ASCO special article abstract

Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer: ASCO Clinical Practice Guideline

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PURPOSE To develop recommendations for duration of adjuvant chemotherapy with a fluoropyrimidine and oxaliplatin for patients with completely resected stage III colon cancer based on the results of trials of 3 months compared with 6 months of treatment.

METHODS ASCO convened an Expert Panel and conducted a systematic review of relevant studies. The guideline recommendations were based on the review of evidence by the Expert Panel.

RESULTS Pooled data from the six International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration randomized controlled trials comprise the evidence base for these guideline recommendations.

RECOMMENDATIONS The recommendations for therapy duration apply to patients with completely resected stage III colon cancer who are being offered adjuvant chemotherapy with oxaliplatin and a fluoropyrimidine. Recommendations are informed by the findings of a recent pooled analysis of clinical trials that compared 6 months versus 3 months of oxaliplatin-based chemotherapy. For patients at a high risk of recurrence (T4 and/or N2), adjuvant chemotherapy should be offered for a duration of 6 months. For patients at a low risk of recurrence (T1, T2, or T3 and N1), either 6 months of adjuvant chemotherapy or a shorter duration of 3 months may be offered on the basis of a potential reduction in adverse events and no significant difference in disease-free survival with the 3-month regimen. In determining duration of therapy, the Expert Panel recommends a shared decision-making approach, taking into account patient characteristics, values and preferences, and other factors and including a discussion of the potential for benefit and risks of harm associated with treatment duration. 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

In 2018, approximately 97,000 people living in the United States will be diagnosed with colon cancer.[1] Of these patients, just less than one third will have stage III disease characterized by spread to regional lymph nodes and absence of distant metastases.[2] The primary treatment option for patients with stage III colon cancer is resection with curative intent; however, recurrence rates can be as high as 50% to 80%[3] with surgery alone. Adjuvant chemotherapy is recommended to improve overall survival for patients who have a high risk of recurrence.

Early trials established the benefit of single-agent chemotherapy compared with surgery alone.[4] Subsequently, oxaliplatin-based combination chemotherapy became the standard based on the results of studies such as the Adjuvant Treatment of Colon Cancer (MOSAIC) phase III randomized trial, which demonstrated a significantly improved disease-free survival (DFS) and overall survival for continuous infusional fluorouracil plus leucovorin and oxaliplatin (FOLFOX4) compared with fluorouracil plus leucovorin alone.[5] Until recently, the standard duration of treatment with oxaliplatin-containing chemotherapy has been 6 months, which is consistent with the time frame used in previously conducted trials.[6] A potential side effect of oxaliplatin-based chemotherapy is peripheral sensory neurotoxicity, which may be severe and/or permanent, and this risk becomes greater with increasing dose and duration of oxaliplatin.[7,8] Some previous analyses of single-agent therapy have shown that shorter duration treatment could confer the same survival advantage as longer duration treatment while reducing the incidence of peripheral sensory neurotoxicity.[7,9,10] Data from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration comparing DFS and incidence of adverse events with different durations of a fluoropyrimidine and oxaliplatin-based chemotherapy have recently been published. This guideline incorporates this new evidence and provides recommendations for duration of chemotherapy for patients with stage III colon cancer who are at high or low risk of recurrence.[7]

THE BOTTOM LINE

Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer: ASCO Clinical Practice Guideline

Guideline Question
What is the optimal duration (3 months *v* 6 months) of oxaliplatin-containing chemotherapy for patients with completely resected stage III colon cancer?

Target Population
Patients with completely resected stage III colon cancer.

Target Audience
Medical oncologists, general surgeons, colorectal surgeons, surgical oncologists, and oncology advanced practice providers who treat patients with colon cancer.

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

Recommendations
For patients with stage III resected colon cancer who are being offered treatment with oxaliplatin-containing chemotherapy:

Recommendation 1
For patients with high-risk (T4 and/or N2) stage III resected colon cancer, adjuvant oxaliplatin-containing chemotherapy should be offered for a duration of 6 months. (Type: Evidence-based; benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 2
For patients with low-risk (T1, T2, or T3 and N1) stage III resected colon cancer, adjuvant oxaliplatin-containing chemotherapy may be offered for a duration of 3 months 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: Intermediate; Strength of recommendation: Moderate).

Recommendation 3
A shared decision-making approach should be used for duration of oxaliplatin-containing chemotherapy for patients with stage III resected colon cancer, taking into account a patient's tumor characteristics, completeness of surgical resection, number of lymph nodes examined, comorbidities, functional status, performance status, values and preferences, age at diagnosis, life expectancy, potential years at risk for long-term sequalae of treatment, and including a discussion of the potential for benefit and risks of harm (Table 2) associated with treatment duration (Type: Consensus-based; benefits outweigh harms; Strength of recommendation: Strong).

Qualifying Statements
Summary of key evidence from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration (n = 12,834)[6]:

- Using a predefined threshold, noninferiority of 3 months compared with 6 months of oxaliplatin-containing chemotherapy was not proven for disease-free survival (DFS), the primary outcome.
- The relative risk of all grade 3 to 4 adverse events and grade 3 to 4 peripheral sensory neurotoxicity up to 1 month post-treatment was significantly lower with 3 months versus 6 months of dual-agent chemotherapy.

Exploratory subgroup analyses by risk of recurrence[6]:

- Within the high-risk group defined in the IDEA Collaboration (T4 and/or N2), superior DFS was found with 6 months versus 3 months duration of dual-agent chemotherapy.
- Within the low-risk group (T1 to 3, N1), DFS was noninferior with 3 months versus 6 months duration of dual-agent chemotherapy.

Prespecified subgroup analysis by type of oxaliplatin-based chemotherapy[6]:

- 3 months of treatment was not inferior to 6 months for patients treated with capecitabine and oxaliplatin (CAPOX).
- 3 months of treatment was inferior to 6 months for patients treated with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Additional Resources

More information, including a Data 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

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.

GUIDELINE QUESTIONS

This clinical practice guideline addresses one clinical question: What is the appropriate duration (3 *v* 6 months) of oxaliplatin-containing adjuvant chemotherapy for patients with completely resected stage III colon cancer?

METHODS

Guideline Development Process

This systematic review–based guideline was developed by a multidisciplinary Expert Panel, which included clinicians with expertise in colorectal surgery and medical oncology as well as a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via teleconference and/or Webinar and corresponded through e-mail. Based upon 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, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic search of PubMed from April 2004 to August 2018 for phase III randomized clinical trials (RCTs) that included a comparison of two or more durations of treatment with FOLFOX or capecitabine and oxaliplatin (CAPOX) chemotherapy. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Patients receiving adjuvant oxaliplatin-containing chemotherapy (FOLFOX or CAPOX) following resection for stage III colon cancer
- Fully published or Meeting presentations or abstracts published within the past 2 years (2017 to 2018)
- English-language reports of phase III RCTs

Within the guideline protocol, the Expert Panel also specified an interest in providing recommendations for subgroups defined by risk of recurrence, including low risk (T1, T2, or T3 and N1 [$\leq$ 3 positive nodes]) and high risk (T4 and/or N2 $\geq$ 4).[6] Outcomes of interest included DFS, overall survival, and adverse events, with a particular interest in rates of peripheral sensory neurotoxicity.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[11] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation. Additional quality elements, including precision, directness, and consistency of outcomes, were also assessed.[12]

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The update search will be guided by the "signals"[13] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help to identify potential signals. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guidelines 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/rwc). 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

The search for phase III RCTs with a comparison of different durations of dual-agent chemotherapy resulted in 266 studies. Two additional studies were identified by Expert Panel members. Studies selected for inclusion were reports from six trials conducted across 12 countries as part of the IDEA Collaboration. The data for these trials have recently been analyzed in a single publication,[6] the results of which comprise the evidence base for recommendations 1 and 2.

Characteristics of Included Studies

Across the six IDEA Collaboration studies, participants were 56% male, with a median age of 64 years (range, 18 to 88 years). American Joint Committee on Cancer Staging, Seventh Edition,[14] nodal status was most commonly N1 (71.4%), and tumor stage of most patients was T3 (65.5%). Eastern Cooperative Oncology Group (ECOG) performance status was favorable for most patients, with 99.6% having ECOG status 0 or 1 (Table 1).

Patients and investigators were permitted to choose treatment with either FOLFOX (60% of all patients) or CAPOX (40% of all patients) in five of the six trials (Cancer and Leukemia Group B [CALGB]/SWOG 80702 only allowed FOLFOX). In none of these trials were patients randomized to FOLFOX versus CAPOX. The proportion of patients receiving FOLFOX ranged from 25% in the Adjuvant Chemotherapy for Colon Cancer With High Evidence (ACHIEVE) trial conducted in Japan to 100% in the North American CALGB/SWOG study.

The primary end point of all trials was 3-year DFS. Across collaborating sites, investigators came to consensus that administration of 3 months of oxaliplatin-based chemotherapy would be deemed noninferior to 6 months of therapy if the upper limit of the two-sided 95% confidence interval did not exceed 1.12,[6] which corresponded to a 2.7% reduction in 3-year DFS from 72% to 69.3%.

More information on the characteristics of the individual IDEA Collaboration studies is available in the Data Supplement.

Study Quality Assessment

Elements that could contribute to risk of bias and overall study quality (ie, certainty of evidence)[15] were assessed for each outcome across IDEA Collaboration studies. Some studies included a central randomization process and allocation concealment, whereas the inclusion of these elements for some studies was unclear. The main analysis was conducted on the patient population that underwent randomization and received at least one dose of a study drug ("modified intention to treat").[6] Studies were open label, with study participants and investigators unblinded to the duration of treatment. Subgroup analyses according to nodal status, tumor stage, and treatment type were prespecified. The subgroups defined as low and high risk were not prespecified and were based on an analysis of likelihood of recurrence. An assessment of consistency of outcomes across trials found that there was no significant heterogeneity ($I^2 < 0.26$; $P > .17$). Within trials, results differed by type of treatment (FOLFOX or CAPOX). Adherence to treatment dose intensity was significantly higher among patients who received 3 months versus 6 months of adjuvant oxaliplatin-based chemotherapy ($P < .001$).

TABLE 1. Combined Characteristics of the IDEA Collaboration Studies

Methods	Pooled data from six individual randomized controlled trials conducted in Italy (TOSCA, n = 2,402), Greece (HORG, n = 708), Japan (ACHIEVE, n = 1,291), North America (CALGB/SWOG 80702, n = 2,440), United Kingdom, Denmark, Spain, Australia, Sweden, New Zealand (SCOT, n = 3,983), and France (IDEA France, n = 2,010).
Participants	44% female, 56% male Median age, 64 years (range, 18-88 years) Extent of bowel invasion (T stage): T1, 3.8%; T2, 9.3%; T3, 65.5%; T4, 20.7% Nodal status: N1, 71.4%; N2, 27.8%; missing data, 0.8% ECOG performance status: 0, 79.0%; 1, 20.6%; 2, 0.4% Median follow-up time: 48 months
Intervention and comparison	Patients were randomized to either 3 months (intervention) or 6 months (comparison) of treatment with[31]: CAPOX (39.5%): Oxaliplatin 130 mg/m^2 IV infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine administered orally at a dose of 1,000 mg/m^2 twice daily (equivalent to a total daily dose of 2,000 mg/m^2 the first evening dose on day 1 and the last morning dose on day 15) given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment) Or FOLFOX (60.5%): FOLFOX4: A 2-hour infusion of LV 200 mg/m^2 followed by a 400 mg/m^2 bolus FU followed by a 22-hour infusion of FU 600 mg/m^2 given on 2 consecutive days plus a 2-hour infusion of 85 mg/m^2 oxaliplatin on day 1 simultaneously with LV using a Y-infusion device Or mFOLFOX6: Oxaliplatin 85 mg/m^2 IV infusion with LV 400 mg/m^2 over 2 hours using a Y-infusion device followed by 400 mg/m^2 bolus FU followed by an IV infusion of FU 2,400 mg/m^2 for 46 hours (N.B. In the SCOT trial, the dose of LV is fixed to 350 mg total dose.)
Outcomes	Primary outcome: DFS at 3 years defined as time from randomization to recurrence, secondary colorectal cancer, or death Preplanned subgroup analyses: DFS according to stage of tumor penetration and nodal status Unplanned subgroup analyses: DFS according to risk level Rates of adverse events, including peripheral sensory neurotoxicity at any time after randomization, diarrhea, febrile neutropenia, neutropenia, thrombocytopenia, nausea, vomiting, mucositis, fatigue, hand-foot syndrome

NOTE. From Grothey et al.[6]

Abbreviations: ACHIEVE, Adjuvant Chemotherapy for Colon Cancer With High Evidence; CALGB, Cancer and Leukemia Group B; CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; HORG, Hellenic Oncology Research Group; IDEA, International Duration Evaluation of Adjuvant Chemotherapy; IV, intravenous; LV, leucovorin; SCOT, Short Course Oncology Therapy; TOSCA, Three or Six Colon Adjuvant.

Lack of blinding, inconsistency of results across treatment types, and lack of an unmodified intention-to-treat analysis resulted in an overall certainty of evidence rating of intermediate for DFS in the overall treatment group. These factors as well as the unplanned exploratory nature of the analysis by risk level resulted in the outcomes reported by risk subgroups being rated down to low certainty of evidence. An additional limitation of the adverse events data is that the data collection period only extends up to 1-month post-treatment; however, due to the large magnitude of effect, the certainty of evidence was upgraded from low to intermediate for the adverse events outcomes (Table 2). Overall, the evidence for recommendations 1 and 2 is rated intermediate quality.

Outcomes

DFS. In the overall study population, the DFS hazard ratio (HR) comparing 6 months to 3 months of adjuvant therapy included the prespecified noninferiority upper 95% CI limit value of 1.12; therefore, 3 months of therapy was not proven noninferior to 6 (Table 2).

Preplanned subgroup analyses were conducted according to treatment type (FOLFOX or CAPOX), T stage (tumor penetration), and N stage (nodal status). Three months of FOLFOX was inferior to 6 months of FOLFOX therapy (HR, 1.16; 95% CI, 1.06 to 1.26), while 3 months of CAPOX met criteria for noninferiority (HR, 0.95; 95% CI, 0.85 to 1.06); there was a significant interaction by treatment type ($P = .0051$), demonstrating statistical difference between these two associations based on treatment. In contrast, there was not a statistically significant interaction by extent of invasion through bowel wall (T stage $P = 0.36$) or N stage ($P = .44$; Data Supplement). However, patients with T4 disease did have a significantly inferior DFS with 3 months versus 6 months of treatment (HR, 1.16; 95% CI, 1.03 to 1.31).

Further unplanned exploratory subgroup analyses were conducted by treatment type and risk of recurrence. T4 and/or N2 cancers were combined into a group that was at higher risk of recurrence or death (approximately 60% 3-year DFS), and T1, T2, or T3 tumors and N1 nodal status were combined to a lower risk group (approximately 80% 3-year DFS). Six months was found to be superior to 3 months of oxaliplatin-containing chemotherapy in the high-risk group (HR, 1.12; 95% CI, 1.03 to 1.23), and 3 months was found to be noninferior to 6 months in the low-risk group (HR, 1.01; 95% CI, 0.9 to 1.12; Table 2).

TABLE 2. Duration of Oxaliplatin-Containing Adjuvant Chemotherapy for Stage III Colon Cancer Intervention: Three-Month Dual-Agent Chemotherapy

Outcome	Study Results, No. of Patients, and Time Frame	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)	Summary
		6 Months	3 Months		
Recurrence or death: overall study population	HR, 1.07 (95% CI, 1.0 to 1.15) Based on data from 12,834 patients in six studies Follow-up, 3 years	**245** per 1,000	**260** per 1,000 Difference: **15 more per 1,000** (95% CI, 0 fewer to 31 more)	**Intermediate** Open-label trials Modified ITT analysis Threshold upper limit of 1.12 corresponds to a 2.7% increase in rate of recurrence or death (from a pre-analysis estimate of 72%-69.3% 3-year DFS);	The upper CI for the hazard associated with 3 *v* 6 months chemotherapy exceeds a predetermined threshold of noninferiority of 1.12. Therefore, 3 months cannot be considered noninferior to 6 months of oxaliplatin-containing chemotherapy.
Recurrence or death: low risk*	HR, 1.01 (95% CI, 0.9 to 1.12) Based on data from 7,471 patients in six studies Follow up, 3 years	**167** per 1,000	**169** per 1,000 Difference: **2 more per 1,000** (95% CI, 17 fewer to 20 more)	**Low** Open-label trials Modified ITT analysis Low- and high-risk levels not prespecified	Low risk: 3 months probably has little or no difference on recurrence or death
Recurrence or death: high risk†	HR, 1.12 (95% CI, 1.03 to 1.23) Based on data from 5,256 patients in six studies Follow-up, 3 years	**356** per 1,000	**373** per 1,000 Difference: **17 more per 1,000** (95% CI, 11 more to 82 more)	**Low** Open-label trials Modified ITT analysis Low- and high-risk levels not prespecified	High risk: 3 months may worsen recurrence or death slightly
Recurrence or death (FOLFOX)	HR, 1.16 (95% CI, 1.06 to 1.26) Based on data from 7,763 patients in six studies Follow-up, 3 years	**240** per 1,000	**264** per 1,000 Difference: **24 more per 1,000** (95% CI, 12 more to 52 more)	**Intermediate** Open-label trials Modified ITT analysis	3 months probably worsens recurrence or death (FOLFOX) slightly
Recurrence or death (CAPOX)	HR, 0.95 (95% CI, 0.85 to 1.06) Based on data from 5,071 patients in six studies Follow-up, 3 years	**252** per 1,000	**241** per 1,000 Difference: **11 fewer per 1,000** (95% CI, 38 fewer to 15 more)	**Intermediate** Open-label trials Modified ITT analysis	3 months probably has little or no difference on recurrence or death (CAPOX)
Any grade 3 or 4 adverse event	RR, 0.66 (95% CI, 0.63 to 0.69) Based on data from 9,381 patients in six studies Follow-up, 1 month post-treatment	**510** per 1,000	**337** per 1,000 Difference: **173 fewer per 1,000** (95% CI, 189 fewer to 158 fewer)	**Intermediate** Open-label trials Modified ITT analysis Only short-term adverse events assessed Upgrade for large magnitude of effect	3 months improves any grade 3 or 4 adverse event

(continued on following page)

TABLE 2. Duration of Oxaliplatin-Containing Adjuvant Chemotherapy for Stage III Colon Cancer Intervention: Three-Month Dual-Agent Chemotherapy (continued)

Outcome	Study Results, No. of Patients, and Time Frame	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)	Summary
		6 Months	3 Months		
Grade 3-4 peripheral sensory neuropathy	RR, 0.18 (95% CI, 0.15 to 0.22) Based on data from 9,245 patients in 6 studies. Follow-up, 1 month post-treatment	**139** per 1,000	**25** per 1,000 Difference: **114 fewer per 1,000** (95% CI, 118 fewer to 108 fewer)	**Intermediate** Open-label trials Modified ITT analysis Only short-term adverse events assessed Upgrade for large magnitude of effect	3 months improves grade 3-4 peripheral sensory neuropathy

NOTE. Comparator: 6-month dual-agent chemotherapy. Table 2 was created using MAGICapp (https://app.magicapp.org/).

Abbreviations: CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; ITT, intention to treat; RR, relative risk.

*Low risk defined as T1, T2, T3, and N1 (80% DFS at 3 years); 58.7% of study population.

†High risk defined as T4 and/or N2 (60% DFS at 3 years); 41.3% of study population.

Adverse events. Grade 3 to 4 adverse events were significantly less likely in the 3-month treatment group versus 6 months (relative risk, 0.66; 95% CI, 0.63 to 0.69). Grade 3 to 4 peripheral sensory neurotoxicity (relative risk, 0.18; 95% CI, 0.15 to 0.22) was also significantly less common in the shorter-duration treatment group (Table 2).

RECOMMENDATIONS

Clinical Question

What is the appropriate duration (3 *v* 6 months) of oxaliplatin-containing adjuvant chemotherapy for patients with completely resected stage III colon cancer?

For patients with stage III resected colon cancer who are being offered treatment with oxaliplatin-containing chemotherapy:

Recommendation 1. For patients with high-risk (T4 and/or N2) stage III resected colon cancer, adjuvant oxaliplatin-containing chemotherapy should be offered for a duration of 6 months. (Type: Evidence-based; benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 2. For patients with low-risk (T1, T2, or T3 and N1) stage III resected colon cancer, adjuvant oxaliplatin-containing chemotherapy may be offered for a duration of 3 months 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: Intermediate; Strength of recommendation: Moderate).

Recommendation 3. A shared decision-making approach should be used for duration of oxaliplatin-containing chemotherapy for patients with stage III resected colon cancer, taking into account a patient's tumor characteristics, completeness of surgical resection, number of lymph nodes examined, comorbidities, functional status, performance status, values and preferences, age at diagnosis, life expectancy, potential years at risk for long-term sequalae of treatment, and including a discussion of the potential for benefit and risks of harm (Table 2) associated with treatment duration (Type: Consensus-based; benefits outweigh harms; Strength of recommendation: Strong).

Literature review and clinical interpretation. The evidence base consists of data from 12,843 patients who participated in six RCTs comprising the IDEA Collaboration.[6]

The risk of grade 3 or greater adverse events, including peripheral sensory neurotoxicity, is significantly reduced with shorter duration of treatment, at least during the time period during and immediately after treatment (Table 2). Using a predetermined threshold, noninferiority of 3 months compared with 6 months of oxaliplatin-containing adjuvant chemotherapy was not proven for DFS. Therefore, despite the potential for reduction in adverse events, 3 months of treatment with oxaliplatin-containing chemotherapy is not recommended within this guideline for all patients.

In a preplanned analysis, there was a significant interaction for these findings based on which chemotherapy regimen was used. Noninferiority for 3 months of therapy was proven when CAPOX was used as oxaliplatin-containing therapy, while inferiority of 3 months was seen with FOLFOX.

The analysis did demonstrate noninferiority for DFS by treatment duration in the group of patients who are at a lower risk of recurrence or death (T1, T2, T3, and N1). Balancing this finding with the significant potential for a reduction in adverse events, the Expert Panel agreed that 3 months of treatment may be recommended for patients who are low risk.

Within the higher-risk group (T4 and/or N2), adverse events would also be significantly lower with 3 months of treatment; however, 3 months of therapy was inferior to 6 months of therapy; therefore, the Expert Panel agreed that 6 months of treatment should be recommended for this subgroup.

Given the limitations of the evidence base, a shared decision-making approach is recommended for all patients.

DISCUSSION

Duration of Therapy

For many years, the standard duration of combination chemotherapy for stage III resected colon cancer has been 6 months; however, oxaliplatin administration is associated with significant risk of peripheral sensory neurotoxicity, which increases with dose and duration and can be long lasting. Previous studies of fluoropyrimidine monotherapy have suggested that there is potential for a shorter duration of chemotherapy to have a similar efficacy with a reduced incidence of neuropathy and other adverse events. This guideline incorporates new data from the IDEA Collaboration group of RCTs, which explored the effect of a reduced duration of oxaliplatin-based combination-agent chemotherapy for stage III resected colon cancer.

Prespecified criteria for noninferiority were not met in the overall study population; however, within the lower risk subgroup, the Expert Panel agrees that 3 months of treatment may be recommended based on findings of a significant reduction in adverse events and no significant difference in DFS.

Within the population defined as high risk (T4 tumor, and/or $\geq$ 4 positive lymph nodes [N2]), there were 33 more recurrences or deaths (95% CI, 8 to 62) and 114 fewer cases of peripheral sensory neurotoxicity (95% CI, 108 to 118) per 1,000 patients with the shorter duration of treatment. This amounts to one additional recurrence or death for every 30 patients and one fewer incidence of peripheral sensory neurotoxicity for every nine patients given the shorter duration of oxaliplatin-containing chemotherapy. Based on this balance of potential for benefit and risk of harm, the 6-month duration of oxaliplatin-containing chemotherapy continues to be recommended for the

higher risk group; however, the Expert Panel recommends a shared decision-making approach given the lower quality of the evidence.

Type of Treatment

An analysis by treatment subgroup (FOLFOX or CAPOX) was also prespecified by the IDEA Collaboration investigators. DFS with 6 months of treatment with FOLFOX was found to be superior to 3 months; however, DFS did not differ significantly by treatment duration for patients who were treated with CAPOX. Further exploratory analysis by risk status and type of chemotherapy found that 6 months of adjuvant therapy was found to be superior for the high-risk subgroup that received FOLFOX (HR, 1.20; 95% CI, 1.07 to 1.3), but no significant difference was found for 3 months of CAPOX in the high-risk subgroup (HR, 1.02; 95% CI, 0.89 to 1.17). These were unexpected findings, according to the IDEA collaborators, and may be attributed to factors such as greater adherence to treatment in the FOLFOX group or to differences in dosing schedule. The question of type of oxaliplatin-based chemotherapy was not included in the protocol for this guideline; however, the Expert Panel discussed the significance of these findings for clinical practice. The Expert Panel agreed that within the recommendation for 3 months of oxaliplatin-containing adjuvant chemotherapy in low-risk patients, it would favor CAPOX over FOLFOX because the data are stronger for the former type of oxaliplatin-based adjuvant chemotherapy. The Expert Panel did not include this as a recommendation within the Bottom Line Box due to the considerations outlined previously and because previous studies comparing CAPOX and FOLFOX in colorectal cancer had not found significant differences between these two treatment options.[16,17]

CONCLUSION

Because of the higher risk of toxicity with 6 months of adjuvant oxaliplatin and fluoropyrimidine-based therapy, the question of reducing adjuvant therapy from 6 months to 3 months was recently examined. Our analysis and interpretation of the data suggest that in general for stage III colorectal cancer, 6 months of adjuvant therapy remains the standard of care for high-risk patients (T4 and/or N2). However, an unplanned subgroup analysis suggests that for patients with low-risk colorectal cancer (T1 to 3, N1), 3 months of adjuvant oxaliplatin and fluoropyrimidine–based therapy may be considered. Because the benefit of adjuvant therapy must be weighed against the toxicity of the therapy, we recommend a shared decision approach when deciding on the duration of therapy. Although 3-year DFS is a validated surrogate outcome for 5-year OS in colon cancer,[18] we await the publication of mature survival data and longer-term data with respect to neurotoxicity from the IDEA Collaboration. ASCO also has plans to update its guideline on systemic chemotherapy for stage II colon cancer in the near future.[19]

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[20]

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.[21-24] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these 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.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. 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. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[25,26] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[27,28]

Discussion of cost can be an important part of shared decision making.[29] 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.[29] The recommendation contained within this guideline that clinicians may offer 3 months rather than 6 months of oxaliplatin-based chemotherapy to low-risk patients is expected to be a less-expensive option in addition to providing a benefit in terms of a reduction in adverse events. A cost table with pricing information for capecitabine and fluorouracil is included (Table 3).

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.[29]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from October 10 through October 24, 2018. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation. All five respondents agreed with recommendation 1 as written. Sixty percent of respondents agreed with recommendation 2 as written. The remaining 40% (two respondents) provided suggested modifications. One respondent suggested that the recommendation say "should" rather than "may," which the Expert Panel agreed with and has modified. Another comment requested that a clarification to indicate that most of the difference in the high-risk group was due to the results of the T4 group (rather than the N2 patients, for which there was no significant difference by duration in the main analysis). These data are included within the text of this article. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline 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 Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site

TABLE 3. Estimated Medicare Prices for Capecitabine and Fluorouracil in the United States

Agent, Route	Dose	Schedule	Price Per Day/Cycle, USD/m^2 BSA	Total Price Per Treatment Cycle, USD/m^2 BSA*
Capecitabine, oral (delivered as CAPOX, Table 1)	1,000 mg/m^2	Twice daily (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment)	500 mg/m^2 at $3.51 $14.04/d $196.56/cycle	3 months (12 weeks, four cycles): $786.24 6 months (24 weeks, eight cycles): $1,572.48
FU, injection (delivered as FOLFOX4, mFOLFOX6, Table 1)	1. FOLFOX4: 400 mg/m^2, 600 mg/m^2 2. mFOLFOX6: 400 mg/m^2, 2,400 mg/m^2	Every 2 weeks: 1. 400 mg/m^2 bolus FU followed by a 22-hour infusion of FU 600 mg/m^2 given on 2 consecutive days 2. 400 mg/m^2 bolus FU followed by an IV infusion of FU 2,400 mg/m^2 for 46 hours	500 mg/m^2 at $1.80 1. $7.20/cycle 2. $10.08/cycle	3 months (12 weeks, six cycles): 1. $43.20 2. $60.48 6 months (24 weeks, 12 cycles): 1. $86.40 2. $120.96

NOTE. Drug prices are dynamic; thus, prices listed may not reflect current prices. Source: Drugs Average Sales Price Data (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html (updated November 29, 2018). Drug price may vary by plan and by pharmacy where a medication is filled (eg, preferred or nonpreferred pharmacies).

Abbreviations: BSA, body surface area; CAPOX, capecitabine and oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; IV, intravenous; USD, US dollars.

*Average BSA is approximately 1.6 m^2 for females and 1.9 m^2 for males.

and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

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 in clinical trials.

ADDITIONAL RESOURCES

More information, including a Data 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[30] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[20] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Adjuvant Chemotherapy for Stage II Colon Cancer[19] (http://ascopubs.org/doi/10.1200/JCO.2004.05.063)

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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 Data 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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer: ASCO Clinical Practice Guideline

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APPENDIX

TABLE A1. Guideline Expert Panel Membership

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Najjia Mahmoud, MD	Penn Medicine, Philadelphia, PA	Colorectal surgery
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Abbreviation: PGIN, Practice Guidelines Implementation Network.