

NCCN Guidelines® Insights

Colon Cancer, Version 2.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Colon Cancer provide recommendations regarding diagnosis, pathologic staging, surgical management, perioperative treatment, surveillance, management of recurrent and metastatic disease, and survivorship. These NCCN Guidelines Insights summarize the NCCN Colon Cancer Panel discussions for the 2018 update of the guidelines regarding risk stratification and adjuvant treatment for patients with stage III colon cancer, and treatment of *BRAF* V600E mutation-positive metastatic colorectal cancer with regimens containing vemurafenib.

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Please Note

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Colon Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Colon Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Al B. Benson III, MD, Panel Chair, has disclosed that he receives grant/research support from Acerta Pharma; Bristol-Myers Squibb Company; Celgene Corporation; Infinity Pharmaceuticals; MedImmune Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Taiho Pharmaceuticals Co., Ltd. He also receives consulting fees/honoraria from and serves as a scientific advisor for AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim GmbH; Boston Biomedical; Bristol-Myers Squibb Company; Celgene Corporation; Eli Lilly and Company; EMO Serono; Exelixis Inc.; Genentech, Inc.; Guidant Corporation; Halozyne, Inc.; Helsinn Therapeutics; ImmunoGen, Inc.; Lexicon Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Opsona Therapeutics; Pfizer Inc.; Purdue Pharma LP; and Taiho Pharmaceuticals Co., Ltd.

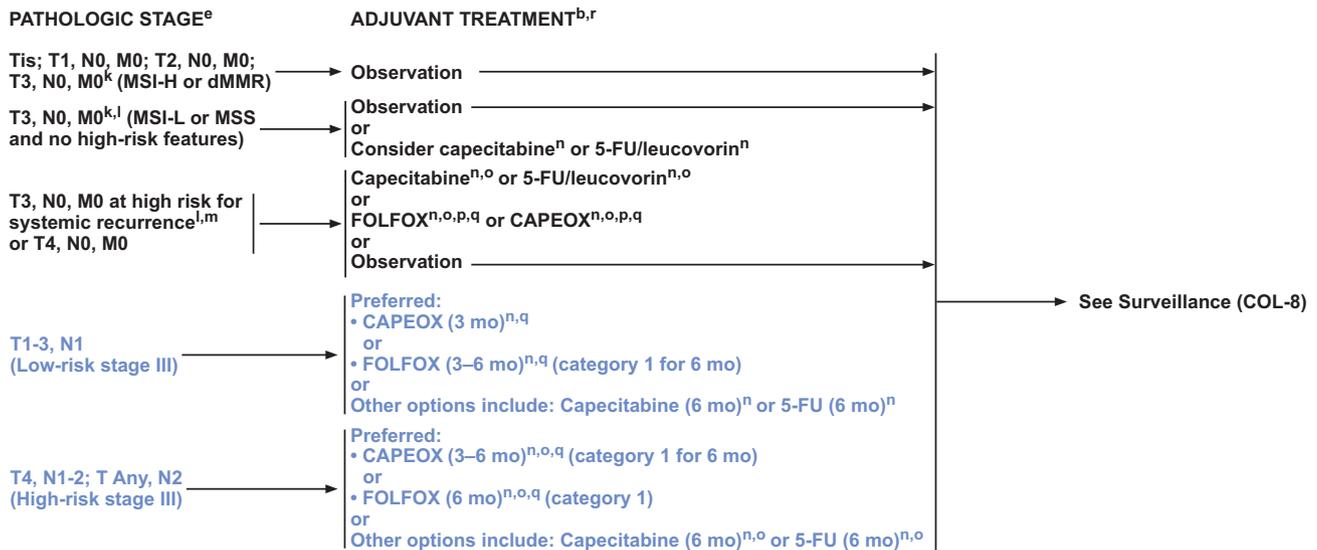
Alan P. Venook, MD, Panel Vice Chair, has disclosed that he serves as a scientific advisor for Bayer HealthCare; Bristol-Myers Squibb Company; Genentech, Inc.; Merck & Co., Inc.; and Taiho Pharmaceuticals Co., Ltd. He also receives grant/research support from Genentech, Inc., and Merck & Co., Inc.

Stacey Cohen, MD, Panel Member, has disclosed that she has no relevant financial relationships.

Deborah A. Freedman-Cass, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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^bSee Principles of Imaging (COL-A).

^cSee Principles of Pathologic Review (COL-B).

^kSee Principles of Risk Assessment for Stage II Disease (COL-F).

^lHigh-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

^mThere are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

ⁿSee Principles of Adjuvant Therapy (COL-G).

^oConsider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-E).

^pA survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012; published online ahead of print on August 20, 2012.

^qA benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

^rIn patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs. 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 vs. 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs. 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX). Shi Q, et al. J Clin Oncol 2017;35 (suppl):LBA1.

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COL-3

NCCN Categories of Evidence and Consensus

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

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

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

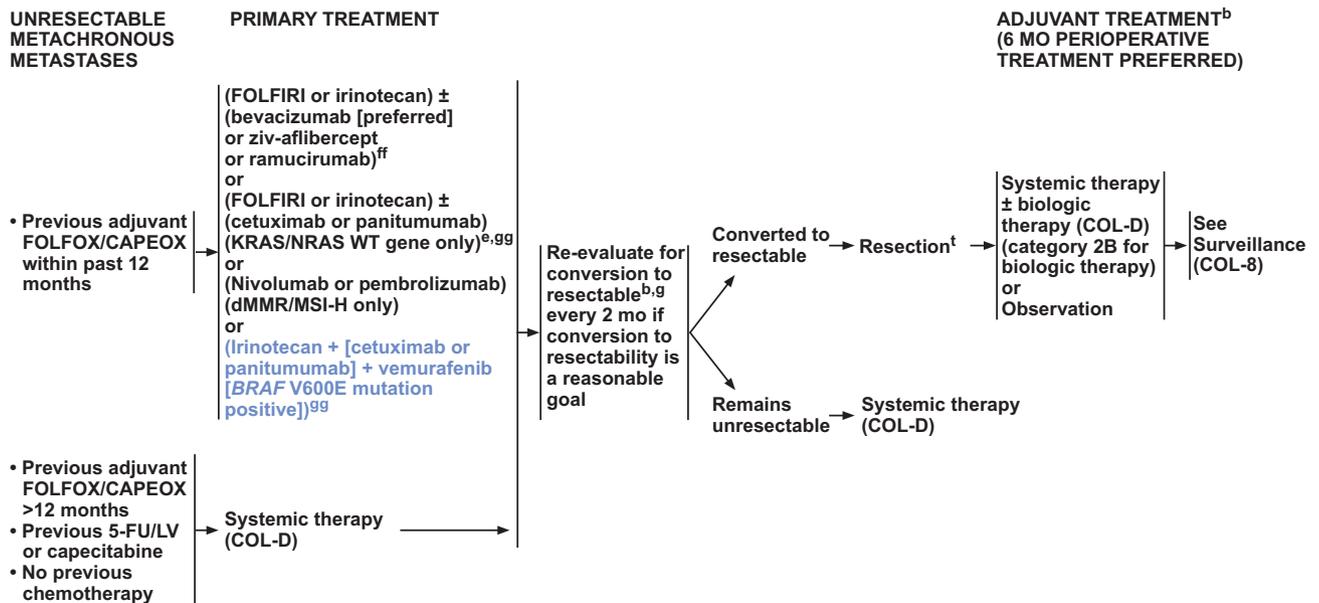
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2018, an estimated 97,220 new cases of colon cancer and approximately 43,030 cases of rectal cancer will be diagnosed. During the same year, an estimated 50,630 people will die of colon and rectal cancers combined.¹ The incidence of CRC has been declining; incidence per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005, and to 40.7 in 2009–2013.^{2,3} In fact, the incidence of CRC decreased at a rate of approximately 3% per year between 2003–2012.⁴ In addition, mortality from CRC decreased by almost 35% from 1990–2007,⁵ and is currently reduced by 51% from peak mortality rates—from 28.6 per 100,000 in 1976 to 14.1 in 2014.³ These improvements in incidence of and mortality from CRC are thought to be a result of shifting patterns of CRC risk factors, cancer prevention and earlier diagnosis through screening, and better treatment modalities.⁶



^bSee Principles of Imaging (COL-A).

^eSee Principles of Pathologic Review (COL-B 4 of 5) - KRAS, NRAS, and BRAF Mutation Testing.

⁹See Principles of Surgery (COL-C 2 of 3).

^tHepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

^{ff}Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

^{9g}BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor.

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COL-11

Despite the observed improvements in the overall CRC incidence rate, its incidence in patients aged <50 years has been increasing.^{3,7} In 2017, approximately 7,550 cases of CRC were diagnosed in this population.³ In a retrospective cohort study of the SEER CRC registry, it was estimated that the incidence rates for colon and rectal cancers in patients aged 20 to 34 years will increase by 90.0% and 124.2%, respectively, by 2030.⁷ The cause of this trend is currently unknown.

2018 Updates to the NCCN Guidelines for Colon Cancer

During the meeting to update the guidelines for 2018, the panel discussed many issues. Most notable were the results of the IDEA collaboration and their impact on adjuvant treatment in patients with stage III colon cancer,⁸ and results of the SWOG S1406 trial and their impact on treatment of patients with BRAF-mutant metastases.⁹

Risk Stratification and Adjuvant Treatment for Stage III Colon Cancer

Nonmetastatic colon cancer is generally treated with curative intent by colectomy and, in some cases, adjuvant chemotherapy.¹⁰ Population and institutional studies have shown that adjuvant therapy may confer a survival advantage in some patients with resected colon cancer (eg, those with stage III or high-risk stage II disease).¹¹⁻¹⁴ Furthermore, randomized controlled trials have shown that the addition of oxaliplatin to these adjuvant regimens benefits some patients.¹⁵⁻¹⁹ However, adjuvant treatment, especially with regimens containing oxaliplatin, is associated with considerable toxicity (notably chemotherapy-induced peripheral neuropathy),^{16,20} and not all patients derive benefit. Consideration of disease stage and pathologic features, microsatellite instability (MSI) status, possible efficacy and toxicity profiles associated with treatment choice, and patient age, comorbidities, and preferences aid in decision-making regarding the use of adjuvant therapy for patients

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PRINCIPLES OF PATHOLOGIC REVIEW

KRAS, NRAS, and BRAF Mutation Testing

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.^{43,44,45} *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.⁴⁶⁻⁴⁸
- Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high-complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.⁴⁹

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing

- Universal MMR* or MSI* testing is recommended in all patients with a personal history of colon or rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- The presence of a *BRAF* V600E mutation in the setting of *MLH1* absence would preclude the diagnosis of Lynch syndrome.
- Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.⁵⁰
- MMR or MSI testing should be performed only in CLIA-approved laboratories.
- Testing for MSI may be accomplished with a validated NGS panel, especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF*.

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-B 1 of 5

See Pathologic Stage on COL-B 2 of 5

See Lymph Node Evaluation on COL-B 3 of 5

*IHC for MMR and DNA analysis for MSI are different assays measuring the same biological effect.

See references on COL-B 5 of 5
(available at NCCN.org)

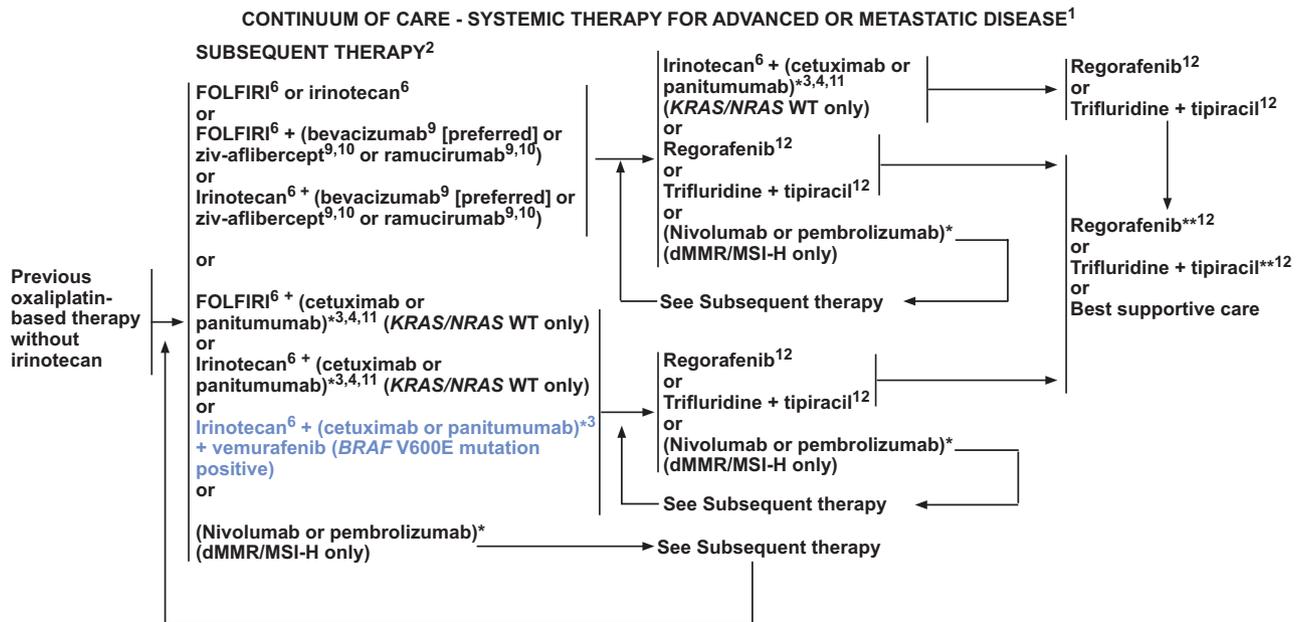
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COL-B
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with colon cancer.²¹⁻²⁵ Better risk stratification could improve adjuvant treatment selection to help patients avoid unnecessary toxicities without compromising outcomes.

The IDEA collaboration investigated whether a shortened duration of adjuvant therapy would be a feasible way to avoid or lessen toxicities associated with oxaliplatin-containing adjuvant therapy in some patients with locoregional colon cancer, without impairing oncologic outcomes. IDEA included >12,000 patients in an international effort that pooled data from 6 concurrently conducted randomized phase III trials to assess the noninferiority of 3 months compared with 6 months of adjuvant FOLFOX or CapeOX in patients with stage III colon cancer.⁸ Median follow-up was 39 months. Importantly, grade ≥ 3 neurotoxicity rates were lower in the 3 months' versus 6 months' treatment arms (3% vs 16% for FOLFOX; 3% vs 9% for CapeOX; $P < .0001$), as were grade 2 neurotoxicity rates (14% vs 32% for FOLFOX; 12% vs 36% for CapeOX; $P < .0001$). Rates

of grades 2 and 3/4 diarrhea were also lower with the shorter duration of therapy ($P < .0001$ for FOLFOX; $P = .01$ for CapeOX). The primary end point of 3-year disease-free survival (DFS) did not meet the pre-specified cutoff for noninferiority, despite the small absolute difference of 0.9% (74.6% for 3 months vs 75.5% for 6 months; hazard ratio [HR], 1.07; 95% CI, 1.00-1.15), which is of questionable clinical significance. Notable differences in 3-year DFS were seen between FOLFOX and CapeOX and between patients with T1-3N1 (low-risk) versus T4 or N2 (high-risk) disease. Specifically, in the T1-3N1 subset, DFS with 3 months of CapeOX was noninferior to that with 6 months of CapeOX (HR, 0.85; 95% CI, 0.71-1.01), whereas noninferiority could not be proven for 3 versus 6 months of FOLFOX (HR, 1.10; 95% CI, 0.96-1.26). In the T4 or N2 subset, DFS with 3 months of FOLFOX was inferior to that of 6 months with FOLFOX (HR, 1.20; 95% CI, 1.07-1.35), whereas noninferiority could not be proven



*if neither previously given
**if not previously given

See footnotes COL-D 6 of 10
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COL-D
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for 3 versus 6 months of CapeOX (HR, 1.02; 95% CI, 0.89–1.17).

The panel discussed several details of the trial and how they believed the results should be translated into guideline recommendations. First, the panel discussed what might account for the unexpected differences seen in DFS between FOLFOX and CapeOX. Oxaliplatin doses are different between the regimens (85 mg/m² every 2 weeks for mFOLFOX6; 130 mg/m² every 3 weeks for CapeOX), which might partially account for the observed difference in outcomes. Although total oxaliplatin exposure is similar, more oxaliplatin is received in the first 4 weeks with CapeOX (260 mg/m²) compared with FOLFOX (170 mg/m²). Also, the panel noted that capecitabine may result in more continuous fluorouracil exposure than 5-FU/leucovorin. One panel member noted that some sites used FOLFOX4; however, panel consensus was that this difference would only account for differences in toxicity, not in efficacy. Treatment compliance was similar between

the CapeOX and FOLFOX arms (percent reaching planned last cycle was 90% for 3-month FOLFOX, 86% for 3-month CapeOX, 71% for 6-month FOLFOX, and 65% for 6-month CapeOX), and therefore compliance is unlikely to account for the differences between the regimens. Importantly, the panel noted that no significant differences have been seen between CapeOX and FOLFOX in randomized adjuvant or metastatic studies.^{26,27} Therefore, the panel discussed the possibility that selection bias may account for the difference in DFS seen between FOLFOX and CapeOX in IDEA. The use of FOLFOX versus CapeOX was by physician's choice, not by randomization; choice of regimen was used as a stratification factor for randomization to 3 or 6 months of treatment duration. The proportion of patients treated with CapeOX varied from 0% to 75% between trial sites.⁸ In the US/Canadian study that used only mFOLFOX6, in fact, 3 months of FOLFOX achieved noninferiority to 6 months of FOLFOX, with an HR for DFS of 1.10. However, in the French trial,⁸ most

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patients (90%) received FOLFOX, and the HR for DFS between 3 and 6 months of FOLFOX was the worst of all trial sites at 1.27. Though the reasons for the different outcomes based on regimen choice are not completely clear, the panel agreed that the data are convincing and that the difference cannot be ignored.

Another point that the NCCN Panel discussed was whether DFS data formed a sufficient basis for guideline recommendations. The panel was unified in its opinion that, although DFS effects have been shown to be larger than overall survival (OS) effects in other trials, the almost complete elimination of oxaliplatin toxicity with a shorter treatment duration justified changes to the guidelines at this time.

The data were sufficient to warrant division of stage III colon cancer into a low-risk (T1–3N1) and a high-risk group (T4N1–2 or TanyN2; see COL-3, page 361). For the low-risk group, the recommended duration of adjuvant therapy is 3 months if CapeOX is chosen, because noninferiority for DFS was proven in IDEA and patients should be spared the increased toxicity, cost, and inconvenience of longer therapy. If FOLFOX is chosen for these patients, then 3 to 6 months of FOLFOX is recommended. The panel believes the shorter duration can be considered to reduce toxicity, cost, and inconvenience, but noninferiority could not be proven for 3 versus 6 months of FOLFOX in this subset. For patients with high-risk stage III colon cancer, 3 to 6 months of adjuvant therapy is recommended if CapeOX is chosen; noninferiority of the shorter duration was not proven in this subset of patients, but the panel believes the shorter duration can be considered to minimize toxicity, cost, and inconvenience. Furthermore, DFS with 3 months of therapy was noninferior to DFS with 6 months for the entire cohort (TanyN1–2) who received CapeOX (HR, 0.95; 95% CI, 0.85–1.06).⁸ Finally, FOLFOX, if chosen, should be given for a full 6 months in the high-risk group because 3 months was shown to be inferior to 6 months for DFS. With these updated and nuanced recommendations, careful discussion and review of the available data between the patient and clinician are important to guide the choice of approach.

The panel then discussed some concerns about the dosing of capecitabine in CapeOX, which they believe is critical if the decision is to give 3 months of CapeOX. Many oncologists, especially in the

United States, routinely reduce the starting dose of capecitabine, but the panel strongly believes that the starting dose used in IDEA⁸ (1,000 mg/m² twice daily) should be used because it is the only validated dose. The panel also discussed that, in practice, oxaliplatin is dropped from FOLFOX and CapeOX after 6 to 10 doses to reduce the risk of severe neurotoxicity. Therefore, it may be reasonable to complete 3 months of CapeOX for patients with high-risk stage III colon cancer and then drop oxaliplatin and continue capecitabine. However, the panel was divided on whether to recommend this approach.

Because of the methodologies and results of IDEA, some of the findings are open to interpretation. However, it will be difficult to generate data that are any more definitive than those from the IDEA analysis. Therefore, the NCCN Guidelines list FOLFOX and CapeOX as equally preferred options without strongly recommending one over the other. Efficacy is similar, FOLFOX is less expensive for US patients, and CapeOX is more convenient for most patients (especially 3 months of CapeOX vs 6 months of FOLFOX). Both regimens are preferred over the other options for adjuvant treatment of patients with stage III colon cancer—6 months of either capecitabine or 5-FU/leucovorin—which are generally only recommended for patients with stage III colon cancer if they cannot tolerate oxaliplatin.

Despite the large number of patients in IDEA, the results were not as definitive as the panel would require for these new recommendations to be listed as category 1. Therefore, these shorter durations are included in the guidelines as category 2A recommendations. The 6-month durations of FOLFOX or CapeOX for patients with stage III colon cancer remain as category 1 recommendations based on older trials.^{15–19}

Finally, the panel also briefly discussed the limited data from IDEA on stage II colon cancer or stage II/III rectal cancer. Only one site included patients with rectal cancer, none of whom had preoperative chemotherapy, and only 2 sites included patients with stage II colon cancer, one of which included mostly those with high-risk stage II. Overall, the panel believed there are not enough data from IDEA to draw any conclusions for patients with rectal or stage II colon cancer.

Treatment of RAS Wild-Type/*BRAF* Mutation–Positive Metastatic CRC

In the 2017 version of the NCCN Guidelines, patients with unresectable, advanced, or metastatic CRC (mCRC) were managed with a continuum of care that included 20 first-line systemic treatment options, 33 second-line options, and 13 options for subsequent therapies in up to 7 lines of treatment.^{28,29} A growing list of factors are considered when choosing therapies for each patient, including the goals of treatment, type and timing of prior therapy, different efficacy and toxicity profiles of the regimens, *KRAS* and *NRAS* mutational tumor status, and patient comorbidities and preferences. MSI status and location of the primary tumor were recently added as additional considerations.^{30–34} Although survival for patients with advanced CRC has improved dramatically over the past decades, the most recently reported 5-year survival rate for patients with stage IV CRC was only 14%.^{1,35} Moreover, patients with *BRAF*-mutated mCRC have a particularly poor prognosis. *BRAF* V600E mutations are present in approximately 8% of mCRC cases and are associated with a more aggressive biology, shorter OS, and decreased response to chemotherapy compared with *BRAF* wild-type tumors.³⁶ Thus, additional treatment options are still needed in mCRC, especially for the *BRAF* mutation–positive subset of patients.

BRAF is downstream of *EGFR* and *RAS* in the MAPK signaling pathway. The *BRAF* V600E mutation results in constitutive MAPK signaling that encourages cellular proliferation.³⁷ Vemurafenib selectively inhibits the V600E-mutated form of the *BRAF* kinase, thereby reducing aberrant MAPK signaling.³⁸ It has an FDA indication for treatment of patients with *BRAF* V600E–mutated, unresectable, or metastatic melanoma.³⁹ However, vemurafenib monotherapy has shown limited activity in mCRC.⁴⁰ Preclinical data suggest that *BRAF* V600E inhibition alone is ineffective because feedback activation of *EGFR* occurs.^{41,42} Therefore, blockage of *EGFR* and *BRAF* V600E together has been speculated to be more effective than *BRAF* V600E inhibition alone. In fact, preclinical studies show a synergistic effect of such dual inhibition.^{41,42} However, vemurafenib in combination with cetuximab- or panitumumab-based therapy has been ineffective in early clinical trials.⁴³ Results from preclinical and early clinical studies suggest that the addition of irinotecan to

BRAF and *EGFR* inhibition may improve antitumor activity.^{44,45}

The combination of vemurafenib, cetuximab, and irinotecan was thus tested in patients with *BRAF* V600E–mutated mCRC in the recent phase II SWOG S1406 trial. In this trial, 99 patients with *BRAF*-mutant, *RAS* wild-type tumors who received 1 or 2 prior regimens were randomized to irinotecan and cetuximab with or without vemurafenib.⁹ The NCCN Panel reviewed updated results of this trial that were presented at the 2017 ASCO annual meeting. The primary end point of median progression-free survival (PFS) was improved in the vemurafenib arm (4.3 vs 2.0 months; HR, 0.48; 95% CI, 0.31–0.75; $P=.001$). Response was also improved, with response rates (only partial responses [PRs] were seen) of 4% vs 16% ($P=.08$) and disease control rates (partial responses + stable disease) of 22% vs 67% ($P=.001$). Grade 3/4 adverse events (AEs) that were higher in the vemurafenib arm included neutropenia (33% vs 7%), anemia (13% vs 0%), and nausea (20% vs 2%). Crossover was allowed for the cetuximab/irinotecan group, and 48% of those patients received vemurafenib at time of progression. Of those who crossed over, the partial response rate was 17% and the stable disease rate was 55%, for a disease control rate of 72%. The HR for the secondary end point of OS, which would be attenuated by the crossover, was 0.73 (95% CI, 0.45–1.17; $P=.19$).

After the panel reviewed these data, one member pointed out that results of the safety lead-in phase of the BEACON CRC trial (ClinicalTrials.gov Identifier: NCT02928224) were to be presented at the ESMO 2017 Congress. This international phase III trial is comparing (1) encorafenib with cetuximab plus or minus binimetinib versus (2) investigator choice of irinotecan/cetuximab or FOLFIRI/cetuximab in patients with *BRAF* V600E–mutant mCRC whose disease has progressed on 1 or 2 prior metastatic regimens. Encorafenib is another inhibitor of mutant *BRAF*, and binimetinib inhibits MEK, which is downstream from *BRAF* in the MAPK pathway.^{37,46} The combination of these 2 drugs has been shown to improve PFS in *BRAF*-mutant melanoma compared with encorafenib monotherapy.⁴⁷ Although the BEACON CRC data had not been presented at the time of panel discussion, several panel members were aware that the results would be better than those seen in SWOG S1406. In fact, the

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now-presented data show that the triplet regimen (encorafenib/cetuximab/binimetinib) was fairly well tolerated in 30 patients, with dose-limiting toxicities in 5 patients (cetuximab infusion reaction, n=2; grade 2 retinopathy, n=2; grade 2 decreased ejection fraction, n=1). Of the 30 patients, 19 (63%) experienced a grade 3 or 4 AE, including fatigue (grade 3 in 4 patients), urinary tract infection (grade 3 in 3 patients), increased aspartate aminotransferase (grade 3 in 2 patients; grade 4 in 1 patient), and increased blood creatine phosphokinase (grade 3 in 3 patients). The most common AEs of any grade were diarrhea (77%), dermatitis acneiform (67%), nausea (63%), and fatigue (63%).^{48,49} In 29 patients with *BRAF* V600E–mutated mCRC, the overall response rate (3 complete responses + 11 partial responses) was 48%. All remaining patients had stable disease, for a disease control rate of 100%. The preliminary estimated median PFS was 8 months. One panel member reasoned that vemurafenib/cetuximab/irinotecan should not be added based on the SWOG S1406 results, but rather the panel should wait for BEACON CRC results and FDA approval of encorafenib and binimetinib. Although the panel members eagerly await more mature data from BEACON CRC and forthcoming FDA approvals, the vast majority of the panel felt that the data from SWOG S1406 were strong enough to warrant the addition of vemurafenib/cetuximab/irinotecan for patients with *BRAF* V600E–mutated mCRC at this time. They believed that this subset of patients is in great need of additional treatment options and saw no justification for waiting for better regimens.

The panel then discussed whether to recommend vemurafenib/panitumumab/irinotecan for these patients by extrapolation from the SWOG S1406 data. In general, the panel believes that panitumumab and cetuximab are interchangeable, and some clinic formularies may only list one or the other agent. Furthermore, panel members pointed out that some patients may experience a severe reaction to cetuximab. Safety of vemurafenib/panitumumab/irinotecan has been shown in a case report of a patient with *BRAF*-mutant cholangiocarcinoma.⁵⁰ Therefore, the panel voted to add this regimen as an additional option for patients with *BRAF* V600E–mutant mCRC.

Next, the panel discussed whether dabrafenib could be substituted for vemurafenib by extrapolation of SWOG S1406 data. However, they do not

believe that dabrafenib and vemurafenib are interchangeable. Dabrafenib was studied in patients with *BRAF* V600E–mutant mCRC in a case report and a few early clinical trials.^{51–54} The largest was a single-arm trial that included 43 patients with *BRAF* V600E–mutant mCRC who received dabrafenib with trametinib.⁵¹ Trametinib is another MEK inhibitor with an FDA indication in *BRAF*-mutated melanoma and non–small cell lung cancer in combination with dabrafenib.⁵⁵ The complete response rate was 2% (1 patient), partial response rate was 9% (4 patients), and stable disease rate was 56% (24 patients). Grade 3 AEs occurred in 58% of patients, with nausea, pyrexia, and fatigue being the most common events of any grade. Four patients (9%) discontinued treatment because of AEs. To the best of the panel's knowledge, however, dabrafenib has not been studied in combination with irinotecan or an EGFR inhibitor, and therefore no safety data for the proposed combination exist. Therefore, the panel declined to add dabrafenib/(cetuximab or panitumumab)/irinotecan to the continuum of care for patients with *BRAF*-mutant mCRC. The panel noted that trametinib/dabrafenib/panitumumab is currently being studied in an open-label phase I/II trial of patients with *BRAF* V600E–mutated mCRC (ClinicalTrials.gov identifier: NCT01750918).

Overall, the panel is gratified by the addition of new treatment options for patients with *BRAF*-mutated mCRC that has progressed on 1 or 2 previous metastatic regimens (see COL-11 and COL-D 2 of 10, pages 362 and 364, respectively, as examples). They are hopeful that ongoing trials will lead to even better options for this difficult-to-treat subset of patients. With the addition of vemurafenib/(cetuximab or panitumumab)/irinotecan to the mCRC continuum of care, the *BRAF* status of the tumor is now another factor that must be considered when choosing therapies for patients with mCRC. *BRAF* status can be determined using any methodology, including next-generation sequencing, which can be used to simultaneously test for MSI and mutations in *RAS* (COL-B 4 of 5, page 363). The panel further notes that *BRAF* and *RAS* mutations are mutually exclusive. Therefore, although the guidelines only indicate that the new regimens are for “*BRAF* V600E mutation–positive” disease, these patients' tumors contain wild-type *RAS*.

Conclusions

Personalizing treatment allows patients to maximize benefits while minimizing harms, thus providing optimal survival and quality of life. In stage III colon cancer, data from the IDEA trial have led to more refined risk stratification that allows some patients to opt for a shorter duration of adjuvant therapy. Thus, they can be spared the associated toxicity, cost, and inconvenience of longer adjuvant treatment without jeopardizing their oncologic outcomes. In

mCRC, data from the SWOG S1406 trial has led to new treatment options specifically for patients with *BRAF* V600E–mutated tumors. These patients have derived little benefit from EGFR-targeted agents in the past and have had poor prognoses. The addition of an inhibitor of the specific *BRAF* mutation provides additional treatment options that include EGFR inhibitors and gives these patients a chance for delayed disease progression.

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Posttest Questions

1. True or False: Patients with stage III colon cancer are now divided into high- and low-risk subsets in the 2018 version of the NCCN Guidelines for Colon Cancer, with different adjuvant treatment recommendations for the 2 groups.
2. In the IDEA collaboration, which of the following was proven to be noninferior for 3-year disease-free survival?
 - a. 3 months of CapeOX was proven to be noninferior to 6 months of CapeOX in patients with T1–3N1 colon cancer
 - b. 3 months of FOLFOX was proven to be noninferior to 6 months of FOLFOX in patients with T1–3N1 colon cancer
 - c. 3 months of CapeOX was proven to be noninferior to 6 months of CapeOX in patients with TanyN2 or T4N1–2 colon cancer
 - d. 3 months of FOLFOX was proven to be noninferior to 6 months of FOLFOX in patients with TanyN2 or T4N1–2 colon cancer
 - e. None of the above
3. Which of the following regimens are included in the 2018 version of the NCCN Guidelines for Colon Cancer for patients with metastatic disease whose tumors contain BRAF V600E mutations?
 - a. Dabrafenib/(cetuximab or panitumumab)/irinotecan
 - b. Dabrafenib/(cetuximab or panitumumab)/trametinib
 - c. Vemurafenib/(cetuximab or panitumumab)/irinotecan
 - d. Encorafenib/(cetuximab or panitumumab)/binimetinib
 - e. All of the above

