

How I Treat Metastatic Colorectal Cancer



Tanios Bekaii-Saab, MD

Professor, Mayo Clinic College of Medicine
and Science
Program Leader, GI Program
Mayo Clinic Cancer Center
Senior Associate Consultant, Mayo Clinic
Phoenix, Arizona

Plus

Highlights in Colorectal Cancer From the 2018
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H&O What factors guide the selection of first-line treatment for metastatic colorectal cancer?

TB The treatment landscape of metastatic colorectal cancer continues to be refined. The selection of first-line therapy for these patients is guided by multiple factors, such as genetic characteristics, microsatellite instability (MSI), the side where the tumor arises, and the patient's age, comorbidities, and performance status.

Two chemotherapy options are available: leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX); and leucovorin, 5-FU, and irinotecan (FOLFIRI). They are typically used in combination with biologic agents. FOLFIRI seems to have a slight edge over FOLFOX, although the numeric improvement is not statistically significant.¹ Younger patients—who have a higher capacity to tolerate more aggressive therapy—are potential candidates for leucovorin, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) plus bevacizumab. However, for most patients, there does not appear to be a significant advantage to FOLFIRINOX vs FOLFOX or FOLFIRI, except for the subgroup with *BRAF*-mutated tumors and possibly those with liver-limited disease.

H&O What is the significance of *BRAF* and *RAS* mutations?

TB Mutations in *BRAF* (V600E) or expanded *RAS*, which includes *KRAS* and *NRAS*, are key genomic factors. In the presence of these mutations, epidermal growth factor receptor (EGFR) inhibitors are excluded as treatment options. In the presence of wild-type *RAS*, tumor sidedness becomes an important consideration. Data consistently indicate that *EGFR* inhibitors lack benefit in the first-line treatment of patients with a *RAS* wild-type colon tumor located on the right side.²

Published and presented data suggest a possible small benefit for EGFR inhibitors, such as cetuximab or panitumumab, in patients with *RAS* wild-type tumors located on the left side of the colon.^{3,4} One should note that the 2 most referenced trials—FIRE-3 (FOLFIRI Plus

Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment for Patients With Metastatic Colorectal Cancer) and trial 80405 from the Cancer and Leukemia Group B and the Southwest Oncology Group—missed their primary endpoints of superiority for cetuximab.^{5,6} The benefit identified for EGFR inhibitors and left-sidedness came through post hoc analyses. As such, for patients with *RAS/RAF* wild-type tumors on the left side, EGFR inhibitors or bevacizumab are both acceptable options. For patients with a tumor on the right side, bevacizumab is the preferred option, when indicated.

As mentioned above, eligible patients with a *BRAF* V600E mutation should be considered for FOLFIRINOX and bevacizumab in the first-line setting. For patients requiring treatment after first-line therapy, there have been some recent gains with combination regimens, including dual- or triple-agent therapy with a mitogen-activated protein kinase (MEK) inhibitor and a *RAF* inhibitor, preferably with the addition of an EGFR inhibitor. One of those regimens is currently included in the colorectal cancer guidelines from the National Comprehensive Cancer Network (NCCN).⁷

H&O How do other factors impact treatment selection?

TB MSI assessment is an additional key element that will impact treatment considerations. Approximately 4% to 5% of patients with metastatic colorectal cancer will have MSI-high disease.⁸ A majority of these patients will respond very well to pembrolizumab or nivolumab, with many having long-term and durable responses.^{9,10} Recently, the US Food and Drug Administration (FDA) approved the combination of ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor) and nivolumab in this group of patients. Unfortunately, with a noticeable absence of a randomized trial, it remains uncertain how to best select patients likely to have an incremental benefit with the addition of ipilimumab to nivolumab, especially when accounting for the added cost and toxicities associated with this drug. In my clinic,

the first treatment option considered for all patients who are MSI-high is a single-agent programmed cell death 1 inhibitor. Patients who eventually develop progressive disease after an initial response may be candidates for combination treatment.

Moreover, the role of amplified human epidermal growth factor receptor 2 (*HER2*) in colorectal cancer has been established in a number of trials. One such study is the HERACLES-A trial (*HER2* Amplification for Colorectal Cancer Enhanced Stratification), which suggested that trastuzumab plus lapatinib can lead to durable responses in patients with heavily pretreated, *HER2*-positive metastatic colorectal cancer.¹¹ The MyPathway study confirmed the presence of durable responses in *HER2*-positive patients treated with trastuzumab and pertuzumab.¹² An ongoing study from the Academic and Community Cancer Research United (ACCRU) network is evaluating a highly specific and potent oral inhibitor of *HER2*, tucatinib, added to trastuzumab in patients with *HER2*-amplified advanced colorectal cancer.¹³ Several other studies underway across the United States and the world are also focusing on targeting this pathway.^{14,15} In addition to providing an opportunity for targeting, amplification of *HER2* seems to predict for lack of response to EGFR inhibitors, as shown in a recent study.¹⁶

Another important consideration for treatment selection is the presence of oligometastatic or organ-limited disease, which applies to a small percentage of patients. These patients may benefit from more-intense systemic therapy, surgical or locoregional options, debulking surgery, hyperthermic intraperitoneal chemotherapy, and radiation therapy. Other considerations, including age, performance status, and comorbidities, will help with selection of treatment options.

H&O What is the goal of treatment?

TB The primary goal of treatment is palliative for the majority of patients with metastatic colorectal cancer. This goal is coupled with that of prolonging survival. The use of currently available therapies has nearly quadrupled survival times from the days when single-agent 5-fluorouracil with or without leucovorin was the mainstay of treatment. Additionally, for some patients with limited oligometastatic disease, treatment can control the disease indefinitely.

H&O What percentage of patients will require second-line treatment, and when is it initiated?

TB More than 90% of patients with metastatic colorectal cancer will require second-line treatment. A rare patient may progress quickly after first-line treatment and never

make it to second-line. The selection of second-line treatment options depends on the type of therapy in the first-line setting. A patient with a *RAS* wild-type tumor located on the right side of the colon who received bevacizumab as first-line treatment will likely receive it again as part of second-line therapy. A patient with a *RAS* wild-type, *BRAF* wild-type tumor on the left side of the colon who receives bevacizumab as a first-line treatment should receive an EGFR inhibitor plus chemotherapy in the second-line setting. In eligible patients treated with EGFR inhibitors in the first-line setting, second-line treatment should include bevacizumab.

Eligible patients with a mutated *RAS* cancer receive bevacizumab as both first-line and second-line therapy, with a chemotherapy switch. For patients with a *BRAF* V600E mutation, subsequent therapy may consist of dual- or triple-agent therapy with a MEK inhibitor and a RAF inhibitor, preferably with the addition of an EGFR inhibitor.

There are currently 3 antiangiogenic agents available for second-line treatment: bevacizumab, ramucirumab, and aflibercept. In the first-line and second-line settings, bevacizumab combination therapy is the antiandrogenic option I tend to use. I do not recommend the use of aflibercept or ramucirumab. The data do not show any historical advantage to aflibercept or ramucirumab vs bevacizumab. In addition, ramucirumab may be more expensive than bevacizumab, and aflibercept may be somewhat more toxic, with no noticeable advantage.

H&O What are the challenges in the management of these patients?

TB The major challenge in the second-line setting is the selection of therapy. For example, how should a patient's biologic treatment change? Do we continue with vascular endothelial growth factor (VEGF) inhibitors, or switch to EGFR inhibitors as indicated? Would it be better to use another line of therapy before the switch to EGFR inhibitors after 2 lines of VEGF inhibitors? When do we consider other targeted or immunotherapeutic options for appropriately selected patients?

H&O What are the treatment options for the third-line setting?

TB The selection of therapy for the third-line setting and beyond is based on factors such as the patient's performance status, treatment history, and capacity to receive further therapy. Approximately half of patients with colon cancer will be well enough to tolerate third-line treatment. There are 2 main treatment options: TAS-102 and regorafenib. These therapies are appropriate for patients with

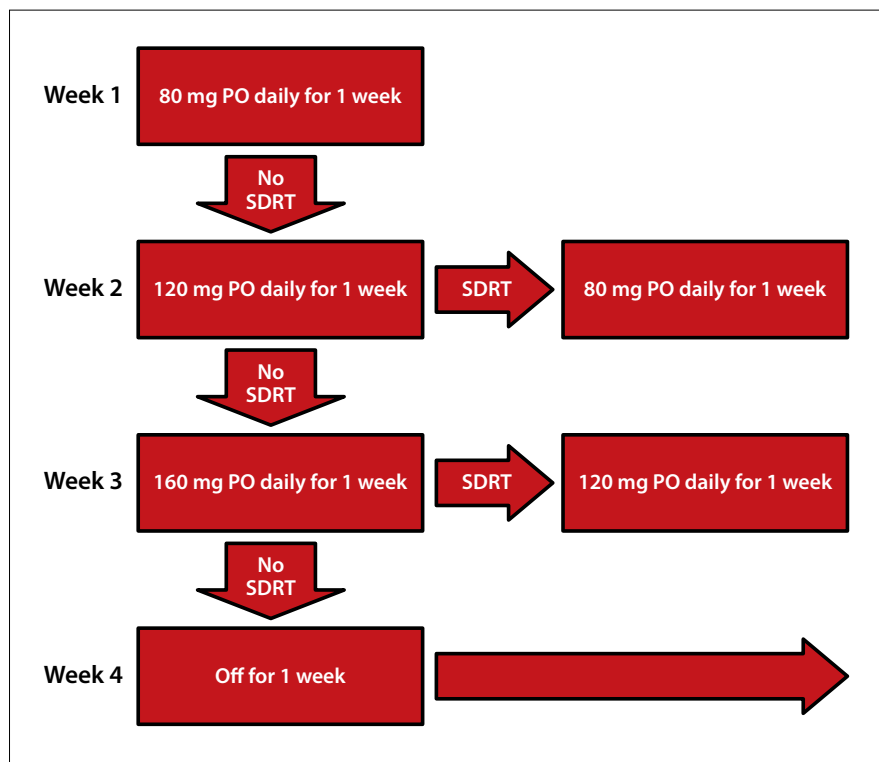


Figure 1. An incremental dose-escalation protocol for administration of regorafenib. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2016;14(suppl 3):8-10.²⁷

refractory disease following treatment with chemotherapy and VEGF or EGFR inhibitors, as indicated, and who are microsatellite stable.

TAS-102 is an oral cytotoxic agent that is part of the “superfamily” of fluoropyrimidines. TAS-102 appears to have activity in cases where 5-fluorouracil or capecitabine fail. In the phase 3 RECURSE trial (Randomized, Double-Blind, Phase 3 Study of TAS-102 Plus Best Supportive Care Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies), median overall survival was 7.1 months with TAS-102 vs 5.3 months with placebo (hazard ratio [HR], 0.68; 95% CI, 0.58-0.81; $P < .001$).¹⁷ TAS-102 is given 5 days on and 2 days off, for 2 weeks in a row every 4 weeks. The toxicities are primarily what one would expect from a cytotoxic agent, and consist primarily of blood count abnormalities. Fatigue and gastrointestinal toxicities may also occur. Interestingly, patients who develop significant neutropenia appear to be more likely to respond to treatment.

Regorafenib is an oral multitargeted tyrosine kinase inhibitor. In the phase 3 CORRECT study (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy), median overall survival was 6.4 months with regorafenib compared with 5.0 months with placebo (HR, 0.77; 95% CI, 0.64-0.94; 1-sided $P = .0052$).¹⁸ Regorafenib is given daily for 3 weeks in a row and then 1 week off.

Toxicities include grade 3 hand-foot skin reaction, which occurs in approximately 10% to 15% of patients. Other adverse events include fatigue, occasional gastrointestinal toxicities, and liver function abnormalities. Typically, the toxicities appear as early as the first 2 weeks of treatment. Interestingly, patients who develop hand-foot skin reaction (any grade), tend to have a better outcome.

H&O What is known about how to sequence agents in the third-line setting?

TB The FDA approved both TAS-102 and regorafenib based on phase 3 studies that compared each with placebo. There are no prospective comparative data for the 2 agents. However, there are hints about how to possibly achieve the most benefit through sequencing. In the RECURSE trial, nearly 20% of patients had prior exposure to regorafenib, and this prior exposure did not appear to impact outcome.¹⁷ Additionally, it appears that the activity of TAS-102 is unaffected by prior exposure. This observation is based on the results of the TERRA trial (Study of TAS-102 in Patients With Metastatic Colorectal Cancer in Asia), which compared TAS-102 with placebo in certain Asian countries.¹⁹ In this group of patients with less preexposure to other biologic agents, the advantage for TAS-102 remained historically very similar to that seen in the RECURSE trial.

With regorafenib, the story appears to be different.

The CONCUR trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was similarly limited to selected Asian countries. Patients in the CONCUR trial were less heavily pretreated.²⁰ In this group of patients with less preexposure to other biologic agents, the advantage for regorafenib appeared to be historically more significant than that seen in CORRECT, perhaps suggesting the need for earlier exposure.

In my own clinic, I tend to start with regorafenib, followed by TAS-102. There are certain exceptions where I tend to use TAS-102 first, such as patients with a history of significant hand-foot skin syndrome following treatment with capecitabine or those with baseline liver dysfunction.

H&O What is known about how to optimize the dosing schedule?

TB One of the biggest challenges with these agents is the dosing and schedule. The dose schedule approved for TAS-102 by the FDA is 35 mg/m² orally twice daily on days 1 through 5 and days 8 through 12 of each 28-day cycle. This schedule can be confusing to many patients. Toxicity can occasionally be significant with the weekly regimen, and some clinicians have changed the schedule to biweekly. There are no currently available data on how to optimize the dosing for TAS-102.

The approved dosing schedule for regorafenib is 160 mg orally every day for 3 weeks on, 1 week off. However, clinicians have used a variety of different dosing/scheduling strategies that are unsubstantiated by data. The benefits to modified dosing strategies were confirmed by the ReDOS study (Regorafenib Dose Optimization Study), which was recently presented at the 2018 European Society for Medical Oncology World Congress on Gastrointestinal Cancer (ESMO GI) and the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.^{21,22} ReDOS compared regorafenib given in the standard regimen of 160 mg vs an escalated dosing strategy, in which the dose began with 80 mg/day, and was escalated weekly up to 160 mg/day in patients without significant drug-related toxicities. The aim was to find the best dose from cycle 1 before moving to cycles 2 and then 3. The study found that more patients treated with the dose-escalation strategy reached cycle 3 (43% vs 24% in the standard-dose arm). The dose-escalation strategy was associated with a numerical improvement in survival (9.0 vs 5.9 months). Patients treated with the escalated strategy also had a slight improvement in progression-free survival (2.5 vs 2.0 months). Quality of life was maintained with the dose-escalation strategy. In contrast, with the standard regimen of 3 weeks on, 1 week

off, quality of life decreased at the 2-week mark, only to recover somewhat after dose adjustments. The ReDOS study showed that the use of regorafenib could be optimized with a dose-escalating strategy that proceeds from 80 mg to 120 mg to 160 mg (Figure 1).

H&O What do you tell patients about treatment?

TB It is important to maintain an honest discussion with patients about the relative benefits of treatment options and the merits of best supportive care as an option. It is necessary to be transparent about a treatment's short-term and long-term toxicities, and cognizant of the balance between treatment tolerability, quality of life, and potential efficacy. Patients should undergo very close follow-up. During the first 1 or 2 months of treatment, they should be seen every week or every other week, when possible. Another topic that has become very important is cost. Patients may face prohibitive copays.

H&O What is known about immunotherapy in microsatellite stable colorectal cancer?

TB The IMblaze370 trial (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma), presented at the ESMO GI meeting, had 3 arms: regorafenib alone; the programmed death ligand 1 inhibitor atezolizumab alone; and atezolizumab in combination with the MEK inhibitor cobimetinib.²³ This study was powered to show survival benefits with the combination of cobimetinib and atezolizumab, a regimen based on the idea that MEK inhibitors would increase the inflammatory aspect of the cancer and thereby enhance the activity of immunotherapy. Results from a phase 1b study were relatively promising.²⁴ However, the phase 3 results were very disappointing, with the combination of cobimetinib plus atezolizumab somewhat underperforming vs regorafenib.

H&O Are there any other new or ongoing clinical trials of interest? ?

TB There are many developmental strategies in the treatment of colorectal cancer, in addition to the ones already discussed. For example, the BEACON study (Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil/Folinic Acid/Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-In of Encorafenib + Binimetinib + Cetuximab in Patients With *BRAF* V600E-Mutant Metastatic Colorectal Cancer) evaluated a triple-drug strategy in patients with a *BRAF* mutation.²⁵ The regimen showed

activity and was well-tolerated. A study from the ACCRU network, known as COLOMATE (Colorectal and Liquid Biopsy Molecularly Assigned Therapy), is assigning patients to molecularly directed arms based on cancer genetic profiling.²⁶ There is additional, ongoing interest in developing studies with innovative immunotherapeutic strategies in patients with microsatellite stable disease.

Disclosure

Dr Bekaii-Saab is a consultant for Merck, AbbVie, Exelixis, Armo, and SillaJen.

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Highlights in Colorectal Cancer From the 2018 American Society of Clinical Oncology Annual Meeting

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REVERCE: Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Metastatic Colorectal Cancer Patients Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan—Biomarker Analysis

The randomized phase 2 REVERCE trial (Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan) evaluated treatment with regorafenib followed by cetuximab vs cetuximab followed by regorafenib in patients with metastatic colorectal cancer (CRC).¹ Biomarker analysis of patient data from the REVERCE trial was conducted to identify liquid biomarkers that correlate with patient outcomes.²

Eligible patients had wild-type *KRAS* exon 2 and were previously treated with fluoropyrimidine, oxaliplatin, and irinotecan. Enrollment criteria excluded patients who had been previously treated with an anti-epidermal growth factor receptor agent.

The trial randomly assigned 101 patients to the 2 treatment arms. Median overall survival (OS) was 17.4 months with regorafenib followed by cetuximab vs 11.6 months with cetuximab followed by regorafenib (hazard ratio [HR], 0.61; 95% CI, 0.39-0.96; $P=.029$; Figure 1). The median progression-free survival (PFS) after completion of study treatment was 5.2 months with regorafenib followed by cetuximab vs 1.8 months with cetuximab followed by regorafenib. In the subset of patients with wild-type *RAS* and *BRAF*, median OS was 18.2 months with regorafenib followed by cetuximab vs 12.7 months with cetuximab followed by regorafenib (HR, 0.60; 95%

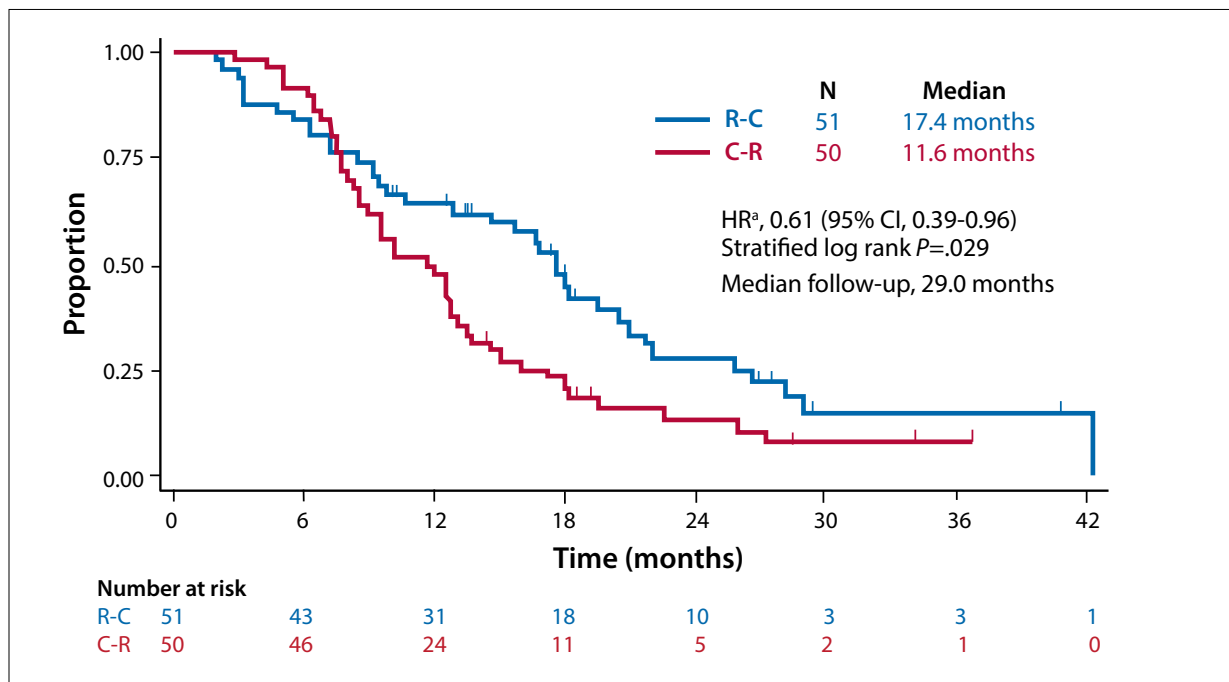


Figure 1. Median overall survival in the phase 2 REVERCE trial, which compared regorafenib followed by cetuximab (R-C) vs cetuximab followed by regorafenib (C-R) in patients with metastatic colorectal cancer. ^aAdjusted by intent to use irinotecan. HR, hazard ratio; REVERCE, Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan. Adapted from Tsuji Y et al. ASCO abstract 3510. *J Clin Oncol.* 2018;36(15 suppl).²

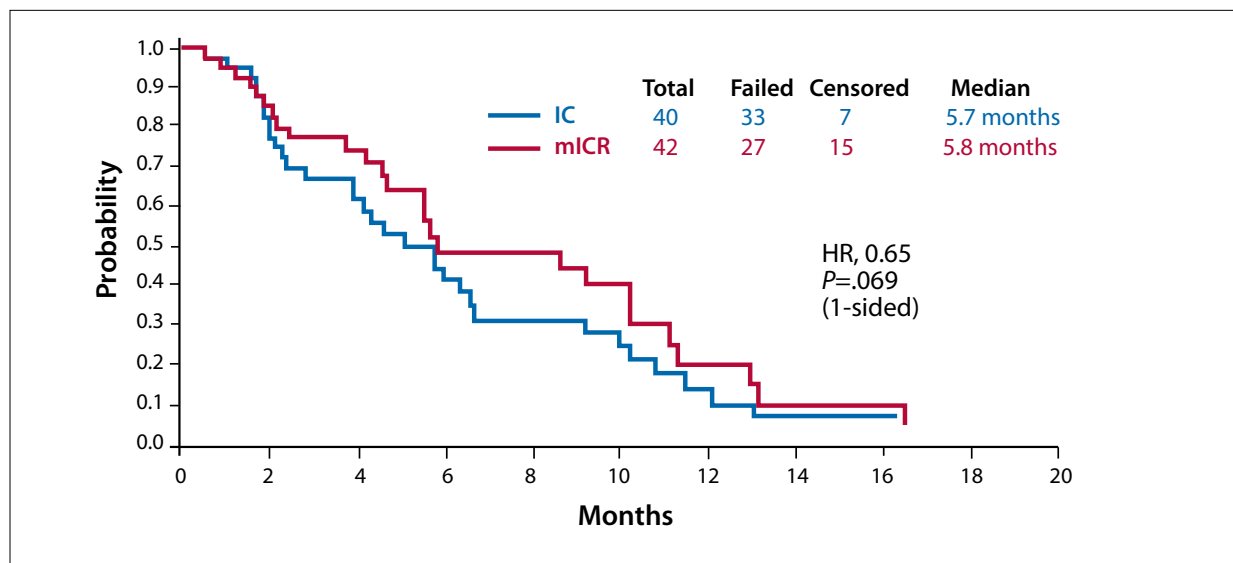


Figure 2. Progression-free survival in a randomized phase 2 study evaluating irinotecan and cetuximab with or without ramucirumab in patients with progressive, metastatic colorectal cancer. HR, hazard ratio; IC, irinotecan and cetuximab; mICR, modified irinotecan, cetuximab, and ramucirumab. Adapted from Hochster HS et al. ASCO abstract 3504. *J Clin Oncol*. 2018;36(15 suppl).¹

CI, 0.37-0.98), and median PFS was 5.2 months vs 1.6 months, respectively (HR, 0.31; 95% CI, 0.17-0.58). In an analysis of patients in both treatment groups, the median OS was 17.7 months in those with no alterations in *RAS*, *BRAF*, *MET*, or *HER2*; 6.3 months in those with preexisting gene alterations; and 10.0 months in those with gene alterations that emerged during treatment.

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Randomized Trial of Irinotecan and Cetuximab Versus Irinotecan, Cetuximab and Ramucirumab as 2nd Line Therapy of Advanced Colorectal Cancer Following Oxaliplatin- and Bevacizumab-Based Therapy: Result of E7208

Ramucirumab is a novel antiangiogenic antibody directed at the ligand binding domain of the vascular endothelial growth factor (VEGF) receptor. Bevacizumab binds to the VEGF ligand. These antibodies therefore have different mechanisms of action, and may not be cross-resistant. A randomized phase 2 study evaluated irinotecan and

cetuximab with or without ramucirumab in metastatic CRC patients who progressed after first-line treatment with oxaliplatin-based chemotherapy plus bevacizumab.¹ Eligible patients had progressed within 90 days of their last dose of bevacizumab and had wild-type *KRAS*.

All patients received standard treatment with irinotecan and cetuximab. Patients in the experimental arm also received ramucirumab (8 mg/kg) every 2 weeks. After a planned interim analysis revealed unacceptable toxicity in the ramucirumab arm, patients in the experimental arm received irinotecan (150 mg/m²), cetuximab (400 mg/m²), and ramucirumab (6 mg/kg) every 2 weeks. The response rate was 28% (95% CI, 16%-43%) with the addition of ramucirumab vs 22% (95% CI, 12%-36%) with irinotecan plus cetuximab alone. The duration of response was 8.1 months vs 5.5 months, respectively. PFS was improved with ramucirumab (HR, 0.63; *P*=.069; (Figure 2) and met the primary endpoint of *P*<.15.

In each arm, 61% of patients left the study owing to progressive disease. The median number of treatment cycles was 11 (range, 1-56) in the ramucirumab arm vs 8 (range, 1-36) in the irinotecan/cetuximab arm (*P*=.12). Grade 3/4 toxicities were observed in 8% to 9% of patients in each arm.

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High Levels of Cell-Free DNA at Baseline and Increase of at Least One Mutation at Day 14 as Independent Prognostic Biomarkers for Patients With Advanced Colorectal Cancer Under Regorafenib

Archival tumor tissue and plasma samples were analyzed to identify markers of early response to regorafenib in patients with advanced CRC.¹ The multicenter study included 141 patients. Samples were collected at baseline and at day 14 after initiation of treatment. Tumor-specific mutations were selected for evaluation based on allele frequency. The most commonly mutated genes in circulating tumor DNA (ctDNA) were *APC* (73%), *TP53* (72%), *KRAS* (66%), and phosphoinositide 3-kinase (*PI3K*) CA (23%). Patients were categorized based on levels of circulating free DNA (cfDNA) at baseline (<1 µg/mL vs ≥1 µg/mL) and the presence or absence of at least 1 tumor-specific mutation level increasing by 50% or more between baseline and day 14.

Among patients with a baseline cfDNA level of at least 1 µg/mL, median PFS was 1.3 months in those without an increase in allele frequency by day 14 vs 1.1 months in those with at least 1 tumor-specific mutation level increasing by 50% or more (HR, 2.36; 95% CI, 1.3-4.4; *P*=.007). Median OS was 6.1 months vs 2.3 months, respectively (HR, 3.23; 95% CI, 1.63-6.40; *P*<.001).

In the subgroup of patients with less than 1 µg/mL cfDNA at baseline, median PFS was 4.1 months in those without an increase in allele frequency vs 1.5 months in those with at least 1 tumor-specific mutation level increasing by 50% or more (HR, 2.33; 95% CI, 1.2-4.4; *P*=.009). Median OS was 13.2 months vs 6.4 months (HR, 2.11; 95% CI, 1.1-3.9; *P*=.02).

Reference

1. Kehagias P, Vandeputte C, Ameye L, et al. High levels of cell-free DNA (cfDNA) at baseline (BL) and increase of at least one mutation at day 14 (D14) as independent prognostic biomarkers for patients (pts) with advanced colorectal cancer (aCRC) under regorafenib [ASCO abstract 3532]. *J Clin Oncol*. 2018;36(15 suppl).

First-Line FOLFOX Plus Panitumumab Followed by 5FU/LV Plus Panitumumab or Single-Agent Panitumumab as Maintenance Therapy in Patients With RAS Wild-Type Metastatic Colorectal Cancer: the VALENTINO Study

The VALENTINO study (Panitumumab-Based Maintenance in Patients With *RAS* Wild-Type, Metastatic Colorectal Cancer) evaluated whether maintenance treatment with panitumumab monotherapy was noninferior to maintenance with leucovorin, 5-fluorouracil (5-FU), and panitumumab after induction with leucovorin, 5-FU, and oxaliplatin (FOLFOX4) plus panitumumab in

patients with metastatic CRC.¹ The primary endpoint was 10-month PFS. The 229 patients, from 29 centers in Italy, were randomly assigned to treatment. Median follow-up was 13.8 months. Baseline patient and disease characteristics were well-balanced between the 2 arms.

The 10-month PFS rate was 62.8% (95% CI, 54.0%-73.1%) with leucovorin/5-FU plus panitumumab maintenance vs 52.8% (95% CI, 43.4%-64.3%) with panitumumab monotherapy. Median PFS was 13.0 months (95% CI, 10.5-16.0 months) vs 10.2 months (95% CI, 8.9-12.2 months), respectively. Subgroup analysis was also generally consistent in showing a slight improvement in PFS with leucovorin/5-FU plus panitumumab compared with panitumumab monotherapy. The overall response rate was 65.8% with leucovorin/5-FU plus panitumumab vs 67.0% with panitumumab monotherapy, and complete response rates were also similar (3.4% vs 3.6%, respectively). Maintenance treatment with the panitumumab combination yielded an increased duration of response compared with panitumumab monotherapy (12.6 vs 9.8 months).

Patients who received the panitumumab combination as maintenance treatment experienced more adverse events (AEs) of any grade and more grade 3/4 AEs. The most common grade 3/4 AEs in the panitumumab combination arm were skin rash (22%, vs 14% in the panitumumab monotherapy arm), stomatitis/oral mucositis (6% vs 1%), and hand-foot syndrome (5% vs 1%).

Reference

1. Pietrantonio F, Morano F, Corallo S, et al. First-line FOLFOX plus panitumumab (pan) followed by 5FU/LV plus pan or single-agent pan as maintenance therapy in patients with *RAS* wild-type metastatic colorectal cancer (mCRC): the VALENTINO study [ASCO abstract 3505]. *J Clin Oncol*. 2018;36(15 suppl).

Circulating Tumor DNA as an Early Marker to Monitor Clinical Benefit of Regorafenib and TAS-102 in Patients With Metastatic Colorectal Cancer

A study of 40 patients with metastatic CRC investigated the use of ctDNA as a biomarker of treatment efficacy.¹ Enrolled patients had consented to a genomic matching protocol and were receiving treatment with regorafenib (n=16) or TAS-102 (n=31). At first restaging, the patients' disease stage was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).

In the subset of patients with *KRAS* or *NRAS* mutations, allele frequency in those genes was evaluated by droplet digital polymerase chain reaction. Because cancer patients tend to show an increase in long ctDNA fragments compared with noncancer controls, a DNA integrity index was calculated to represent the relative amount of long ctDNA fragments (≥265 bp) vs short ctDNA fragments (≥80 bp). Progressive disease by ctDNA analysis

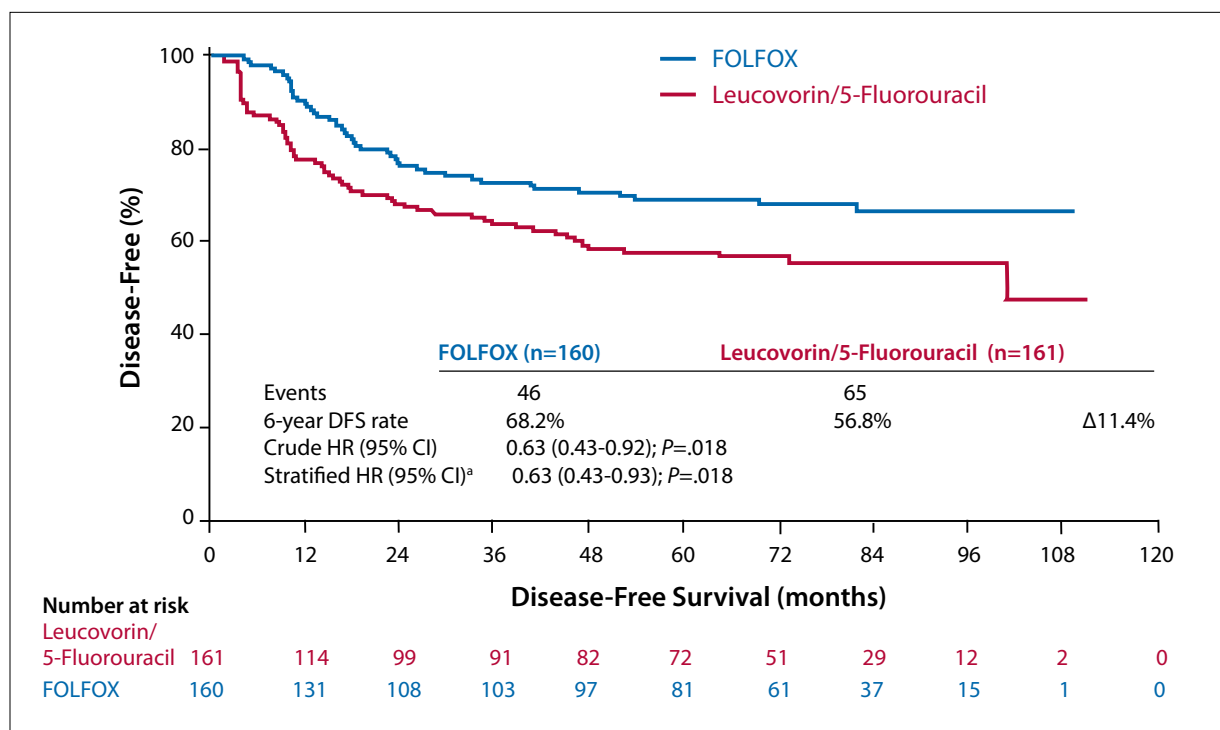


Figure 3. Disease-free survival in the phase 2 ADORE trial, which compared adjuvant FOLFOX vs 5-fluorouracil/leucovorin. ^aStratified by predefined stratification factors (yp stage and participating centers). ADORE, Adjuvant Oxaliplatin, Leucovorin, and 5-Fluorouracil Versus 5-Fluorouracil and Leucovorin After Preoperative Chemoradiotherapy and Surgery for Locally Advanced Rectal Cancer; DFS, disease-free survival; FOLFOX, oxaliplatin, leucovorin, and 5-fluorouracil; HR, hazard ratio. Adapted from Hong YS et al. ASCO abstract 3501. *J Clin Oncol.* 2018;36(15 suppl).¹

was defined as any increase in allele frequency and any increase in DNA integrity index.

Serial monitoring, requiring at least 2 serial plasma samples, was available for 22 treatments. At baseline, the median allele frequency was 18.1%, and the median DNA integrity index was 0.112. Digital droplet polymerase chain reaction in patients with a *KRAS* or *NRAS* mutation showed a sensitivity of 61.5% and a specificity of 100% in detecting progressive disease according to RECIST. The DNA integrity index showed a sensitivity of 47.4% and a specificity of 100%. Therefore, no false positive results were produced by either assay. The findings suggested that evaluation of ctDNA can be used to predict progressive disease.

Reference

1. Lima Pereira AA, Lam M, Marie PK, et al. Circulating tumor DNA (ctDNA) as an early marker to monitor clinical benefit of regorafenib and TAS-102 in patients with metastatic colorectal cancer (mCRC) [ASCO abstract 3533]. *J Clin Oncol.* 2018;36(15 suppl).

Long-Term Results of the ADORE Trial: Adjuvant Oxaliplatin, Leucovorin, and 5-Fluorouracil (FOLFOX) Versus 5-Fluorouracil and Leucovorin After Preoperative Chemoradiotherapy and Surgery for Locally Advanced Rectal Cancer

Long-term results from the phase 2 ADORE trial (Adjuvant Oxaliplatin, Leucovorin, and 5-Fluorouracil Versus 5-Fluorouracil and Leucovorin After Preoperative Chemoradiotherapy and Surgery for Locally Advanced Rectal Cancer) showed a significant improvement in disease-free survival (DFS) with FOLFOX vs 5-FU plus leucovorin.¹ The study included 321 patients with resected rectal cancer. Eligible patients had received preoperative chemotherapy with fluoropyrimidines alone, along with mesorectal excision. Patients were staged after chemoradiotherapy (y) and pathologic examination (p) to derive a “yp” stage. Patients with yp stage II or III disease were enrolled.

After stratification by yp stage and the participating center, patients were randomly assigned to receive adjuvant FOLFOX (every 2 weeks for 8 cycles) or adjuvant 5-FU/leucovorin (every 4 weeks for 4 cycles). After a median follow-up of 74.1 months, the 6-year DFS rate was 68.2% with adjuvant FOLFOX vs 56.8% with adjuvant 5-FU/leucovorin (HR, 0.63; 95% CI, 0.43-0.93; *P*=.018; Figure 3). Adjuvant FOLFOX improved DFS in patients with yp stage III disease (63.2% vs 48.3%; HR, 0.59; 95% CI, 0.38-0.92; *P*=.019). In patients with yp stage II disease, adjuvant FOLFOX yielded a numerically higher DFS rate, but the difference was not significant (77.8% vs

69.5%; HR, 0.64; 95% CI, 0.30-1.36; $P=.245$). Further analysis showed a benefit with adjuvant FOLFOX over 5-FU/leucovorin in several subgroups, including men; patients younger than 65 years; and those with pathologic T stage 3 or 4, a pathologic N stage of 1b or 2, a poorly differentiated/mucinous/signet ring cell tumor, minimal or no regression, no lymphovascular invasion, and no perineural invasion. Both arms showed similar rates of treatment exposure and AEs.

Reference

1. Hong YS, Kim SY, Lee JS, et al. Long-term results of the ADORE trial: adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer [ASCO abstract 3501]. *J Clin Oncol*. 2018;36(15 suppl).

Modified FOLFOX6 With or Without Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Multicenter Randomized Trial

The Chinese FOWARC study (Neoadjuvant FOLFOX6 Chemotherapy With or Without Radiation in Rectal Cancer) evaluated the impact of chemotherapy with or without concurrent radiotherapy on DFS in patients with locally advanced, resectable adenocarcinoma of the rectum.^{1,2} The multicenter, open-label, phase 3 study enrolled patients with stage II/III rectal cancer. Patients in arm 1 received modified FOLFOX6 without concurrent radiotherapy. Patients in arm 2 received modified FOLFOX6 with concurrent radiotherapy. Patients in arm 3 received 5-FU, based on the de Gramont regimen, along with concurrent radiotherapy. Radiotherapy (46.0-50.4 Gy) was delivered in 23 to 25 fractions during chemotherapy cycles 2 through 4. Patients then underwent surgery followed by 6 to 8 more cycles of the same chemotherapy. The trial randomly assigned 165 patients to each treatment arm. Between 73.8% and 84.4% of patients in each arm had stage III disease.

Local recurrence rates were 8.7% \pm 2.4% in arm 1, 8.0% \pm 2.3% in arm 2, and 10.3% \pm 2.7% in arm 3 ($P=.832$). The primary endpoint of 3-year DFS was similar for all 3 arms and ranged from a low of 75.7% \pm 3.8% in arm 3 to a high of 77.1% \pm 3.6% in arm 2 ($P=.970$). Based on multivariate analysis, risk factors associated with DFS included disease stage ($P=.002$), tumor deposits ($P=.004$), and perineural invasion ($P=.008$). OS was similar for all 3 treatment regimens ($P=.926$).

References

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multicenter, open-label, randomized three-arm phase III trial. *J Clin Oncol*. 2016;34(26):3300-3307

2. Deng Y, Chi P, Lan P, et al. Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: final results of the Chinese FOWARC multicenter randomized trial [ASCO abstract 3502]. *J Clin Oncol*. 2018;36(15 suppl).

Preoperative Chemoradiotherapy and Postoperative Chemotherapy With Capecitabine +/- Oxaliplatin in Locally Advanced Rectal Cancer: Final Results of PETACC-6

The PETACC-6 trial (Chemotherapy and Radiation Therapy Before Surgery Followed by Capecitabine With or Without Oxaliplatin in Treating Patients With Locally Advanced Rectal Cancer) investigated the addition of oxaliplatin to neoadjuvant and adjuvant treatment in patients with locally advanced, stage II/III rectal cancer.¹ After randomization, patients in the control arm received capecitabine and radiotherapy, followed by surgery and subsequent capecitabine. Patients in the investigational arm received the same regimen, with oxaliplatin added to neoadjuvant and adjuvant capecitabine. The trial randomly assigned 1094 patients to treatment.

All 6 cycles of treatment were completed by 69% of patients in the control arm and 57% of patients in the investigational arm. In 2014, after a median follow-up of 31 months, an early analysis recommended by the independent data monitoring committee showed no difference in DFS (adjusted HR, 1.04; 95% CI, 0.81-1.33; $P=.781$). After a median follow-up of 68 months, the rate of locoregional relapse was 8.7% in the capecitabine monotherapy arm vs 6.0% in the capecitabine plus oxaliplatin arm ($P=.238$). Rates of distant relapse were also similar (21.4% vs 19.2%, respectively; $P=.261$). Five-year DFS was 71.3% in the control arm vs 70.5% in the investigational arm (HR, 1.02; 95% CI, 0.82-1.28; $P=.84$). Six- and 7-year DFS rates were also similar. Similar DFS rates were observed in both treatment arms for patients with stage II disease ($P=.82$) and stage III disease ($P=.78$). Long-term OS was similar for capecitabine monotherapy or capecitabine plus oxaliplatin ($P=.252$). A notable observation was made in the subgroup analysis: there was a superior DFS in German patients treated without oxaliplatin (HR, 1.25; 95% CI, 0.95-1.64) and in non-German patients treated with oxaliplatin (HR, 0.71; 95% CI, 0.48-1.03). The authors found these differences between Germany and other countries unexplainable.

Reference

1. Schmoll H-J, Haustermans K, Price TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: final results of PETACC-6 [ASCO abstract 3500]. *J Clin Oncol*. 2018;36(15 suppl).

