX4 proved to be superior to LV5FU2 and oxaliplatin monotherapy in terms of ORR (9.9% for FOLFOX4 vs 1.3% for oxaliplatin monotherapy vs 0% for LV5FU2 [FOLFOX4 vs LV5FU2: Fisher's exact test, $P<.0001$]). Median TTP was 4.6 months for FOLFOX4 vs 2.7 months for LV5FU2 vs 1.6 months for oxaliplatin monotherapy (FOLFOX4 vs LV5FU2: 2-sided, stratified log rank test, $P<.0001$). These data led to the FDA approval of oxaliplatin in combination with LV5FU2 as second-line therapy for mCRC in the United States.

The combination of irinotecan and oxaliplatin also was tested. Haller and colleagues reported a randomized phase 3 trial comparing oxaliplatin plus irinotecan with irinotecan alone in the second-line therapy of mCRC.[20] Patients with mCRC that had progressed or recurred during or after adjuvant or first-line fluoropyrimidine therapy (5-FU/LV or capecitabine) were randomly assigned to either irinotecan 200 mg/m^2 plus oxaliplatin 85 mg/m^2 every 3 weeks (IROX) or irinotecan 350 mg/m^2 alone every 3 weeks. There was a significant improvement in median OS in the IROX arm compared with the irinotecan-alone arm (13.4 vs 11.1 months; HR, 0.78 [95% CI, 0.65-0.94]; $P=.0072$). Also better in the IROX arm were ORR (22% vs 7%; $P<.0001$), median TTP (5.3 vs 2.8 months; $P<.0001$), and tumor-related symptoms (32% vs 19%; $P=.0072$). As well, the rates of grade 3/4 toxicities were higher in IROX arm than in the irinotecan-alone arm; these included neutropenia (25% vs 13%), diarrhea (28% vs 23%), and sensory neuropathy (5% vs 0%). Because of its toxicity profile, IROX is not commonly used in general practice.

FOLFIRI vs FOLFOX: The GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) Study

Debates over the choice between FOLFOX vs FOL-FIRI, as well as the sequencing of these regimens, have occurred because of limited data, a lack of head-to-head trials, different toxicity profiles, and the personal preferences of oncologists. Therefore, Tournigand and colleagues conducted a randomized phase 3 trial to examine 2 sequences of the combination chemotherapies in the first- and second-line settings.[2] Patients with

chemotherapy-naive mCRC were randomly assigned either to FOLFIRI followed by FOLFOX6 at the time of tumor progression, or to the reverse sequence of FOLFOX6 as first-line therapy followed by FOLFIRI as second-line therapy. Importantly, there was no significant difference in OS (median OS, 20.4 vs 21.5 months) between the 2 study arms. In terms of safety profile, both treatments were well tolerated. Based on this study, there does not appear to be an optimal combination regimen sequence because the OS rates were virtually identical in the 2 treatment arms. The study also demonstrated that patients should receive all 3 different classes of cytotoxic agents (fluoropyrimidine, oxaliplatin, and irinotecan) if possible to achieve the best outcome.

Antiangiogenic Therapy

The VEGF family of ligands and receptors is one of the best-characterized pathways for its role in pathological angiogenesis in CRC. VEGF-A and its structurally related VEGF ligands (VEGF-B, VEGF-C, VEGF-D, and placental growth factor) mediate biological effects through different cellular receptors: VEGFR-1, VEGFR-2, and VEGFR-3. The FDA has approved 3 monoclonal antibodies targeting VEGF-VEGFR interaction for the second-line treatment of mCRC.

Bevacizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against VEGF-A. It binds all isoforms of VEGF-A and blocks the subsequent binding of VEGF-A to its cognate receptors, thereby inhibiting its biological activity.[21,22] Ziv-aflibercept is a soluble decoy receptor molecule composed of the critical ligand-binding domains of human VEGFR-1 and VEGFR-2 fused with the Fc portion of IgG, binding VEGF-A, VEGF-B, and placental growth factor.[23,24] Ramucirumab is a humanized IgG1 monoclonal antibody targeting the extracellular domain of VEGFR-2. Ramucirumab blocks the binding of multiple VEGF ligands to VEGFR-2, inhibiting the VEGFR-2 signaling pathway.

There are 4 key clinical trials that provide support for the current use of antiangiogenic agents in the second-line setting. E3200 was a randomized study conducted by the Eastern Cooperative Oncology Group (ECOG) that investigated bevacizumab in combination with FOLFOX4 in patients with mCRC that had progressed on initial irinotecan-based chemotherapy in the first-line setting.[25] ML18147 investigated the use of bevacizumab in the second-line setting in patients whose disease had progressed on a previous bevacizumab-containing regimen.[26] VELOUR (Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen) was the registration

trial to examine ziv-aflibercept in combination with FOL-FIRI in patients whose disease had failed to respond to a prior oxaliplatin-containing regimen in the first-line setting.[27] Lastly, RAISE (A Study in Second Line Metastatic Colorectal Cancer) was the registration trial to evaluate ramucirumab in combination with FOLFIRI in patients with mCRC and disease progression during or within 6 months after the last dose of first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.[28]

E3200

E3200 was a pivotal randomized phase 3 clinical trial that formed the basis for the FDA approval of bevacizumab in the second-line setting. Patients with mCRC and tumor progression on a fluoropyrimidine/irinotecan-based regimen, but no prior bevacizumab exposure, were randomly assigned either to bevacizumab (10 mg/kg every 2 weeks) plus FOLFOX4 or to FOLFOX4 alone.[25] In the bevacizumab/FOLFOX4 arm, there was a significant improvement in OS (median OS, 12.9 vs 10.8 months; P=.0011), PFS (median PFS, 7.3 vs 4.7 months; P<.0001), and ORR (22.7% vs 8.6%; P<.0001).[25] Grade 3/4 toxicities, including peripheral neuropathy, hypertension, bleeding, and vomiting, were somewhat more frequent in the FOLFOX/bevacizumab arm. The study was not designed to address whether bevacizumab could be continued beyond first progression for patients who had received bevacizumab in the first-line setting.

ML18147

The observational BriTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety)[29] and ARIES[30] (The Avastin Registry—Investigation of Effectiveness and Safety) studies suggested that the continuation of bevacizumab in patients with mCRC beyond disease progression while they were on bevacizumab-containing chemotherapy in the first line was beneficial in terms of survival. ML18147 was designed in an effort to confirm this observation. This was an open-label, multicenter, phase 3 trial that evaluated the continued use of bevacizumab as second-line therapy in patients with mCRC that had progressed after a first-line bevacizumab-containing regimen.[26] Patients with mCRC progressing up to 3 months after they had discontinued first-line chemotherapy with bevacizumab were randomly assigned (1:1) either to second-line chemotherapy alone (411 patients) or to chemotherapy plus bevacizumab (409 patients). The choice of oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen. The primary endpoint was OS. The continuation of bevacizumab in the second-line treatment improved OS (median OS, 11.2 vs 9.8 months; HR, 0.81 [95% CI, 0.69-0.94]; unstratified log rank test, P=.0062). Toxicities

of grade 3 or higher were slightly more frequent in the bevacizumab-plus-chemotherapy arm: hemorrhage (2% vs <1%), gastrointestinal perforation (2% vs <1%), and venous thromboembolism (5% vs 3%). In an exploratory subgroup analysis, a benefit of bevacizumab in terms of PFS was also observed irrespective of *KRAS* mutation status (for wild-type *KRAS*: HR, 0.61; P<.0001; for mutant *KRAS*: HR, 0.70; P=.003).[26] The findings demonstrated that continuation of the antiangiogenic agent bevacizumab with an accompanying change in the cytotoxic chemotherapy backbone after disease progression conferred clinical benefit in terms of OS and PFS.

VELOUR

VELOUR was a randomized, double-blind, phase 3 study to evaluate the efficacy and safety of FOLFIRI plus ziv-aflibercept in the second-line treatment of patients with mCRC after disease progression or the completion of treatment with an oxaliplatin-based regimen.[27] Patients were randomly assigned either to FOLFIRI plus ziv-aflibercept (612 patients) or to FOLFIRI plus placebo (614 patients). The primary endpoint was OS. Significant improvements were observed for FOLFIRI plus ziv-aflibercept compared with FOLFIRI plus placebo in OS (median OS, 13.50 vs 12.06 months; HR, 0.817 [95% CI, 0.713-0.937]; P=.0032), PFS (median PFS, 6.90 vs 4.67 months; HR, 0.758 [95% CI, 0.661-0.869]; P<.0001), and ORR (19.8% vs 11.1%; P=.0001). Patients who received FOLFIRI plus ziv-aflibercept experienced the characteristic toxicities of anti-VEGF agents and an increased incidence of some chemotherapy-related toxicities. A prespecified subgroup analysis of patients previously treated with bevacizumab showed that median OS was 12.5 months in the arm given FOLFIRI plus ziv-aflibercept (186 patients) and 11.7 months in the arm given FOLFIRI plus placebo (187 patients).[31] Median OS in patients without prior exposure to bevacizumab was 13.9 months in the arm given FOLFIRI plus ziv-aflibercept (426 patients) and 12.4 months in the arm given FOLFIRI plus placebo (427 patients).

About 10% of patients enrolled in VELOUR had a history of cancer recurrence during or within 6 months after completing oxaliplatin-based adjuvant therapy (adjuvant fast relapsers). A better-efficacy subgroup was identified in a VELOUR post hoc multivariate analysis. This subgroup consisted of fast relapsers after adjuvant therapy with an ECOG performance status (PS) of 0 or a PS of 1 with fewer than 2 metastatic sites. Increased benefits were seen in this subgroup, with median OS of 16.2 vs 13.1 months (adjusted HR, 0.73 [95% CI, 0.61-0.86]), median PFS of 7.2 vs 4.8 months (adjusted HR, 0.68 [95% CI, 0.57-0.80]), and ORR of 24% vs 11%. In the poor-efficacy subgroup, no benefit was seen with the addition of ziv-aflibercept.[32]

RAISE

RAISE was a multicenter, randomized, double-blind phase 3 trial to evaluate the efficacy and safety of ramucirumab in combination with FOLFIRI chemotherapy in the second-line treatment of patients with mCRC who had disease progression during or within 6 months after the last dose of first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.[28] A total of 1072 patients were randomly assigned (1:1) either to FOLFIRI plus ramucirumab (536 patients) or to FOLFIRI alone (536 patients). The results showed a significant improvement of OS with the combination of FOLFIRI plus ramucirumab (median OS, 13.3 vs 11.7 months; HR, 0.844 [95% CI, 0.730-0.976]; log rank test, *P*=.0219). This survival benefit was consistent across all subgroups of the study patients in the FOLFIRI-plus-ramucirumab arm. Grade 3/4 toxicities were reported more frequently in the FOLFIRI-plus-ramucirumab arm: severe neutropenia (38% vs 23%) and hypertension (11% vs 3%). Severe diarrhea (11% vs 10%) and fatigue (12% vs 8%) were seen in more than 5% of the patients in both arms.

It is interesting to note that the 3 trials based on the use of anti-VEGF agents as second-line treatment of mCRC found similar improvements in OS (ML18147, 1.4 months; VELOUR, 1.4 months; RAISE, 1.6 months) and PFS (ML18147, 1.7 months; VELOUR, 2.2 months; RAISE, 1.2 months). The stratified HRs for OS also were quite similar (ML18147, 0.83; VELOUR, 0.82; RAISE, 0.84). Moreover, the toxicity profiles of these agents overlapped, with a higher incidence of anti-VEGF–associated adverse events (eg, hemorrhage, hypertension, and proteinuria) in the antiangiogenesis agent arms, as was expected.

However, some differences among these trials need to be pointed out. First, in VELOUR and RAISE, all patients received a regimen based on oxaliplatin and a fluoropyrimidine as first-line treatment. Approximately 60% of patients in ML18147 received irinotecan-based therapy, and the remaining 40% received an oxaliplatin-based regimen as first-line therapy. Second, all patients in ML18147 and RAISE had received previous treatment with bevacizumab, whereas only 30% of patients in VELOUR had received such previous treatment. The anti-VEGF agents used in these trials also differed with respect to their mechanisms of action and pharmacokinetic properties. Despite these differences, data from the 3 trials provide confirmatory evidence that the inhibition of tumor angiogenesis beyond initial disease progression after first-line treatment is an effective treatment strategy in mCRC. However, what we do not know is whether cross-resistances exist between these agents, or whether combinations of these different agents may improve the efficacy of antiangiogenesis.

Anti-EGFR Therapy

The EGFR signaling pathway is one of the key growth factor signaling pathways in the progression of CRC. Cetuximab and panitumumab are monoclonal antibodies approved by the FDA for the treatment of mCRC. Cetuximab is a chimeric IgG1 monoclonal antibody targeting the external cell surface domain of EGFR. It competitively inhibits binding of the natural ligands to EGFR, thereby blocking downstream growth factor pathway signaling. Panitumumab is a fully human IgG2 monoclonal antibody that binds with high affinity to EGFR and inhibits EGFR downstream signaling. Several clinical trials have evaluated the role of anti-EGFR antibodies in the second-line therapy of mCRC. One critical point should be emphasized: that some of the earlier studies were performed before the identification of *RAS* mutations as negative predictive markers for anti-EGFR monoclonal antibody therapy in patients with mCRC.

Cetuximab Plus Irinotecan

EPIC (Erbitux Plus Irinotecan for Metastatic Colorectal Cancer) was a multicenter, open-label, phase 3 study to determine whether the addition of cetuximab to irinotecan improves OS in patients who have mCRC previously treated with oxaliplatin and 5-FU.[33] A total of 1298 patients with EGFR-expressing mCRC that had progressed on oxaliplatin plus 5-FU were randomly assigned either to cetuximab (400 mg/m^2 on day 1 followed by 250 mg/m^2 weekly) plus irinotecan (350 mg/m^2 every 3 weeks) or to irinotecan alone (350 mg/m^2 every 3 weeks). The study showed that the addition of cetuximab to irinotecan significantly improved both PFS (median PFS, 4.0 vs 2.6 months; HR, 0.692 [95% CI, 0.617-0.776]; *P*=.0001) and ORR (16.4% vs 4.2%; *P*<.0001). However, there was no significant improvement in OS (median OS, 10.7 vs 10.0 months; HR, 0.975 [95% CI, 0.0854-1.114]; *P*=.71). This lack of difference is most likely due to crossover of therapy because 46.9% of the study patients in the irinotecan-alone arm eventually received cetuximab. There was a higher incidence of acneiform rash, diarrhea, hypomagnesemia, and electrolyte imbalance in the cetuximab-plus-irinotecan arm. This study was performed before the role of *RAS* mutations as negative predictive markers for anti-EGFR therapy was fully appreciated, and there is no further information about the efficacy of cetuximab in the wild-type *RAS* subgroup.

Cetuximab Plus FOLFOX

CAPRI-GOIM (Cetuximab After Progression in KRAS Wild-Type Colorectal Cancer Patients-Gruppo Oncologico dell'Italia Meridionale) was a randomized phase 2 study to evaluate the efficacy of cetuximab plus chemotherapy in the second-line treatment of patients with wild-type *KRAS* exon 2 mCRC after disease progression with first-line chemotherapy

and an EGFR inhibitor.[34] A total of 153 patients were randomly assigned (1:1) either to FOLFOX plus cetuximab (74 patients) or to FOLFOX alone (79 patients) after disease progression with FOLFIRI plus cetuximab in the first-line setting. There was no significant difference in PFS between the FOLFOX-plus-cetuximab group and the FOLFOX-alone group (median PFS, 6.4 vs 4.5 months; HR, 0.81 [95% CI, 0.58-1.12]; log rank test, P=.19).

Subsequent next-generation sequencing analysis of available archival tumor blocks from 117 of the 153 enrolled patients (76.5%) revealed that only 75 of the 117 patients had "all-RAS" wild-type tumors; the remaining 42 patients had KRAS (exon 2, 3, or 4) or NRAS (exon 2, 3, or 4) mutations, which are known negative predictive markers for anti-EGFR therapy. Of note, subgroup analysis of the all-RAS wild-type population showed that these patients did not benefit from the addition of cetuximab either (median PFS, 6.8 months in the FOLFOX-plus-cetuximab arm vs 5.5 months in the FOLFOX-alone arm; HR, 0.80 [95% CI, 0.50-1.29]; log rank test, P=.36). Further next-generation sequencing analysis of BRAF and PIK3CA genes revealed that only 66 of the 117 patients had no mutation in KRAS, NRAS, BRAF, or PIK3CA genes ("quadruple" wild-type) in their tumors. Interestingly, significant improvement of PFS with the addition of cetuximab to FOLFOX was shown in the "quadruple" wild-type population (median PFS, 6.9 in the FOLFOX-plus-cetuximab arm vs 5.3 months in the FOLFOX-alone arm; HR, 0.56 [95% CI, 0.33-0.94]; log rank test, P=.025).

This was the first study to demonstrate that the continuation of anti-EGFR therapy in combination with chemotherapy as second-line therapy significantly prolongs PFS in highly selected patients with "quadruple" wild-type mCRC after progression with FOLFIRI plus cetuximab as first-line treatment. This result warrants further evaluation in a randomized phase 3 study to evaluate the clinical benefit of continuing anti-EGFR antibody therapy in the second-line therapy of patients with "quadruple" wild-type mCRC after progression despite initial FOLFIRI plus cetuximab.

Panitumumab Plus Irinotecan
PICCOLO (Panitumumab and Irinotecan Versus Irinotecan Alone for Patients With KRAS Wild-Type, Fluorouracil-Resistant Advanced Colorectal Cancer) was an open-label, randomized trial performed in the United Kingdom to evaluate the role of panitumumab plus irinotecan in the second-line therapy of wild-type KRAS mCRC that had progressed on a fluoropyrimidine with or without oxaliplatin in the first-line setting.[35] A total of 460 patients with wild-type KRAS codons 12, 13, and 61 and no previous EGFR-targeted therapy were randomly assigned either to irinotecan plus panitumumab (230 patients) or to irinotecan alone (230 patients). Patients in both arms received iri-

notecan 350 mg/m² every 3 weeks (300 mg/m² if aged ≥70 years or with a PS of 2). Patients randomly assigned to the irinotecan-plus-panitumumab arm received panitumumab 9 mg/kg IV every 3 weeks in addition to irinotecan. The primary endpoint was OS. There was no difference in OS between the irinotecan-plus-panitumumab arm and the irinotecan-alone arm (median OS, 10.5 vs 10.4 months; HR, 1.01 [95% CI, 0.83-1.23]; P=.91). However, PFS was significantly better in the irinotecan-plus-panitumumab arm (HR, 0.78 [95% CI, 0.64-0.95]; P=.015), and ORR was also better in the combination arm (34% vs 12%; P<.0001). Treatment-related grade 3/4 toxicities were more frequent in the combination arm: diarrhea (29% vs 18%), skin toxicity (19% vs 0%), lethargy (21% vs 11%), infection (19% vs 10%), and hematologic toxicity (22% vs 12%). This was the first randomized trial introducing prospective testing of KRAS mutation status for the selection and randomization of patients with mCRC for anti-EGFR monoclonal antibody treatment.

Panitumumab Plus FOLFIRI
Peeters and colleagues reported a phase 3 randomized study to evaluate the efficacy and safety of panitumumab plus FOLFIRI chemotherapy compared with FOLFIRI alone after the failure of first-line treatment.[36,37] The endpoints were PFS and OS. A total of 1186 patients with mCRC were randomly assigned (1:1) either to FOLFIRI plus panitumumab or to FOLFIRI alone every 2 weeks. KRAS mutation status at codons 12 and 13 was available in 1083 patients (91%): 597 (55%) with wild-type KRAS tumors and 486 (45%) with mutant KRAS tumors.

In the wild-type KRAS codon 12 and 13 subgroup, the addition of panitumumab to FOLFIRI chemotherapy improved PFS significantly in comparison with FOLFIRI alone (median PFS, 6.7 vs 4.9 months; HR, 0.82 [95% CI, 0.69-0.97]; P=.023). The improvement in PFS with the addition of panitumumab to FOLFIRI chemotherapy was significant in patients in the wild-type KRAS subgroup whose disease had progressed on prior oxaliplatin (6.0 vs 3.7 months; HR 0.72 [95% CI, 0.58-0.88]; P=.001) or on an oxaliplatin/bevacizumab-containing regimen in the first-line setting (6.4 vs 3.7 months; HR, 0.58 [95% CI, 0.37-0.90]; P=.014). The tumor response rate also was improved with the addition of panitumumab to FOLFIRI in the same subgroup (36% vs 10%; P <.0001). However, there was no significant improvement in OS with the addition of panitumumab in the wild-type KRAS codon 12 and 13 subgroup (median OS, 14.5 vs 12.5 months; HR, 0.85 [95% CI, 0.70-1.04]; P=.12). These OS results may have been confounded by crossover because 34% of patients in the FOLFIRI-alone arm received subsequent anti-EGFR therapy. Toxicities were generally comparable across arms, with the exception of toxicities known to be associated with anti-EGFR therapy.

FOLFIRI Plus Panitumumab vs FOLFIRI Plus Bevacizumab

Although most of the available data on combinations of chemotherapy regimens with targeted agents (eg, cetuximab vs bevacizumab) have looked at first-line therapy, some data are available for these combinations as the second-line therapy as well.[38] SPIRITT (Second-Line Panitumumab Irinotecan Treatment Trial) was a randomized, multicenter phase 2 study of FOLFIRI plus panitumumab vs FOLFIRI plus bevacizumab in the second-line treatment of patients with wild-type *KRAS* exon 2 mCRC.[39] A total of 182 patients with disease progression during oxaliplatin-based chemotherapy and bevacizumab in the first-line setting were randomly assigned either to FOLFIRI plus panitumumab or to FOLFIRI plus bevacizumab. There was no significant difference in PFS between the 2 arms (median PFS, 7.7 in the FOLFIRI-plus-panitumumab arm vs 9.2 months in the FOLFIRI-plus-bevacizumab arm; HR, 1.01 [95% CI, 0.68-1.50]; *P*=.97). OS was also similar between the 2 arms (median OS, 18.0 months in the FOLFIRI-plus-panitumumab arm vs 21.4 months in the FOLFIRI-plus-bevacizumab arm; HR, 1.06 [95% CI, 0.75-1.49]; *P*=.75). The ORR was 32% in the FOLFIRI-plus-panitumumab arm and 19% in the FOLFIRI-plus-bevacizumab arm. Skin disorders, diarrhea, hypomagnesemia, hypokalemia, dehydration, and hypotension were more frequent in the FOLFIRI-plus-panitumumab arm. Neutropenia was more frequent in the bevacizumab-containing arm. This study reinforced the concept that patients who have had bevacizumab in combination with chemotherapy may continue to benefit from either antiangiogenesis-based or anti-EGFR–based second-line chemotherapy.

Recommendations and Suggestions for Clinical Practice

The therapeutic options for the second-line treatment of patients with mCRC depend on previous therapies in the first-line setting.[40] In current practice, most of the patients with mCRC receive first-line combination chemotherapy consisting of a 5-FU/LV–based or capecitabine-based regimen with either oxaliplatin or irinotecan. The currently available biologic agents for second-line therapy are antiangiogenic agents (including bevacizumab, ramucirumab, and ziv-aflibercept) and anti-EGFR agents (eg, cetuximab and panitumumab) for patients with wild-type *KRAS*/*NRAS* tumors only.

For patients with mCRC that has progressed with an oxaliplatin-plus-fluoropyrimidine (5-FU or capecitabine) regimen without any biologics in the first-line setting, chemotherapy (FOLFIRI or irinotecan monotherapy) is recommended, either alone or with one of the biologics. In those patients whose disease progressed after an irinotecan-plus-fluoropyrimidine (5-FU or capecitabine) regimen without any biologics in the first-line setting, chemotherapy (FOLFOX or XELOX) alone or with one of the biologics is recommended. For those patients who had only a fluoropyrimidine (5-FU or capecitabine) without oxaliplatin or irinotecan in the first-line setting, chemotherapy (FOLFOX, XELOX, FOLFIRI, IROX, or irinotecan monotherapy) alone or with one of the biologics should be considered based on their condition and PS. An anti-EGFR agent (cetuximab or panitumumab) as monotherapy or in combination with irinotecan can be considered in patients with wild-type *KRAS*/*NRAS* whose disease progressed with oxaliplatin/irinotecan/5-FU/LV (FOLFOXIRI) in the first-line setting.

For patients with mCRC whose disease progressed with maintenance therapy (fluoropyrimidine plus bevacizumab or an anti-EGFR antibody)[41-45] after the first-line setting, the traditional paradigm of first-line vs second-line treatment may not apply well to the choice of optimal systemic therapy. If there are no significant residual toxicities from induction chemotherapy, the resumption of the same first-line induction chemotherapy (either FOLFOX/XELOX or FOLFIRI) is commonly suggested until further tumor progression, and the same algorithm discussed earlier will be recommended at the time of tumor progression on the resumed induction chemotherapy. However, to avoid rapid recurrence of the toxicity/side effects of previous exposure to a chemotherapy agent, switching to a different chemotherapy agent (or using a different regimen) may also be suggested. For example, to avoid peripheral neuropathy from oxaliplatin in a patient initiated with FOLFOX, the physician may choose to add irinotecan to 5-FU when disease has progressed on 5-FU maintenance.

Based on the recent development of checkpoint blockade therapy in patients with mismatch repair–deficient CRC,[38] it may be necessary to modify this paradigm of recommendations for second-line therapy in patients with mismatch repair–deficient mCRC in the near future.[46]

It also needs to be pointed out that the traditional concepts of *first-line therapy* and *second-line therapy* may no longer easily fit into clinical practice as treatment evolves toward a model of personalized management based on the specific cancer biology and genetic characteristics of individual patients.

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