ASCO special articles

Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update

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abstract

PURPOSE To develop recommendations for adjuvant therapy for patients with resected stage II colon cancer.

METHODS ASCO convened an Expert Panel to conduct a systematic review of relevant studies and develop recommendations for clinical practice.

RESULTS Twenty-one observational studies and six randomized controlled trials met the systematic review inclusion criteria.

RECOMMENDATIONS Adjuvant chemotherapy (ACT) is not routinely recommended for patients with stage II colon cancer who are not in a high-risk subgroup. Patients with T4 tumors are at higher risk of recurrence and should be offered ACT, whereas patients with other high-risk factors, including sampling of fewer than 12 lymph nodes in the surgical specimen, perineural or lymphovascular invasion, poorly or undifferentiated tumor grade, intestinal obstruction, tumor perforation, or grade BD3 tumor budding, may be offered ACT. The addition of oxaliplatin to fluoropyrimidine-based ACT is not routinely recommended, but may be offered as a result of shared decision making. Patients with mismatch repair deficiency/microsatellite instability tumors should not be routinely offered ACT; if the combination of mismatch repair deficiency/microsatellite instability and high-risk factors results in a decision to offer ACT, oxaliplatin-containing chemotherapy is recommended. Duration of oxaliplatin-containing chemotherapy is also addressed, with recommendations for 3 or 6 months of treatment with capecitabine and oxaliplatin or fluorouracil, leucovorin, and oxaliplatin, with decision making informed by key evidence of 5-year disease-free survival in each treatment subgroup and the rate of adverse events, including peripheral neuropathy.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

An estimated 105,000 new cases of colon cancer were diagnosed in the United States in 2021,[1] of which approximately 39% were localized.[2] Stage II cancers are characterized by a lack of metastatic spread or lymph node involvement, and the main treatment is surgical resection of the primary tumor. Prognosis after resection is relatively favorable, with an estimated 5-year disease-free survival rate of approximately 68%-83% with surgery alone.[3] To eradicate micrometastatic disease after surgery, adjuvant therapy may be considered for patients with a high risk of recurrence; however, the extent to which established prognostic factors can predict response to treatment is not well defined.[4]

In 2004, ASCO published a guideline on adjuvant therapy for stage II colon cancer, which recommended against routine use of adjuvant chemotherapy (ACT) for patients with stage II colon cancer. This recommendation was based on a meta-analysis showing a 5-year survival benefit on average in patients of not more than 5%.[5] However, on the basis of indirect evidence from patients with stage III colon cancer, the consideration of fluorouracil-based ACT was recommended for select stage II patients who were at higher risk of recurrence, defined by the presence of prognostic factors, including fewer than 13 sampled lymph nodes, T4 tumor stage, clinical bowel obstruction at the time of diagnosis, perforation of the colon at the tumor site, poor histologic grade, and lymphovascular invasion (LVI). As further indirect evidence, the recurrence rate in high-risk stage II patients is 40%-50%, which is similar to the rate in stage III patients, for whom adjuvant therapy is recommended.[6] Despite the

THE BOTTOM LINE

Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update

Guideline Question

Is adjuvant therapy recommended for patients with stage II colon cancer?

Target Population

Patients with stage II colon cancer.

Target Audience

The target audience includes medical oncologists, surgical oncologists, and other clinicians treating patients with stage II colon cancer.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Recommendation 1.1. Adjuvant chemotherapy (ACT) should not routinely be offered to patients with stage II colon cancer (Type: Evidence-based; harms outweigh benefits; Evidence quality: moderate; Strength of recommendation: strong).

Note: See Recommendations 1.3 and 1.4 for scenarios where ACT may be appropriate for specific subgroups of patients with stage II colon cancer.

Recommendation 1.2. ACT should not routinely be offered to patients who are at low risk for recurrence, including patients with stage IIA (T3) tumors with at least 12 sampled lymph nodes of the surgical specimen, tumors without perineural or lymphovascular invasion, poor or undifferentiated tumor grade, clinical intestinal obstruction, tumor perforation, and less than grade BD3 tumor budding (Type: Evidence-based; harms may outweigh benefits; Evidence quality: low; Strength of recommendation: weak).

Qualifying statement: There is no compelling evidence to suggest that age of patient should alter this recommendation. Specifically, there is no evidence that younger low-risk stage II patients should be offered ACT on the basis of their age alone.

Recommendation 1.3. ACT should be offered to patients with stage IIB and stage IIC colon cancer (ie, T4, lesions either penetrating visceral peritoneum or invasive of surrounding organ, respectively), with a discussion of the potential benefits and risks of harm associated with ACT (Type: Evidence-based; benefits may outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

Recommendation 1.4. ACT may be offered to patients with stage IIA (ie, T3) colon cancer with high-risk features, including sampling of fewer than 12 lymph nodes in the surgical specimen, perineural or lymphovascular invasion, poorly or undifferentiated tumor grade, intestinal obstruction, tumor perforation, and/or grade BD3 tumor budding (≥ 10 buds) (Type: Evidence-based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Qualifying statements:

- The number of risk factors should be considered as part of the shared decision-making process. The presence of more than one risk factor may increase the risk of recurrence[9]; in an exploratory analysis of International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration data, the 5-year disease-free survival (DFS) was 74.8% for stage II patients with two or more risk factors, compared with 87.3% for patients with one risk factor.[10]
- Circulating tumor DNA (ctDNA) was identified as an emerging potential predictive factor; however, insufficient evidence of predictive value of chemotherapy was available to warrant its inclusion in the list of high-risk features within the main recommendation. The Expert Panel anticipates that data on ctDNA will be forthcoming through prospective clinical trials and included in a future version of this guideline.
- The Expert Panel notes that there is controversy around the timing of chemotherapy; data on this topic were not reported in the included observational studies. In the MOSAIC trial of oxaliplatin in addition to fluoropyrimidine-based chemotherapy, patients were required to have started ACT within 7 weeks of surgery.[11,12] In the QUASAR trial of ACT with fluorouracil and folinic acid, therapy was initiated within 6 weeks of surgery, where possible.[13]

Recommendation 2.1. Adjuvant fluoropyrimidine-only chemotherapy is not routinely recommended for patients with exhibit mismatch repair deficiency (dMMR) or high microsatellite instability (MSI) tumors (Type: Evidence-based; harms outweigh benefits; Evidence quality: moderate; Strength of recommendation: strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Qualifying statements:

- For patients with dMMR or MSI and T4 tumors and/or other high-risk features (with the exception of poor differentiation), oxaliplatin-containing chemotherapy may be considered (see Recommendation 3.1, qualifying statements). This qualifying statement is based on indirect evidence of a DFS benefit with the addition of oxaliplatin in the population of patients with stage II or stage III colon cancer in the MOSAIC trial.[14]
- Poor differentiation is not considered a high-risk prognostic factor in patients with dMMR or MSI tumors.[15]
- Patients with proficient mismatch repair/microsatellite stable (pMMR or MSS) tumors are included within guideline Recommendations 1.1-1.4.

Recommendation 3.1. There is insufficient evidence to routinely recommend the addition of oxaliplatin to fluoropyrimidine-based chemotherapy for patients with high-risk stage II colon cancer (Type: Evidence-based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Qualifying statements:

- The Expert Panel notes the significant time to recurrence (TTR) benefit with oxaliplatin-containing ACT in exploratory analyses of the MOSAIC trial. The Panel recommends a shared decision-making approach to guide the choice of therapy that includes discussion of potential for benefit and risks of harm with the addition of oxaliplatin to fluoropyrimidine-based chemotherapy (Table 5).
- As stated in the qualifying statement to Recommendation 2.1, for patients with dMMR or MSI who have T4 tumors and/or other high-risk features (with the exception of poor differentiation), when shared decision-making results in the choice to proceed with ACT, the Expert Panel recommends oxaliplatin-containing chemotherapy. This statement is based on indirect evidence of benefit in the combined population of patients with stage II and III colon cancer.[14]

Recommendation 4.1. In patients who are candidates for adjuvant doublet chemotherapy, adjuvant oxaliplatin-containing chemotherapy may be offered for a duration of 3 or 6 months, after a discussion with the patient of the potential benefits and risks of harm associated with the options for treatment duration (Type: Evidence-based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

Note:

- Recommendation 4.1 is based on a subgroup analysis of four randomized trials from the IDEA collaboration.[10] The choice of therapy with capecitabine and oxaliplatin (CAPOX) or fluorouracil, leucovorin, and oxaliplatin (FOLFOX) was non-randomized and made by treating clinicians before random assignment to 3 or 6 months duration of treatment. In high-risk stage II patients, 5-year DFS, the primary study outcome, was 81.7% versus 82.0% ($P = .09$) with 3 versus 6 months of CAPOX, respectively (hazard ratio [HR], 1.02; 80% CI, 0.88 to 1.17). The 5-year DFS was 79.2% versus 86.5% ($P = .88$) with 3 versus 6 months of FOLFOX, respectively (HR, 1.41; 80% CI, 1.18 to 1.68). Among all patients, the prevalence of peripheral neuropathy of grade 2 or higher during treatment was 13% versus 36% with 3 months versus 6 months of treatment, respectively. These findings should be considered during the shared decision-making process.

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

uncertainty, chemotherapy after resection with curative intent is prescribed for approximately 20% of stage II patients regardless of the presence or absence of high-risk features.[7,8] Because of the relatively low risk of recurrence, many of these patients will experience adverse events and inconvenience with no possibility of benefit from treatment. The purpose of this guideline update is to examine the latest evidence on the impact of chemotherapy for subgroups of patients with varying levels of recurrence risk within the population of patients with stage II colon cancer. Risk factors of interest include those discussed in the previous version of this guideline and others that have been more recently identified. In addition, the scope of the evidence review includes studies that looked at microsatellite instability (MSI) status, the addition of oxaliplatin to adjuvant therapy, and duration of oxaliplatin-containing chemotherapy in patients with stage II colon cancer.

GUIDELINE QUESTIONS

This update to ASCO's clinical practice guideline on adjuvant therapy for stage II colon cancer addresses the following clinical questions:

1. Is there a benefit of fluoropyrimidine-based ACT for patients with resected stage II colon cancer compared with surgery alone?
   Subpopulations include the following:
   a. All patients with stage II colon cancer.
   b. Patients at low risk of recurrence, defined by the absence of the high-risk features listed subsequently.
   c. Patients at high risk of recurrence, characterized by sampling of fewer than 12 lymph nodes in the surgical specimen, T4 tumor (having adherence to or invasion of local organs), tumor perforation, clinical intestinal obstruction, poorly differentiated histology, LVI and/or perineural invasion (PNI), ctDNA, and tumor budding.
2. Is there a benefit of fluoropyrimidine-based ACT for patients with tumors that exhibit dMMR or MSI, or pMMR or MSS?
3. If adjuvant therapy is recommended, is there a benefit to adding oxaliplatin to fluoropyrimidine-based chemotherapy?
4. If adjuvant oxaliplatin-containing chemotherapy is considered, are outcomes affected by reducing the treatment duration from 6 to 3 months?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline. All ASCO guidelines are ultimately reviewed and approved by the ASCO Evidence Based Medicine Committee (EBMC) before submission for editorial review and consideration for publication in the *Journal of Clinical Oncology*. All funding for the administration of the project was provided by ASCO.

Evidence Search

A search for existing guidelines with systematic reviews was conducted using the Guidelines International Network International Guidelines Library and a scan of the websites of known guideline developers, such as the Scottish Intercollegiate Guidelines Network, the UK National Institute for Care Excellence, and Cancer Care Ontario (CCO). This initial search led to the identification of the CCO guideline Adjuvant Systemic Chemotherapy for stage II and III Colon Cancer Following Complete Resection; this guideline was based on a high-quality systematic review of randomized controlled trials, included clinical questions that encompassed the scope of this ASCO guideline, and used a search strategy that was current to May 2018. The CCO systematic review was included in the ASCO evidence base for questions 1a, 2, and 3, and an update search of PubMed was conducted for more recent systematic reviews and randomized control trials (RCTs) that addressed these questions (June 2018-April 2021). A broader search from 2010 to April 2021 of prospective or retrospective nonrandomized studies was conducted for the questions related to ACT for risk subgroups, as outlined in clinical questions 1b-1c. High-risk subgroups were defined according to the previous version of the guideline. In addition, a scan of the literature to determine whether this list was current resulted in the addition of ctDNA level, PNI, and tumor budding (ie, "the presence of isolated single cancer cells or clusters of up to four cancer cells at the invasive tumour front"[16 (p101)]) to this list. The minimum recommended number of lymph nodes retrieved was also updated to align with the College of American Pathologists consensus statement[17] and other guidelines.[3,18]

Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Population: Patients with curatively resected stage II colon cancer, including subgroups of patients identifiable by the presence or absence of risk factors.
- Interventions: Fluoropyrimidine-based adjuvant therapy with or without oxaliplatin; studies of administration of ACT for a duration of 3 versus 6 months.
- Comparison: Observation, placebo, and other types of chemotherapy.
- Outcomes: Overall survival (OS), progression-free survival, and adverse events (specifically peripheral neuropathy for duration studies).

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals within 2 years of publication; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; (3) and published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* methodology.[19] In addition, a guideline implementability review is conducted.

Assessment of Data Quality

Evidence quality (ie, certainty of the evidence) for each outcome was assessed using the Cochrane Risk of Bias

tool[20] and elements of the Grading of Recommendations, Assessment, Development and Evaluation quality assessment and recommendations development process.[21] To facilitate the quality assessment ratings, MAGIC App guideline development software was used; within this framework, outcomes from randomized controlled trials are rated high quality and can subsequently be downgraded as factors that affect quality are identified. Observational nonrandomized studies are rated as low quality and can be upgraded for factors such as large magnitude of effect. Grading of Recommendations, Assessment, Development and Evaluation quality assessment labels of high, moderate, low, or very low and a recommendation strength of strong or weak were assigned by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel. Definitions for these ratings are provided in Table A2.

Data Analysis

HRs were extracted where available for time-to-event data; for dichotomous outcomes, relative risk (RR) was extracted where available or calculated using reported events and population totals in the treatment and control groups. Statistics were based on numbers from multivariate analyses, where available. Where more than one study was available, data were pooled in meta-analyses using a random or fixed effects model and the generic inverse variance function in RevMan 5.3. Where HRs were combined in a meta-analysis, log of the HR (logHR) and its standard error were calculated and entered in RevMan 5.3. Heterogeneity was assessed using the I^2 statistic and informally categorized according to the Cochrane Handbook as low: $\leq$ 40%, moderate: 30%-60%, substantial: 50%-90%, or considerable: 75%-100%.[22]

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Thirteen observational studies,[23–35] one RCT,[36] and one RCT subgroup analysis were[37] included in the evidence base for the clinical question related to high- and low-risk patients. Nine of these observational studies and one RCT were found in the reference list of a systematic review[38] that addressed the impact of ACT in patient subpopulations with various high-risk factors,[23–25,27,31–36] and five additional newer

studies were added through the PubMed search.[26,28–30,37] Six observational studies[22,39,40–43] and two subgroup analyses of RCTs[44,45] informed the research question related to treatment by mismatch repair status. The evidence base for the addition of oxaliplatin included one RCT,[11,46] and one additional RCT met the inclusion criteria for the question related to the duration of chemotherapy.[10] Most observational studies were retrospective cohort studies, conducted at single institutions, multiple centers, or using records from large databases such as the National Cancer Database (NCDB) or Surveillance, Epidemiology and End Results Database, with sample sizes ranging from 349 to more than 90,000. Studies of high- and low-risk patients with stage II colon cancer mostly used data collected over the past 20 years; however, some studies used older records dating back to the early 1990s.[33,41,44] Further details related to study characteristics, such as geographic location, follow-up, patient numbers, and variables included in multivariate analyses, are included in the Data Supplement (online only). Detailed study outcomes and quality assessment are included in the subsequent Recommendations section.

RECOMMENDATIONS

Clinical Question 1

Is there a benefit of fluoropyrimidine-based ACT for patients with resected stage II colon cancer compared with surgery alone?

Subpopulations include the following:

a. All patients with stage II colon cancer.
b. Patients at low risk of recurrence, defined by the absence of the high-risk features listed subsequently.
c. Patients at high risk of recurrence, characterized by nodal sampling in the surgical specimen (< 12 nodes sampled), T4 tumor (having adherence to or invasion of local organs), tumor perforation, clinical intestinal obstruction, poorly differentiated histology, LVI or PNI, ctDNA, and tumor budding.

Recommendation 1.1. ACT should not routinely be offered to patients with stage II colon cancer (Type: Evidence-based; harms outweigh benefits; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. The recommendations contained in the original version of this guideline were based on a 1997 CCO systematic review and meta-analysis, which found that ACT resulted in a small DFS advantage, but no increase in OS, compared with surgery alone.[5,13] Since that time, a 3%-5% survival benefit has been established with single-agent 5-flourouracil adjuvant therapy in patients with high-risk stage II colon cancer.[3] In a recent meta-analysis, the estimated overall DFS for patients with stage II colon cancer treated with ACT was 79.3% (95% CI, 75.6 to 83.1), compared with 81.4% (95% CI, 75.4 to 87.4) for patients who did not receive ACT.[9] Thus, a significant subgroup of patients with stage II colon cancer are not expected to benefit from ACT. No new data in this update were found to alter the original 2004 ASCO recommendation against routine use of ACT in patients with stage II colon cancer. The subsequent recommendations in this section address patients who are at low or high risk of stage II colon cancer recurrence.

Recommendation 1.2. ACT should not routinely be offered to patients who are at low risk for recurrence, including patients with stage IIA (T3) tumors with at least 12 sampled lymph nodes of the surgical specimen, tumors without perineural or lymphatic invasion, poor or undifferentiated tumor grade, clinical intestinal obstruction, tumor perforation, and less than grade BD3 tumor budding (Type: Evidence-based; harms may outweigh benefit; Evidence quality: low; Strength of recommendation: weak).

Qualifying statement. There is no compelling evidence to suggest that age of patients should alter this recommendation. Specifically, there is no evidence that younger low-risk stage II patients should be offered ACT on the basis of their age alone.

Literature review and analysis. A small number of retrospective cohort studies reported data on low-risk patients (ie patients with an absence of high-risk factors):

- In the study by Kumar et al, the 3-year recurrence-free survival (RFS), 5-year disease-specific survival, and 5-year OS results were 84.1% versus 92.5% ($P = .115$), 87.1% versus 92.0% ($P = .180$), and 82.9% versus 83.3% ($P = .561$), for low-risk patients who received ACT versus no ACT, respectively. The use of ACT in low-risk patients was correlated with poorer outcomes, including worse RFS (HR, 2.18; 95% CI, 1.00 to 4.97 [$P = .05$]) and disease-specific survival (HR, 3.01; 95% CI, 1.10 to 8.23 [$P = .03$]), compared with patients not receiving ACT.
- Babaei et al reported that in three low-risk populations of patients in the European Union, there was no significant difference in survival for patients treated with ACT versus surgery alone for the patients in Belgium and Sweden (approximately 78% in treatment and control groups); however, patients in the Netherlands had worse outcomes with ACT versus surgery alone (approximately 64% *v* 78%, respectively).
- In the study by Kim et al, ACT was associated with reduced RR of death in low-risk patients after adjusting for other factors (RR, 0.74; 95% CI, 0.61 to 0.89; $P = .002$, 5-year OS 88% *v* 90%).
- Casadaban et al found that in low-risk patients, the 5-year OS rate improved from 68% to 86% with ACT ($P < .001$), compared with 57% to 76% ($P < .001$) in high-risk patients.
- In the study by Jee et al, the survival results of the ACT group in low-risk patients were also significantly better than those of the surgery-alone group (OS, 97.7% *v* 88.2%, $P < .0001$; DFS, 93.0% *v* 80.0%, $P = .001$).

Clinical interpretation. Mixed results, with high variability depending on the underlying patient population, characterize the limited data for patients with low-risk stage II colon cancer. Considering the overall modest potential for benefit for average-risk patients with stage II colon cancer as outlined in Recommendation 1.1, low likelihood of recurrence, and thus a large proportion of the population realizing no benefit but associated adverse events, the consensus of the Expert Panel does not recommend ACT for patients in the low-risk subgroup.

Recommendation 1.3. ACT should be offered to patients with stage IIB and stage IIC colon cancer (ie, T4 lesions either penetrating visceral peritoneum or invasive of surrounding organ, respectively), with a discussion of the potential benefits and risks of harm associated with ACT (Type: Evidence-based; benefits may outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

T4 tumors—literature review and analysis. Across six studies of patients with T4 tumors, there was an OS advantage (HR, 0.64; 95% CI, 0.56 to 0.75, $I^2 = 60\%$),[23–25,27,30,33] and across two studies, an RFS advantage was found (HR, 0.70; 95% CI, 0.63 to 0.77, $I^2 = 0$)[25,30] with ACT compared with surgery alone (Table 1 and the Data Supplement). There was no recurrence-free survival advantage found in an RCT of patients treated with tegafur and uracil (UFT) versus surgery alone, in which the overall stage II 5-year OS rates were 94.3% and 94.5%, respectively (HR for RFS, 1.31; 95% CI, 0.85 to 2.01).[36]

T4 tumors—clinical interpretation. All studies included in the meta-analyses found a positive effect of ACT on OS in patients with this risk factor although heterogeneity was present ($I^2 = 60\%$). In addition, a highly consistent ($I^2 = 0$) significant benefit of ACT on RFS was found. The demonstrated concordance between OS and RFS is important because RFS is the outcome most affected by ACT and less likely to be affected by patient selection.[25,28,30] In a matched-pair analysis by Teufel et al,[30] the 5-year survival rates for patients with T4 tumors were 70.9% for those receiving ACT versus 59.8% for those not receiving ACT. On the basis of this consistent effect across a considerable combined sample, including large and small studies, as well as the established prognostic significance of this factor[9] and evidence of a low 5-year OS rate within the untreated patient population, the Expert Panel recommends ACT for patients with stage IIB and IIC.

Recommendation 1.4. ACT may be offered to patients with stage IIA (ie, T3) colon cancer with high-risk features, including sampling of fewer than 12 lymph nodes in the surgical specimen, perineural or lymphatic invasion, poorly or undifferentiated tumor grade, intestinal obstruction, tumor perforation, and/or grade BD3 tumor budding (≥10 buds) (Type: Evidence-based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

(See Recommendation 2.1 in the subsequent section with guidance for patients with dMMR or MSI.)

Qualifying statements:

- The number of risk factors should be considered as part of the shared decision-making process. The presence of more than one risk factor may increase the risk of recurrence[9]; in an exploratory analysis of IDEA collaboration data, the 5-year DFS was 74.8% for stage II patients with two or more risk factors, compared with 87.3% for patients with one risk factor.[10]
- ctDNA was identified as an emerging potential predictive factor; however, insufficient evidence of predictive value of chemotherapy was available to warrant its inclusion in the list of high-risk features within the main recommendation. The Expert Panel anticipates that data on ctDNA will be forthcoming through prospective clinical trials and included in a future version of this guideline.

TABLE 1. Effect of ACT in Patients With T4 Stage II Colon Cancer

Population: T4 stage II colon cancer
Intervention: ACT
Comparator: surgery alone

Outcome	Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Surgery Alone	ACT		
OS	HR: 0.64 (95% CI, 0.56 to 0.75) (18,517 patients in six studies) Follow-up: 5 years	483 deaths per 1,000	344 deaths per 1,000	Low ($I^2 = 60\%$)	ACT probably improves OS for patients with pT4 tumors
		Difference: 139 fewer per 1,000 (95% CI, 174 fewer to 93 fewer)			
RFS	HR: 0.7 (95% CI, 0.63 to 0.77) (7,711 patients in two studies) Follow-up: 5 years	541 recurrences or deaths per 1,000	420 recurrences or per 1,000	Low ($I^2 = 0$)	ACT probably improves RFS for patients with pT4 tumors
		Difference: 121 fewer per 1,000 (95% CI, 153 fewer to 90 fewer)			

Abbreviations: ACT, adjuvant chemotherapy; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.

- The Expert Panel notes that there is controversy around the timing of chemotherapy; data on this topic were not reported in the included observational studies. In the MOSAIC trial of oxaliplatin in addition to fluoropyrimidine-based chemotherapy, patients were required to have started ACT within 7 weeks of surgery.[11,12] In the QUASAR trial of ACT with fluorouracil and folinic acid, therapy was initiated within 6 weeks of surgery, where possible.[13]

Other risk factors—Literature review and analysis. ***Number of lymph nodes sampled.*** In the pooled analysis of four studies, the HR for OS was 0.67 (95% CI, 0.57 to 0.77, $I^2 = 30\%$; Table 2 and the Data Supplement).[23,25,34,35] The HR estimate for RFS/DFS was 0.71 (95% CI, 0.61 to 0.82, $I^2 = 0\%$), on the basis of three studies.[25,35,36] The study by Wells et al,[34] which found a significant impact of ACT on patients with fewer sampled lymph nodes, was conducted in a population of patients with T3 tumors.

Poorly/undifferentiated tumors. Four studies were included in the analysis of OS for patients with poor or undifferentiated tumors.[23–25,27] There was no significant difference overall between the intervention and control groups although the HR favored ACT (HR, 0.88; 95% CI, 0.61 to 1.27, $I^2 = 86\%$). Given the high heterogeneity, a sensitivity analysis was conducted that eliminated the only study to find a significantly worse outcome with adjuvant therapy, thereby reducing the heterogeneity to zero.[23] Among the remaining three studies, the HR was 0.78 (0.70 to 0.88, $P < .0001$).[24,25,27] Pooling of the three studies that reported DFS or RFS resulted in an HR of 0.79 (95% CI, 0.60 to 1.04).[25,26,36]

Intestinal obstruction. In a pooled analysis of three studies, the HR for OS significantly favored ACT, compared with surgery alone (HR, 0.57; 95% CI, 0.38 to 0.85, $I^2 = 0\%$) in patients with clinical obstructing tumors.[25,28,33] In the study by Sabbagh et al,[28] a study in which all patients had obstructing colon cancer that was defined clinically and confirmed by imaging (N = 504), the 5-year OS was 92.1% (95% CI, 86.9 to 97.6) for patients who received ACT and 80.1% (95% CI, 72.3 to 88.8) for the non-ACT group. Across two studies, the pooled estimate for RFS[25] and DFS[28] was 0.63 (95% CI, 0.44 to 0.89, $I^2 = 0\%$) in favor of the ACT group. In a related outcome measure, Verhoeff et al[27] report a crude 3-year survival of 79% in the non-ACT group versus 95% in the ACT group in high-risk patients who underwent emergency surgery; however, they report potentially being underpowered to detect a difference in survival (457 ACT *v* 74 no ACT; HR, 0.43; 95% CI, 0.15 to 1.21).

Tumor perforation. In a pooled analysis of two studies with a small number of patients (100 and 86, respectively), the HR for OS significantly favored ACT, compared with surgery alone (HR, 0.31; 95% CI, 0.16 to 0.60).[38] Kumar et al[25] evaluated RFS in this subgroup and found a nonsignificant HR in favor of ACT of 0.48 (95% CI, 0.23 to 1.00).

PNI. A pooled analysis of four studies resulted in an HR of 0.74 (95% CI, 0.41 to 1.35, $I^2 = 93\%$).[23,25,32,33] Three of four studies indicated a survival advantage with AC compared with surgery alone in patients with PNI, although this finding was only significant in the largest study, on the basis of the NCBD, which reported an HR of 0.57 (95% CI, 0.48 to 0.67); in this study, the 5-year survival for those with PNI was 49.1% (no ACT) versus 81.1% (ACT).[32] Results from 100 patients in a study on the basis of the California Cancer Registry showed a significantly worse outcome for patients treated with ACT. Given the high heterogeneity, a sensitivity analysis was conducted to remove the outlier study. The HR across the three remaining studies was 0.57 (95% CI, 0.48 to 0.67, $I^2 = 0\%$).[25,32,33] Kumar et al[25] also reported RFS results, finding an HR of 0.93 (95% CI, 0.44 to 1.98) in a group of 89 patients.

LVI. In a pooled analysis of three studies, the HR for OS significantly favored ACT, compared with surgery alone for LVI (HR, 0.65; 95% CI, 0.44 to 0.98, $I^2 = 28\%$).[25,33,36] This analysis included the RCT by Matsuda et al[36] of UFT versus surgery alone, in which the HR for LVI was nonsignificant. Kumar et al[25] evaluated RFS in this subpopulation and found no significant difference between groups.

Inadequate surgical margins. The systematic review by Zhang et al[38] included one study that reported an HR of 2.37 (95% CI, 0.91 to 6.17) with ACT versus no ACT in patients with positive margins.[23] One additional study on the basis of the NCDB reported an HR of 0.89 (95% CI, 0.78 to 1.00).[24] These two studies were based on data from large databases that did not include details regarding what margins were evaluated, ie proximal/distal versus retroperitoneal.

Tumor budding. This variable was assessed in one study with a small number of patients who were participants in a randomized controlled trial of UFT. The authors found a nonsignificant improvement in recurrence-free survival for patients with BD2 (5-9 buds, intermediate grade) and BD3 (≥10 buds, high grade).[37]

ctDNA. No studies of the predictive effect of ACT versus no ACT in patients with high ctDNA content were found in the literature review although this factor is known as an effective predictor of short-term recurrence; Tie et al detected radiologic recurrence in 78.6% of patients with positive postoperative ctDNA, whereas 9.8% of patients testing negative for ctDNA experienced recurrence.

Multiple risk factors. In the study by Babcock et al,[23] a significant benefit for ACT was found for T4 tumors in combination with a smaller number of sampled lymph nodes, poorly differentiated tumors, and LVI. Kumar et al[25] found that patients with two or more risk factors did not significantly benefit from ACT, and this finding was more pronounced in patients who did not have T4 tumors. In an exploratory analysis of IDEA collaboration data, the 5-year DFS was 74.8% for stage II patients with two or more risk

TABLE 2. Effect of ACT in Patients With High-Risk Factors

Population: High-risk stage II colon cancer
Intervention: ACT
Comparator: Surgery alone

Outcome	Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Surgery Alone	ACT		
OS fewer than 12 sampled lymph nodes	HR: 0.67 (95% CI, 0.57 to 0.77) (6,800 patients in four studies) Follow-up: 5 years	483 deaths per 1,000	357 deaths per 1,000	Low (I^2 = 30%)	ACT probably improves OS for patients with fewer than 12 sampled lymph nodes
		Difference: 126 fewer per 1,000 (95% CI, 170 fewer to 85 fewer)			
DFS/RFS fewer than 12 sampled lymph nodes	HR: 0.71 (95% CI, 0.61 to 0.82) (6,554 patients in three studies) Follow-up: 5 years	541 recurrences/new tumors or deaths per 1,000	425 recurrences/new tumors or deaths per 1,000	Low (I^2 = 0)	ACT probably improves DFS/RFS for patients with fewer than 12 sampled lymph nodes
		Difference: 116 fewer per 1,000 (95% CI, 163 fewer to 69 fewer)			
OS tumor perforation	HR: 0.31 (95% CI, 0.16 to 0.6) (186 patients in two studies) Follow-up: 5 years	483 deaths per 1,000	185 deaths per 1,000	Low (I^2 = 29%)	ACT probably improves OS for patients with tumor perforation
		Difference: 298 fewer per 1,000 (95% CI, 383 fewer to 156 fewer)			
RFS tumor perforation	HR: 0.48 (95% CI, 0.23 to 1.0) (100 patients in one study) Follow-up: 5 years	541 recurrences per 1,000	312 recurrences per 1,000	Very low[a,b]	The impact of ACT on RFS for patients with tumor perforation is uncertain
		Difference: 229 fewer per 1,000 (95% CI, 377 fewer to 0 fewer)			
OS intestinal obstruction	HR: 0.57 (95% CI, 0.38 to 0.85) (911 patients in three studies) Follow-up: 5 years	199 deaths per 1,000	119 deaths per 1,000	Low (I^2 = 0%)	ACT probably improves OS for patients with intestinal obstruction
		Difference: 80 fewer per 1,000 (95% CI, 118 fewer to 27 fewer)			
DFS or RFS intestinal obstruction	HR: 0.63 (95% CI, 0.44 to 0.89) (796 patients in two studies) Follow-up: 5 years	461 recurrences/new tumors or deaths per 1,000	323 recurrences/new tumors or deaths per 1,000	Low (I^2 = 0%)	ACT probably improves DFS/RFS for patients with intestinal obstruction
		Difference: 138 fewer per 1,000 (95% CI, 223 fewer to 38 fewer)			
OS urgent surgery	HR: 0.43 (95% CI, 0.15 to 1.21— (531 patients in one study)	201 deaths per 1,000	92 deaths per 1,000	Very low[a]	The impact of ACT on OS for patients undergoing emergency surgery is uncertain
		Difference: 109 fewer per 1,000 (95% CI, 168 fewer to 37 more)			
OS LVI	HR: 0.65 (95% CI, 0.44 to 0.98) (1,371 patients in three studies) Follow-up: 5 years	460 deaths per 1,000	330 deaths per 1,000	Low (I^2 = 28%)	ACT probably improves OS in patients with LVI
		Difference: 130 fewer (95% CI, 223 fewer to 7 fewer)			
RFS LVI	HR: 0.62 (95% CI, 0.29 to 1.32) (155 patients in one study) Follow-up: 3 years	196 recurrences per 1,000	250 recurrences per 1,000	Very low[a]	The impact of ACT on RFS for patients with LVI is uncertain
		Difference: 54 more per 1,000 (95% CI, 89 fewer to 325 more)			
OS PNI	HR: 0.74 (95% CI, 0.41 to 1.35) (1,371 patients in four studies) Follow-up: 5 years	620 deaths per 1,000	511 deaths per 1,000	Very low[c] (I^2 = 93%)	The impact of ACT on OS for patients with PNI is uncertain
		Difference: 109 fewer per 1,000 (95% CI, 293 fewer to 109 more)			

(continued on following page)

TABLE 2. Effect of ACT in Patients With High-Risk Factors (continued)

Population: High-risk stage II colon cancer
Intervention: ACT
Comparator: Surgery alone

Outcome	Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Surgery Alone	ACT		
RFS PNI	HR: 0.93 (95% CI, 0.44 to 1.98) (89 patients in one study) Follow-up: 5 years	456 recurrences per 1,000	432 recurrences per 1,000	Very low[a,b]	The impact of ACT on RFS in patients with PNI is uncertain
		Difference: 24 fewer per 1,000 (95% CI, 221 fewer to 244 more)			
OS poorly or undifferentiated histology	HR: 0.88 (95% CI, 0.61 to 1.27) (27,815 patients in four studies) Follow-up: 5 years	307 deaths per 1,000	276 deaths per 1,000	Very low[c] (I^2 = 86%)	The impact of ACT on OS in patients with poorly or undifferentiated histology is uncertain
		Difference: 31 fewer per 1,000 (95% CI, 107 fewer to 65 more)			
DFS/RFS poorly or undifferentiated histology	HR: 0.79 (95% CI, 0.6 to 1.04) (7,961 patients in three studies) Follow-up: 3 years	196 recurrences or new tumors or deaths per 1,000	158 recurrences or new tumors or deaths per 1,000	Low (I^2 = 0)	ACT may improve DFS/RFS for patients with poorly differentiated histology
		Difference: 38 fewer per 1,000 (95% CI, 73 fewer to 7 more)			

NOTE. Downgrade for the following: [a]Only data from one study. [b]Low number of patients. [c]Considerable heterogeneity (ie inconsistency, according to the following categories: low: ≤ 40%, moderate: 30%-60%, substantial: 50%-90%, and considerable: 75%-100%).

Abbreviations: ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; LVI, lymphovascular invasion; OS, overall survival; PNI, perineural invasion; RFS, recurrence-free survival.

factors, compared with 87.3% for patients with one risk factor.[10]

Other risk factors—clinical interpretation. Fewer than 12 sampled lymph nodes. All studies included in the meta-analysis found a positive effect of ACT on OS, and a highly consistent (I^2 = 0) significant benefit of ACT on RFS was demonstrated. As mentioned previously, the concordance between OS and RFS is important because RFS is the outcome most affected by ACT and less likely to be affected by patient selection.[25,28,30] On the basis of this evidence, as well as the established prognostic significance of this risk factor,[47] ACT may be recommended for patients with stage II cancer with fewer than 12 sampled lymph nodes.

Other high-risk factors. For other high-risk factors including poorly differentiated tumors, PNI, LVI, perforation, obstruction, and inadequate surgical margins, low- to very low-quality evidence was found for the effect of ACT versus surgery alone. Evidence quality was limited by a variety of factors, such as inconsistent direction of effect across studies, limited data resulting in wide CIs, or bias because of patient selection. Detailed reasons for evidence quality ratings are included in footnotes in Table 2. Although the evidence for these outcomes was of lower quality, a consistent positive effect of ACT was found for RFS and OS for intestinal obstruction, and treatment with ACT in patients with tumor perforation was associated with a positive effect on OS, whereas the HR for RFS, on the basis of 100 patients in one study, was 0.48 (95% CI, 0.23 to 1.00). This evidence, along with previously established prognostic information, was deemed sufficient to suggest that ACT may be recommended for patients with intestinal obstruction or tumor perforation.

One study noted that as tumor size increased, so did incidence of LVI and PNI, which suggests that these two factors could be indicative of an early stage of nodal metastases.[29] In this analysis, OS for LVI was significantly improved with the addition of ACT, whereas RFS, on the basis of only one study, showed no significant difference, resulting in high uncertainty regarding the effect of ACT in this patient subpopulation.

For PNI, the heterogeneity across studies for the OS outcome was very high (I^2 = 93%); when an outlier study was removed, the heterogeneity was reduced to zero and the HR was 0.57 (95% CI, 0.48 to 0.67). It is unclear why the outlier study,[23] on the basis of data from the California Cancer Registry, produced inconsistent results. Results were also variable for other outcomes: RFS for patients with PNI on the basis of one small study did not find a significant difference between ACT and non-ACT patients;[25] however, DFS was significantly better for patients treated with ACT versus no ACT in another small study (83.2% of 36 *v* 54.4% of 21, respectively). These data indicate that there is a high level of uncertainty regarding the predictive value of PNI.

Similarly, heterogeneity was high across the four studies included in the meta-analysis for poorly or undifferentiated

histology, which included two studies that were also part of the analysis of PNI.[23,25] When the same outlier study as previously mentioned was removed in a sensitivity analysis,[23] the heterogeneity was reduced to zero and the estimate indicated significant improvement with ACT (HR, 0.78; 95% CI, 0.70 to 0.88, $P < .0001$). The lack of significant difference in the RFS and DFS outcomes and high heterogeneity result in very low-quality evidence and uncertainty about the effect of ACT in this group of patients.

Although there are significant limitations to the evidence base for these other high-risk factors, including intestinal obstruction, tumor perforation, PNI, LVI, and poorly/undifferentiated tumors, the Expert Panel agrees that it is reasonable to offer ACT, on the basis of the established poorer prognosis expected for these patient subpopulations.[9]

Tumor budding. Very low-quality evidence, on the basis of subgroups from one RCT with nonsignificant results, was available to inform the predictive significance of tumor budding. Thus, the Expert panel endorses results from the International Tumor Budding Consensus Conference, which concluded that ACT should be considered for patients with the highest grade of tumor budding (ie, BD3: ≥ 10), on the basis of the prognostic significance of this factor.[48] Results of a systematic review show that resected colorectal cancer specimens with tumor budding are more likely to develop disease recurrence (odds ratio [OR], 5.50; 95% CI, 3.64 to 8.29, <.00001) and more likely to lead to cancer-related death at 5 years (OR, 4.51; 95% CI, 2.55 to 7.99, $P < .00001$).[49] The International Tumor Budding Consensus Conference also endorsed a three-tier grading system for tumor budding; specimens with grade BD3 budding are associated with an increased risk of recurrence in stage II colorectal cancer.[16]

ctDNA. This is an emerging prognostic factor, and trials are currently underway to determine its utility, such as the DYNAMIC trial (ACTRN12615000381583).[50,51]

CLINICAL QUESTION 2

Is there a benefit of fluoropyrimidine-based ACT for patients with tumors that exhibit dMMR or MSI, or pMMR or MSS?

Recommendation 2.1

Adjuvant fluoropyrimidine-only chemotherapy is not routinely recommended for patients with dMMR or MSI tumors (Type: Evidence-based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Qualifying statements:

- For patients with dMMR or MSI and T4 tumors and/or other high-risk features (with the exception of poor differentiation), oxaliplatin-containing chemotherapy may be considered (see Recommendation 3.1, qualifying statements). This qualifying statement is based on indirect evidence of a DFS benefit with the addition of oxaliplatin in the population of patients with stage II or stage III colon cancer in the MOSAIC trial.[14]
- Poor differentiation is not considered a high-risk prognostic factor in patients with dMMR or MSI tumors.[15]
- Patients with pMMR or MSS tumors are included within guideline Recommendations 1.1-1.4.

Microsatellite stability status. Literature review and analysis (Table 3, Table 4, and Data Supplement).

dMMR or MSI tumors. One included guideline with systematic review recommends against adjuvant fluoropyrimidine-only therapy for patients with dMMR or MSI, on the basis of the pooled RCT subgroup analysis by Sargent et al,[6] showing a potential detrimental effect of ACT on DFS. This analysis included 102 patients, data from RCTs conducted several decades ago, and had imprecise estimates, and therefore, it is rated as very low-quality evidence.[45] For the current review, the study by Sargent et al was combined with more recent observational studies. The pooled analysis of three studies found no difference in the HR for DFS (HR, 0.89; 95% CI, 0.45 to 1.74) in patients with dMMR or MSI.[39,42,45] The heterogeneity in this analysis was high ($I^2 = 75\%$), which might have been due to the difference in patient populations, with Tougeron et al including high-risk stage II patients who had received oxaliplatin, Sargent et al including patients who had received FU with levamisole or leucovorin, and Kim et al including a mix of treatments, the majority of which did not include oxaliplatin, as well as the differing timeframes for data collection across studies. A pooled analysis also found no difference in OS, with an HR of 1.03 (95% CI, 0.53 to 2.02, $I^2 = 76\%$).[41,42,45]

In addition, data from the study by Yang et al[43] for mostly stage IIA (95%) patients with dMMR or MSI showed no difference between OS (116 patients, 40.33 *v* 40.02 months [$P = .143$]) and DFS (116 patients, 38.52 *v* 34.42 months [$P = .187$]), with and without ACT, respectively. In the study by Baek et al,[40] there was no statistically significant difference in survival outcomes in the dMMR or MSI group between mostly stage IIB or IIC (92%) patients who received ACT and who did not (76 patients, DFS, $P = .124$; OS, $P = .225$). Finally, in a subset analysis of the QUASAR trial, there was no difference in 2-year recurrence in the overall stage II dMMR population with the addition of ACT (OR, 0.81; 95% CI, 0.29 to 2.22).[44] One study found that there was no effect of ACT on the subset of dMMR or MSI patients with T4 tumors (HR, 0.84; 95% CI, 0.27 to 2.63).[22]

pMMR or MSS tumors. This review also included an analysis of the pMMR or MSS subgroup. As this status is more prevalent than dMMR or MSI (approximately 80% *v* 20% prevalence, respectively), the analysis of this subgroup included a larger number of patients. In a pooled analysis of two studies, DFS was not significantly different (1,162 patients; HR, 0.56; 95% CI, 0.25 to 1.26; $I^2 = 88\%$)[42,45] and OS was significantly improved (1,093 patients; HR, 0.31; 95% CI, 0.18 to 0.52; $I^2 = 46\%$) with the addition of ACT to

TABLE 3. Effect of ACT in Patients With Stage II Colon Cancer and dMMR or MSI

Population: dMMR or MSI
Intervention: ACT
Comparator: Surgery alone

Outcome	Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Surgery Alone	ACT		
OS	HR: 1.03 (95% CI, 0.53 to 2.02) (320 patients in three studies) Follow-up: 5 years	190 per 1,000	195 per 1,000	Very low[a] (I^2 = 76%)	We are uncertain whether ACT improves or worsens OS for patients with dMMR or MSI
		Difference: 5 more per 1,000 (95% CI, 84 fewer to 157 more)			
DFS	HR: 0.89 (95% CI, 0.45 to 1.74) (368 patients in three studies) Follow-up: 5 years	240 per 1,000	217 per 1,000	Very low[a] (I^2 = 75%)	We are uncertain whether ACT improves or worsens DFS for patients with dMMR or MSI
		Difference: 23 fewer per 1,000 (95% CI, 124 fewer to 140 more)			

Abbreviations: ACT, adjuvant chemotherapy; DFS, disease-free survival; dMMR, deficient mismatch repair; HR, hazard ratio; MSI, high microsatellite instability; OS, overall survival.

[a]Downgrade for point estimates varying widely and considerable heterogeneity (ie, inconsistency, according to the following categories: low: ≤ 40%, moderate: 30%-60%, substantial: 50%-90%, and considerable: 75%-100%).

surgery alone.[41,42] Similarly, Yang et al[43] showed a significantly improved median OS with ACT in an earlier stage population (82% stage IIA; 557 patients, 36.17 months *v* 34.33 months [*P* = .007]), whereas DFS was not significantly different: 29.2 versus 28.6 months (*P* = .075). Hutchins et al[44] demonstrated a significantly improved 2-year recurrence rate in the pMMR or MSS population with the addition of ACT (OR, 0.59; 95% CI, 0.45 to 0.77).

Studies reporting data by microsatellite stability status—clinical interpretation. High heterogeneity, differing directions of the HR estimates, and small samples in included studies, with the majority of results showing no significant differences between groups, result in a recommendation against ACT in the dMMR or MSI population. This recommendation is supported by the reduced risk of recurrence, which is approximately half that of pMMR or MSS tumors, as well as a relatively higher survival rate.[9,52]

The ASCO Expert Panel recommends observation or consideration of chemotherapy in patients with pMMR or MSS where high-risk factors are present, on the basis of the demonstrated improvement in OS, as outlined in Recommendations 1.3 and 1.4.

TABLE 4. Effect of ACT in Patients With Stage II Colon Cancer and Proficient Mismatch Repair

Population: pMMR or MSS
Intervention: ACT
Comparator: Surgery alone

Outcome	Results	Absolute Effect Estimates		Quality of Evidence (heterogeneity)	Plain Language Summary
		Surgery Alone	ACT		
OS	HR: 0.31 (95% CI, 0.18 to 0.52) (1,093 patients in two studies) Follow-up: 5 years	380 per 1,000	138 per 1,000	Low (I^2 = 46%)	ACT may improve OS
		Difference: 242 fewer per 1,000 (95% CI, 298 fewer to 160 fewer)			
DFS	HR: 0.56 (95% CI, 0.25 to 1.26) (1,162 patients in two studies) Follow-up: 5 years	470 per 1,000	299 per 1,000	Very low (I^2 = 88%)[a]	We are uncertain whether ACT improves or worsens DFS
		Difference: 171 fewer per 1,000 (95% CI, 323 fewer to 81 more)			

Abbreviations: ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; MS, microsatellite stable; OS, overall survival; pMMR, proficient mismatch repair.

[a]Downgrade for considerable heterogeneity (ie, inconsistency, according to the following categories: low: ≤ 40%, moderate: 30%-60%, substantial: 50%-90%, and considerable: 75%-100%).

CLINICAL QUESTION 3

If adjuvant therapy is recommended, is there a benefit to adding oxaliplatin to fluoropyrimidine-based chemotherapy?

Recommendation 3.1

There is insufficient evidence to routinely recommend the addition of oxaliplatin to fluoropyrimidine-based chemotherapy for patients with high-risk stage II colon cancer (Type: Evidence-based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Qualifying statements:

- The Expert Panel notes the significant TTR benefit with oxaliplatin-containing ACT in exploratory analyses of the MOSAIC trial. The Panel recommends a shared decision-making approach to guide the choice of therapy that includes discussion of potential for benefit and risks of harm with the addition of oxaliplatin to fluoropyrimidine-based chemotherapy (Table 5).
- As stated in the qualifying statement to Recommendation 2.1, for patients with dMMR or MSI who have T4 tumors and/or other high-risk features (with the exception of poor differentiation), when shared decision-making results in the choice to proceed with ACT, the Expert Panel recommends oxaliplatin-containing chemotherapy. This statement is based on indirect evidence of benefit in the combined population of patients with stage II and III colon cancer.[14]

Literature review and analysis. One randomized controlled trial (MOSAIC) assessed the addition of oxaliplatin to FU + LV in patients with stage II colon cancer at high risk of recurrence, defined as at least one of the following: T4 stage, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes examined (Table 5). The evidence quality for these outcomes is rated low, and the results of this subgroup analysis are considered exploratory. There was no significant benefit of the addition of oxaliplatin for OS (HR, 0.91; 95% CI, 0.61 to 1.36) or DFS (HR, 0.72; 95% CI, 0.51 to 1.01); however, TTR, defined as time from random assignment to recurrence of the same cancer, was significantly improved (HR, 0.62; 95% CI, 0.41 to 0.93).[46]

Clinical interpretation. On the basis of a TTR benefit found in an exploratory analysis, oxaliplatin-containing chemotherapy may be considered an option for some patients, following a discussion of the lack of demonstrated OS benefit and potential for harms (Table 5).

CLINICAL QUESTION 4

If adjuvant oxaliplatin-containing chemotherapy is considered, are outcomes affected by reducing the treatment duration from 6 to 3 months?

Recommendation 4.1. In patients who are candidates for adjuvant doublet chemotherapy, adjuvant oxaliplatin-containing chemotherapy may be offered for a duration of 3 or 6 months, after a discussion with the patient of the potential benefits and risks of harm associated with the options for treatment duration (Type: Evidence-based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

Note:

- Recommendation 4.1 is based on a subgroup analysis of four randomized trials from the IDEA collaboration.[10] The choice of therapy with CAPOX or FOLFOX was nonrandomized and made by treating clinicians before random assignment to 3 or 6 months duration of treatment. In high-risk stage II patients, 5-year DFS, the primary study outcome, was 81.7% versus 82.0% (P = .09) with 3 versus 6 months of CAPOX, respectively (HR, 1.02; 80% CI, 0.88 to 1.17). The 5-year DFS was 79.2% versus 86.5% (P = .88) with 3 versus 6 months of FOLFOX, respectively (HR, 1.41; 80% CI, 1.18 to 1.68). Among all patients, the prevalence of peripheral neuropathy of grade 2 or higher during treatment was 13% versus 36% with 3 versus 6 months of treatment, respectively. These findings should be considered during the shared decision-making process (Table 6).

Literature review and analysis. Analysis of six randomized controlled trials of 3 months versus 6 months of treatment with FOLFOX or CAPOX was carried out by the IDEA collaboration to compare efficacy and safety (Table 6). Iveson et al[10] pooled results from four IDEA collaboration studies that included patients with high-risk stage II colon cancer (ie, patients with T4 tumors, fewer than 10 (Short Course Oncology Treatment) or fewer than 12 sampled lymph nodes (Three or Six Colon Adjuvant, Hellenic Oncology Research Group, and Adjuvant Chemotherapy for Colon Cancer with High Evidence 2), poor differentiation, obstruction, perforation, or vascular/PNI). These four studies included 3,273 patients from the United Kingdom, Denmark, Spain, Sweden, Australia, and New Zealand (Short Course Oncology Treatment), Greece (Hellenic Oncology Research Group), Italy (Three or Six Colon Adjuvant), and Japan (Adjuvant Chemotherapy for Colon Cancer with High Evidence 2). DFS was the primary outcome, and a noninferiority boundary of 1.2 was set, on the basis of results from the MOSAIC trial.[46] Noninferiority of 3 versus 6 months of oxaliplatin-containing chemotherapy was not met for DFS, as this threshold was exceeded by the upper CI (HR, 1.17; 95% CI, 1.05 to 1.31). The test for interaction between treatment duration and regimen type (FOLFOX or CAPOX) was not significant (P = .07). The 5-year survival rate for patients treated with 3 months of CAPOX was 81.7% (95% CI, 79.2 to 84.3), compared with 82.0% (95% CI, 79.3 to 84.7) for 6 months of CAPOX. The 5-year survival rates were 79.2% (95% CI, 75.9 to 82.7) and 86.5% (95% CI, 83.7 to 89.3), respectively, for patients treated with 3 or 6 months of FOLFOX.

TABLE 5. Addition of Oxaliplatin to ACT

Population: Patients with high-risk stage II colon cancer
Intervention: FOLFOX
Comparator: FU + LV

Outcome	Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		FU + LV	FOLFOX		
Grade 3 peripheral sensory neuropathy	RR: 69.0 (95% CI, 17.0 to 278.0) (2,219 patients in one study during treatment)	2 per 1,000	138 per 1,000	Moderate[a]	FOLFOX worsens grade 3 peripheral sensory neuropathy during treatment
		Difference: 136 more per 1,000 (95% CI, 32 more to 554 more)			
OS	HR: 0.91 (95% CI, 0.61 to 1.36) (569 patients in one study) Follow-up median: 80 months	167 per 1,000	153 per 1,000	Low[b]	FOLFOX may have little or no effect on OS in patients at high risk of recurrence
		Difference: 14 fewer per 1,000 (95% CI, 62 fewer to 53 more)			
DFS	HR: 0.72 (95% CI, 0.51 to 1.01) (569 patients in one study) Follow-up median: 63 months	254 per 1,000	190 per 1,000	Low[b]	FOLFOX may have little or no effect on DFS in patients at high risk of recurrence
		Difference: 64 fewer per 1,000 (95% CI, 115 fewer to 2 more)			
TTR	HR: 0.62 (95% CI, 0.41 to 0.92) (569 patients in one study) Follow-up median: 63 months	212 per 1,000	137 per 1,000	Low[b]	FOLFOX may improve TTR in patients at high risk of recurrence
		Difference: 75 fewer per 1,000 (95% CI, 119 fewer to 13 fewer)			

Abbreviations: DFS, disease-free survival; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; HR, hazard ratio; LV, leucovorin calcium; OS, overall survival; PSN, peripheral sensory neuropathy; RR, relative risk; TTR, time to recurrence.

[a]Downgrade for wide CI. Grade 3 PSN during treatment was reported in 138 patients (12.5%) in the FOLFOX4 group and 0.2% of the patients in the LV + FU group. At 18 and 48 months, 0.7% of FOLFOX-treated patients experienced Grade 3 PSN.

[b]Indirectness: population includes stage III patients (MOSAIC trial, 2009). MOSAIC analyses conducted in high-risk subpopulation are considered exploratory.

Clinical interpretation. The noninferiority threshold of 1.2 was exceeded in the overall study population of patients undergoing treatment with CAPOX or FOLFOX, and therefore, 3 months of treatment cannot be considered noninferior to 6 months of treatment. Although the test for interaction between the treatment regimen and duration was nonsignificant, the absolute difference in 5-year survival was 0.3% for patients treated with CAPOX for 3 months (81.7%) versus 6 months (82.0%). Because of the difficulty in obtaining an adequate number of events, an 80% CI was also reported by investigators; at 1.17, the upper limit of this CI for CAPOX was below the threshold for noninferiority. Given the small absolute difference, similar findings in the stage III population,[53] and reduced toxicity, the Expert Panel considers it reasonable to offer 3 months of CAPOX, rather than 6 months, to patients who are candidates for adjuvant doublet-based chemotherapy. The absolute difference in 5-year survival in the FOLFOX subgroup for 6 versus 3 months of treatment was 7.3%, and noninferiority was not demonstrated. These results along with the incidence of peripheral sensory neuropathy (Table 6) should be discussed as part of the shared decision-making process.

DISCUSSION

ASCO's original 2004 guideline for stage II colon cancer recommended against ACT, on the basis of evidence showing that the 5-year survival benefit did not exceed 5%.[5] However, ACT could be considered for higher risk subgroups, such as for patients with T4 tumors, fewer than the recommended number of sampled lymph nodes, poor differentiation, or LVI. This guideline update includes a meta-analysis of current data on the effect of ACT in high-risk patients. The data for these comparisons are mostly of lower quality, and therefore, as in 2004, recommendations

TABLE 6. Population: Patients With High-Risk Stage II Colon Cancer

Intervention: 3-month ADCT
Comparator: 6-month ADCT

Outcome	Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		6-Month ADCT	3-Month ADCT		
DFS (overall study population)	HR: 1.17 (80% CI, 1.05 to 1.31) (95% CI, 0.99 to 1.38) (3,273 patients in four studies[a]) Follow-up: 5 years	161 per 1,000	186 per 1,000	Low[b]	3-Month ADCT probably has little or no effect on DFS compared with 6-month ADCT
		Difference: 25 more per 1,000 (95% CI, 7 more to 44 more)			
DFS (CAPOX)	HR: 1.02 (80% CI, 0.88 to 1.17) (95% CI, 0.83 to 1.28) (2,019 patients in four studies[a]) Follow-up: 5 years	159 per 1,000	162 per 1,000	Low[b]	3-Month ADCT probably has little or no effect on DFS (CAPOX) compared with 6-Month ADCT
		Difference: 3 more per 1,000 (95% CI, 18 fewer to 24 more)			
DFS (FOLFOX)	HR: 1.41 (80% CI, 1.18 to 1.68) (95% CI, 1.08 to 1.84) (1,254 patients in four studies[a]) Follow-up: 5 years	150 per 1,000	205 per 1,000	Low[b]	3-Month ADCT probably worsens DFS (FOLFOX) compared with 6-month ADCT
		Difference: 55 more per 1,000 (95% CI, 25 more to 89 more)			
Grade ≥ 2 peripheral neuropathy	RR: 0.36 (95% CI, 0.31 to 0.42) (3,273 patients in four studies[a]) Follow-up during treatment	360 per 1,000	130 per 1,000	Moderate	Patients experience significantly less peripheral neuropathy with 3 months of ADCT compared with 6 months of ADCT
		Difference: 230 fewer per 1,000 (95% CI, 248 fewer to 209 fewer)			

Abbreviations: ACHIEVE2, Adjuvant Chemotherapy for Colon Cancer with High Evidence 2; ADCT, adjuvant doublet chemotherapy; CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HORG, Hellenic Oncology Research Group; HR, hazard ratio; RR, relative risk; SCOT, Short Course Oncology Treatment; TOSCA, Three or Six Colon Adjuvant.

[a]SCOT (NCT00749450), ACHIEVE2 (UMIN000013036), TOSCA (NCT0064660), and HORG (NCT01308086).

[b]Choice of CAPOX or FOLFOX was nonrandomized (chosen by treating clinician); noninferiority threshold of 1.2 not met; modified intention-to-treat analysis including only patients who received at least one dose of chemotherapy. Ninety percent of patients assigned to 3-month treatment received all planned doses, compared with 65% of 6-month patients. Analyses by T4 (yes or no), inadequate nodal harvest (yes or no), and poorly differentiated histology (yes or no) were not significant. Test for interaction between duration and the regimen was not significant ($P = .07$); adjusted for multiple hypothesis tests.

are largely based on the prognostic significance of these indicators and indirect evidence from studies that included stage III patients. In this update, the Expert Panel recommends that ACT is offered to patients with T4 tumors, on the basis of the prognostic significance of this factor, and a higher number of observational studies to support it as a potential predictive factor, compared with other risk factors included in the review. The Expert Panel continues to suggest that ACT may be offered to patients with other high-risk factors, as listed in Recommendation 1.4, and includes patients with BD3 tumor budding, a new addition since the previous version of this guideline. Evidence for the newer prognostic factor ctDNA was explored in this update, and although there was not sufficient evidence to include it in the list of risk factors at this time, the Expert Panel will continue to monitor emerging evidence and consider adding this risk factor to a future update. This update also recommends that ACT is not routinely used for tumors that have dMMR or MSI, although a qualifying statement is included indicating that if a shared decision-making approach results in the choice to use ACT, for example, in the case of T4 tumors, oxaliplatin-containing chemotherapy is recommended, on the basis of indirect evidence from patients with stage III colon cancer. When considering the use of oxaliplatin-containing ACT in the patient population that does not have dMMR or MSI, a shared decision-making approach should be used to weigh a potential TTR benefit against the potential for adverse events. At the time of the previous guideline, results from randomized controlled trials addressing duration of chemotherapy were not available, and this update addresses this topic with the incorporation of data from the IDEA collaboration.[10] The duration of single-agent chemotherapy was not explored in the updated systematic review, but remains 6 months, on the basis of earlier trials of ACT compared with surgery alone.[13]

In addition, the Expert Panel acknowledges the development of tumor-based profiling tools that provide prognostic and predictive information, which can aid in decision making regarding the choice to proceed with ACT.[54,55] Although these tools are not ready for routine use, they may be considered for endorsement in a future version of this guideline when further evidence of their effectiveness becomes available.

PATIENT AND CLINICIAN COMMUNICATION

For general recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[56] Communication strategies that are specific to patients with stage II colon cancer can be found in the previous version of this guideline.[5]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans. Some racial and ethnic minorities, including Black residents of the United States, experience higher colon cancer incidence and mortality than patients who are non-Hispanic White.[57] One study of colorectal cancer attributes disparities to lack of family history knowledge, unequal access to care, and insufficient data on movement patterns and clinical records, which limit efforts to reduce disparities.[58] There may also be differences in the biologic behavior of colorectal cancer, for example, Black patients are more likely than White patients to be diagnosed before age 50 years (10.6% *v* 5.5%).[57] Travel burden may also be more of a barrier for non-Hispanic Black patients, who were more likely than non-Hispanic White patients to experience treatment delay associated with this factor in a Chicago-area study.[59] Treatment delays have also been associated with lower socioeconomic status in a UK study.[60] A targeted approach is recommended for different populations, to address varying challenges and limitations.[58] Awareness of disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.[61–64]

MULTIPLE CHRONIC CONDITIONS

Many patients for whom guideline recommendations apply present with multiple chronic conditions (MCCs). In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs.

Treatment plans need to consider the complexity and uncertainty created by the presence of MCCs, which is reflected in qualifying statements that highlight the importance of shared decision making when implementing guideline recommendations. In addition, patient age is not considered in these guideline recommendations because it is considered more useful to base decisions on functional status and incidence of comorbidities, while acknowledging that these factors are correlated with patient age.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[65,66] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[67,68]

Discussion of cost can be an important part of shared decision making.[69] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[69]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[69]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data, agents that are not currently available in either the United States or Canada, and/or are industry-sponsored. As noted in the ASCO guideline on duration of oxaliplatin-containing ACT in stage III colon cancer, the option of 3 months of ACT is expected to be more cost-effective than 6 months of ACT, in addition to the benefit of fewer adverse events.[53] A recent cost-effectiveness analysis found that the cost of 3 months of CAPOX per person (€37,645) was lower than that of 6 months of CAPOX (€41,257) and 3 months (€47,135) or 6 months of FOLFOX (€44,389).[70]

OPEN COMMENT

The draft recommendations were released to the public for open comment from September 23, 2021, through October 6, 2021. Ten responses were received to the open comment survey. All respondents agreed or agreed with minor modifications to the draft guideline recommendations. Suggestions from this response were incorporated before EBMC review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation that a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[71] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[56] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Duration of Oxaliplatin-containing Adjuvant Therapy in Patients with Stage II Colon Cancer[53] (https://ascopubs.org/doi/pdf/10.1200/JCO.19.00281)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

EQUAL CONTRIBUTION

N.N.B. and J.A.M. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update

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Jordan Berlin
Consulting or Advisory Role: Bayer Health, QED Therapeutics, Clovis Oncology, Ipsen, Mirati Therapeutics, Insmed
Research Funding: Bayer (Inst), Incyte (Inst), Karyopharm Therapeutics (Inst), EMD Serono (Inst), Boston Biomedical (Inst), Macrogenics (Inst), PsiOxus Therapeutics (Inst), Pfizer (Inst), Lilly (Inst), Dragonfly Therapeutics (Inst), AbbVie (Inst), I-MAB (Inst), Astellas Pharma (Inst), Atreca (Inst), Day One Biopharmaceuticals (Inst), Bristol Myers Squibb/Celgene (Inst)
Travel, Accommodations, Expenses: Boston Biomedical
Other Relationship: Novocure, Pancreatic Cancer Action Network, Karyopharm Therapeutics

Thomas J. George
Consulting or Advisory Role: Tempus, Pfizer
Research Funding: Bristol Myers Squibb (Inst), Merck (Inst), AstraZeneca/MedImmune (Inst), Lilly (Inst), Bayer (Inst), Incyte (Inst), Ipsen (Inst), Seattle Genetics (Inst), Genentech (Inst), Astellas Pharma (Inst), BioMed Valley Discoveries (Inst), GlaxoSmithKline (Inst), GlaxoSmithKline (Inst)
Open Payments Link: https://https://openpaymentsdata.cms.gov/physician/321938

Sharlene Gill
Honoraria: Amgen, Taiho Oncology, Eisai
Consulting or Advisory Role: Taiho Pharmaceutical, Amgen, Roche Canada, Eisai, Ipsen, Pfizer, Merck, Bristol Myers Squibb Canada, Bayer
Research Funding: Taiho Pharmaceutical (Inst)

Lee Jones
Honoraria: Bayer, Guardant Health

Christopher Lieu
Consulting or Advisory Role: Ipsen (Inst), HalioDx (Inst), Pfizer (Inst)
Research Funding: Merck (Inst)

Najjia Mahmoud
Employment: Johnson & Johnson, Johnson & Johnson/Janssen
Honoraria: Johnson & Johnson, Johnson & Johnson/Janssen
Consulting or Advisory Role: Johnson & Johnson

Erika Ruiz-Garcia
Consulting or Advisory Role: Roche/Genentech, Amgen, BMS, Bayer
Travel, Accommodations, Expenses: Sanofi/Aventis

Jeffrey A. Meyerhardt
Honoraria: Cota Healthcare, Taiho Pharmaceutical
Research Funding: Boston Biomedical (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Adjuvant Therapy for Stage II Colon Cancer: Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
Nancy N. Baxter, MD, PhD (cochair)	University of Melbourne, Melbourne, Australia	Colorectal Surgery
Jeffrey A. Meyerhardt, MD, MPH (cochair)	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Emily Bergsland, MD	UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA	Medical Oncology
Jordan Berlin, MD	Vanderbilt University Medical Center, Nashville, TN	Medical Oncology
Thomas J. George, MD	University of Florida, Gainesville, FL	Medical Oncology
Sharlene Gill, MD, MPH, MBA	BC Cancer, Vancouver, Canada	Medical Oncology
Philip J. Gold, MD	Swedish Cancer Institute, Seattle, WA	Medical Oncology
Alex Hantel, MD	Edward Elmhurst Healthcare, Naperville, IL	Practice Guidelines Implementation Network Representative
Lee Jones, MBA	Arlington, VA	Patient Representative
Christopher Lieu, MD	University of Colorado Cancer Center, Aurora, CO	Medical Oncology
Najjia Mahmoud, MD	Penn Medicine, Philadelphia, PA	Colorectal Surgery
Arden M. Morris, MD, MPH	Stanford University Medical Center, Palo Alto, CA	Colorectal Surgery
Erika Ruiz-Garcia, MD, MS	Instituto Nacional de Cancerologia, Mexico City, Mexico	Medical Oncology
Y. Nancy You, MD, MHSc	University of Texas M.D. Anderson Cancer Center, Houston, TX	Colorectal Surgery
Erin B. Kennedy, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guidelines Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects
	All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists
	Most informed people would choose the recommended course of action, but a substantial number would not