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# Colon Cancer, Version 1.2017

## Clinical Practice Guidelines in Oncology

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**Abstract**

This portion of the NCCN Guidelines for Colon Cancer focuses on the use of systemic therapy in metastatic disease. Considerations for treatment selection among 32 different monotherapies and combination regimens in up to 7 lines of therapy have included treatment history, extent of disease, goals of treatment, the efficacy and toxicity profiles of the regimens, *KRAS/NRAS* mutational status, and patient comorbidities and preferences. Location of the primary tumor, the *BRAF* mutation status, and tumor microsatellite stability should also be considered in treatment decisions.

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### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

**Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

## Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2016, an estimated 95,270 new cases of colon cancer and approximately 39,220 cases of rectal cancer will occur. During the same year, an estimated 49,190 people will die of colon and rectal cancer combined.[1] Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from

### Please Note

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### Disclosures for the NCCN Colon Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Colon Cancer Panel members can be found on page 398. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

60.5 in 1976 to 46.4 in 2005.[2] In fact, the incidence of CRC decreased at a rate of approximately 3% per year between 2003 and 2012.[1] The incidence rate for CRC reported by the CDC for 2011 is 40.0 per 100,000 persons.[3] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[4] and is currently down by approximately 50% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.

Despite the observed improvements in the overall CRC incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients <50 years of age has been increasing.[5] The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years by 2030. The cause of this trend is currently unknown.

This portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM staging system (Table 1 [ST-1], available in these guidelines at NCCN.org).[6] Furthermore, all recommendations are classified as category 2A

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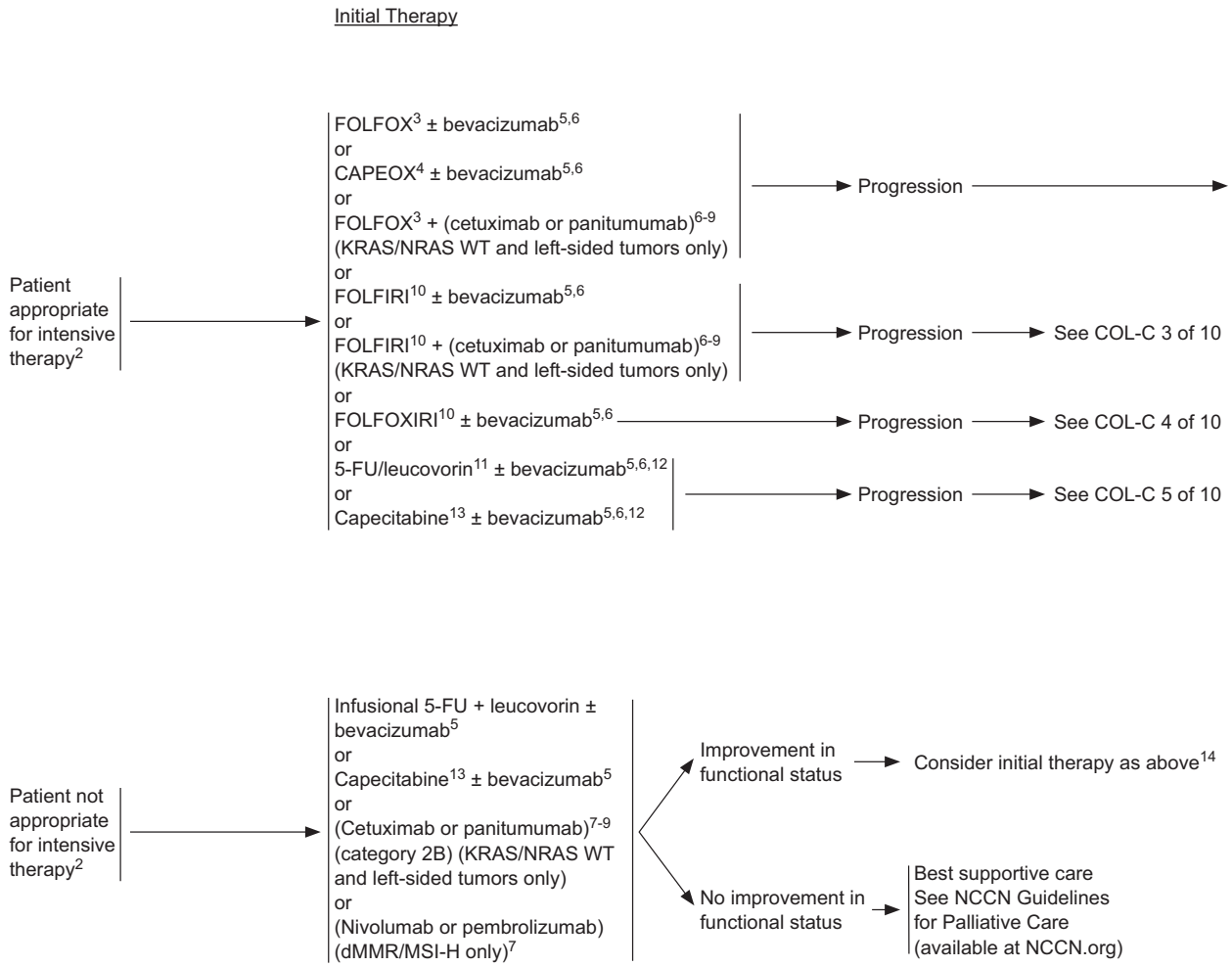
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 10)

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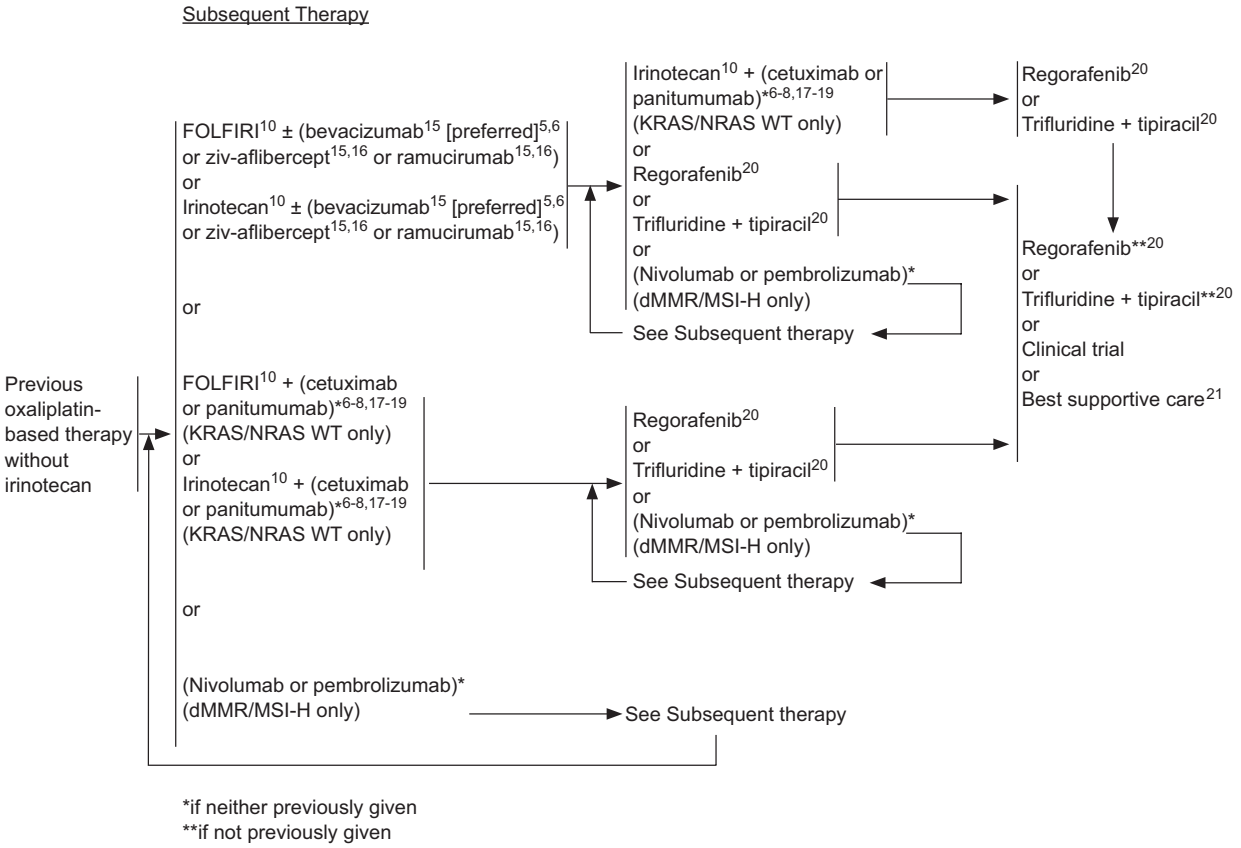


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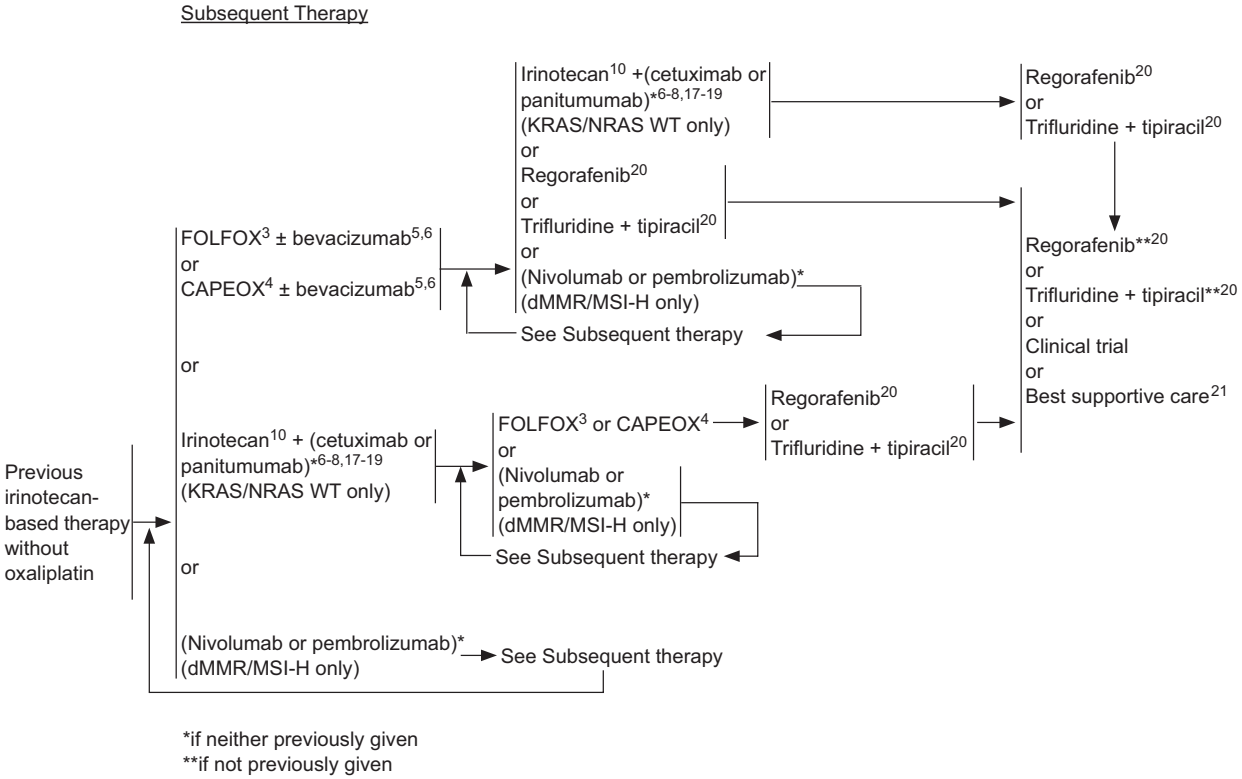


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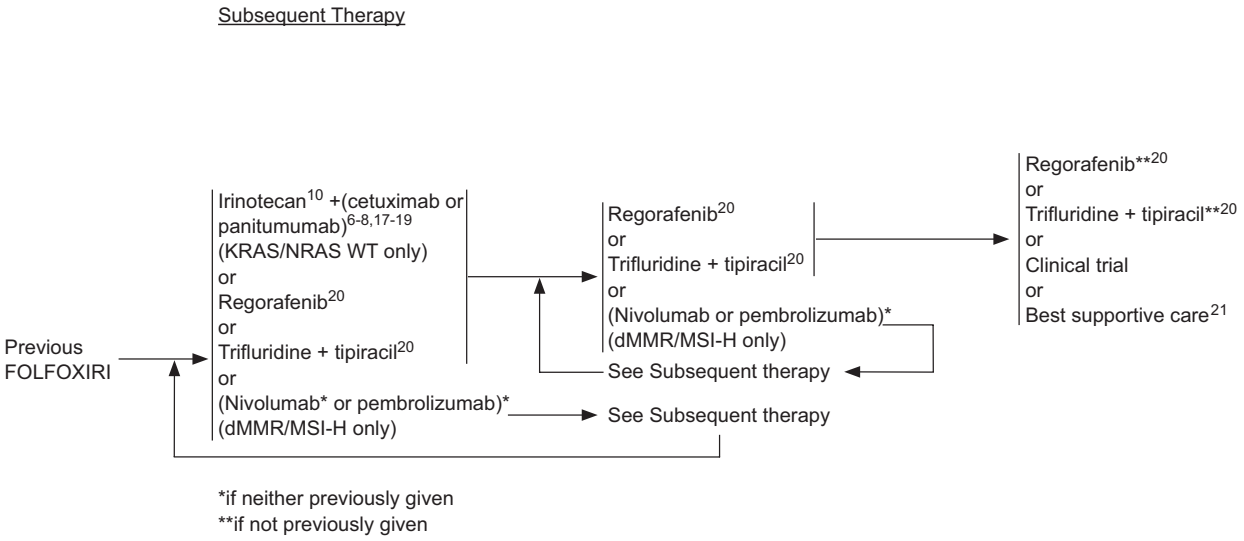


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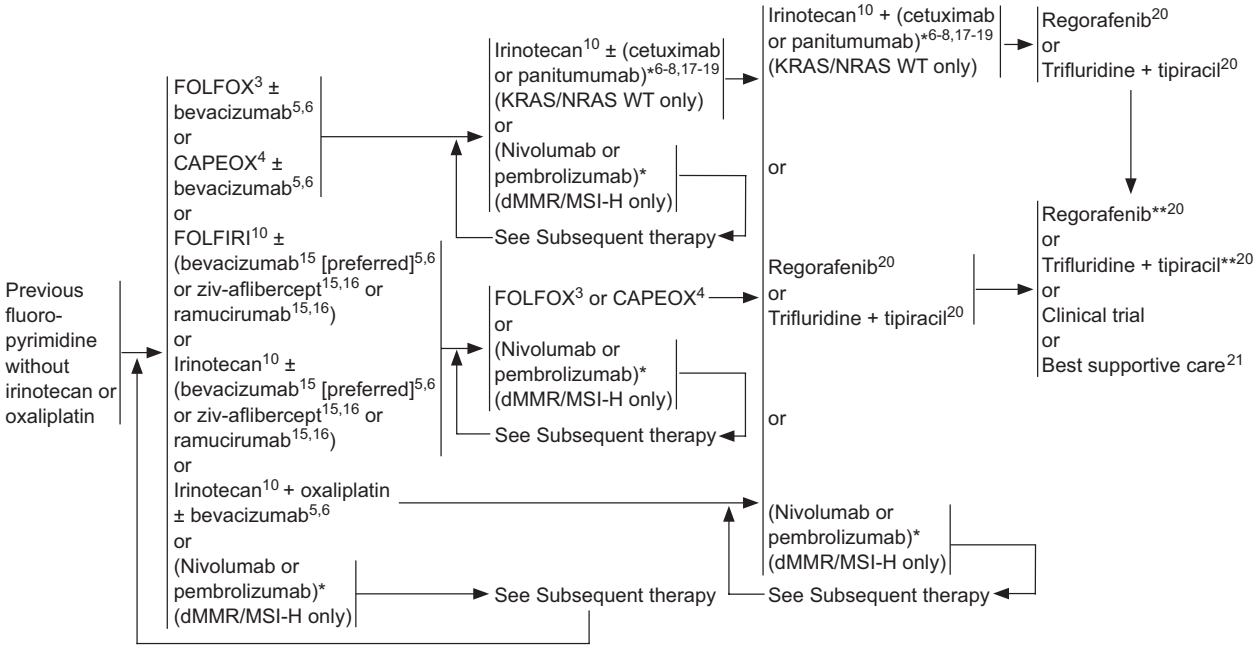
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 5 of 10)

Subsequent Therapy

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 10)

[1]For chemotherapy references, see Chemotherapy Regimens and References (COL-C 7-10).

[2]Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used.

[3]Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CAPEOX after 3–4 months of therapy (or sooner if significant neurotoxicity develops ≥ grade 2) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2006;24:394-400. There are no data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity and therefore it should not be done.

[4]The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CAPEOX with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.

[5]There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.

[6]Combination therapy involving cytotoxics, anti-EGFRs, and anti-VEGFs is not recommended. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-80. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360(6):563-572.

[7]See Principles of Pathologic Review (COL-A 4 of 5; available online, in these guidelines, at NCCN.org).

[8]Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely.

[9]There is a preponderance of data to suggest lack of activity of cetuximab and panitumumab in initial therapy for patients whose primary tumors originated on the right side of the colon.

[10]Irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.

[11]Infusional 5-FU is preferred.

[12]A treatment option for patients not able to tolerate oxaliplatin or irinotecan.

[13]Patients with diminished creatinine clearance may require dose modification of capecitabine.

[14]The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.

[15]Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

[16]There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

[17]Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

[18]EGFR testing has no demonstrated predictive value; therefore, routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

[19]There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.

[20]Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

[21]Single-agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.

Cont. from page 371.

except where noted in the text or algorithm. Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

## Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents: 5-FU/leucovorin (LV), capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, trifluridine-tipiracil, pembrolizumab, and nivolumab.[7–48] The putative mechanisms of action of these agents are varied and include interference with DNA replication and inhibition of the activities of vascular endothelial growth factor (VEGF) and epidermal growth factors (EGFRs).[49–52] The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[25] For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

Principles to consider at the start of therapy include preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based partly on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for this therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (ie, mFOLFOX6),[34,53] FOLFIRI,[8] CapeOx,[11,54,55] infusional 5-FU/LV or capecitabine,[8,30,37,48] or FOLFOXIRI,[21,40] with or without targeted agents.[56]

### Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Before the use of targeted agents, several studies randomized patients to different schedules.[53,57–59] The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given in first line or if less intensive therapy is given first followed by more intensive combinations.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first progression showed neither sequence to be significantly superior with respect to progression-free survival (PFS) or median overall survival (OS).[53] A combined analysis of data from 7 recent phase III clinical trials in advanced CRC provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, irinotecan) at some point in the continuum of care.[60] Furthermore, OS was not found to be associated with the order in which these drugs were received.

A study of 6,286 patients from 9 trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of metastatic CRC treatment according to patient performance status showed similar therapeutic efficacy for patients with performance status of 2 or 1 or less compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[61]

Overall, the panel does not consider one regimen (ie, FOLFOX, CapeOx, FOLFIRI, 5-FU/LV, capecitabine, FOLFOXIRI) to be preferable over the

others as initial therapy for metastatic disease. The panel also does not indicate a preference for biologic agents used as part of initial therapy (ie, bevacizumab, cetuximab, panitumumab, none).

## Maintenance Therapy

Interest in the use of a maintenance therapy approach after first-line treatment of unresectable, metastatic CRC is growing. In general, this approach involves intensive first-line therapy, followed by less intensive therapy until progression in patients with good response to initial treatment.

The CAIRO3 study was an open-label, phase III, multicenter randomized controlled trial assessing maintenance therapy with capecitabine/bevacizumab versus observation in 558 patients with metastatic CRC and with stable disease or better after first-line treatment with CapeOx/bevacizumab.[62] After first progression, both groups were to receive CapeOx/bevacizumab again until second progression (PFS2). After a median follow-up of 48 months, the primary end point of PFS2 was significantly better in the maintenance arm (8.5 vs 11.7 months; hazard ratio [HR], 0.67; 95% CI, 0.56–0.81; *P*<.0001), with 54% of patients overall receiving CapeOx/bevacizumab the second time. Quality of life was not affected by maintenance therapy, although 23% of patients in the maintenance group developed hand-foot syndrome during the maintenance period. A nonsignificant trend toward improved OS was seen in the maintenance arm (18.1 vs 21.6 months; adjusted HR, 0.83; 95% CI, 0.68–1.01; *P*=.06).

The AIO 0207 trial was an open-label, noninferiority, randomized phase III trial that randomized 472 patients whose disease did not progress on induction FOLFOX/bevacizumab or CapeOx/bevacizumab to no maintenance therapy or to maintenance therapy with fluoropyrimidine/bevacizumab or with bevacizumab alone.[63] The planned protocol included reintroduction of primary therapy after first progression. The primary end point was time to failure of strategy, defined as time from randomization to second progression, death, and initiation of treatment with a new drug. After a medium follow-up of 17 months, the median time to failure of strategy was 6.4 months (95% CI, 4.8–7.6) for the no treatment group, 6.9 months (95% CI, 6.1–8.5) for the fluoropyrimidine/bevacizumab group, and 6.1 months (95% CI, 5.3–7.4) for the bevacizumab alone group. Compared with fluoropyrimidine/bevacizumab, bevacizumab alone was noninferior, whereas the absence of maintenance therapy was not. However, only approximately one-third of trial participants received the reinduction therapy, thus limiting the interpretation of results. OS was one of the secondary end points of the trial, and no relevant difference was seen between the arms.

The randomized phase III noninferiority SAKK 41/06 trial addressed the question of continuing bevacizumab alone as maintenance therapy after chemotherapy plus bevacizumab in first-line treatment.[64] The primary end point of time to progression was not met (4.1 months for bevacizumab continuation vs 2.9 months for no continuation; HR, 0.74; 95% CI, 0.58–0.96), and no difference in OS was observed (25.4 vs 23.8 months; HR, 0.83; 95% CI, 0.63–1.1; *P*=.2). Therefore, noninferiority for treatment holidays versus bevacizumab maintenance therapy was not demonstrated.

The GERCOR DREAM trial (OPTIMOX3) was an international, open-label, phase III study that randomized patients with metastatic CRC without disease progression on bevacizumab-based therapy to maintenance therapy with bevacizumab or bevacizumab plus erlotinib.[65] Intention-to-treat analysis revealed an advantage in PFS (5.4 vs 4.9 months; stratified HR, 0.81; 95% CI, 0.66–1.01; *P*=.06) and OS (24.9 vs 22.1 months; stratified HR, 0.79; 95% CI, 0.63–0.99; *P*=.04) with combination therapy. A smaller randomized trial, however, showed no difference in PFS or OS between bevacizumab and bevacizumab/erlotinib maintenance therapy in patients with KRAS wild-type tumors.[66] A meta-analysis identified 3 randomized trials (682 patients) and concluded that maintenance therapy with bevacizumab/erlotinib significantly increases OS and PFS, with manageable toxicity.[67]

Another phase III trial investigated the role of capecitabine in the maintenance phase, after initial treatment with FOLFOX or CapeOx.[68] PFS, the primary end point, was 6.4 months in the capecitabine maintenance group and 3.4 months in the group that was observed until progression (HR, 0.54; 95% CI, 0.42–0.70; *P*<.001). A non–statistically significant difference in the median OS was also seen (HR, 0.85; 95% CI, 0.64–1.11; *P*=.2247). Toxicities associated with the capecitabine maintenance therapy were acceptable.

## Bevacizumab

Bevacizumab is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis.[69] Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved OS in patients with unresectable metastatic CRC compared with those receiving these regimens without bevacizumab.[70–72] A combined analysis of the results of these trials showed that the addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab ($P$=.008).[31] A study of previously untreated patients receiving bevacizumab plus irinotecan/fluorouracil/leucovorin (IFL) also provided support for the inclusion of bevacizumab in initial therapy.[70] In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs 15.6 months; HR, 0.66; $P$<.001).

Results have also been reported from a large, head-to-head, randomized, double-blind, placebo-controlled, phase III study (NO16966) in which CapeOx (capecitabine dose, 1000 mg/m$^2$, twice daily for 14 days) with bevacizumab or placebo was compared with FOLFOX with bevacizumab or placebo in 1,400 patients with unresectable metastatic disease.[39] The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; $P$=.0023), and the difference in OS, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; $P$=.077).[39] Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although these hypotheses are conjectural.[39] However, in this 1,400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab, and this finding could not have been influenced by the early withdrawal rates, which would have occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOx indicated that bevacizumab was associated with improvements in PFS when added to CapeOx but not FOLFOX.[39]

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced CRC has been studied, although no randomized controlled trials have compared FOLFIRI with and without bevacizumab. A recent systematic review with a pooled analysis (29 prospective and retrospective studies, 3,502 patients) found that the combination gave a response rate of 51.4%, a median PFS of 10.8 months (95% CI, 8.9–12.8), and a median OS of 23.7 months (95% CI, 18.1–31.6).[73] FOLFOXIRI with bevacizumab is also an accepted combination (see section on "FOLFOXIRI," available online, in these guidelines, at NCCN.org [MS-37]), although no randomized controlled trials have compared FOLFOXIRI with and without bevacizumab.

A prospective observational cohort study (ARIES) included 1,550 patients who received first-line therapy with bevacizumab with chemotherapy for metastatic CRC and 482 patients treated with bevacizumab in second-line therapy.[74] Median OS was 23.2 months (95% CI, 21.2–24.8) for the first-line cohort and 17.8 months (95% CI, 16.5–20.7) in the second-line group. A similar cohort study (ETNA) of first-line bevacizumab use with irinotecan-based therapy reported a median OS of 25.3 months (95% CI, 23.3–27.0).[75]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for metastatic CRC.[76–84] A meta-analysis of 6 randomized clinical trials (3,060 patients) that assessed the efficacy of bevacizumab in first-line treatment of metastatic CRC found that bevacizumab gave a PFS (HR, 0.72; 95% CI, 0.66–0.78; $P$<.00001) and OS (HR, 0.84; 95% CI, 0.77–0.91; $P$<.00001) advantage.[85] However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In addition, a recent analysis of the SEER-Medicare database found that bevacizumab added a modest improvement to OS of patients with stage IV colorectal cancer diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).[86] The survival advantage was not evident when bevacizumab was combined with oxaliplatin-based chemotherapy, but was evident in irinotecan-based regimens. Limitations of this analysis have been discussed,[87,88] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

No data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease. Recent data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer[89,90] have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. However, the panel does not recommend the use of bevacizumab in the perioperative stage IV setting.

A recent meta-analysis of randomized controlled trials showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (relative risk [RR], 1.33; 95% CI, 1.02–1.73; *P*=.04), with hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) being the most common causes of fatality.[91] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[92] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension and gastrointestinal hemorrhage and perforation, although the overall risk for hemorrhage and perforation is low.[93] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged ≥65 years. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.[94,95] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of gastrointestinal perforation when treated with bevacizumab.[96] This result illustrated that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.[69]

Use of bevacizumab may interfere with wound healing.[69,94,95] A retrospective evaluation of data from 2 randomized trials of 1,132 patients undergoing chemotherapy with or without bevacizumab as initial therapy for metastatic CRC indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; *P*=.28).[95] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered before surgery, with a delay between bevacizumab administration and surgery of at least 6 weeks, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; *P*=.63). Similarly, results of a single-center, nonrandomized phase II trial of patients with potentially resectable liver metastases showed no increase in bleeding or wound complications when the bevacizumab component of CapeOx plus bevacizumab therapy was stopped 5 weeks before surgery (ie, bevacizumab excluded from the sixth cycle of therapy).[97] In addition, no significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped at ≤8 weeks versus at >8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[98] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[69]) between the last dose of bevacizumab and any elective surgery.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and increased mortality. A recent retrospective meta-analysis of 5 placebo-controlled, randomized phase III trials including 4,205 patients with metastatic colorectal, breast, renal, or pancreatic cancer found no difference in time to disease progression and mortality with discontinuation of bevacizumab versus discontinuation of placebo.[99] Although this meta-analysis has been criticized,[100,101] the results are supported by recent results from the NSABP Protocol C-08 trial.[89] This trial included patients with stage II and III CRC, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus those in the control arm. These results suggest that no "rebound effect" is associated with bevacizumab use.

## Cetuximab and Panitumumab

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways. Panitumumab is a fully human monoclonal antibody, whereas cetuximab is a chimeric monoclonal antibody.[102,103] Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of metastatic CRC. Recent meta-analyses of randomized controlled trials have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-type metastatic CRC.[104,105] Individual trials and the role of *KRAS*, *NRAS*, and *BRAF* are discussed herein.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[102,103] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[106–108] Skin toxicity is a side effect of both of these agents and is not considered part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab seem to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs have been shown to predict increased response and survival.[44,109–113] An NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[114] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious adverse events.[115,116]

Based on the results of the PACCE and CAIRO2 trials, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see "Bevacizumab," page 380).[41,117] Several trials that assessed EGFR inhibitors in combination with various chemotherapy agents are discussed herein.

***The Role of Primary Tumor Sidedness:*** A growing body of data has shown that the location of the primary tumor can be both prognostic and predictive of response to EGFR inhibitors in metastatic CRC.[118–125] For example, outcomes of 75 patients with metastatic CRC treated with cetuximab, panitumumab, or cetuximab/irinotecan in first-line or subsequent lines of therapy at 3 Italian centers were analyzed based on sidedness of the primary tumor.[119] No responses were seen in the patients with right-sided primary tumors, compared with a response rate of 41% in those with left-sided primaries ($P$=.003). The median PFS was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (HR, 3.97; 95% CI, 2.09–7.53; $P$<.0001).

The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial.[125,126] The study showed that patients with all *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in the first line (HR, 1.36; 95% CI, 0.93–1.99; $P$=.10), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; $P$=.04).[126] OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 vs 32.6 months) but shortened in the right-sided primary group (13.6 vs 29.2 months).

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with metastatic CRC if the primary tumor originated on the right side.[118,119,121,122] The panel believes that primary tumor sidedness is a surrogate for the nonrandom distribution of molecular subtypes across the colon and that the ongoing analysis of tumor specimens from the study will enable a better understanding of the biologic explanation of the observed difference in response to EGFR inhibitors. Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy,[118,119,122] but the panel awaits more definitive studies. Until such data are available, all patients with *RAS* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

***The Role of* KRAS, NRAS, *and* BRAF *Status:*** The receptor for EGFR has been reported to be overexpressed in 49% to 82% of colorectal tumors.[127–130] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of re-

sponse to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[14] A similar conclusion was drawn with respect to panitumumab.[131] Therefore, routine EGFR testing is not recommended, and no patient should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using immunohistochemistry is not predictive of treatment efficacy.[14,132] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with CRC.[14,45,132] The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to cetuximab or panitumumab therapy (see "*KRAS* Exon 2 Mutations," this page).[7,44,110,133–138] More recent evidence shows mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab (see "*NRAS* and Other *KRAS* Mutations," page 384).[105,139]

The panel therefore strongly recommends *KRAS/NRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic CRC. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by *KRAS/NRAS* wild-type genes. ASCO released a provisional clinical opinion update on extended *RAS* testing in patients with metastatic CRC that is consistent with the NCCN panel's recommendations.[140]

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic CRC for *RAS* (*KRAS* exon 2 and non-exon 2; *NRAS*) and *BRAF* at diagnosis of stage IV disease. The recommendation for *KRAS/NRAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *KRAS/NRAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non–time-sensitive manner and the patient and provider can discuss the implications of a *KRAS/NRAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *KRAS/NRAS* genotyping of CRC at these earlier stages is not recommended.

*KRAS* mutations are early events in CRC formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[141–143] For this reason, *KRAS/NRAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS/NRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS*, *NRAS*, and *BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[144] No specific testing methodology is recommended.[145]

KRAS *Exon 2 Mutations:* Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[7,146] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[7,44,110,133–138,147] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of CRC characterized by these mutations.[102,103] Results are mixed regarding the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter disease-free survival than patients without such mutations.[148] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al[149] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive

of nonresponse. Another retrospective study showed similar results.[138] However, more recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[150] Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory metastatic CRC whose tumors contained *KRAS* G13D mutations.[151] The primary end point of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the phase II AGITG ICECREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.[152] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

NRAS *and Other* KRAS *Mutations:* In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.[153] In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; *P*=.008) and OS (HR, 1.21; 95% CI, 1.01–1.45; *P*=.04) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared with those who received FOLFOX alone.[139] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in "Cetuximab or Panitumumab Versus Bevacizumab in First-Line," page 387) was recently published.[154] When all *RAS* (*KRAS*/*NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than in patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 vs 12.2 months; *P*=.004). On the other hand, patients with *KRAS*/*NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 vs 10.2 months; *P*=.54). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was recently updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation–positive disease in combination with oxaliplatin-based chemotherapy.[103] The NCCN Colon Cancer Panel believes that non–exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.

BRAF *V600E Mutations:* Although mutations of *KRAS*/*NRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS*/*NRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS*/*NRAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E).[155,156] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[155,157] Activation of the protein product of the nonmutated *BRAF* gene occurs downstream of the activated *KRAS* protein in the EGFR pathway; the mutated BRAF protein product is believed to be constitutively active,[158–160] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with metastatic CRC treated in the first-line setting suggest that, although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.[156,161] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of metastatic CRC.[139] On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental one in patients with *BRAF*-mutated tumors treated with CapeOx or FOLFOX in the first-line setting.[157]

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non–first-line setting of metastatic disease.[162–164] A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; *P*=.0012).[165] Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non–first-line setting in the small subset of patients with *BRAF* mutations.[166]

A meta-analysis published in 2015 identified 9 phase III trials and 1 phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care, including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).[167] The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14; *P*=.33), OS (HR, 0.91; 95% CI, 0.62–1.34; *P*=.63), or overall response rate (RR, 1.31; 95% CI, 0.83–2.08, *P*=.25) compared with control arms. Similarly, another meta-analysis identified 7 randomized controlled trials and found that cetuximab and panitumumab did not improve PFS (HR, 0.86; 95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF* mutations.[168]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[146,156,157,169–174] A prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with microsatellite instability–low (MSI-L) or microsatellite stable (MSS) tumors (HR, 2.2; 95% CI, 1.4–3.4; *P*=.0003).[146] Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.[156] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (95% CI, 0.33–0.73; *P*=.001).[170] The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, whereas those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 and 20.1 months, respectively.[157] Results from a recent systematic review and meta-analysis of 21 studies, including 9,885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[175] In particular, an association was observed between *BRAF* mutation and proximal tumor location (odds ratio [OR], 5.22; 95% CI, 3.80–7.17; *P*<.001), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; *P*=.007), and poor differentiation (OR, 3.82; 95% CI, 2.71–5.36; *P*<.001).

Overall, the panel believes that evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely. The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[176]) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by polymerase chain reaction (PCR) amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

***HER2 Overexpression:*** HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely overexpressed in CRC (approximately 3% overall), but the prevalence is higher in *RAS*/*BRAF* wild-type tumors (reported at 5%–14%).[177,178] Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,[179] and various therapeutic approaches are being tested in patients with tumors that have HER2 overexpression (eg, trastuzumab plus lapatinib, trastuzumab plus pertuzumab).[177,180] These approaches are currently considered investigational, and enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.[181] However, initial results indicate HER2 overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.[178,182] For example, in a cohort of 97 patients with *RAS*/*BRAF* wild-type metastatic CRC, median PFS on first-line therapy without an EGFR inhibitor was similar regardless of HER2 status.[178] However, in second-line therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2

amplification compared with those without (2.9 vs 8.1 months; HR, 5.0; *P*<.0001). Larger confirmatory studies are needed, and the panel does not recommend HER2 testing for prognostication or treatment planning at this time.

***Cetuximab With FOLFIRI:*** Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial, in which patients were randomly assigned to receive FOLFIRI with or without cetuximab.[44] Retrospective analyses of the subset of patients with known *KRAS* exon 2 tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the wild-type (9.9 vs 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; *P*=.02).[44] The statistically significant benefit in PFS for patients with *KRAS* exon 2 wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.[156] This recent study included a retrospective analysis of OS in the *KRAS* exon 2 wild-type population and found an improvement with the addition of cetuximab (23.5 vs 20.0 months; *P*=.009). Importantly, the addition of cetuximab did not affect the quality of life of participants in the CRYSTAL trial.[183] As has been seen with other trials, when DNA samples from the CRYSTAL trial were reanalyzed for additional *KRAS* and *NRAS* mutations, patients with *RAS* wild-type tumors derived a clear OS benefit (HR, 0.69; 95% CI, 0.54–0.88), whereas those with any *RAS* mutation did not (HR, 1.05; 95% CI, 0.86–1.28).[184]

***Panitumumab With FOLFIRI:*** FOLFIRI with panitumumab is listed as an option for first-line therapy in metastatic CRC based on extrapolation from data in second-line treatment.[36,166,185,186]

***Cetuximab With FOLFOX:*** Three trials have assessed the combination of FOLFOX and cetuximab in first-line treatment of metastatic CRC. In a retrospective evaluation of the subset of patients with known tumor *KRAS* exon 2 status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs 37%; OR, 2.54; *P*=.011) and a very slightly lower risk of disease progression (7.7 vs 7.2 months [a 15-day difference]; HR, 0.57; 95% CI, 0.36–0.91; *P*=.016) compared with FOLFOX alone in the subset of patients with *KRAS* exon 2 wild-type tumors.[134] Although data supporting the statistically significant benefits in objective response rate and PFS for patients with tumors characterized by *KRAS* wild-type exon 2 were upheld in an update of this study, no median OS benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm vs 18.5 months in the arm undergoing chemotherapy alone; HR, 0.85; *P*=.39).[187]

Furthermore, in the recent randomized phase III MRC COIN trial, no benefit in OS (17.9 vs 17.0 months; *P*=.067) or PFS (8.6 months in both groups; *P*=.60) was seen with the addition of cetuximab to FOLFOX or CapeOx as first-line treatment of patients with locally advanced or metastatic CRC and wild-type *KRAS* exon 2.[157] Exploratory analyses of the COIN trial, however, suggest that there may be a benefit to the addition of cetuximab in patients who received FOLFOX instead of CapeOx.[157] Similarly, a recent pooled analysis of the COIN and OPUS studies found that a benefit was suggested in response rate and PFS with the addition of cetuximab to FOLFOX in patients with *KRAS* exon 2 wild-type tumors, although there was no OS benefit.[188]

Notably, more recent trials examining the efficacity of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced or metastatic CRC and wild-type *KRAS* exon 2 have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no OR or PFS benefit in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.[189]

However, results from the recent randomized phase III CALGB/SWOG 80405 trial of >3,000 patients (discussed in "Cetuximab or Panitumumab Versus Bevacizumab in First-Line," page 387) showed that the combination of FOLFOX with cetuximab can be effective in the first-line treatment of metastatic CRC.[190] The panel thus added a recommendation for the use of cetuximab with FOLFOX as initial therapy for patients with advanced or metastatic disease to the 2015 version of these guidelines.

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI).[191] In fact, with fewer than half

of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs 24.2 months; HR, 1.50; 95% CI, 1.00–2.25; *P*<.048). The panel thus cautions that cetuximab in the perioperative setting may harm patients. The panel therefore does not recommend the use of FOLFOX plus cetuximab in patients with resectable disease and should be used with caution in those with unresectable disease that could potentially be converted to a resectable status.

***Panitumumab With FOLFOX:*** Panitumumab in combination with either FOLFOX[20,139] or FOLFIRI[33] has also been studied in the first-line treatment of patients with metastatic CRC. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS/NRAS* wild-type advanced CRC showed a statistically significant improvement in PFS (HR, 0.72; 95% CI, 0.58–0.90; *P*=.004) and OS (HR, 0.77; 95% CI, 0.64–0.94; *P*=.009) with the addition of panitumumab.[139] Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. Importantly, the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS/NRAS* in the PRIME trial (discussed further in "*NRAS* and Other *KRAS* Mutations," page 384).[139]

## Cetuximab or Panitumumab Versus Bevacizumab in First-Line

The randomized, open-label, multicenter FIRE-3 trial from the German AIO group compared the efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.[154] This trial did not meet its primary end point of investigator-read objective response rate in the 592 randomized patients (62.0% vs 58.0%; *P*=.18). PFS was nearly identical between the arms of the study, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs 25.0 months; HR, 0.77; 95% CI, 0.62–0.96; *P*=.017). The panel has several criticisms of the trial, including the lack of third-party review and low rates of second-line therapy.[192,193] Although the rate of adverse events was similar between the arms, more skin toxicity was observed in those receiving cetuximab.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were recently reported.[190] In this study, patients with wild-type *KRAS* exon 2 received either FOLFOX (73%) or FOLFIRI (27%) and were randomized to receive cetuximab or bevacizumab. The primary end point of OS was equivalent between the arms: 29.0 months (95% CI, 25.7–31.2 months) in the bevacizumab arm versus 29.9 months (95% CI, 27.6–31.2 months) in the cetuximab arm (HR, 0.92; 95% CI, 0.78–1.09; *P*=.34).

Results were also published for the randomized multicenter phase II PEAK trial, which compared FOLFOX/panitumumab with FOLFOX/bevacizumab in first-line treatment of patients with wild-type *KRAS* exon 2.[194] In the subset of 170 participants with wild-type *KRAS/NRAS* based on extended tumor analysis, PFS was better in the panitumumab arm (13.0 vs 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; *P*=.03), and a trend toward improved OS was seen (41.3 vs 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; *P*=.06). Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[195]

Economic analyses suggest that bevacizumab may be more cost-effective than EGFR inhibitors in first-line therapy for metastatic CRC.[196,197]

At this time, the panel considers the addition of cetuximab, panitumumab, or bevacizumab to chemotherapy as equivalent choices in the first-line, *RAS* wild-type, metastatic setting.

## Therapy After Progression

Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as therapy in patients exhibiting disease progression after treatment with standard therapies. These agents have not been shown to be effective in this setting. Furthermore, no objective responses were observed when single-agent capecitabine was administered in a phase II study of patients with CRC resistant to 5-FU.[198]

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based therapy are dependent on the initial treatment regimen and are outlined in the guidelines.

Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care[15] or infusional 5-FU/LV.[199] In the study of Rougier et al,[199] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (*P*=.030), whereas Cunningham et al[15] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive care group (*P*=.0001). Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of metastatic CRC.[200]

A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[201] Another meta-analysis showed an OS and PFS benefit to continuing an antiangiogenic agent after progression on an antiangiogenic agent in first-line treatment.[202] Data relating to specific biologic therapies are discussed below.

***Cetuximab and Panitumumab in the Non–First-Line Setting:*** For patients with wild-type *KRAS/NRAS* CRC who experienced progression on therapies not containing an EGFR inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab[136] is recommended. For patients with wild-type *KRAS/NRAS* CRC progressing on therapies that did contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice.

Panitumumab has been studied as a single agent in the setting of metastatic CRC for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy.[45] In a retrospective analysis of the subset of patients in this trial with known *KRAS* exon 2 tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[7] PFS was 12.3 versus 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumab were 17% versus 0% in the wild-type and mutant arms, respectively.[7]

Panitumumab has also been studied in combination therapy in the setting of progressing metastatic CRC. Among patients with *KRAS* exon 2 wild-type tumors enrolled in the large study 181 comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for metastatic CRC, addition of the biologic agent was associated with improvement in median PFS (5.9 vs 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; *P*=.004), although differences in OS between the arms did not reach statistical significance.[36] These results were confirmed in the final results of study 181.[186] Furthermore, reanalysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.[203] In addition, secondary analysis from the STEPP trial showed that panitumumab in combination with irinotecan-based chemotherapy in second-line therapy has an acceptable toxicity profile.[185] The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary end point of improved OS in patients with wild-type *KRAS/NRAS* tumors.[166]

Cetuximab has been studied both as a single agent[14,109,132,136] and in combination with irinotecan[14] in patients experiencing disease progression on initial therapy not containing cetuximab or panitumumab for metastatic disease. Results of a large phase III study comparing irinotecan with or without cetuximab did not show a difference in OS, but showed significant improvement in response rate and median PFS with irinotecan and cetuximab compared with irinotecan alone.[204] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[204]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[109] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[136] For those patients, median PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30–0.54; *P*<.001) and median OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41–0.74; *P*<.001), in favor of the cetuximab arm.[136]

The recently published randomized, multicenter, open-label, noninferiority phase III ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[205] The primary noninferiority OS end

point was reached, with a median OS of 10.4 months (95% CI, 9.4–11.6) with panitumumab and 10.0 months (95% CI, 9.3–11.0) with cetuximab (HR, 0.97; 95% CI, 0.84–1.11). The incidence of adverse events was similar between the groups.

***Bevacizumab in the Non–First-Line Setting:*** In the ML18147 (TML) trial, patients with metastatic CRC that progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[206] This study met its primary end point, with patients continuing on bevacizumab having a modest improvement in OS (11.2 vs 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; *P*=.0062). Subgroup analyses from this trial found that these treatment effects were independent of *KRAS* exon 2 status.[207]

Similar results were reported from the GONO group's phase III randomized BEBYP trial, in which the PFS of patients who continued on bevacizumab plus a different chemotherapy regimen after progression on bevacizumab was 6.8 versus 5.0 months in the control arm (HR, 0.70; 95% CI, 0.52–0.95; *P*=.001).[208] An improvement in OS was also seen in the bevacizumab arm (HR, 0.77; 95% CI, 0.56–1.06; *P*=.04). The EAGLE trial randomized 387 patients with disease progression after oxaliplatin-based therapy with bevacizumab to second-line therapy with FOLFIRI plus either 5 or 10 mg/kg of bevacizumab.[209] No difference was seen in PFS or time to treatment failure between the arms, indicating that 5 mg/kg of bevacizumab is an appropriate dose in second-line treatment of metastatic CRC.

The continuation of bevacizumab after progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from US Oncology's iKnowMed electronic medical record system.[210] Bevacizumab beyond progression was associated with a longer OS (HR, 0.76; 95% CI, 0.61–0.95) and a longer postprogression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis. Analyses of the ARIES observational cohort found similar results, with longer postprogression survival with continuation of bevacizumab (HR, 0.84; 95% CI, 0.73–0.97).[211]

Overall, these data (along with data from the VELOUR trial, discussed later) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant OS benefit. The panel added the continuation of bevacizumab to the second-line treatment options in the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers. It may be added to any regimen that does not contain another targeted agent. The panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this setting, but believes that the option is acceptable, especially in patients whose disease progressed on a 5-FU– or capecitabine-based regimen. When an angiogenic agent is used in second-line therapy, bevacizumab is preferred over ziv-aflibercept and ramucirumab (discussed later), based on toxicity and/or cost.[212]

It may also be appropriate to consider adding bevacizumab to chemotherapy after progression of metastatic disease if it was not used in initial therapy.[23] The randomized phase III ECOG E3200 study in patients who experienced progression through a first-line non–bevacizumab-containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.[23] Median OS was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months for patients treated with FOLFOX alone (*P*=.0011).[23] Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[23]

***Ziv-Aflibercept:*** Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1.[213] It is designed to function as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with metastatic CRC that progressed after one regimen containing oxaliplatin. The trial met its primary end point with a small improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; *P*=.003).[47] A prespecified subgroup analysis from the VELOUR trial found that median OS in the ziv-aflibercept arm versus the placebo arm was 12.5 months (95% CI, 10.8–15.5) versus 11.7 months (95% CI, 9.8–13.8) in patients with prior bevacizumab treatment and 13.9 months (95% CI, 12.7–15.6) versus 12.4 months (95% CI, 11.2–13.5) in patients with no prior bevacizumab treatment.[214]

Adverse events associated with ziv-aflibercept treatment in the VELOUR trial led to discontinu-

ation in 26.6% of patients compared with a 12.1% discontinuation in the placebo group.[47] The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who progressed on FOLFIRI plus bevacizumab or vice versa, and no data suggest activity of single-agent ziv-aflibercept. Furthermore, the addition of ziv-aflibercept to FOLFIRI in first-line therapy of patients with metastatic CRC in the phase II AFFIRM study had no benefit and increased toxicity.[215] Thus, the panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only after progression on therapy not containing irinotecan. However, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab in this setting, based on toxicity and/or cost.[212]

***Ramucirumab:*** Another antiangiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGF receptor 2 to block VEGF signaling.[216] In the multicenter, phase III RAISE trial, 1,072 patients with metastatic CRC whose disease progressed on first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo.[217] The primary end point of OS in the intent-to-treat population was met at 13.3 and 11.7 months in the ramucirumab and placebo groups, respectively, for an HR of 0.84 (95% CI, 0.73–0.98; *P*=.02). PFS was also improved with the addition of ramucirumab, at 5.7 and 4.5 months for the 2 arms (HR, 0.79; 95% CI, 0.70–0.90; *P*<.0005).

Rates of discontinuation due to adverse events in the RAISE trial were 11.5% in the ramucirumab arm and 4.5% in the placebo arm. The most common grade 3 or worse adverse events were neutropenia, hypertension, diarrhea, and fatigue.

Considering the results of the RAISE trial, the panel added ramucirumab as a second-line treatment option in combination with FOLFIRI or irinotecan after progression on therapy not containing irinotecan. As with ziv-aflibercept, no data suggest activity of FOLFIRI plus ramucirumab in patients whose disease progressed on FOLFIRI plus bevacizumab or vice versa, and no data suggest activity of single-agent ramucirumab. When an angiogenic agent is used in this setting, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab, because of toxicity and/or cost.[212]

***Regorafenib:*** Regorafenib is a small molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor [FGF] receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes, including tumor growth and angiogenesis.[218] The phase III CORRECT trial randomized 760 patients whose disease progressed on standard therapy to best supportive care with placebo or regorafenib.[27] The trial met its primary endpoint of OS (6.4 months for regorafenib vs 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; *P*=.005). PFS was also significantly but modestly improved (1.9 vs 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; *P*<.000001).

The randomized, double-blind, phase III CONCUR trial was performed in China, Hong Kong, South Korea, Taiwan, and Vietnam.[219] Patients with progressive metastatic CRC were randomized 2:1 to receive regorafenib or placebo after ≥2 previous treatment regimens. After a median follow-up of 7.4 months, the primary end point of OS was met in the 204 randomized patients (8.8 months in the regorafenib arm vs 6.3 months in the placebo arm; HR, 0.55; 95% CI, 0.40–0.77; *P*<.001).

Regorafenib has only shown activity in patients whose disease has progressed on all standard therapy. Therefore, the panel added regorafenib as an additional line of therapy for patients with metastatic CRC refractory to chemotherapy. It can be given before or after trifluridine/tipiracil; no data inform the best order of these therapies.

The most common ≥grade 3 adverse events in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[27] Severe and fatal liver toxicity occurred in 0.3% of 1,100 patients treated with regorafenib across all trials.[218] In a meta-analysis of 4 studies that included 1,078 patients treated with regorafenib for CRC, gastrointestinal stromal tumor, renal cell carcinoma, or hepatocellular carcinoma, the overall incidence of all-grade and high-grade hand-foot skin reactions was 60.5% and 20.4%, respectively.[220] In the subset of 500 patients with CRC, the incidence of all-grade hand-foot skin reaction was 46.6%.

The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2,872 patients from 25 countries with refractory metastatic CRC.[221] The REBECCA study also assessed the safety and efficacy of regorafenib in a cohort of 654 patients with metastatic CRC within a compassionate use program.[222] The safety profile of regorafenib in both of these trials was consistent with that seen in the CORRECT trial.

***Trifluridine/Tipiracil (TAS-102):*** Trifluridine/tipiracil is an oral combination drug, consisting of a cytotoxic thymidine analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, which prevents the degradation of trifluridine. Early clinical studies of the drug in patients with CRC were promising.[223,224]

Results of the double-blind randomized controlled international phase III RECOURSE trial were published in 2015,[35] followed shortly thereafter by FDA approval of trifluridine/tipiracil.[225] In this trial, which involved 800 patients with metastatic CRC who progressed through at least 2 prior regimens randomized 2:1 to receive trifluridine/tipiracil or placebo, the primary end point of OS was met (5.3 vs 7.1 months; HR, 0.68; 95% CI, 0.58–0.81; *P*<.001).[35] Improvement was also seen in the secondary end point of PFS (1.7 vs 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; *P*<.001). The most common adverse events associated with trifluridine/tipiracil were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred. A postmarketing surveillance study did not reveal any unexpected safety signals.[226]

The panel added trifluridine/tipiracil as an additional treatment option for patients whose disease has progressed through standard therapies. It can be given before or after regorafenib; no data inform the best order of these therapies. The 144 patients in RECOURSE who had prior exposure to regorafenib obtained similar OS benefit from trifluridine/tipiracil (HR, 0.69; 95% CI, 0.45–1.05) as the 656 patients who did not (HR, 0.69; 95% CI, 0.57–0.83).

***Pembrolizumab and Nivolumab:*** The percentage of stage IV colorectal tumors characterized as MSI-H (mismatch repair–deficient [dMMR]) ranged from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.[227–229] dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed cell death ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells can suppress the immune response by binding to programmed cell death protein 1 (PD-1) receptor on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.[230] Therefore, it has been hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors.

Pembrolizumab is a humanized, IgG4 monoclonal antibody that binds to PD-1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus allowing immune recognition and response. Pembrolizumab is FDA-approved for the treatment of some patients with unresectable or metastatic melanoma or metastatic non–small cell lung cancer.[231]

A recent phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR CRC, 21 patients with MMR-proficient CRC, and 9 patients with dMMR non–colorectal carcinomas.[232] All patients had progressive metastatic disease; the patients in the CRC arms had progressed through 2 to 4 previous therapies. The primary end points were the immune-related objective response rate and the 20-week immune-related PFS rate. The immune-related objective response rates were 40% (95% CI, 12%–74%) in the dMMR CRC group, 0% (95% CI, 0%–20%) in the MMR-proficient CRC group, and 71% (95% CI, 29%–96%) in the dMMR non–colorectal carcinoma group. The 20-week immune-related PFS rates were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were not reached in the arm with dMMR CRC, and were 2.2 and 5.0 months, respectively, in the MMR-proficient CRC group (HR for disease progression or death, 0.10; *P*<.001).

Nivolumab is another humanized IgG4 PD-1 blocking antibody, with FDA indications in melanoma and non–small cell lung cancer.[233] Nivolumab was studied with or without ipilimumab in patients with metastatic CRC in a phase II trial.[234] The median PFS was 5.3 months (95% CI, 1.4–not estimable) in the patients with MMR-deficient CRC who received nivolumab monotherapy, not reached in the patients with MMR-deficient CRC who received

nivolumab plus ipilimumab, and 1.4 months (95% CI, 1.2–1.9) in the pooled MMR-proficient group.

Based on these data, the panel recommends pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient CRC in second- or third-line therapy. Patients who experience disease progression on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.

Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions—many immune-mediated—occur in as many as 21% to 41% of patients.[232,234,235] The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.[236–238] Pneumonitis, occurring in approximately 3% to 7% of patients on pembrolizumab or nivolumab, is one of the most serious side effects of PD-1 inhibitors.[236,239–241]

***Cetuximab or Panitumumab Versus Bevacizumab in Second-Line:*** The randomized, multicenter, phase II SPIRITT trial randomized 182 patients with *KRAS* wild-type tumors whose disease progressed on first-line oxaliplatin-based therapy plus bevacizumab to FOLFIRI plus bevacizumab or FOLFIRI plus panitumumab.[242] No difference was seen in the primary end point of PFS between the arms (7.7 months in the panitumumab arm vs 9.2 months in the bevacizumab arm; HR, 1.01; 95% CI, 0.68–1.50; *P*=.97).

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**Individual Disclosures for the Colon Cancer Panel**

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[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict:
Sunil Sharma, MD: Beta Cat Pharmaceuticals; ConverGene; and Salarius Pharmaceuticals
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