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Colon Cancer, Version 3.2014

Clinical Practice Guidelines in Oncology

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Abstract

The NCCN Guidelines for Colon Cancer address diagnosis, pathologic staging, surgical management, perioperative treatment, posttreatment surveillance, management of recurrent and metastatic disease,and survivorship. This portion of the guidelines focuses on the use of systemic therapy in metastatic disease. The management of metastatic colorectal cancer involves a continuum of care in which patients are exposed sequentially to a variety of active agents, either in combinations or as single agents. Choice of therapy is based on the goals of treatment, the type and timing of prior therapy, the different efficacy and toxicity profiles of the drugs, the mutational status of the tumor, and patient preference. (*J Natl Compr Canc Netw* 2014;12:1028–1059)

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 2013, an estimated 102,480 new cases of colon cancer and approximately 40,340 cases of rectal cancer will occur. During the same year, an estimated 50,830 people will die of colon and rectal cancers combined.[1] Despite these high numbers, the incidence of colon

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 1059. (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.

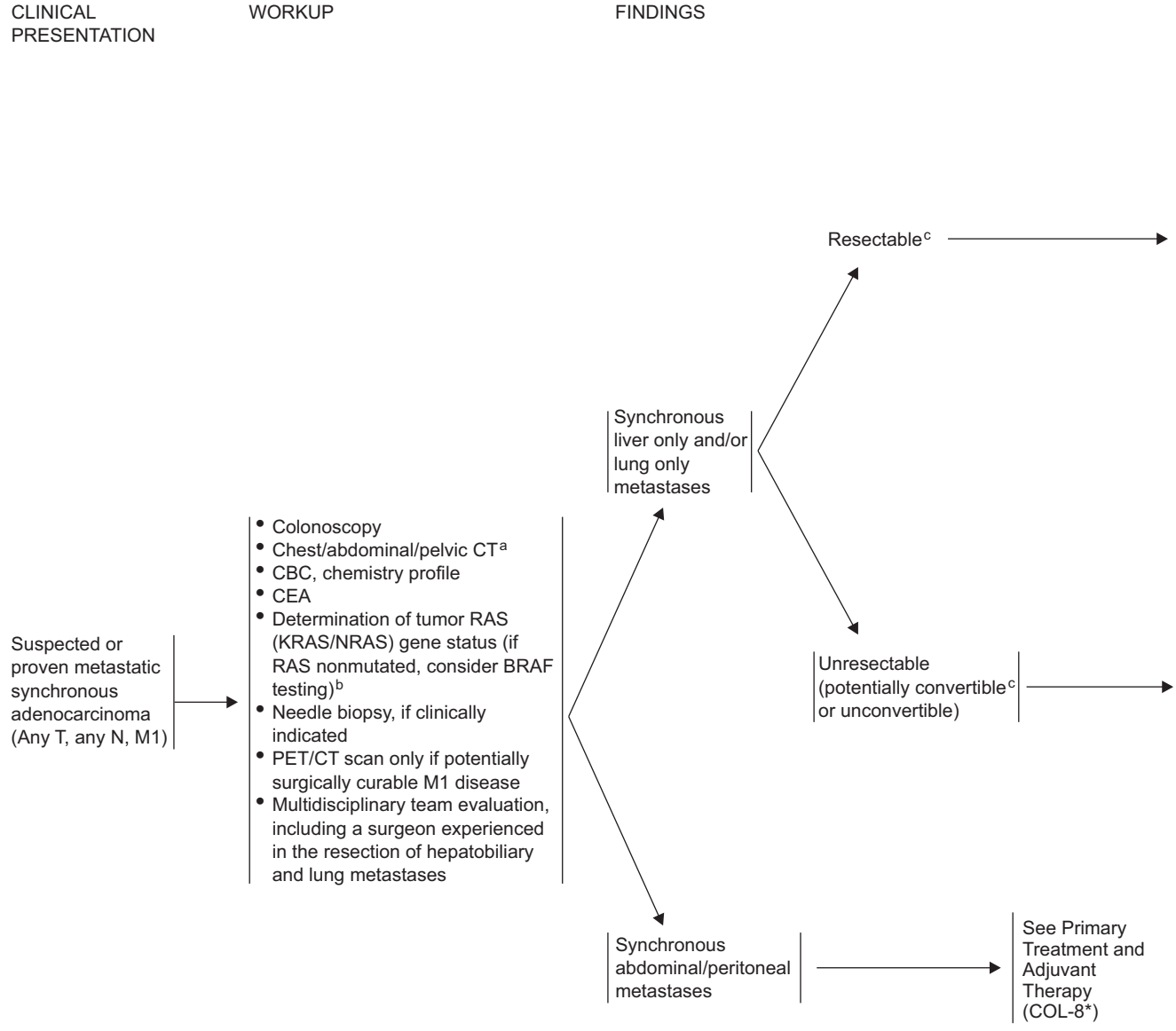
and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[2] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[3] possibly because of earlier diagnosis through screening and better treatment modalities.

This discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy. For other topics related to colon or rectal cancer, please refer to the full NCCN Guidelines for Colon and Rectal Cancers (available at NCCN.org). All recommendations are classified as category 2A 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.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC develop colorectal metastases,[4–6] and 80% to 90% of these patients have unresectable metastatic liver disease.[5,7–10] Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver being the most common site of involvement.[11] However, 20% to 34% of patients with CRC present with synchronous liver metastases.[10,12] Some evidence indicates that synchronous metastatic colorectal liver disease is as-

Text cont. on page 1036.



*Available online, in these guidelines, at NCCN.org.

[a]CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.
[b]See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.
[c]See Principles of Surgery (COL-B 2 of 3*).

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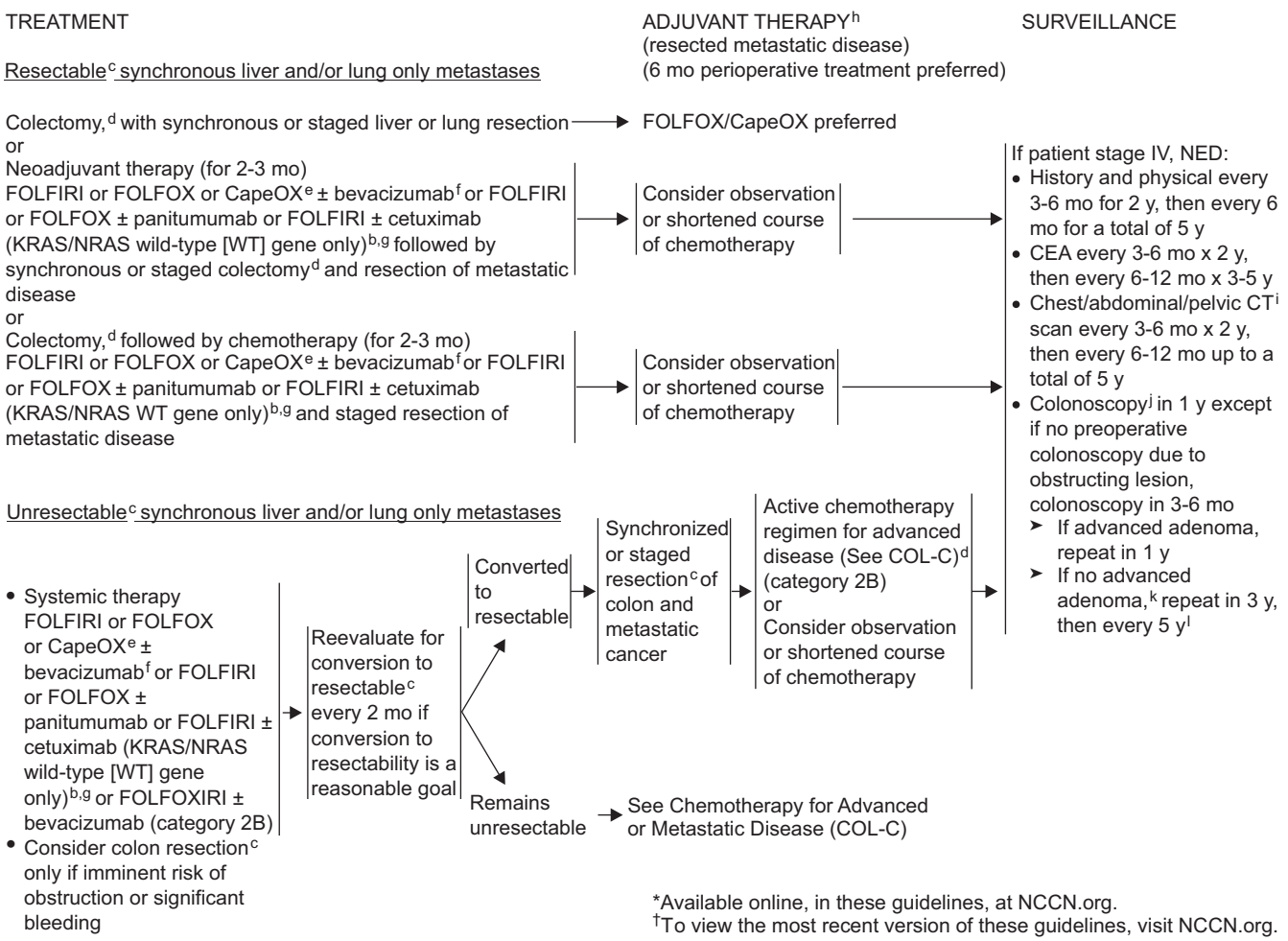

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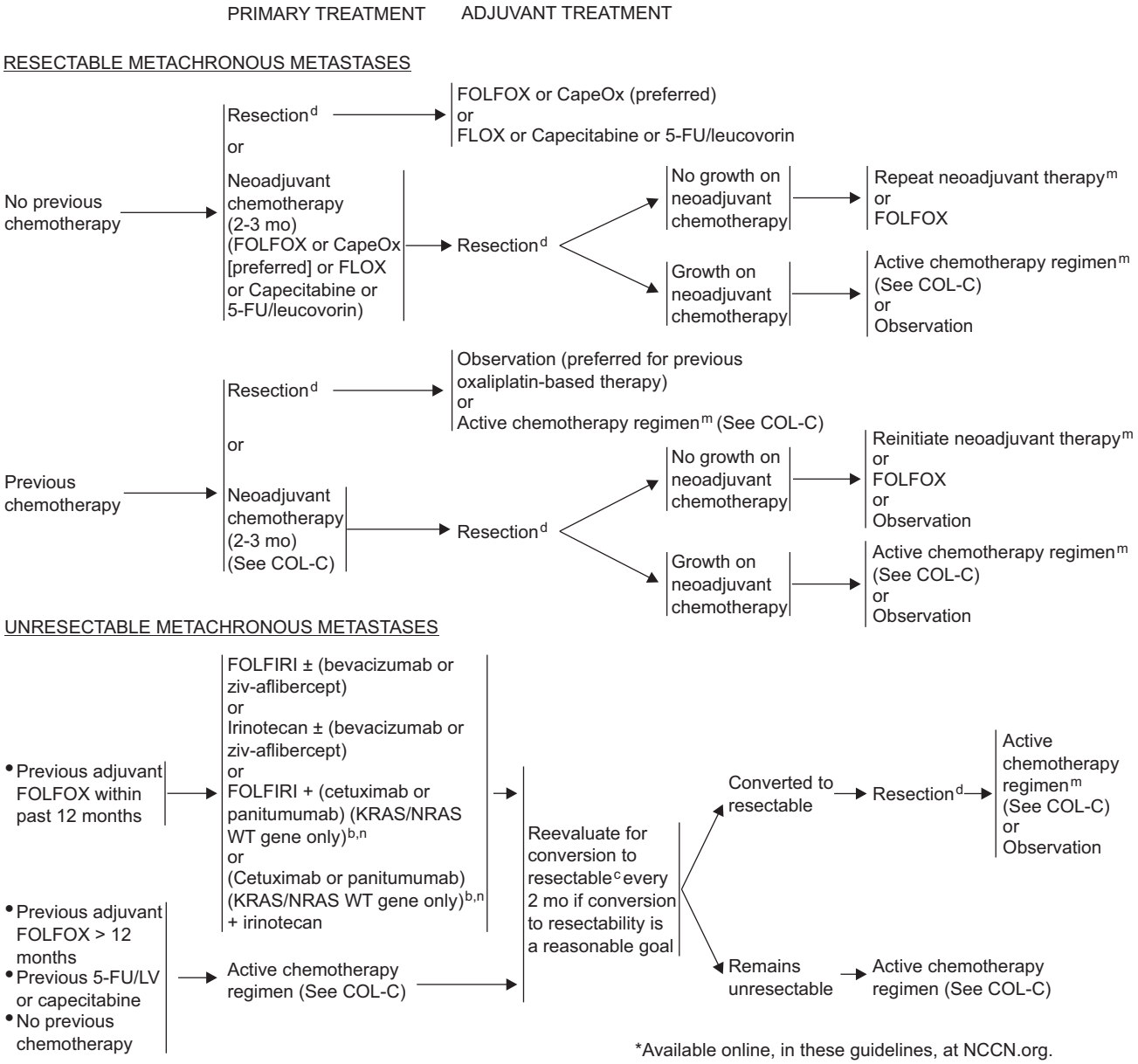
[b] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.
[c] See Principles of Surgery (COL-B 2 of 3*).
[d] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[e] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and 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.
[f] The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-wk interval between the last dose of bevacizumab and elective surgery and reinitiation of bevacizumab at least 6-8 wk postoperatively. 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.
[g] There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.
[h] Testing for mismatch repair proteins (MMR) should be considered for all patients <50 years of age.
[i] CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a noncontrast chest CT if either CT of abdominal/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
[j] All patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†.
[k] Villous polyp, polyp >1 cm, or high grade dysplasia.
[l] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-1871.

COL-6, COL-7



*Available online, in these guidelines, at NCCN.org.

[b] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
[c] See Principles of Surgery (COL-B 2 of 3*).
[d] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[m] Perioperative therapy should be considered for up to a total of 6 months.
[n] Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest a lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.

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PRINCIPLES OF PATHOLOGIC REVIEW

KRAS and NRAS Mutation Testing

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS mutations (KRAS and NRAS). At the very least, exon 2 KRAS mutation status should be determined. Whenever possible, non-exon 2 KRAS mutation status and NRAS mutation status should also be determined. Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.[1-3]
- Testing for KRAS and NRAS mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS and NRAS mutations are similar in both specimen types.[4]

BRAF Mutation Testing

- Patients with a V600E BRAF mutation appear to have a poorer prognosis. There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.[5-6]
- Testing for the BRAF V600E mutation can be performed on formalin-fixed paraffin-embedded tissues. This is usually performed by amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform high complexity clinical laboratory (molecular pathology) testing.

MSI Testing - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†

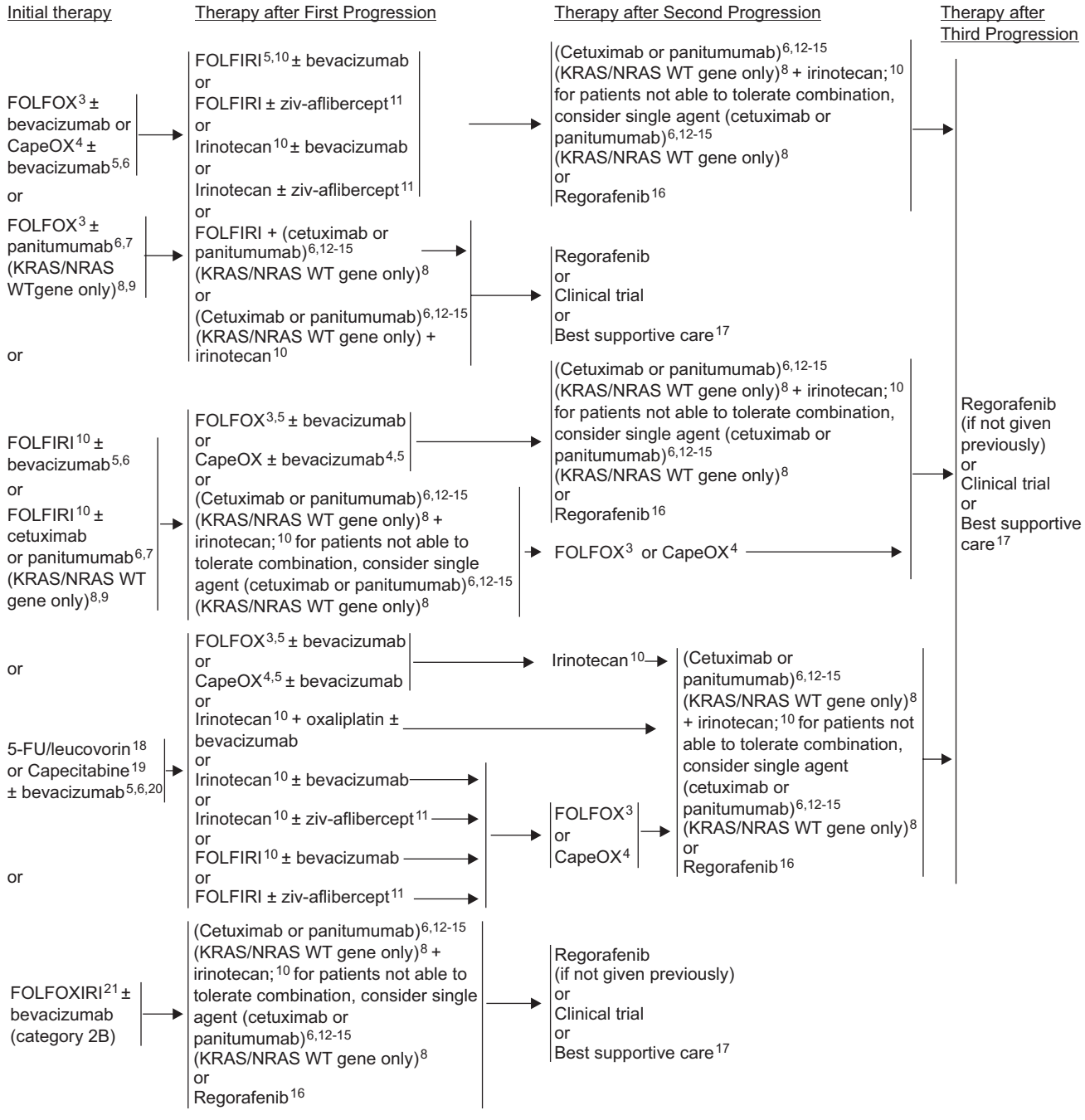
- Lynch syndrome tumors screening (ie, IHC or MSI) should be considered for CRC patients diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines.[7]

†To view the most recent version of these guidelines, visit NCCN.org.

[1] Lievre A, Bachatte JB, Blige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colon cancer with cetuximab. J Clin Oncol 2008;26:374-379.
[2] Amado IG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitunumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634.
[3] Douillard JY, Oliner KS, Siena S, et al. Panitumumab--FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034.
[4] Etienne-Gimeldi MC, Formenta JL, Francoual M, et al. KRAS mutations in treatment outcome in colorectal cancer in patients receiving exclusive fluoropyrimidine. Clin Cancer Research 2008;14:4830-4835.
[5] Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-5712.
[6] Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466-1475.
[7] Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565.

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1]

Patient appropriate for intensive therapy[2]



See footnotes on facing page.

COL-C
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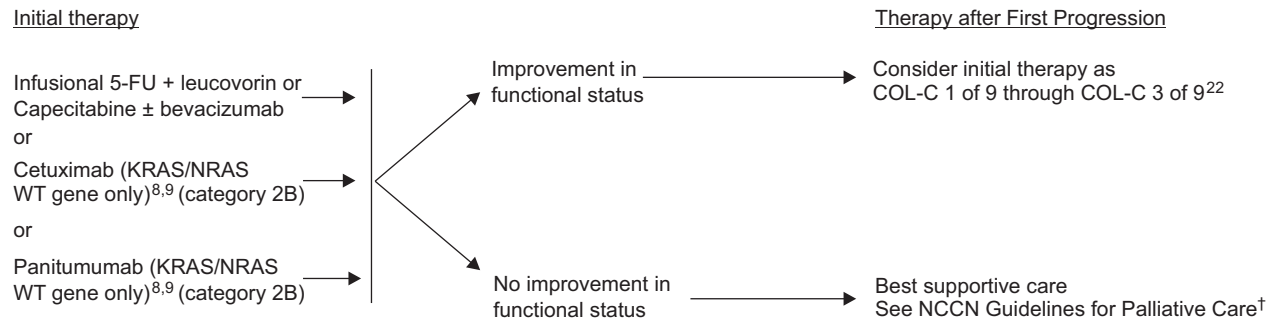
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1]

Patient not appropriate for intensive therapy[2]



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FOOTNOTES

[1] For chemotherapy references, see Chemotherapy Regimens and References (COL-C 6-9*).

[2] PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended.

[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 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/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and 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;27:672-680. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572.

[7] If cetuximab or panitumumab is used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.

[8] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS, and BRAF Mutation Testing.

[9] There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.

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

[12] Cetuximab is indicated in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

[13] 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.

[14] 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.

[15] Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.

[16] Regorafenib is a treatment option for patients who have progressed through all available regimens (eg, KRAS/NRAS mutant or KRAS/NRAS WT with previous exposure to anti-EGFR inhibitor.)

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

[18] Infusional 5-FU is preferred.

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

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

[21] Data are not mature for the addition of biologic agents to FOLFOXIRI.

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

*Available online, in these guidelines, at NCCN.org.

Text cont. from page 1029.

sociated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (*P*=.008) and more bilobar metastases (*P*=.016) than patients diagnosed with metachronous liver metastases.[13]

Estimates show that more than half of patients who die of CRC have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.[14] Reviews of autopsy reports of patients who died from CRC showed that the liver was the only site of metastatic disease in one-third of patients.[9] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[5,15] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with CRC.[12,16–20]

Conversion to Resectability

Most patients diagnosed with metastatic CRC have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply based on a favorable response to chemotherapy, because the probability of complete eradication of a metastatic deposit by chemotherapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status.[21]

Any active metastatic chemotherapeutic regimen can be used in an attempt to convert an unresectable patient to a resectable status, because the goal is not specifically the eradication of micrometastatic disease, but rather the obtaining of optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.[22–26] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed in this section.

In the study of Pozzo et al,[27] it was reported that chemotherapy with irinotecan combined with 5-FU/leucovorin (LV) enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection. The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the NCCTG,[7] 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 initially unresectable patients with colorectal liver disease were treated with chemotherapy, which included oxaliplatin in most cases, and 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection.[16] The 5-year disease-free survival rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic CRC enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.[28] The median overall survival (OS) time in this group was 42.4 months.

In addition, FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials in unresectable patients.[29,30] In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, *P*=.033 in the Gruppo Oncologico Nord Ovest (GONO) trial[29]; and 4% versus 10%, *P*=.08 in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[30] In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs 8%), with a median OS of 23.4 versus 16.7 months (*P*=.026).[31]

More recent favorable results have been reported of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversing unresectable disease to resectable disease in combination with anti–epidermal growth factor receptor (EGFR) inhibitors.[32,33] For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[32] Retrospective analysis showed that in both treatment arms, combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab ($P<.0001$). Another recent randomized controlled trial compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab versus chemotherapy alone in patients with unresectable CRC metastatic to the liver.[34] The primary end point was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 (29%) patients in the cetuximab arm and 9 of 68 (13%) patients in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm ($P<.01$). In addition, surgery improved the median survival time compared with unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs 25.7 months; $P=.007$ for the cetuximab arm and 36.0 vs 19.6 months; $P=.016$ for the control arm). A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11% to 18%; relative risk [RR], 1.59; $P=.04$), and progression-free survival (PFS), but not OS in patients with wild-type *KRAS* exon 2–containing tumors.[35]

The role of bevacizumab in the unresectable patient, whose disease is believed to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.[36,37] Thus, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration. On the other hand, a 1400-patient randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed absolutely no benefit in terms of response rate or tumor regression with the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.[38] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this "convert to resectability" setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical reevaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical reevaluation every 2 months thereafter.[26,39–41] Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[22] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends that a course of an active systemic chemotherapy regimen for metastatic disease, administered for a total perioperative treatment time of approximately 6 months, be considered for most patients undergoing liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated. A recent meta-analysis identified 3 randomized clinical trials comparing surgery alone versus surgery plus systemic therapy among 642 evaluable patients with colorectal liver metastases.[42] The pooled analysis showed a benefit of chemotherapy in PFS (pooled hazard ratio [HR], 0.75; CI, 0.62–0.91; $P=.003$) and disease-free survival (pooled HR, 0.71; CI, 0.58–0.88; $P=.001$), but not in OS (pooled HR, 0.74; CI, 0.53–1.05; $P=.088$).

The choice of chemotherapy regimen in the preoperative and postoperative settings depends on several factors, including the previous chemotherapy regimens used and the response rates and safety/toxicity issues associated with the regimens. Regimens recommended for adjuvant therapy and neoadjuvant therapy are the same (see the next section). However, if the tumor grows on neoadjuvant treatment, an active regimen for advanced disease or observation is recommended.

The optimal sequencing of chemotherapy remains unclear. Patients with resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) chemotherapy can be used.[43,44]

Potential advantages of preoperative chemotherapy include: earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include missing the "window of opportunity" for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[9,45,46] In fact, results from a recent study of patients with CRC receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically, despite achievement of a complete response as evaluated on CT scan.[46,47] Therefore, during treatment with preoperative chemotherapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative chemotherapy regimen and facilitates an appropriately timed surgical intervention.[22]

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[22–26] To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

Chemotherapy 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/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, and regorafenib.[29,30,48–86] 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 EGFRs.[87–90] The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy 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.[65] 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 in patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy in 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, 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),[74,91] FOLFIRI,[49] CapeOx,[52,92,93] infusional 5-FU/LV or capecitabine,[49,70,76,86] or FOLFOXIRI.[29,30]

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Before the use of targeted agents, 3 studies randomized patients to different schedules.[94–96] The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given as first-line therapy or if less intensive therapy is given first followed by more intensive combinations.

A study of 6286 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 a 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.[97]

Although use of FOLFOXIRI as initial therapy is a category 2B recommendation, the panel does not consider one of the other regimens (ie, FOLFOX, CapeOx, FOLFIRI, 5-FU/LV, capecitabine) to be preferable over the others as initial therapy for metastatic disease. Biologic agents used as part of initial therapy can include bevacizumab, cetuximab, or panitumumab.

FOLFOX: The phase III EORTC 40983 study, evaluating the use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, showed absolute improvements in 3-year PFS of 8.1% (P=.041) and 9.2% (P=.025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[98] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery-only arm and 59% of the patients in the chemotherapy arm.[99]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[100] Results of the OPTIMOX1 study showed that a "stop-and-go" approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect OS in patients receiving FOLFOX as initial therapy for metastatic disease.[101] Other trials have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.[102] Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this adverse effect. Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.[103–110] However, the phase III randomized, double-blind N08CB study, which randomized 353 patients with colon cancer receiving adjuvant FOLFOX to calcium/magnesium infusion or placebo, found that calcium/magnesium did not reduce cumulative sensory neurotoxicity.[111] The panel therefore recommends against calcium/magnesium infusions for this purpose.

In the phase II OPTIMOX2 trial, patients were randomized to receive either an OPTIMOX1 approach (discontinuation of oxaliplatin after 6 cycles of FOLFOX to prevent or reduce neurotoxicity, with continuance of 5-FU/LV, followed by reintroduction of oxaliplatin on disease progression) or an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX.[112] Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, preplanned, chemotherapy-free interval (median OS, 23.8 vs 19.5 months; P=.42). However, the median duration of disease control, which was the primary end point of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval (P=.046).[112]

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[38,113] as is the addition of panitumumab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on "Bevacizumab," "Cetuximab and Panitumumab," and "The Role of *KRAS*, *NRAS*, and *BRAF* Status," pages 1041, 1043, and 1044, respectively).[61,114] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, panel consensus is that FOLFOX and CapeOx can be used interchangeably.

CapeOx: The combination of capecitabine and oxaliplatin, known as CapeOx or XELOX, has been studied as an active first-line therapy for patients with metastatic CRC.[52,92,93,115,116] In a randomized phase III trial comparing CapeOx and FOLFOX in 2034 patients,

the regimens showed similar median PFS intervals of 8.0 and 8.5 months, respectively, and CapeOx was determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.[52] A recent meta-analysis of 3603 patients from 7 randomized controlled trials also showed that CapeOx and FOLFOX had similar benefits for patients with metastatic CRC.[117]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see "FOLFOX," page 1039).[118] Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[101]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. Data are insufficient to support the routine use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.[103–108]

Regarding the toxicities associated with capecitabine use, the panel noted that (1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification;[119] (2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV;[113,119] and (3) North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[120] These toxicities may necessitate modifications in the dosing of capecitabine,[113,119,121] and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects, such as hand-foot syndrome. Interestingly, a recent analysis of patients from the AIO's KRK-0104 trial and the Mannheim rectal cancer trial found that capecitabine-related hand-foot skin reactions were associated with an improved OS (75.8 vs 41.0 months; P=.001; HR, 0.56).[122]

The addition of bevacizumab is an option if CapeOx is chosen as initial therapy.[38,113] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the panel is that FOLFOX and CapeOx can be used interchangeably.

FOLFIRI: Evidence for the comparable efficacy of FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and then were switched to the other regimen at disease progression.[91] Similar response rates and PFS times were obtained when these regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX and FOLFIRI regimens in previously untreated patients with metastatic CRC.[54] No differences were observed in response rate, PFS times, and OS between the treatment arms.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[123,124] Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates, such as bilirubin, into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or an elevated serum bilirubin level. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,[124–127] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[127] Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression.[128] Also, a warning has been added to the label for irinotecan indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[123] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[127] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing in patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

Results from a recent phase IV trial in 209 patients with metastatic CRC who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab combined with other 5-FU–based therapies.[129] Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for tumors characterized by wild-type *KRAS*/*NRAS*) can be added to this regimen.[61,73,75,82,130]

Infusional 5-FU/LV and Capecitabine: For patients with impaired tolerance to aggressive initial therapy, the guidelines recommend infusional 5-FU/LV or capecitabine with or without bevacizumab as an option.[49,69,71,81,84,113] Patients with metastatic cancer with no improvement in functional status after this less intensive initial therapy should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for initial therapy for advanced or metastatic disease. Toxicities associated with capecitabine use are discussed earlier (see "CapeOx," page 1039).

In a pooled analysis of results from 2 randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone after surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR, 1.32; 95% CI, 1.00–1.76; *P*=.058), with no significant difference in OS.[131]

Results were recently published from the open-label phase III AVEX trial, in which 280 patients aged 70 years or older were randomized to capecitabine with or without bevacizumab.[132] The trial met its primary end point, with the addition of bevacizumab giving a significantly improved median PFS (9.1 vs 5.1 months; HR, 0.53; 95% CI, 0.41–0.69; *P*<.0001).

FOLFOXIRI: FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease (category 2B).[29,30] Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.[29,30] In the GONO study, statistically significant improvements in PFS (9.8 vs 6.9 months; HR, 0.63; *P*=.0006) and median OS (22.6 vs 16.7 months; HR, 0.70; *P*=.032) were observed in the FOLFOXIRI arm,[29] although no OS difference was seen between treatment arms in the HORG study (median OS, 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; *P*=.337).[30] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[29] diarrhea, alopecia, and neurotoxicity[30]), but no differences in the rate of toxic death were reported in either study. Long-term outcomes of the GONO trial with a median follow-up of 60.6 months were recently reported.[31] The improvements in PFS and OS were maintained.

For the 2014 version of these guidelines, the panel included the possibility of adding bevacizumab to FOLFOXIRI for initial therapy of patients with unresectable metastatic disease (category 2B). Results of the GONO group's phase III TRIBE trial found that FOLFOXIRI/bevacizumab significantly increased PFS (12.2 vs 9.7 months; *P*=.0012) and response rate (65% vs 53%; *P*=.006) compared with FOLFIRI/bevacizumab in patients with unresectable metastatic CRC.[133,134] Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy. Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. Results were recently reported from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab and FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver metastases.[135] Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs 23%; *P*=.017). The panel recommends that this aggressive combination only be used in very select patients who could potentially be converted to a resectable state.

Bevacizumab: Bevacizumab[136] is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis. 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.[37,137,138] 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).[71] A study of previously untreated patients receiving bevacizumab plus irinotecan, fluorouracil, and LV (IFL) also provided support for including bevacizumab in initial therapy.[37] 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 1400 patients with unresectable metastatic disease.[38] 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).[38] 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.[79] However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab (see later discussion), and this finding would not have been potentially 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.[38] The randomized phase III trial HEPATICA, which is comparing CapeOx with and without bevacizumab as adjuvant therapy in patients with liver metastases, is currently recruiting patients (ClinicalTrials.gov identifier: NCT00394992).[139]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for metastatic CRC.[140–144] A recent meta-analysis of 6 randomized clinical trials (3060 patients) that assessed the efficacy of bevacizumab in first-line treatment of metastatic CRC found that bevacizumab was associated with 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.[145] 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 CRC diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).[146] 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,[147,148] but, overall, the addition of bevacizumab to first-line chemotherapy seems 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[149,150] have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. The panel does not recommend the use of bevacizumab in the postresection stage IV adjuvant setting, unless a response to bevacizumab was seen in the neoadjuvant 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 (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.[151] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[152] Another meta-analysis showed that bevacizumab was associated with a statistically significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is low.[153] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.[113,154] 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 un-

acceptably high rate of gastrointestinal perforation when treated with bevacizumab.[155] 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 this risk. 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.[156]

Use of bevacizumab may interfere with wound healing.[113,136,154] A retrospective evaluation of data from 2 randomized trials of 1132 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).[154] 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).[157] 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 or less versus at more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[158] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[136]) between the last dose of bevacizumab and 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 4205 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.[159] Although this meta-analysis has been criticized,[160,161] the results are supported by recent results from the NSABP protocol C-08 trial.[149] 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.

Results from 2 randomized phase III trials have shown that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity.[162,163] In the PACCE trial, the addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both *KRAS* exon 2 wild-type and mutant gene groups.[162] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[163] Therefore, the panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent (cetuximab or panitumumab) and an anti-VEGF agent (bevacizumab).

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.[164] Cetuximab and panitumumab have been studied in combination with FOLFIRI[73,82] and FOLFOX[61,114] as initial therapy options for treatment of metastatic CRC. A recent meta-analysis of 14 randomized controlled trials concluded that there is a clear benefit to using EGFR inhibitors in patients with *KRAS* exon 2 wild-type metastatic CRC.[165] Individual trials and the role of *KRAS*, *NRAS*, and *BRAF* are discussed in this section.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[164,166] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion

reactions to cetuximab.[167–169] 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 seems 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.[82,170–175] An NCCN Task Force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[176] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious adverse events.[177,178]

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 1041).[162,163] A recent editorial summarizes trials that assessed EGFR inhibitors in combination with various chemotherapy agents.[179] These data are also discussed herein. The consensus of the panel is that cetuximab and panitumumab are not necessarily interchangeable because they have never been compared head-to-head and may have different interactions with chemotherapy regimens. The panel separately assessed the data pertaining to each antibody when making its recommendations.

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.[180–183] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response 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.[55] A similar conclusion was drawn with respect to panitumumab.[184] Therefore, routine EGFR testing is not recommended, and no patient should be either 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.[55,185] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with CRC.[55,83,185] 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, facing page).[48,82,114,172,186–190] 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," facing page).[191] 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. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS*, this testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see "*BRAF* V600E Mutations," facing page).

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic CRC *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 CRCs 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.[192–194] 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.[195] No specific testing methodology is recommended.[196]

KRAS Exon 2 Mutations: Approximately 40% of CRCs are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[48,197] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[48,82,114,172,186–190,198] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of CRC characterized by these mutations.[164,166] Results are mixed as far as the prognostic value of *KRAS* mutations, and the test is not recommended for prognostic reasons.

A recent retrospective study from De Roock et al[199] raised the possibility that codon 13 mutations (G13D) may not be absolutely predictive of nonresponse. Another recent retrospective study showed similar results.[200] However, as the article by De Roock et al[199] states, these findings are hypothesis-generating only, and prospective studies are needed to determine if patients with *KRAS* G13D mutations can, in fact, benefit from anti-EGFR therapy. Furthermore, a recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[201] Currently, use of anti-EGFR agents in patients whose tumors have G13D mutations remains investigational, and is not endorsed by the panel for routine practice.

NRAS and Other *KRAS* Mutations: It was recently reported that 17% of 641 patients from the PRIME trial 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 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.[191] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

An updated analysis of the FIRE-3 trial (discussed in "Cetuximab Versus Bevacizumab in First-Line," page 1047) was recently presented.[202] When all *RAS* (*KRAS/NRAS*) mutations were considered, PFS was significantly worse in *RAS*-mutant patients receiving FOLFIRI plus cetuximab than *RAS*-mutant patients receiving FOLFIRI plus bevacizumab (6.1 vs 12.2 months; *P*=.004). On the other hand, no difference in PFS was seen between the regimens in *KRAS/NRAS* wild-type patients (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.[166] The NCCN Colon/Rectal Cancer Panel believes that non–exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined whenever possible. 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 certain 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).[130,203] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[203,204] 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,[205–207]

thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

The utility of *BRAF* status as a predictive marker is unclear. 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.[208,209] 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 the first-line treatment of metastatic CRC.[191] On the other hand, results from the randomized phase III 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.[204] Overall, the panel believes that data are insufficient to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on *BRAF* V600E mutation status.

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.[210–212] A retrospective study of 773 primary tumor samples from chemotherapy-refractory patients 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).[213] Furthermore, recently reported prospective data from the multicenter, randomized, controlled PICCOLO trial are consistent with this conclusion, with a detrimental effect seen for the addition of panitumumab to irinotecan in the non–first-line setting in patients with *BRAF* mutations.[214]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[197,204,209,215–219] A recent 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 or microsatellite stable tumors (HR, 2.2; 95% CI; 1.4–3.4; *P*=.0003).[197] 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.[209] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73; *P*=.001).[215] 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.[204]

For patients with *KRAS/NRAS* wild-type tumors, the panel includes the option of *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[220]) at diagnosis of *KRAS/NRAS* wild-type stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed using PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

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.[82] 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 group with disease characterized by *KRAS* wild-type exon 2 (9.9 vs 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; *P*=.02).[82] 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.[209] 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, this addition did not affect the quality of life of participants in the CRYSTAL trial.[221]

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.[75,214,222,223]

Cetuximab With FOLFOX: Three trials have assessed the combination of FOLFOX and cetuximab in the 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%; odds ratio, 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.[114] 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 a recent update of this study,[224] 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).[224]

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.[204] 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.[204] 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 *KRAS* exon 2 wild-type patients, although no OS benefit was seen.[225]

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 benefit in OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.[226]

In summary, the negative COIN trial showed a marginal benefit in the FOLFOX subset of patients, the NORDIC trial showed negative results, and the only positive results came from a phase II trial with a primary end point of response rate (OPUS). Because of the lack of convincing benefit and the increased incidence of grade 3 adverse events seen in the COIN trial, the panel does not recommend the use of cetuximab with FOLFOX as initial therapy for patients with advanced or metastatic disease.

In addition, the New EPOC trial, which was stopped early because of a lack of futility, recently found a lack of benefit for cetuximab with chemotherapy (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI) in the perioperative metastatic setting.[227] In fact, with less than half of the 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, although the data are not strong enough to prohibit its use, cetuximab in the perioperative setting may harm patients.

Panitumumab With FOLFOX: Panitumumab in combination with either FOLFOX[61,228] or FOLFIRI[73] 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.[191] 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 1045).[191]

Cetuximab 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 to FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.[229,230] 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 (28.8 vs 25.0 months; HR, 0.77; *P*=.016; 95% CI, 0.62–0.95). The panel has several criticisms of the trial, including regarding the lack of third-party review and low rates of second-line therapy. 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 Intergroup 80405 trial, comparing FOLFOX/FOLFIRI with cetux-

imab or bevacizumab (ClinicalTrials.gov identifier: NCT00265850) are pending and will provide more information regarding whether these targeted drugs confer significantly different outcomes.

Therapy After Progression: Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of capecitabine, mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as salvage 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.[231]

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:

- For patients who received a FOLFOX or CapeOx-based regimen for initial therapy, FOLFIRI or irinotecan alone or with cetuximab or panitumumab (*KRAS/NRAS* wild-type tumor only), bevacizumab, or ziv-aflibercept are recommended options.
- For patients who received a FOLFIRI-based regimen as initial treatment, FOLFOX or CapeOx alone[115] or with bevacizumab; cetuximab or panitumumab plus irinotecan; or single-agent cetuximab or panitumumab (for those not appropriate for the combination with irinotecan) are recommended options.
- For patients who received 5-FU/LV or capecitabine without oxaliplatin or irinotecan as initial therapy, options after first progression include FOLFOX, CapeOx, FOLFIRI, single-agent irinotecan, or irinotecan plus oxaliplatin (IROX). These can be varyingly combined with bevacizumab or ziv-aflibercept.
- For patients who received FOLFOXIRI as initial therapy, cetuximab or panitumumab plus irinotecan or cetuximab or panitumumab alone are recommended options for those with wild-type *KRAS/NRAS*.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX6 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 PFS or median OS.[91] 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.[232] Furthermore, OS was not found to be associated with the order in which these drugs were received. Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care[56] or infusional 5-FU/LV.[233] In the study of Rougier et al,[233] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=.030), whereas Cunningham et al[56] 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.[234]

Bevacizumab in the Non–First-Line Setting: In the TML (ML18147) trial, patients with metastatic CRC who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[235] 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.[236]

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 6.7 months compared with 5.2 months in the control arm (HR, 0.66; 95% CI, 0.49–0.90; P=.0072).[237]

The continuation of bevacizumab after progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system.[238] Bevacizumab beyond progression was associated with a longer OS

(HR, 0.76; 95% CI, 0.61–0.95) and a longer post-progression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis.

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 an EGFR inhibitor or ziv-aflibercept. 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 for whom a 5-FU– or capecitabine-based regimen failed.

It may also be appropriate to consider adding bevacizumab to chemotherapy after progression of metastatic disease if it was not used in initial therapy.[63] 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.[63] 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).[63] 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.[63]

Cetuximab and Panitumumab in the Non–First-Line Setting: For patients with wild-type *KRAS/NRAS* 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[188] is recommended. For patients with wild-type *KRAS/NRAS* progressing on therapies that did contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. Although no head-to-head studies have compared cetuximab and panitumumab, similar response rates have been observed when each agent was studied as monotherapy after progression. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice. If the patient does not experience response to oxaliplatin, irinotecan, and an EGFR inhibitor, the panel recommends best supportive care or enrollment in a clinical trial.

Panitumumab has been studied as a single agent in the setting of metastatic CRC chemotherapy.[83] 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.[48] 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.[48]

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.[75] These results were confirmed in the final results of Study 181.[223] 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.[222] 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.[239]

Cetuximab has been studied both as a single agent[55,171,185,188] and in combination with irinotecan[55,240] 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.[241] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[241]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving ce-

tuximab monotherapy as second-line therapy,[171] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[188] 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.[188]

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.[242] 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 for whom one regimen containing oxaliplatin failed. 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).[85]

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 experienced disease progression on FOLFIRI plus bevacizumab or vice versa, and no data suggest activity of single-agent ziv-aflibercept. 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.

Adverse events associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared with 12.1% discontinuation in the placebo group.[85] The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

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.[243] The phase III CORRECT trial randomized 760 patients who experienced disease progressin on standard therapy to best supportive care with placebo or regorafenib.[67] The trial met its primary end point 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).

Regorafenib has only shown activity in patients who experienced disease progression on all standard therapy. Therefore, the panel added regorafenib as an additional line of therapy for patients with metastatic CRC refractory to chemotherapy. For patients with mutant *KRAS/NRAS*, regorafenib can be used in the third-line setting; patients with wild-type *KRAS/NRAS* can receive regorafenib as a third or fourth line of therapy.

The most common grade 3 or higher 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%).[67] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[243]

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Individual Disclosures of the NCCN Colon Cancer Panel					
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The NCCN guidelines staff have no conflicts to disclose.