Colon Cancer, Version 2.2021

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ABSTRACT

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer focuses on systemic therapy options for the treatment of metastatic colorectal cancer (mCRC), because important updates have recently been made to this section. These updates include recommendations for first-line use of checkpoint inhibitors for mCRC, that is deficient mismatch repair/microsatellite instability-high, recommendations related to the use of biosimilars, and expanded recommendations for biomarker testing. The systemic therapy recommendations now include targeted therapy options for patients with mCRC that is HER2-amplified, or *BRAF* V600E mutation–positive. Treatment and management of nonmetastatic or resectable/ablatable metastatic disease are discussed in the complete version of the NCCN Guidelines for Colon Cancer available at NCCN.org. Additional topics covered in the complete version include risk assessment, staging, pathology, posttreatment surveillance, and survivorship.

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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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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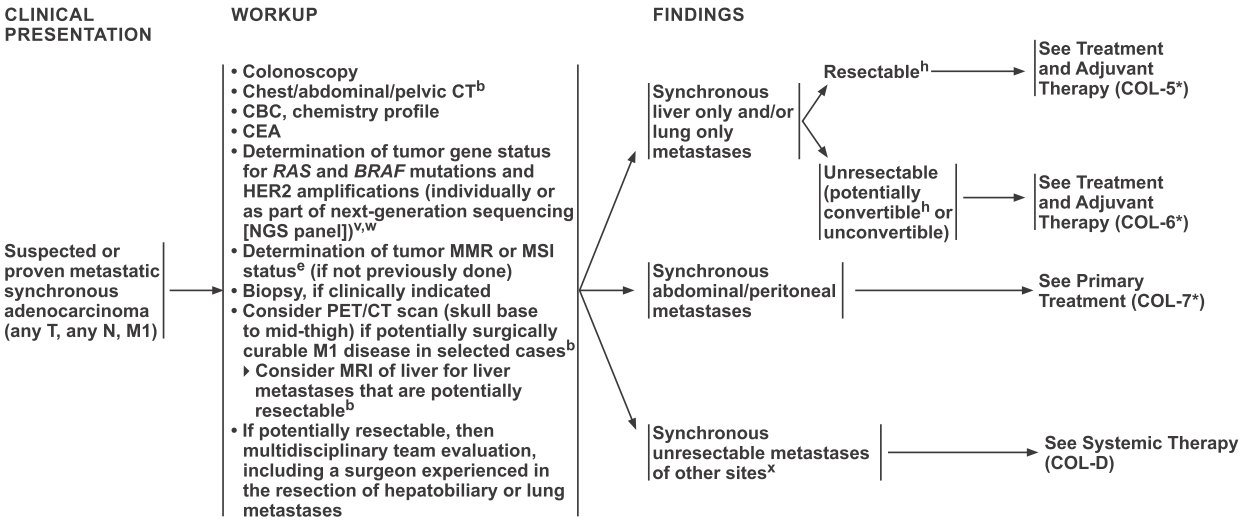
The complete NCCN Guidelines for Colon Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

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 359. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[b] See Principles of Imaging (COL-A*).
[e] See Principles of Pathologic Review (COL-B 4 of 8*) - MSI or MMR Testing.
[h] See Principles of Surgery (COL-C 2 of 3*).
[v] See Principles of Pathologic Review (COL-B 4 of 8*) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[w] If known *RAS/RAF* mutation, HER2 testing is not indicated. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[x] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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

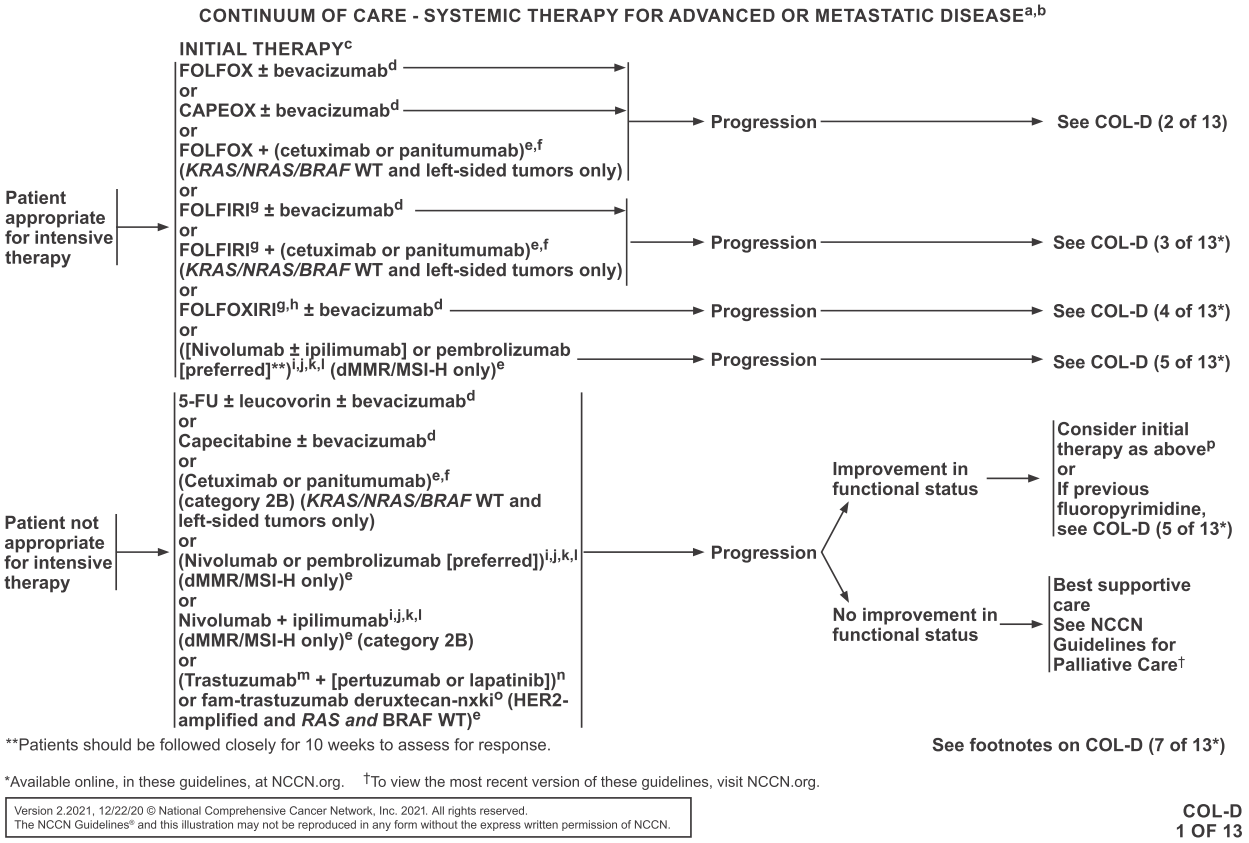
Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2020, an estimated 104,610 new cases of colon cancer and 43,340 cases of rectal cancer will occur. During the same year, an estimated 53,200 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 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016.[2,3] In addition, mortality from CRC has been decreasing for decades (since 1947 in women and since 1980 in men) and is currently down by more than 50% from peak mortality rates.[1,3] 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. Recent data show continued rapid declines in incidence among those aged 65 years or older, with a decrease of 3.3% annually between 2011 and 2016.[3]

Conversely, incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those 65 years and older, compared with a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years.[3] A retrospective cohort study of the SEER CRC registry also found that the incidence of CRC in patients younger than 50 years has been increasing.[4] 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 of age by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population is different, there would be a need to develop specific treatment strategies for this population.[5]

Management of Metastatic Disease

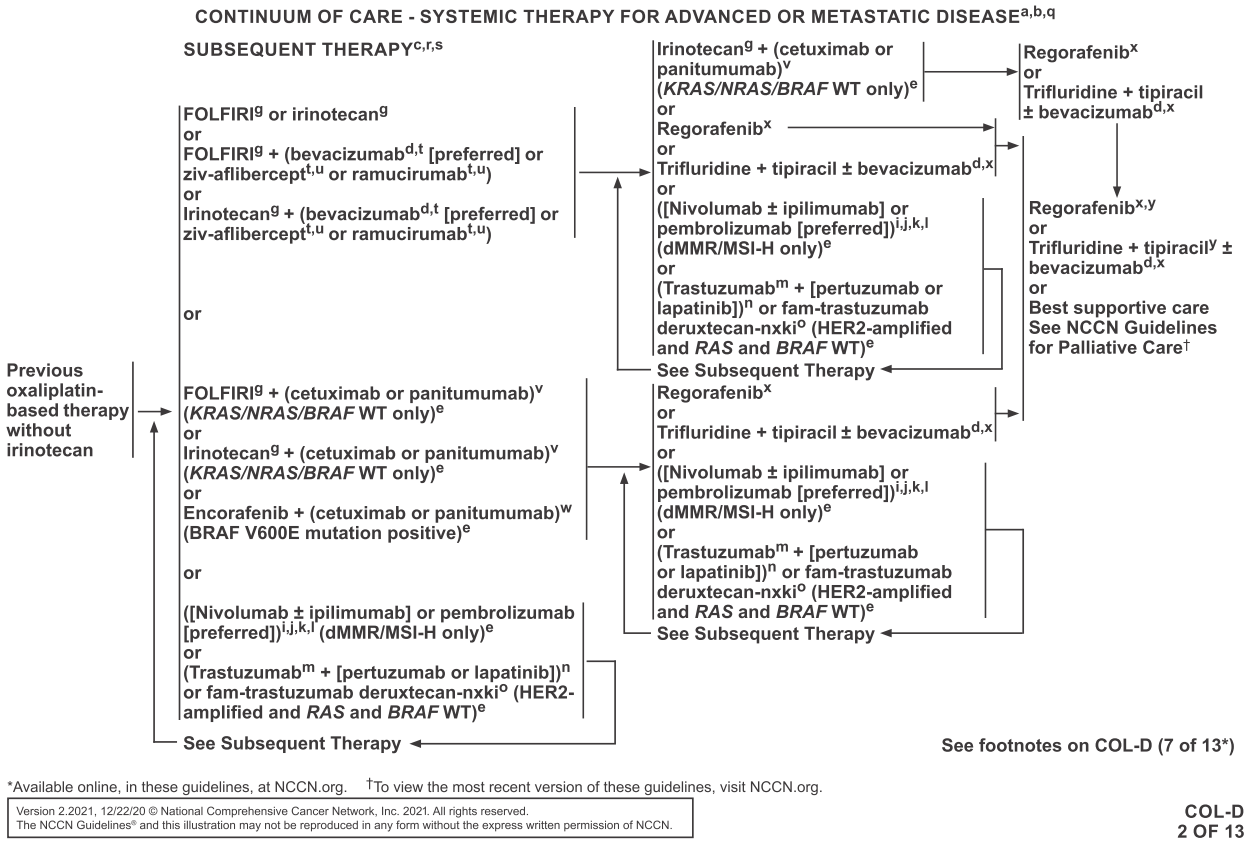
Approximately 50%–60% of patients diagnosed with CRC develop colorectal metastases,[6–8] and 80%–90% of these



patients have unresectable metastatic liver disease.[7,9–12] Metastatic disease most frequently develops metachronously after treatment of locoregional CRC, with the liver being the most common site of involvement.[13] However, 20%–34% of patients with CRC present with synchronous liver metastases.[12,14] Some evidence indicates that synchronous metastatic colorectal liver disease is associated 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.[15]

It has been estimated 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.[16] Reviews of autopsy reports of patients who died of CRC showed that the liver was the only site of metastatic disease in one-third of patients.[11] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[7,17] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of >3 tumors, and a disease-free interval of <12 months, have been associated with a poor prognosis in patients with CRC.[14,18–22]

Other groups, including ESMO, have established guidelines for the treatment of metastatic CRC (mCRC).[23] For the specific NCCN recommendations, see "Workup and Management of Synchronous Metastatic Disease" and "Workup and Management of Metachronous Metastatic Disease" in the complete version of these guidelines at NCCN.org. Additionally, this selection only covers systemic therapy recommendations for advanced or metastatic disease that is not amenable to resection. For additional discussion related to metastatic disease, see "Surgical Management of Colorectal Metastases," "Local Therapies for Metastases," "Peritoneal Carcinomatosis," "Determining Resectability," "Conversion to Resectability," and "Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease" in the complete version of these guidelines (available at NCCN.org).



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2 OF 13

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. 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.[24] 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: (1) preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive; and (2) 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, in part, 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 a 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.

Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Prior to the use of targeted agents, several studies randomized patients to different schedules.[25–28] 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).[28] 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.[29] 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 mCRC treatment showed similar therapeutic efficacy for patients with a performance status of 2 or 1 or less as compared with control groups. However, the risks of certain gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[30]

Overall, the panel does not consider one regimen to be preferable over another 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).

Therapy Retreatment/Rechallenge

Due to few efficacious options in later lines of therapy, there has been considerable interest in the possibility of retreating with a systemic therapy used during an earlier line of treatment. Most studies that have reported on this approach have been retrospective, detailing institutional experiences retreating with chemotherapeutics[31–33] or targeted therapies (eg, epidermal growth factor receptor [EGFR] inhibitors)[31,34–38] and concluded that a retreatment approach was feasible, based on response and/or toxicity data. However, these studies were mainly small and did not differentiate between patients who stopped therapy due to progression compared with other reasons, limiting the quality of these data. The randomized FIRE-4 trial (ClinicalTrials.gov identifier: NCT02934529) is currently under recruitment and will seek to address this question.

Therefore, until stronger data become available, the panel agrees that for patients who had therapy stopped for a reason other than progression (eg, use as adjuvant therapy, cumulative toxicity, treatment break, patient preference), rechallenge with this therapy would be an option. However, based on the current lack of evidence, retreatment with a therapy following progression on that regimen is not recommended. For discussion of the data on maintenance strategies, see "Maintenance Therapy" in the complete version of these guidelines (available at NCCN.org). Given the PFS benefit seen in some studies but the probable lack of OS benefit, maintenance therapy may be discussed as part of shared decision-making with patients with observation an acceptable alternative.

Biosimilars

A biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences from an existing biologic therapy.[39–45] Several biosimilars are now available in the United States market, including biosimilars to 2 biologics that are recommended in the NCCN Guidelines for Colon Cancer: bevacizumab and trastuzumab. The NCCN Panel has agreed that an FDA-approved biosimilar may be substituted for either bevacizumab or trastuzumab wherever these therapies are recommended within the NCCN Guidelines for Colon Cancer.

Biomarkers for Systemic Therapy

As the role of targeted therapy for treatment of advanced or mCRC has become increasingly prominent, the NCCN Panel has expanded its recommendations regarding biomarker testing (see COL-4, page 330, and "Principles of Pathologic Review" [COL-B] in the complete version of these guidelines at NCCN.org). Currently, determination of tumor gene status for *KRAS/NRAS* and *BRAF* mutations, as well as HER2 amplifications and microsatellite instability high (MSI)/mismatch repair (MMR) status (if not previously done), are recommended for patients with mCRC. Testing may be performed for individual genes or as part of a next-generation sequencing (NGS) panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (*NTRK*) fusions. Specific information about each of these biomarkers may be found in the subsequent sections.

KRAS *and* NRAS *Mutations*

The MAPK pathway of RAS/RAF/MEK/ERK is downstream of EGFR; mutations in components of this pathway are now established to be strong negative predictive markers, essentially precluding efficacy of these therapies. A sizable body of literature has shown that tumors with a mutation in exons 2, 3, or 4 of either the *KRAS* or *NRAS* genes are essentially insensitive to cetuximab or panitumumab therapy.[46–56] The panel therefore strongly recommends *RAS* (*KRAS/NRAS)* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with mCRC. 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. ASCO released a "Provisional Clinical Opinion Update" on extended *RAS* testing in patients with mCRC that is consistent with the NCCN Panel's recommendations.[57] A guideline on molecular biomarkers for CRC developed by the ASCP, CAP, AMP, and ASCO also recommends *RAS* testing consistent with the NCCN recommendations.[58]

The recommendation for *RAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* 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 *RAS* 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, *RAS* 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.[59–61] For this reason, *RAS* 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 *RAS* 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.[62] No specific testing methodology is recommended.[63] The three genes can be tested individually or as part of an NGS panel.

Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.[64] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study by De Roock et al[65] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of nonresponse. Another retrospective study showed similar results.[53] 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.[66] Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory mCRC whose tumors contained *KRAS* G13D mutations.[67] The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICE CREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.[68] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of 8 randomized control trials (RCTs) came to the same conclusion: that tumors with *KRAS* G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other *KRAS* mutations.[69] The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

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.[70] 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 (hazard ratio [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.[55] 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 Therapy," page 343) has been published.[71] 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). Conversely, 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 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.[72] The NCCN Colon and Rectal Cancers Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *RAS* mutation should not be treated with either cetuximab or panitumumab.

BRAF *V600E Mutations*

Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS*

still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5%–9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E)[73,74] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *RAS* mutations.[73–75] Activation of the protein product of the nonmutated *BRAF* gene occurs downstream of the activated RAS protein in the EGFR pathway. The mutated BRAF protein product is believed to be constitutively active,[76–78] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with mCRC 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.[74,79] 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 mCRC.[55] 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 effect in patients with *BRAF*-mutated tumors treated with CAPEOX or FOLFOX in the first-line setting.[75]

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.[80–82] 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).[83] 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.[84]

A meta-analysis published in 2015 identified 9 phase III trials and one 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).[85] 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 (ORR; RR, 1.31; 95% CI, 0.83–2.08; P=.25) compared with control arms. Similarly, another meta-analysis identified 7 RCTs 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.[86]

In addition to its role as a predictive marker for BRAF-targeted therapy, it is clear that mutations in *BRAF* are a strong prognostic marker.[74,75,87–93] 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 MSI-L or microsatellite stable tumors (HR, 2.2; 95% CI, 1.4–3.4; P=.0003).[89] 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.[74] 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).[88] The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[75] In addition, a secondary analysis of the N0147 and C-08 trials found that *BRAF* mutations were significantly associated with worse survival after recurrence of resected stage III colon cancer, with a stronger association for primary tumors located in the distal colon.[94] 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.[95] In particular, an association was observed between *BRAF* mutation and proximal tumor location (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, unless given as part of a BRAF inhibitor regimen (see "Encorafenib Plus Cetuximab or Panitumumab for *BRAF* V600E Mutation–Positive Disease in the Non–First-Line Setting," page 346). The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[96]) 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 amplification and direct DNA sequence analysis. Allele-specific polymerase chain reaction, NGS, or immunohistochemistry (IHC) are other acceptable methods for detecting this mutation.

HER2 Amplification/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 amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5%–14%).[97,98] Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,[99] and HER2-targeted therapies are now recommended as subsequent therapy options in patients with tumors that are both *RAS* and *BRAF* wild-type and have HER2 overexpression (see "Systemic Therapy Options for HER2-Amplified Disease," page 347).[97,100] Based on this, the NCCN Guidelines recommend testing for HER2 amplifications for patients with mCRC. If the tumor is already known to have a *KRAS*/*NRAS* or *BRAF* mutation, HER2 testing is not indicated. Because HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.[101] In addition to its role as a predictive marker for HER2-targeted therapy, initial results indicate HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.[98,102,103] For example, in a cohort of 98 patients with *RAS/BRAF*–wild type mCRC, median PFS on therapy without an EGFR inhibitor was similar regardless of HER2 status.[103] However, in therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.8 vs 8.1 months; HR, 7.05; 95% CI, 3.4–14.9; $P<.001$).

dMMR/MSI-H Status

The percentage of stage IV colorectal tumors characterized as MSI-H (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.[104–106] 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 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.[107] It was therefore hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors. Subsequently, this hypothesis was confirmed in clinical trials, leading to the addition of recommendations for checkpoint inhibitors for dMMR/MSI-H disease (see "Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease" in the first-line and non–first-line settings, pages 343 and 347, respectively). The NCCN Guidelines recommend universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced CRC setting, MMR/MSI status can also help to identify individuals with Lynch syndrome (see "Lynch Syndrome" in the complete version of these guidelines at NCCN.org), and to inform adjuvant therapy decisions for patients with stage II disease (see "Microsatellite Instability under Adjuvant Chemotherapy for Resectable Colon Cancer," in the complete version of these guidelines, at NCCN.org).

NTRK *Fusions*

Three *NTRK* genes encode the tropomyosin receptor kinase (TRK) proteins. TRK expression is primarily in the nervous system where these kinases help to regulate pain, perception of movement/position, appetite, and memory. *NTRK* gene fusions lead to overexpression of the TRK fusion protein, resulting in constitutively active downstream signaling.[108] Recent studies have estimated that about 0.2%–1% of CRCs carry *NTRK* gene fusions.[109,110] A study of 2,314 CRC specimens, of which 0.35% had *NTRK* fusions, found that *NTRK* fusions were limited to cancers that were wild-type for *KRAS*, *NRAS*, and *BRAF*. Furthermore, a majority of the CRCs harboring *NTRK* fusions were also MMR-deficient.[111] These results may support limiting testing for *NTRK* fusions to those with wild-type *KRAS*, *NRAS*, and *BRAF*. TRK inhibitors are treatment options for patients with mCRC that is *NTRK* gene fusion-positive (see "Larotrectinib or Entrectinib for *NTRK* Fusion–Positive Disease in the Non–First-Line Setting," page 348).

Tumor Mutation Burden

Tumor mutation burden (TMB) measures the total amount of somatic coding mutations within a given coding area of the tumor genome and can be quantified using NGS techniques.[112] Research has identified TMB as a potential biomarker for response to immunotherapy and pembrolizumab has been FDA-approved for patients with unresectable or metastatic, TMB-high solid tumors that have progressed after prior treatment and have no satisfactory alternative treatment options.[113] TMB-high is defined in the label as ≥10 mutations/megabase by an FDA-approved test. This approval was based off results of the phase 2, KEYNOTE-158 study which enrolled patients with advanced solid tumors.[114] Patients with TMB-H tumors who were treated with pembrolizumab had an ORR of 29% compared with 6% of those with non–TMB-high tumors. However, of the 796 patients who were evaluated for efficacy on this study, none had colorectal cancers. An abstract on the phase II TAPUR basket study reported results for 27 patients with TMB-H advanced CRC who were treated with pembrolizumab.[115] One partial response and 7 cases with

stable disease for at least 16 weeks were reported, for a disease control rate of 28% and an ORR of 4%.

Based on the limited data in the CRC population, the NCCN Panel does not currently recommend TMB biomarker testing for CRC, unless measured as part of a clinical trial.

Severe Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines.[116,117] Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine.[118–122] Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1%–2% of the population with truncating alleles that may herald an increased risk of severe toxicity.[123] These patients could receive dose reductions or could be offered non-fluoropyrimidine regimens, although it is not certain that every one of these patients is at risk.[117]

Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective.[124–126] In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2,038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17%–91% (median 48%).[126] Results showed a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs 73%; $P<.001$). None of the patients died of drug toxicity, compared with a 10% death rate in the historical control group. Another prospective study identified 85 patients with any of the 4 *DPYD* variant alleles (8% of 1,103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele.[125] This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared with the historical cohorts. However, because fluoropyrimidine are a pillar of therapy in CRC and it is not known with certainty that given *DYPD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time.

First-Line Systemic Therapy

FOLFOX for First-Line Therapy

The phase III EORTC 40983 study, evaluating 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.[127] 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.[128]

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[129,130] as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on bevacizumab, page 340, and on cetuximab and panitumumab, pages 342 and 343).[48,131,132] 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. Results from a recent registry-based cohort analysis of >2,000 patients support the equivalence of these combinations.[133]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[134] 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.[135] 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.[136] A recent meta-analysis of RCTs also concluded that intermittent delivery of systemic therapy does not compromise OS compared with continuous treatment.[137] Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this AE. 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 time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

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.[138] 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 endpoint 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).[138]

The CONcePT trial also tested an intermittent oxaliplatin approach in patients with advanced CRC and found that it improved acute peripheral sensory neuropathy (P=.037) over continuous oxaliplatin.[139] The addition of oxaliplatin breaks also improved time to treatment failure (HR, 0.581; P=.0026) and time to tumor progression (HR, 0.533; P=.047).

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.[140–147] 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.[148] The panel therefore recommends against calcium/magnesium infusions for this purpose.

CAPEOX for First-line Therapy

The combination of capecitabine and oxaliplatin, known as CAPEOX or XELOX, has been studied as an active first-line therapy for patients with mCRC.[149–153] 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.[149] Meta-analyses of RCTs also showed that CAPEOX and FOLFOX had similar benefits for patients with mCRC.[154,155]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see section on FOLFOX, page 337).[156] Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[135]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A recent Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line therapy with CAPEOX/bevacizumab.[157] Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. The panel recommends against the use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.[148]

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[158]; (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[129,158]; and (3) North American patients may experience a higher incidence of adverse events (AEs) with certain doses of capecitabine compared with patients from other countries.[159] These toxicities may necessitate modifications in the dosing of capecitabine.[129,158,160] 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).[161]

The addition of bevacizumab is an option if CAPEOX is chosen as initial therapy.[129,130] 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. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[133]

FOLFIRI for First-line Therapy

Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at disease progression.[28] 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 mCRC.[162] No differences were observed in response rate, PFS times, and OS between the treatment arms.

A randomized phase III study compared FOLFIRI to 5-FU/LV in first-line treatment of elderly patients with mCRC.[163] In this population of patients, aged ≥75 years, grade 3–4 toxicities were increased with the addition of irinotecan (52.2% vs 76.3%), without an improvement in PFS or OS.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[164,165] 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 elevated serum bilirubin. 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,[165–167] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[167] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[168] The maximum tolerated dose of intravenous irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*/28, and *28/*28 genotypes, respectively.

Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression. Also, a warning was 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.[164] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[167] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on 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 mCRC who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab with other 5-FU–based therapies.[169] A phase III trial in Japan also showed that FOLFIRI plus bevacizumab is noninferior to mFOLFOX6 plus bevacizumab with regard to PFS.[170] Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for left-sided tumors characterized by wild-type *RAS/BRAF*) can be added to this regimen (see subsequent sections on bevacizumab, page 340, and on cetuximab and panitumumab, pages 342 and 343).[54,74,131,171,172]

Infusional 5-FU/LV and Capecitabine for First-Line Therapy

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 (see COL-D 1 of 13, page 331).[129,173–177] 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 previously (see section on CAPEOX, page 338).

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.[178]

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.[179] The trial met its primary endpoint, 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 for First-Line Therapy

FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease. Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.[180,181] In a trial by the GONO group, 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,[180] although no OS difference was seen between treatment arms in the HORG study (median OS was 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; P=.337).[181] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[180] diarrhea, alopecia, and neurotoxicity[181]), 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 later reported.[182] The improvements in PFS and OS were maintained.

The panel includes the possibility of adding bevacizumab to FOLFOXIRI for initial therapy of patients with unresectable metastatic disease. Results of the GONO

group's phase III TRIBE trial showed that FOLFOXIRI/bevacizumab significantly increased PFS (12.1 vs 9.7 months; HR, 0.75; 95% CI, 0.62–0.90; P=.003) and response rate (65% vs 53%; P=.006) compared with FOLFIRI/ bevacizumab in patients with unresectable mCRC.[183] Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy (64% of cases included oxaliplatin in the adjuvant regimen). Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. In an updated analysis on the TRIBE trial, investigators reported the median OS at 29.8 months (95% CI, 26.0–34.3) in the FOLFOXIRI plus bevacizumab arm and 25.8 months (95% CI, 22.5–29.1) in the FOLFIRI plus bevacizumab arm (HR, 0.80; 95% CI, 0.65–0.98; P=.03).[184]

The randomized, phase III TRIBE2 compared first-line FOLFOXIRI plus bevacizumab to a sequential strategy of first-line FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab after progression in 679 patients with unresectable, previously untreated mCRC.[185] The primary endpoint of median PFS was 19.2 months for FOLFOXIRI compared with 16.4 months for the sequential strategy (HR, 0.74; 95% CI, 0.63–0.88; P=.0005). Serious AEs were reported in 25% of patients in the FOLFOXIRI group compared with 17% in the sequential therapy group.

Results from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab to FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver metastases, were also reported.[186] Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs 23%; 95% CI, 4%–48%) and in the primary endpoint of overall (R0/R1/R2) resection rate (61% vs 49%; 95% CI, −11%–36%). Other phase II trials, including CHARTA and STEAM, have also reported improved outcomes for FOLFOXIRI plus bevacizumab when compared with a chemotherapy doublet plus bevacizumab for first-line treatment of mCRC.[187,188]

A pooled analysis of TRIBE and TRIBE2[189] and a meta-analysis of individual patient data from CHARTA, OLIVIA, STEAM, TRIBE, and TRIBE2[190] reached similar conclusions as the clinical trials. These analyses concluded that first-line treatment with FOLFOXIRI plus bevacizumab yields significantly better outcomes, albeit at the expense of higher toxicity, compared with sequential treatment with chemotherapy doublets in combination with bevacizumab. Based on these results, the NCCN Panel strongly recommends first-line FOLFOXIRI for patients with excellent performance status who can withstand the higher toxicity of the triplet regimen.

Bevacizumab for First-Line Therapy

Bevacizumab is a humanized monoclonal antibody that blocks the activity of vascular endothelial growth factor (VEGF), a factor that plays an important role in tumor angiogenesis.[191] The NCCN Panel notes that FDA-approved biosimilars may be substituted for bevacizumab wherever the therapy is recommended within these guidelines (see "Biosimilars," page 333, for more information). 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 mCRC compared with those receiving these regimens without bevacizumab.[192–194] 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).[175] A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.[192] 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.[130] 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).[130] 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.[130] 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.[130]

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced CRC has been studied, although no RCTs have compared FOLFIRI with and without bevacizumab. A recent systematic review with a pooled analysis (29 prospective and retrospective studies, 3502 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).[195] FOLFOXIRI with bevacizumab is also an accepted combination (see section on FOLFOXIRI, page 339), although no RCTs 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 mCRC and 482 patients treated with bevacizumab in second-line.[196] 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).[197]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for mCRC.[198–206] A meta-analysis of 6 randomized clinical trials (3,060 patients) that assessed the efficacy of bevacizumab in first-line treatment of mCRC 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.[207] 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).[208] 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,[209,210] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

Only limited data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease.[211] The randomized phase III HEPATICA trial, which closed prematurely due to poor accrual, found that global quality of life scores were higher in patients receiving CAPEOX plus bevacizumab than those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.[212] Furthermore, data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer[213,214] 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 meta-analysis of RCTs 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.[215] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[216] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[217] 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.[129,218] 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.[219] 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.[191]

Use of bevacizumab may interfere with wound healing.[129,191,218] A retrospective evaluation of data from 2 randomized trials of 1132 patients undergoing chemotherapy with or without bevacizumab as initial therapy for mCRC 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; $P=.28$).[218] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered after surgery, with a delay between surgery and bevacizumab administration 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).[220] 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.[221] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[191]) between the last dose of bevacizumab and any elective surgery. Additionally, reinitiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

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.[222] Although this meta-analysis has been criticized,[223,224] the results are supported by recent results from the NSABP Protocol C-08 trial.[213] This trial included patients with stage II and stage III CRC, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that no "rebound effect" is associated with bevacizumab use.

Cetuximab or Panitumumab for First-Line Therapy in KRAS/NRAS *Wild-Type Disease*

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.[72,225] Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of mCRC. The randomized, phase II PLANET-TTD trial comparing patients treated with panitumumab plus either FOLFOX or FOLFIRI found no significant differences in efficacy between the two regimens.[226]

Recent meta-analyses of RCTs have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-type mCRC.[56,227] 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 (see "Biomarkers for Systemic Therapy" and "*KRAS* and *NRAS* Mutations," page 333).

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[72,225] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[228–230] 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.[52,54,231–234] A recent NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[235] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious AEs.[236,237]

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 section on bevacizumab, page 340).[238,239] Several trials that assessed EGFR inhibitors in combination with various chemotherapy agents are discussed in the sections on "Cetuximab with FOLFIRI," "Panitumumab with FOLFIRI," "Cetuximab with FOLFOX," and "Panitumumab with FOLFOX", in the complete version of these guidelines at NCCN.org.

Cetuximab/Panitumumab and 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 mCRC.[240–248] For example, outcomes of 75 patients with mCRC 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.[241] 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.[245] The study showed that patients with *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in 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 if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; P=.04).[249] 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). Retrospective

analyses of other contemporary studies have confirmed this finding.[248]

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with mCRC if the primary tumor originated on the right side.[240,241,243] 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 genomic differences between right- and left-sided tumors[250] 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,[240,241,243] but the panel awaits more definitive studies. Until such data are available, all patients with *RAS/BRAF* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

Cetuximab or Panitumumab Versus Bevacizumab in First-Line Therapy

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.[71] This trial did not meet its primary endpoint 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.[251,252] Although the rate of AEs 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.[132] 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 endpoint of OS was equivalent between the arms, at 29.0 months in the bevacizumab arm versus 30.0 months in the cetuximab arm (HR, 0.88; 95% CI, 0.77–1.01; P=.08).

Results 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, were also published.[253] 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). A trend toward improved OS was seen (41.3 vs 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; P=.06). The final analysis of the PEAK trial confirmed that FOLFOX/panitumumab showed a longer PFS compared with FOLFOX/bevacizumab in patients with wild-type *RAS* (12.8 vs 10.1 months; HR, 0.68; 95% CI, 0.48–0.96; P=.029).[254] Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[255]

Economic analyses suggest that bevacizumab may be more cost effective than EGFR inhibitors in first-line therapy for mCRC,[256] although more recent analyses have shown the opposite.[257,258]

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

Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the First-Line Setting

The phase III, randomized open-label KEYNOTE-177 study evaluated the use of pembrolizumab compared with chemotherapy with or without bevacizumab or cetuximab as first-line therapy for 307 patients with MSI-H/dMMR mCRC.[259] Median PFS was found to be longer with pembrolizumab compared with chemotherapy (16.5 vs 8.2 months; HR, 0.60; 95% CI, 0.45-0.80; P=.0002). Confirmed ORR was 43.8% with pembrolizumab versus 33.1% with chemotherapy. Grade ≥3 treatment-related AEs were reported in 22% of patients treated with pembrolizumab compared with 66% of those treated with chemotherapy.

Likewise, the phase II CheckMate-142 trial evaluated the role of nivolumab in combination with ipilimumab for first-line treatment of dMMR/MSI-H mCRC. A 2019 abstract reporting results for 45 patients on this trial found ORR to be 60% (95% CI, 44.3%–74.3%), with a median follow-up of 13.8 months.[260] After 19.9 months of follow-up, investigator-assessed ORR was 64% (95% CI, 49%–78%), disease control rate was 84% (95% CI, 71%–94%), and duration of response had not been reached. After 19.9 months of follow-up, 20% of patients had grade 3 or 4 treatment-related AEs, and AEs led to discontinuation in 11% of patients. A 2020 abstract reported results from a longer follow-up of this same trial.[261] With a median follow-up of 29.0 months, the ORR increased to 69% and the CR rate was 13%. While median PFS and OS were not yet reached, 24-months rates for these outcome measures were 74% and 79%, respectively. Treatment-related AE and discontinuation rates were similar to the earlier analysis. Additional results

from CheckMate-142 (including nivolumab alone or in combination with ipilimumab as subsequent therapy) are discussed in "Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the Non–First-Line Setting" (page 347).

Based on these data, the panel recommends pembrolizumab or nivolumab, alone or in combination with ipilimumab, as first-line treatment options for patients with MSI-H/dMMR mCRC, whether they are eligible for intensive therapy. The recommendation for nivolumab plus ipilimumab for patients not appropriate for intensive therapy is category 2B due to concerns about potential toxicity from the combination therapy.

Second-Line or Subsequent Systemic Therapy

Decisions regarding therapy after progression of metastatic disease depend on previous therapies (for subsequent therapy following FOLFOX, see "COL-D 2 of 13," page 332; for other subsequent therapy recommendations, see COL-D 3 through 6 of 13, in the complete version of these guidelines at NCCN.org). 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.[262]

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[263] or infusional 5-FU/LV.[264] In the study of Rougier et al,[264] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=.030), whereas Cunningham et al[263] 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). A meta-analysis of five RCTs showed that there was no OS benefit to FOLFIRI over that obtained with irinotecan alone.[265] Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of mCRC.[266]

A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[267] Another meta-analysis showed an OS and PFS benefit to continuing an antiangiogenic agent after progression on an antiangiogenic agent in first-line.[268] Data relating to specific biologic therapies are discussed subsequently.

Cetuximab and Panitumumab in the Non–First-Line Setting

For patients with wild-type *KRAS/NRAS/BRAF* 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[50] is recommended. For patients with wild-type *KRAS/NRAS/BRAF* 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 mCRC for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy in an open-label phase III trial.[269] 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.[46] 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.[46] A more recent phase III trial compared single-agent panitumumab to best supportive care in patients with wild-type *KRAS* exon 2 mCRC and disease progression on oxaliplatin- and irinotecan-based chemotherapy.[270] The primary endpoint of OS was improved with panitumumab (10.0 vs 7.4 months; HR, 0.73; 95% CI, 0.57–0.93; P<.01).

Panitumumab has also been studied in combination therapy in the setting of progressing mCRC. 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 mCRC, 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.[172] These results were confirmed in the final results of Study 181.[271] Furthermore, reanalysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.[272] 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.[273] The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary

endpoint of improved OS in patients with wild-type *KRAS/NRAS* tumors.[84]

Cetuximab has been studied both as a single agent[50,231,274,275] and in combination with irinotecan[274] 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 in median PFS with irinotecan and cetuximab compared with irinotecan alone.[276] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[276]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[231] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[50] 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.[50]

The randomized, multicenter, open-label, noninferiority phase III ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[277] The primary noninferiority OS endpoint 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 AEs was similar between the groups. The final analysis of ASPECCT came to the same conclusion, reporting a median OS of 10.2 months with panitumumab and 9.9 months with cetuximab (HR, 0.98; 95% CI, 0.82–1.07).[278]

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.[279] No difference was seen in the primary endpoint 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; $P=.97$).

Bevacizumab in the Non–First-Line Setting

In the TML (ML18147) trial, patients with mCRC who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[280] This study met its primary endpoint, 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.[281]

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 following progression on bevacizumab was 6.8 months compared with 5.0 months in the control arm (HR, 0.70; 95% CI, 0.52–0.95; $P=.001$).[282] 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 following oxaliplatin-based therapy with bevacizumab to second-line therapy with FOLFIRI plus either 5 or 10 mg/kg bevacizumab.[283] 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 mCRC.

The continuation of bevacizumab following 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.[284] 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).[285]

Overall, these data (along with data from the VELOUR trial, discussed subsequently) 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 subsequently), based on toxicity and/or cost.[286] Beyond the second-line setting, bevacizumab may be combined with trifluridine-tipiracil (see "Trifluridine-Tipiracil," page 349, for more information).

It may also be appropriate to consider using bevacizumab with second-line therapy after progression on a first-line regimen that did not contain bevacizumab.[287] However, there are no data to support adding bevacizumab to a regimen after progression on that same regimen. 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.[287] 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).[287] 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.[287]

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.[288] 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 mCRC that progressed after one regimen containing oxaliplatin. The trial met its primary endpoint 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).[289] 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.[290]

AEs associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared with a 12.1% discontinuation in the placebo group.[289] 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 mCRC in the phase II AFFIRM study had no benefit and increased toxicity.[291] 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 (discussed subsequently) in this setting, based on toxicity and/or cost.[286]

Ramucirumab

Another antiangiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGF receptor 2 to block VEGF signaling.[292] In the multicenter, phase III RAISE trial, 1,072 patients with mCRC whose disease progressed on first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo.[293] The primary endpoint of OS in the ITT population was met at 13.3 months 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 months and 4.5 months for the 2 arms (HR, 0.79; 95% CI, 0.70–0.90; P<.0005). A subgroup analysis of the RAISE trial subsequently reported similar efficacy and safety among patient subgroups with different *KRAS* mutation status, time to progression on first-line therapy, and age.[294]

Rates of discontinuation due to AEs 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 AEs were neutropenia, hypertension, diarrhea, and fatigue. In addition, a meta-analysis of 6 phase III trials showed that ramucirumab did not increase the risk of arterial thromboembolic events, venous thromboembolic events, high-grade bleeding, or high-grade gastrointestinal bleeding compared with placebo controls.[295] These results suggest that ramucirumab may be distinct among antiangiogenic agents in that it does not increase the risk of these events.

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 who 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.[286]

Encorafenib Plus Cetuximab or Panitumumab for BRAF *V600E Mutation–Positive Disease in the Non–First-Line Setting*

A combination of the BRAF inhibitor, encorafenib, and the MEK inhibitor, binimetinib, with cetuximab has been investigated in the randomized, phase III BEACON trial for metastatic, *BRAF* V600E mutation–positive CRC.[296,297] The safety lead-in of the BEACON trial showed promising efficacy results with an ORR of 48% (95% CI, 29.4%–67.5%) among the 29 patients included in the efficacy analysis. Among the 30 treated patients in the safety lead-in, the most common grade 3 or 4 AEs were fatigue (13%), anemia (10%), increased creatine phosphokinase (10%), increased AST (10%), and urinary tract infections (10%).[296]

Subsequently, the randomized portion of the BEACON trial reported similarly encouraging results, including a positive OS result.[297] Within this portion of the study, 665 patients were randomized to receive either the triplet combination, an encorafenib and cetuximab doublet, or a control regimen of cetuximab plus either irinotecan or FOLFIRI. The final results of BEACON reported a median OS of 5.9 months, 9.3 months, and 9.3 months for the control, doublet, and triplet arms, respectively, after a median follow-up of 12.8 months.[298] The ORRs were 2%, 20%, and 27%, respectively, and grade 3 or higher AE rates were highest in the triplet arm, although the addition of binimetinib did not improve OS or ORR over the doublet. Quality of life assessments showed that the doublet and triplet regimens led to a similarly longer maintenance of quality of life compared with control. Based on this report, the NCCN Panel concluded that only the doublet regimen of encorafenib with either cetuximab or panitumumab should be recommended for patients with *BRAF* V600E-mutated mCRC.

Data exist on the use of cetuximab or panitumumab in combination with irinotecan and vemurafenib[299] as well as dabrafenib plus trametinib[300] for *BRAF* V600E mutation–positive mCRC. However, based on superior data and/or lower toxicity with the encorafenib-containing doublets, the panel voted to not include recommendations for these regimens within the current version of the guidelines.

Systemic Therapy Options for HER2-Amplified Disease

Three different regimens are recommended by the panel as options for subsequent treatment of mCRC with HER2 amplifications: fam-trastuzumab deruxtecan-nxki (T-DXd) monotherapy or trastuzumab in combination with either pertuzumab or lapatinib. These regimens may also be appropriate for patients with previously untreated HER2-amplified mCRC who are not appropriate for intensive therapy. The NCCN Panel notes that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within these guidelines (see "Biosimilars," page 333). The results of clinical trials supporting each of these regimens are detailed subsequently.

Trastuzumab Plus Pertuzumab

A combination regimen of the HER2 inhibitors trastuzumab and pertuzumab was studied in a subset analysis of MyPathway, a phase IIa multiple basket study.[301] This subset included 57 patients with previously treated, HER2-amplified mCRC who were treated with the combination of pertuzumab and trastuzumab. ORR was 32% (95% CI, 20%–45%), with 1 complete response and 17 partial responses. Thirty-seven percent of patients treated with trastuzumab plus pertuzumab had grade 3 or 4 AEs, with hypokalemia and abdominal pain being most common. Another phase II basket study, TAPUR, also investigated the combination of trastuzumab and pertuzumab in HER2-amplified mCRC.[302] In this study, 28 patients with heavily pretreated, HER2-amplified advanced CRC were treated with the combination. Four partial responses and 10 cases of stable disease for at least 16 weeks were reported, leading to a disease control rate of 50% and an ORR of 14%. Two patients had at least one grade 3 AE, including anemia, infusion reaction, and left ventricular dysfunction.

Trastuzumab Plus Lapatinib

The combination of trastuzumab plus the dual HER2/EGFR inhibitor, lapatinib, was studied in the multicenter, phase II HERACLES trial.[97] This trial included 27 patients with previously treated, HER2-positive tumors that were treated with trastuzumab and lapatinib. ORR was 30% (95% CI, 14%–50%), with 1 complete response, 7 partial responses, and 12 patients with stable disease. Twenty-two percent of patients treated with trastuzumab plus lapatinib had grade 3 AEs, including fatigue (4 patients), skin rash (1 patient), and increased bilirubin (1 patient).[97]

T-DXd

The HER2-directed antibody and topoisomerase inhibitor conjugate was studied in the phase II, multicenter DESTINY-CRC01 trial of 78 patients with HER2-expressing, *RAS/BRAF* wild-type unresectable and/or mCRC that had already progressed on at least 2 prior regimens.[303] Patients were split into 3 cohorts based on the level of tumor HER2 expression (cohort A: IHC 3+ or IHC 2+/ISH+; cohort B: IHC 2+/ISH−; cohort C: IHC 1+). In cohort A, the primary endpoint of ORR was 45.3%, with one complete response and 23 partial responses. Median PFS in this group was 6.9 months, median OS had not yet been reached. No responses were reported in cohorts B or C. 20.5% of patients had received prior anti-HER2 therapy; for these patients ORR was 43.8%. Grade ≥3 treatment-emergent AEs occurred in 61.5% of patients, with decreased neutrophil count and anemia most common. Of note, 5 patients on this trial developed interstitial lung disease related to T-Dxd, including 2 deaths due to this complication (2.6% of all patients).

Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the Non–First-Line Setting

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.[113]

A phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR CRC, 21 patients with pMMR CRC, and 9 patients with dMMR noncolorectal

carcinomas.[304] All patients had progressive metastatic disease; the patients in the colorectal arms had progressed through 2 to 4 previous therapies. The primary endpoints 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 pMMR CRC group, and 71% (95% CI, 29%–96%) in the dMMR noncolorectal 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 pMMR CRC group (HR for disease progression or death, 0.10; $P<.001$). Another phase II study, KEYNOTE-164, investigated the efficacy of pembrolizumab in 124 patients with MSI-H/dMMR mCRC which had been treated with at least one previous line of therapy.[305] The patients on this study were divided into 2 cohorts based on whether they had received ≥2 lines of therapy including a fluoropyrimidine, oxaliplatin, and irinotecan (cohort A) or ≥1 line of therapy (cohort B). ORR was reported as 33% for both cohorts, with the median duration of response not reached at the time of publication. Median PFS was 2.3 months and 4.1 months, for cohorts A and B, respectively. Median OS was 31.4 months for cohort A and had not been reached for cohort B. Treatment-related AEs of grade ≥3 occurred in 16% of patients in cohort A and 13% in cohort B, with pancreatitis, fatigue, increased alanine aminotransferase, and increased lipase most common.

Nivolumab is another humanized IgG4 PD-1 blocking antibody,[306] which was studied with or without ipilimumab in patients with mCRC in the phase II, multicohort CheckMate-142 trial.[307,308] One cohort of this trial included 74 patients with dMMR CRC who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8–42.9) with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related AEs occurred in 20% of patients, with increased amylase and increased lipase being most common.[308] Another cohort of the CheckMate-142 included 119 patients with dMMR CRC who were treated with nivolumab in combination with ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related AEs occurred in 32% of patients, but were manageable.[307] An in-depth analysis of the safety profile of nivolumab plus ipilimumab on the CheckMate-142 trial reported that AEs predefined in the study protocol as being of special clinical interest (eg, endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin events) tended to occur early in treatment, were managed using evidence-based treatment algorithms, and resolved.[309]

Based on these data, the panel recommends pembrolizumab, nivolumab, or nivolumab plus ipilimumab as subsequent-line treatment options in patients with metastatic MMR-deficient CRC. These therapies are only options for patients who have not previously received a checkpoint inhibitor. 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%–41% of patients.[304,307,308,310] The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.[311–313] Pneumonitis, occurring in approximately 3%–7% of patients on checkpoint inhibitor therapy, is one of the most serious side effects of PD-1 inhibitors.[311,314–316]

Larotrectinib or Entrectinib for NTRK *Fusion–Positive Disease in the Non–First-Line Setting*

Recent studies have estimated that about 0.2%–1% of CRCs carry *NTRK* gene fusions.[109,110] Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor.[317,318]

A pooled analysis of 3 studies (a phase I study including adults, a phase I/II study involving children, and the phase II NAVIGATE study involving adolescents and adults) studied the safety and efficacy of larotrectinib in 55 patients with *NTRK* gene fusion-positive tumors, including four patients with colon cancer.[108] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment,[108] although the package insert cites a 25% ORR for colon tumors specifically.[318] Larotrectinib was found to be well-tolerated as the majority (93%) of AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in more than 5% of patients.[108] A subsequent analysis of these 3 studies included 159 patients, 8 with colon cancer, and reported similar results compared with the earlier analysis.[319] In this later analysis, the ORR was 79% (95% CI, 72%–85%) by investigator assessment with 16% complete responses. An analysis of 14 patients with gastrointestinal cancer who were treated with larotrectinib in the NAVIGATE study reported a median PFS of 5.3 months

(95% CI, 2.2–9.0) and a median OS of 33.4 months (95% CI, 2.8–36.5).[320] Responses were ongoing for 5 patients, leading their results to be censored. Of the 8 patients with colon cancer, 50% showed a partial response and 50% had stable disease.

An integrated analysis of 3 global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic *NTRK* gene fusion-positive solid tumors.[321] For the whole population, ORR was 57% (95% CI, 43.2%–70.8%), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9–not estimable) by independent review. Median DOR was 10 months (95% CI, 7.1–not estimable). Of the 4 patients with CRC on this study, one was recorded as having a response. Notably, a similar ORR (50% vs 60%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs.

Based on these results the panel added larotrectinib and entrectinib as subsequent treatment options for patients with *NTRK* gene fusion-positive disease, acknowledging that these therapies will not be appropriate for most patients due to the rarity of the *NTRK* fusion in CRC.

Regorafenib

Regorafenib is a small-molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, BRAF, KIT, and RET) that are involved with various processes including tumor growth and angiogenesis.[322] The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.[323] 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.[324] Patients with progressive mCRC were randomized 2:1 to receive regorafenib or placebo after 2 or more previous treatment regimens. After a median follow-up of 7.4 months, the primary endpoint 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; $P<.001$).

The most common grade 3 or higher AEs in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[323] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[322] In a meta-analysis of four studies that included 1078 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.[325] In the subset of 500 patients with CRC, the incidence of all-grade hand-foot skin reaction was 46.6%.

Other studies have also investigated regorafenib for treatment of refractory mCRC. The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2872 patients from 25 countries with refractory mCRC.[326] The REBECCA study assessed the safety and efficacy of regorafenib in a cohort of 654 patients with mCRC within a compassionate use program.[327] The prospective, observational CORRELATE study assessed the safety and efficacy of regorafenib in 1037 patients with mCRC in real-world clinical practice.[328] The safety and efficacy profiles of regorafenib in all of these trials were consistent with that seen in the CORRECT trial.

The randomized, phase II ReDOS trial investigated the use of an alternative dose schedule to reduce the toxicities related to regorafenib treatment.[329] Of the 116 evaluable patients, the dose-escalation group had a higher percentage of patients who initiated cycle 3 of regorafenib (43%) compared with the standard dosing group (26%). Rates of several of the most common AEs were also lower among the dose-escalation group compared with the standard dosing group. Based on these results, the panel agreed that a dose-escalation strategy is an appropriate alternative approach for regorafenib dosing.

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

Trifluridine-Tipiracil

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.[330,331]

Results of the double-blind, randomized, controlled, international phase III RECOURSE trial were published in 2015,[332] followed shortly thereafter by approval of trifluridine-tipiracil by the FDA.[333] With 800 patients with mCRC who progressed through at least 2 prior regimens randomized 2:1 to receive trifluridine-tipiracil or placebo, the primary endpoint of OS was met (5.3 vs

7.1 months; HR, 0.68; 95% CI, 0.58–0.81; $P<.001$).[332] Improvement was also seen in the secondary endpoint of PFS (1.7 vs 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; $P<.001$). The most common AEs associated with trifluridine-tipiracil in RECOURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred.[332] A post-marketing surveillance study did not reveal any unexpected safety signals[334] and a subgroup analysis of the RECOURSE trial reported similar efficacy and safety regardless of age, geographical origin, or *KRAS* mutation status.[335]

The combination of trifluridine-tipiracil and bevacizumab has also been studied in the non-first-line setting. C-TASK FORCE was on open-label, single-arm phase I/II study of trifluridine-tipiracil plus bevacizumab for patients with mCRC who had previously received a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF therapy, and an anti-EGFR therapy, if eligible.[336] Patients on this study had not been previously treated with regorafenib. The primary endpoint of PFS at 16 weeks was 42.9% and treatment-related serious AEs were reported in 12% of patients. Based on the results from C-TASK FORCE, a randomized phase II trial of 93 patients was initiated to compare trifluridine-tipiracil with and without bevacizumab in this patient population.[337] On the phase II trial, previous treatment with a VEGF inhibitor and/or regorafenib were permitted, but not required for study eligibility. After a median follow-up of 10 months, the median PFS was 2.6 months for trifluridine-tipiracil alone compared with 4.6 months in combination with bevacizumab (HR, 0.45; 95% CI, 0.29-0.72; $P=.0015$). Toxicity was similar between the two groups, with serious AEs reported in 45% of patients who received trifluridine-tipiracil alone and 41% of those who received trifluridine-tipiracil in combination with bevacizumab. A retrospective study of 57 patients with refractory mCRC showed similar results, with an improved median OS for trifluridine-tipiracil with bevacizumab versus without (14.4 vs 4.5 months; $P<.001$).[338]

Based on these data, the panel added trifluridine-tipiracil, with or without bevacizumab, as a treatment option for patients who have progressed through standard therapies. It can be given before or after regorafenib; no data inform the best order of these therapies, although real-world data have shown that patients show better adherence to trifluridine-tipiracil compared with regorafenib.[339] 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).

Summary

The panel believes that a multidisciplinary approach is necessary for managing mCRC. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at initiation of therapy include preplanned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. In addition to fluoropyrimidine-, oxaliplatin-, and/or irinotecan-containing chemotherapy regimens, immunotherapy and targeted therapy regimens are becoming an increasingly important part of the mCRC treatment landscape. Combination of a biologic agent (eg, bevacizumab, cetuximab, panitumumab) with some of the chemotherapy regimens is an option, depending on available data. Systemic therapy options for patients with progressive disease depend on the choice of initial therapy and biomarker status of the tumor.

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The NCCN Guidelines Staff have no conflicts to disclose.
[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
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