Optimal Duration of Adjuvant Therapy for Stage III Colon Cancer

Kunal C. Kadakia, MD, William M. Worrilow, BA, Harris Coley, BS, and Mohamed E. Salem, MD

The authors are affiliated with the Department of Solid Tumor Oncology of the Levine Cancer Institute at Atrium Health in Charlotte, North Carolina. Drs Kadakia and Salem are medical oncologists, Mr Worrilow is an oncology data research coordinator, and Mr Coley is a research assistant.

Corresponding author:
Mohamed E. Salem, MD
Department of Solid Tumor Oncology
Levine Cancer Institute
1021 Morehead Medical Drive
Charlotte, NC 28204
Tel: (704) 403-1322
E-mail: mohamed.salem@atriumhealth.org

Keywords
Adjuvant, CAPOX, chemotherapy, colon cancer, FOLFOX, oxaliplatin, XELOX

Abstract: Colon cancer remains a major cause of mortality worldwide. Following adequate surgical resection of lymph node–positive colon cancer, the standard of care since 2004 has been to administer an oxaliplatin-containing regimen (eg, FOLFOX or CAPOX) for 6 months. These regimens have consistently improved oncologic outcomes compared with non-oxaliplatin therapies in multiple adjuvant randomized controlled trials. However, oxaliplatin-induced cumulative dose-dependent neurotoxicity is a major cause of morbidity that can persist years after treatment. The IDEA collaboration is a study that pooled data from 6 concurrent phase 3 trials comparing 3 vs 6 months of adjuvant FOLFOX or CAPOX to evaluate whether a shorter duration of therapy could maintain efficacy while reducing neurotoxicity. In this article, we review the history of adjuvant therapy in stage III colon cancer and comprehensively detail the results of the IDEA collaboration. A risk-based approach focusing on efficacy, toxicity, and patient selection is emphasized to guide discussions regarding the optimal duration of adjuvant therapy in stage III colon cancer.

Introduction

Nearly 100,000 patients in the United States receive a diagnosis of colon cancer each year,[1] and approximately 30% to 35% of these patients present with regional lymph node metastases that are consistent with stage IIIA-C colon cancer as defined by the American Joint Committee on Cancer (AJCC). In the absence of adjuvant systemic therapy, stage III colon cancer often confers a poor prognosis. Fluoropyrimidines were first shown in 1990 to reduce the risk of death in the adjuvant colon cancer setting.[2] Oxaliplatin combined with fluoropyridine-based therapy was subsequently found to improve both disease-free survival (DFS) and overall survival (OS) compared with fluoropyrimidines alone in 3 large, randomized controlled trials (RCTs).[3-5] Based on these data, the standard of care since 2004 has been to administer 6 months of 5-fluorouracil/leucovorin (5-FU/LV) with oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (CAPOX, also called XELOX) for resected stage III colon cancers.

Despite improved outcomes with oxaliplatin, this agent is associated with a cumulative dose-dependent neurotoxicity that can persist months to years after the completion of adjuvant therapy. Neurotoxicity, other non-neurotoxic adverse effects, and inconvenience led to efforts to evaluate whether a shorter duration of therapy might maintain efficacy while mitigating toxicities. The culmination of such efforts was the formation of the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration.[6] The IDEA study was a prospective, preplanned, pooled analysis of 6 parallel phase 3 trials that compared 3 vs 6 months of FOLFOX or CAPOX. In this article, we review the history of adjuvant therapy in stage III colon cancer and comprehensively detail the results of the IDEA pooled analysis. A risk-based approach to guide discussions regarding the optimal duration of adjuvant therapy in stage III colon cancer is highlighted.

Prognosis of Stage III Colon Cancer by Tumor and Node Stage

Although all stage III colon cancers share the presence of nodal involvement, the varied prognoses by differing tumor (T1-4ab) and node (N1ac-N2ab) AJCC stage groups (Table 1) highlight the heterogeneity within these cancers. Stage III colon cancers can be associated with high rates of relapse and death, with 5-year relative survival rates of 70% to 90% for stage IIIA (T1-2N1/N1c, T1N2a), 45% to 70% for stage IIIB (T3-4N1/N1c, T2-3N2a, T1-2N2b), and 15% to 40% for stage IIIC (T4aN2a, T3-4aN2b, T4bN1-2).[7]

Major Historic Trials of Adjuvant Chemotherapy in Stage III Colon Cancer

Fluoropyrimidines

The Intergroup INT-0035 study (Intergroup Study of Fluorouracil Plus Levamisole as Adjuvant Therapy for Stage II/Dukes' B2 Colon Cancer) was the first RCT to observe a significant reduction in the risk of death (33%; 95% CI, 10%-50%; *P*=.006) with 12 months of 5-FU/levamisole compared with observation in Dukes C (stage III) colon cancer.[8] Subsequent trials observed that 6 months of 5-FU/LV was as effective as 12 months of 5-FU/levamisole and that levamisole conferred no benefit over 5-FU/LV.[9, 10] The Oncology Multidisciplinary Research Group (GERCOR) C96.1 study found no improvement with 9 months of 5-FU/LV as compared with 6 months.[11] Although these trials established the 6-month duration that is commonly used in adjuvant trials, toxicities of bolus 5-FU remained significant. Subsequent dose and schedule modifications to 5-FU/LV, such as the de Gramont regimen (LV at 200 mg/m^2 as a 2-hour infusion, followed by bolus 5-FU at 400 mg/m^2, and then a 22-hour infusion of 5-FU at 600 mg/m^2, every 2 weeks), improved tolerance.

The oral fluoropyridine capecitabine was evaluated in the European/Canadian X-ACT trial (Xeloda in Adjuvant

Table 1. Relevant AJCC 2017 T and N Definitions in Stage III Colon Cancer

Primary tumor (T)			
T category	**T criteria**		
T1	Tumor invades the submucosa		
T2	Tumor invades the muscularis propria		
T3	Tumor invades into pericolorectal tissues		
T4	Tumor invades the visceral peritoneum or invades or adheres to an adjacent organ or structure		
T4a	Tumor invades through the visceral peritoneum		
T4b	Tumor directly invades or adheres to adjacent organs or structures		
Regional lymph nodes (N)			
N category	**N criteria**		
N1a	One regional lymph node is positive		
N1b	Two or 3 regional lymph nodes are positive		
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, nonperitonealized pericolic, or perirectal/mesorectal tissues		
N2	Four or more regional lymph nodes are positive		
N2a	Four to 6 regional lymph nodes are positive		
N2b	Seven or more regional lymph nodes are positive		
Prognostic stage groups			
T category	**N category**	**TNM Stage**	**5-Year Relative Survival Rates[7]**
T1-T2	N1/N1c	IIIA	70%-90%
T1	N2a	IIIA	
T3-T4a	N1/N1c	IIIB	45%-70%
T2-T3	N2a	IIIB	
T1-T2	N2b	IIIB	
T4a	N2a	IIIC	15%-40%
T3-T4a	N2b	IIIC	
T4b	N1-N2	IIIC	
Based in part on the AJCC cancer staging manual.[36]			

AJCC, American Joint Committee on Cancer; TNM, primary tumor (T), regional lymph nodes (N), distant metastasis (M).

Table 2. Seminal Phase 3 Trials of Oxaliplatin-Based Adjuvant Therapy for Resected Colon Cancer and Associated Neurotoxicity

Trial	Oxaliplatin Arm	5-Year DFS[a]	DFS HR (95% CI)	OS	OS HR (95% CI)	Median Oxaliplatin Dose Per Protocol	Median Oxaliplatin Dose Received	Any-Grade CIPN/ G3	Chronic CIPN
MOSAIC[3,14]	FOLFOX4	73.3%	0.80 (0.68-0.93)	72.9%	0.80 (0.65-0.97)	1020 mg/m^2	810 mg/m^2	92%/13%	At 48 months, G1=12%, G2=3%, G3=0.7%
	5-FU/LV	67.4%		68.7%					
NSABP C-07[15,37]	FLOX	69.4%	0.82 (0.72-0.93)	80.2%[a]	0.88 (0.75-1.02)[b]	765 mg/m^2	667 mg/m^2	Not reported/ 8.2%	At 27.2 months, 10% with persistent CIPN[c]
	5-FU/LV	64.2%		78.4%					
NO16968[5,16]	CAPOX	63%	0.80 (0.69-0.93)	73%	0.83 (0.7-0.91)	1040 mg/m^2	873 mg/m^2	78%/11%	At end of treatment, 68% any-grade CIPN, 5% G3/4 CIPN
	Capecitabine	56%		67%					

5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CIPN, chemotherapy-induced peripheral neuropathy; DFS, disease-free survival; FLOX, Roswell Park regimen plus oxaliplatin 85 mg/m^2 on weeks 1, 3, and 5 of each 8-week cycle; G, grade; HR, hazard ratio; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; LV, leucovorin; OS, overall survival.

[a]7-year DFS and OS for NO16968.

[b]Not statistically significant.

[c]Common Terminology Criteria for Adverse Events (CTCAE) grading not reported.

Colon Cancer Therapy), in which 1987 patients with resected stage III colon cancer were randomly assigned to capecitabine (1250 mg/m^2 twice daily for 14 days of every 21-day cycle) or bolus 5-FU/LV given as the Mayo regimen (5-FU at 425 mg/m^2 and LV at 20 mg/m^2 daily on days 1-5, once per month).[12] The primary endpoint of noninferiority in 3-year DFS was confirmed (64% vs 61%; *P*=.05) and led to US Food and Drug Administration (FDA) approval of capecitabine for adjuvant colon cancer.

Oxaliplatin

The benefit of oxaliplatin in addition to 5-FU/LV was initially observed in first-line metastatic colorectal cancer.[13] This prompted the undertaking of 3 large adjuvant RCTs comparing 5-FU/LV plus oxaliplatin vs 5-FU/LV alone: MOSAIC (Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer),[3,14] the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial,[4,15] and the NO16968 study (A Study of Xeloda Plus Oxaliplatin in Patients With Colon Cancer).[5,16]

The key oncologic findings, median number of planned and received oxaliplatin doses per protocol, and chemotherapy-induced peripheral neuropathy rates are detailed in Table 2. These 3 large trials consistently show a relative improvement of approximately 18% to 20% in DFS and approximately 12% to 20% in OS with the addition of oxaliplatin to fluoropyrimidine therapy. In 2004, based largely upon the initial publication of MOSAIC, oxaliplatin received FDA approval in combination with 5-FU/LV for adjuvant therapy of resected stage III colon cancer.

The IDEA Collaboration

Rationale for IDEA

The overarching purpose of the IDEA collaboration was to prospectively pool data from 6 concurrent phase 3 trials comparing 3 vs 6 months of adjuvant FOLFOX or

CAPOX to evaluate whether a shorter duration of therapy could maintain efficacy (ie, confirm noninferiority) while reducing neurotoxicity. The initial suggestion that a duration of less than 6 months might not negatively impact outcomes was observed in an adjuvant trial comparing 3 months of protracted venous infusion 5-FU with 6 months of bolus 5-FU/LV.[17] No statistically significant differences in 5-year relapse-free survival (73.3% vs 66.7%; hazard ratio [HR], 0.8; 95% CI, 0.62-1.04; *P*=.10) or OS (75.7% vs 71.5%; HR, 0.79; 95% CI, 0.61-1.03; *P*=.08) were found. This was the first trial to suggest that decreasing the duration of adjuvant therapy to less than 6 months might not negatively affect outcomes, while reducing toxicities. Additionally, despite differences in the per-protocol median oxaliplatin dosing in MOSAIC and NSABP C-07 (1020 vs 765 mg/m^2), the median oxaliplatin dose received was relatively similar (810 vs 667 mg/m^2), and the studies found comparable relative reductions in DFS (HR, 0.80-0.82). Similar findings were observed when considering the median oxaliplatin dose received in NO16968 (Table 2). These data, along with real-world data suggesting that nearly one-third of patients do not receive more than 3 months of therapy, provided the background to test whether 3 months of adjuvant therapy might be noninferior to 6 months while reducing toxicity, cost, and inconvenience.[18]

Trial Design

To adequately test the hypothesis that 3 months of adjuvant therapy with an oxaliplatin-based chemotherapy regimen is noninferior to 6 months in stage III colon cancer, the researchers determined that at least 10,500 patients would be needed. Based on prior logistical issues surrounding conducting a single, global trial, the IDEA collaborators decided that 6 individual but concurrent international trials—all of which shared specific requirements—would allow for a pooled analysis with adequate power. Although each trial could have additional hypotheses and secondary endpoints, the main requirements were the same in all trials. First, all patients had to have stage III colon cancer (although 2 of the trials also included patients with stage II colon cancer). Second, patients were randomly assigned to a control group consisting of 6 months of FOLFOX4 (oxaliplatin plus the de Gramont regimen of 5-FU/LV), modified FOLFOX6 (mFOLFOX; 12 treatments every 2 weeks), or CAPOX (8 treatments every 3 weeks); or an experimental group consisting of 3 months of FOLFOX4 or mFOLFOX6 (6 treatments every 2 weeks) or 3 months of CAPOX (4 treatments every 3 weeks). Third, the primary endpoint was 3-year DFS. Finally, the leaders of each trial agreed to provide its data to the pooled analysis. The characteristics of the 6 trials included in IDEA are presented in Table 3.

Three-year DFS was chosen as the primary efficacy endpoint based largely on findings from an analysis by the Adjuvant Colon Cancer End Points (ACCENT) group, which evaluated 20,898 patients from 18 RCTs and found that DFS was an acceptable surrogate for 5-year OS and would allow for more prompt results from adjuvant clinical trials.[19] A noninferiority trial design was undertaken given that there was no expectation of superiority of reduced-duration therapy. The initial noninferiority margin, with an HR of 1.10, was based primarily on DFS rates observed in MOSAIC and NSABP C-07. However, owing to a lower number of events than expected (the number of disease-free events was adjusted from 4700 to 3400), the IDEA committee amended the target noninferiority margin in 2013 so that the upper boundary of a 2-sided 95% CI of the HR could not exceed 1.12.[6] This noninferiority margin of HR equaling 1.12 would be equivalent to an absolute difference in 3-year DFS of 2.7% (from 72% to 69.3%).

IDEA Results

The primary and major subgroup analyses from the pooled IDEA analysis are detailed in Figures 1 to 3. Of the 12,834 patients randomly assigned to 3 vs 6 months of chemotherapy, 60% received FOLFOX and 40% received CAPOX according to physician's choice. After a median duration of 41.8 months, the trial failed to observe noninferiority despite the absolute difference in 3-year DFS for 3 vs 6 months being only 0.9% (74.6% vs 75.5%; HR, 1.07; 95% CI, 1.00-1.15; *P*=.11 for noninferiority of 3 months). However, a significant 30% absolute reduction in grade 2 or higher chemotherapy-induced peripheral neuropathy occurred with the shorter duration of therapy.

In the preplanned subgroup analysis of 3-year DFS by chemotherapy regimen, noninferiority of 3 months was observed for CAPOX but not for FOLFOX. Of the patients who received CAPOX, 3 months was found to be noninferior to 6 months (75.9% vs 74.8%; HR, 0.95; 95% CI, 0.85-1.06). However, for patients receiving FOLFOX, 6 months was found to be superior to 3 months by 2.4% (73.6% for 3 months vs 76% for 6 months; HR, 1.16; 95% CI, 1.06-1.26; *P*=.001).

IDEA Results by Low-Risk and High-Risk Groups

In an exploratory analysis, the investigators compared outcomes in patients with low-risk tumors, defined as T1-T3 and N1, vs high-risk tumors, defined as T4, N2, or both. These tumors account for approximately 60% and 40% of the population, respectively. Among patients with low-risk tumors (Figure 2), noninferiority of 3 months was established, with only a 0.2% absolute difference in 3-year DFS (83.1% vs 83.3%; HR, 1.01; 95% CI, 0.90-1.12). However, there was a modest 1.7% absolute difference in

Table 3. Characteristics of the 6 Randomized Trials Included in the IDEA Pooled Analysis

Trial	Participating Country	Years of Accrual	Included in IDEA/Total Number	Risk Groups (%)	Chemotherapy Regimens (%)	Additional Trial Comparisons
SCOT[20]	United Kingdom, Denmark, Spain, Australia, Sweden, New Zealand	2008-2013	3983/6088	T1-T3/N1 (51)	CAPOX (67)	None
				T4, N2, or both (49)	mFOLFOX6 (33)	
TOSCA[22]	Italy	2007-2013	2402/3759	T1-T3/N1 (65)	CAPOX (35)	FOLFOX4 + bevacizumab vs FOLFOX4
				T4, N2, or both (35)	FOLFOX4 (65)	
CALGB 80702[24]	United States, Canada	2010-2015	2440/2500	T1-T3/N1 (64)	mFOLFOX6 (100)	Celecoxib for 3 years vs placebo
				T4, N2, or both (36)		
IDEA France[23]	France	2009-2014	2010/2022	T1-T3/N1 (62)	CAPOX (10)	None
				T4, N2, or both (38)	mFOLFOX6 (90)	
HORG[24]	Greece	2009-2015	708/708	T1-T3/N1 (59)	CAPOX (58)	None
				T4, N2, or both (41)	FOLFOX4 (42)	
ACHIEVE[24]	Japan	2012-2014	1291/1313	T1-T3/N1 (56)	CAPOX (75)	None
				T4, N2, or both (44)	mFOLFOX6 (25)	

CAPOX, capecitabine and oxaliplatin; FOLFOX4, leucovorin, 5-fluorouracil, and oxaliplatin; IDEA, International Duration Evaluation of Adjuvant Chemotherapy; mFOLFOX6, modified FOLFOX regimen in which the day 1 bolus 5-fluorouracil is given with a 46-hour infusion of 5-fluorouracil over days 1-2; N, regional lymph node stage; OS, overall survival; T, primary tumor stage.

3-year DFS in high-risk patients (Figure 3), supporting superiority of 6 months over 3 months in this population (62.7% vs 64.4%; HR, 1.12; 95% CI, 1.03-1.23; *P*=.01 for superiority of 6 months). Although no statistically significant interaction according to risk group was identified (*P*=.11), it appears that among the high-risk group, those with T4 appeared to have a differential effect greater than N2 patients with 6 months of adjuvant treatment (3-year DFS with 3 vs 6 months: 58.1% vs 61.4% for T4; HR, 1.16; and 61.6% vs 61.8% for N2; HR, 1.07).

Compliance and Toxicity in IDEA

As expected, some notable differences in adherence and toxicity existed between 3 and 6 months of FOLFOX and CAPOX. Although the majority (84%-89%) completed the 3-month course for either treatment regimen, fewer patients completed 6 months of CAPOX compared with FOLFOX (64% vs 70%).

No deaths owing to chemotherapy-induced toxicities were reported. Chemotherapy-induced peripheral neuropathy findings are noted in Figure 1. The rates of chemotherapy-induced peripheral neuropathy at grade 2 (moderate symptoms—limiting instrumental activities of daily living) or higher were considerably lower with 3 vs 6 months of therapy (FOLFOX: 17% vs 48% and CAPOX: 14% vs 45%). A specific analysis of grade 3 chemotherapy-induced peripheral neuropathy (severe symptoms—limiting self-care activity of daily living) showed that these rates were notable as well (FOLFOX: 3% vs 16% and CAPOX: 3% vs 9%). Extensive quality-of-life analyses comparing 3 vs 6 months have thus far been reported from the SCOT trial (Short Course Oncology Treatment), including results from a neurotoxicity-specific questionnaire (FACT/GOG-Ntx4; Functional Assessment of Cancer Treatment Gynecologic Oncology Group - Neurotoxicity).[20] Of 2871 patients completing this questionnaire, the observed peak of neuropathic symptoms occurred at 6 months in the 3-month group and 9 months in the 6-month group, which is consistent with a prior detailed analysis of oxaliplatin-induced CIPN.[21]

Heterogeneity Within IDEA

As detailed in Table 3, there was heterogeneity among the 6 participating trials within the IDEA collaboration. An important distinction among the trials was the variable

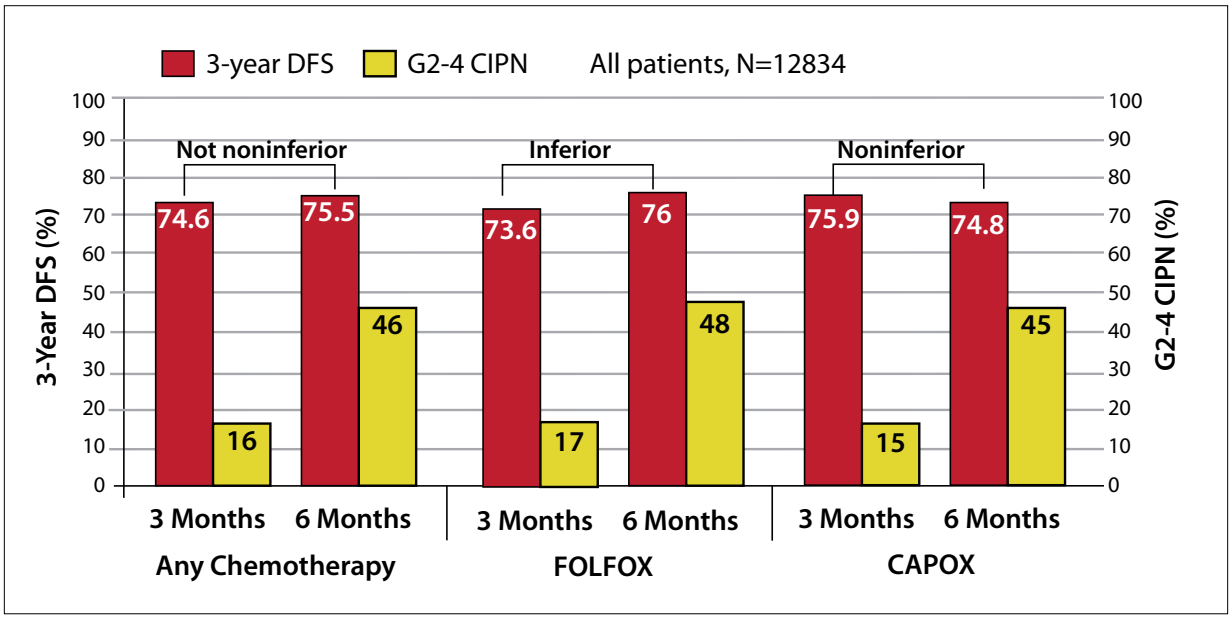

Figure 1. Three-year disease-free survival and chemotherapy-induced peripheral neuropathy by chemotherapy type for all patients. Statistical significance for noninferiority noted as *noninferior, inferior,* or *not proven.*

CAPOX, capecitabine and oxaliplatin; CIPN, chemotherapy-induced peripheral neuropathy; DFS, disease-free survival; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; G, grade.

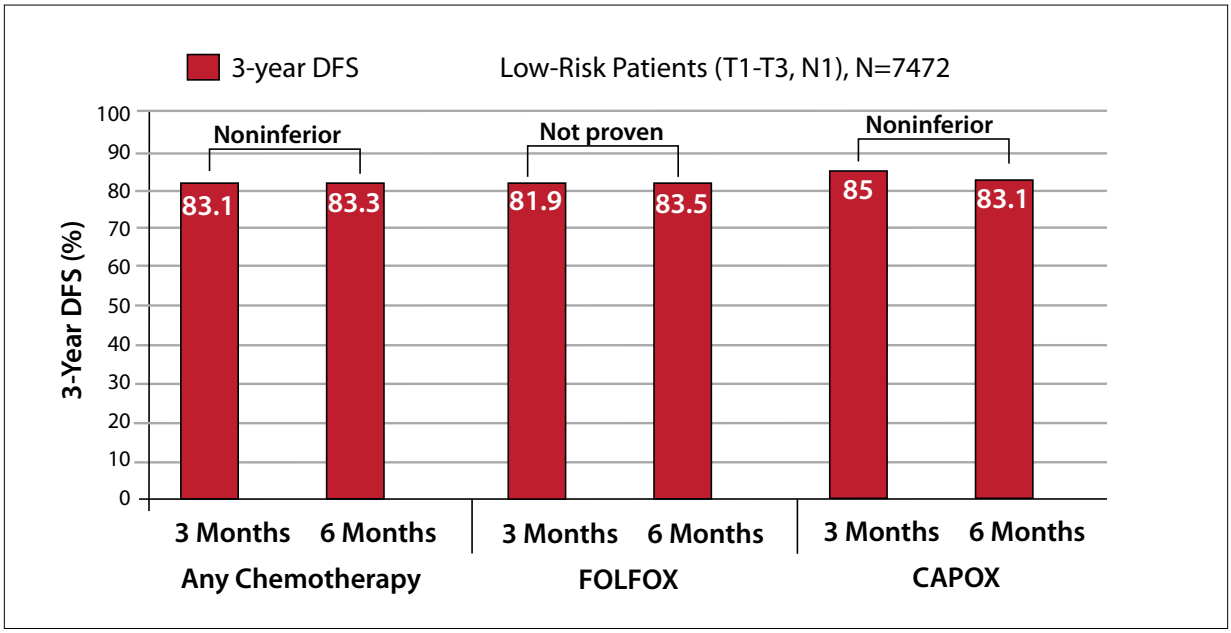

Figure 2. Three-year disease-free survival by chemotherapy type for low-risk patients. Statistical significance noted as *noninferior, inferior,* or *not proven.*

CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin.

use of CAPOX compared with FOLFOX, which was dictated by the discretion of the treating physician and nonrandomized. For example, the largest trial, SCOT, had the greatest use of CAPOX (67%),[17] whereas in TOSCA (Three Of Six Colon Adjuvant)[18] and IDEA France,[19] CAPOX was given to only 35% and 10% of patients, respectively. In contrast, the Cancer and Leukemia Group B (CALGB) 80702 trial, which enrolled a

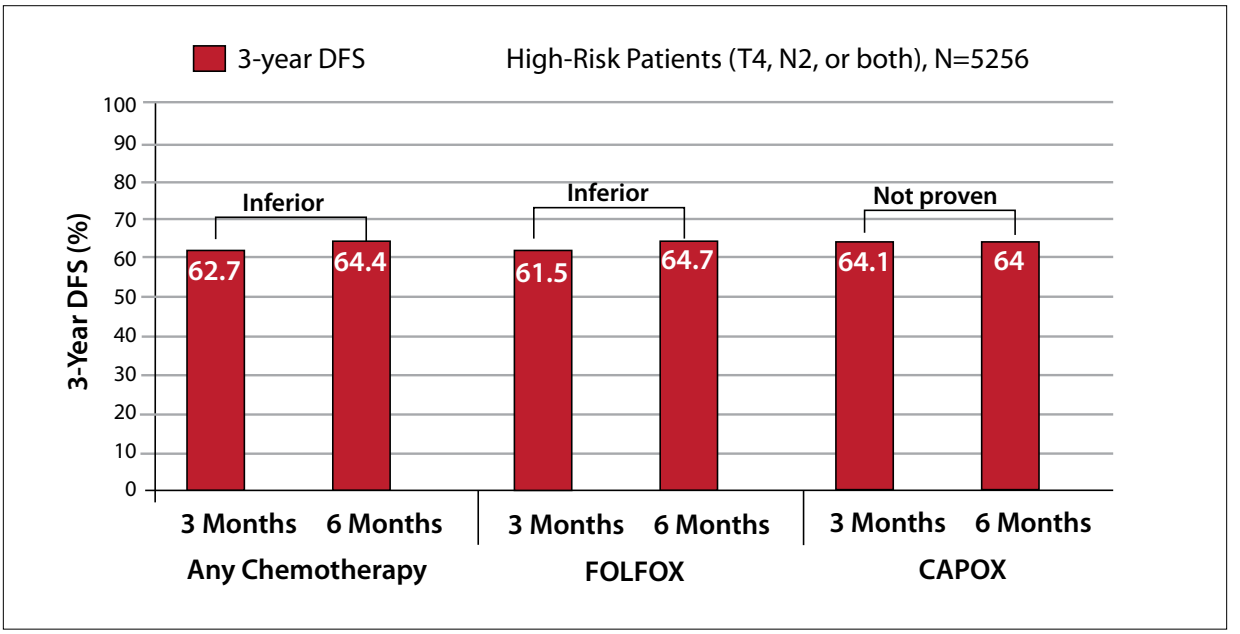

Figure 3. Three-year disease-free survival by chemotherapy type for high-risk patients. Statistical significance for noninferiority noted as *noninferior, inferior*, or *not proven*.

CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin.

US population, only utilized FOLFOX. These treatment decisions certainly increase the potential for selection bias when considering the exploratory findings of efficacy by chemotherapy regimen. Some trials also included high-risk stage II colon cancer (SCOT and TOSCA) as well as rectal cancer (SCOT), but these cohorts were not included in the IDEA analysis.

Although some important differences existed in the designs and populations within these trials, the IDEA collaborators attempted to limit bias by confirming certain aspects that were consistent within all the included trials: inclusion of patients with stage III colon cancer, randomization to either 3 or 6 months of FOLFOX or CAPOX, 3-year DFS as the primary endpoint, and an a priori agreement to be included in the final IDEA analysis. Thus far, SCOT,[20] TOSCA,[22] and IDEA France[23] have been published and provide insight into the individual trial findings and detailed subgroup analyses. These trials were underpowered to establish noninferiority for the primary endpoint of 3-year DFS, however. We await the results of the 3 trials that have yet to be fully published: CALGB 80702, HORG (Hellenic Oncology Research Group), and ACHIEVE (Adjuvant Chemotherapy for Colon Cancer With High Evidence).

National Guidelines

The IDEA investigators suggested a risk-based approach when recommending adjuvant therapy, with 3 months of CAPOX appropriate for low-risk stage III colon cancer patients (T1-T3, N1) and 6 months of CAPOX or FOLFOX for high-risk patients (T4, N2, or both).[24] The most recent National Comprehensive Cancer Network (NCCN) guidelines support a similar risk-based approach. These guidelines recommend 3 months of CAPOX or 3 to 6 months of FOLFOX for low-risk patients (T1-T3, N1), noting a category 1 level of evidence for 6 months of treatment.[25] For high-risk patients, defined similarly by the NCCN, the guidelines recommend CAPOX for 3 to 6 months or FOLFOX for 6 months, noting again category 1 level evidence for 6 months with either regimen.

Unresolved Issues and Ongoing Investigations

Despite the massive efforts undertaken to conduct these 6 international randomized trials included in IDEA, several issues remain unresolved when considering adjuvant chemotherapy for resected stage III colon cancer.

Capecitabine in the US Population

Although the suggestion of a differential effect by chemotherapy regimen (FOLFOX vs CAPOX) is provocative, these exploratory findings were based on nonrandomized physician's choice, and inapparent selection bias might be a confounding variable. It is plausible that the increased intensity of oxaliplatin earlier during adjuvant therapy or the pharmacologic effect of differing fluoropyrimidine

scheduling with CAPOX compared with FOLFOX might account for these findings. Further studies from the IDEA investigators regarding these issues are eagerly awaited.

Of note, the application of these findings to the US population is less clear because the CALGB 80702 cohort, which included all the US patients, allowed only FOLFOX. The capecitabine dosing evaluated in the CAPOX arms was 1000 mg/m^2 twice daily on days 1 to 14 every 21 days, a dose that is lower than the current FDA-approved adjuvant capecitabine monotherapy dosing (1250 mg/m^2), but still higher than what has been observed to be tolerable in most US cohorts (eg, 825 mg/m^2 twice daily, or approximately 1500 mg twice daily).[5,26,27] If CAPOX is used in the United States for adjuvant therapy in low-risk or high-risk stage III patients, we do recommend starting therapy at standard dosing as per the IDEA trial (capecitabine at 1000 mg/m^2 twice daily on days 1 to 14 every 21 days), but with close and frequent toxicity evaluation to intervene early and minimize severe adverse effects.

High-Risk Subgroups

The proposed distinction between low-risk and high-risk stage III colon cancers provides a simple-to-use distinction when considering duration of therapy and has clear clinical validity. However, the heterogeneity within stage III colon cancer is striking. A prognostic distinction appears to exist between T4 and N2 disease, with a high T stage possibly leading to worse prognosis. Further analyses will hopefully detail which patients among these subgroups—including distinguishing between T4a and T4b—might be most likely to benefit from longer-duration adjuvant therapy. Until these data are available, we agree with recommending 6 months of oxaliplatin-based adjuvant therapy for all high-risk patents, especially those with T4N+ disease. The common practice of continuing the fluoropyridine for 6 months despite discontinuing oxaliplatin is a strategy that cannot be directly elucidated by the IDEA analysis. However, for high-risk patients with progressive neuropathy necessitating oxaliplatin discontinuation, it is reasonable to consider completion of 6 months with fluoropyridine monotherapy. The ongoing IROCAS study (Irinotecan and Oxaliplatin for Colon Cancer in Adjuvant Setting; NCT02967289) of modified folinic acid, 5-FU, irinotecan, and oxaliplatin (mFOLFIRINOX) vs mFOLFOX6 in high-risk stage III colon cancer, defined similarly as pT4N1 or pT1-T4N2, is actively recruiting.[28]

Elderly Patients

Not surprising for a clinical trial population, the median age of 64 years in the IDEA analysis was younger than the median age of 69 years at diagnosis for colon cancer (36% of diagnoses occur at age 75 years or older).[29] Detailed analyses by age will be forthcoming from the IDEA studies. Thus far, TOSCA and IDEA France have reported subgroup analyses of patients younger than 70 years vs 70 years or older. In TOSCA, no statistical difference existed between relapse-free survival by the age subgroups, although confidence intervals had wide overlaps with a nonsignificant test of interaction.[22] In IDEA France, both age subgroups appeared to favor 6 months over 3 months.[23] Details on adherence and toxicity by age have not been reported thus far from either trial.

Chemotherapy is not as frequently offered to or received by elderly patients, which is not entirely unexpected given the conflicting results by age between NSABP C-07 and NO16968. This is further confounded by opposing findings from large retrospective analyses as to the benefit of oxaliplatin-based therapy in elderly patents.[30,31] Whether oxaliplatin-related adverse effects are more likely in the elderly is also not fully clarified. A large retrospective analysis found modest increases in neutropenia and nausea and vomiting, but no differences in hospitalizations or early death as compared with fluoropyrimidine alone.[32] For elderly patients who appear physically fit and have normal organ function, we recommend a similar risk-based approach to adjuvant therapy as done in younger patients. However, capecitabine should be used with caution, particularly in those 80 years or older and/or with diminished renal function. A randomized phase 2 trial of capecitabine vs no therapy for stage III colon cancer in 170 elderly (>75 years) patients called ACE (Adjuvant Chemotherapy in Elderly With Colon Cancer Stage III; NCT02978612) is ongoing. Until these data are reported, the relative tolerability of capecitabine in the elderly can be ascertained from a phase 3 trial of elderly patients in the first-line metastatic colorectal cancer setting randomly assigned to capecitabine (dosed at 1000 mg/m^2 on days 1-14 every 21 days) vs capecitabine with bevacizumab. The median age of the 280 patients was 76 years (range, 70-87 years). Grade 3 or worse adverse events were present in 22% of the capecitabine-only group, with the most common grade 3 or worse events being hand-foot syndrome and diarrhea (both 7%).[33]

Surrogate Endpoints

As discussed above, the primary endpoint of 3-year DFS used in the IDEA analysis was based on the ACCENT database examination of more than 20,000 patients in RCTs that was published in 2007. Since that analysis, multiple newer agents in the metastatic setting have significantly improved OS and impacted the time from recurrence to death, referred to as survival after recurrence (SAR). Although additional studies are forthcoming, 2 studies from the ACCENT investigators suggest that

the near doubling of SAR (14.8 months in 1998-2003 vs 26.4 months in 2004-2009) might obviate the previously accepted correlation of 3-year DFS and OS in colon cancer.[34,35] As such, the long-term OS and DFS results of IDEA are eagerly awaited.

Molecular Subtypes

The prognostic heterogeneity within stage III colon cancers does not appear to be isolated to the varied T and N stages. Molecular underpinnings (eg, consensus molecular subtypes, RAS/RAF status, and microsatellite instability status), tumor-sidedness, and histopathologic findings all appear to have prognostic implications. Future and ongoing studies will elucidate the predictive nature of these variables, with the goal of allowing a more personalized approach to adjuvant therapy for resected stage III colon cancer.

Conclusions

Owing to the important and significant efforts from the IDEA collaborators, we now have strong evidence, based on nearly 13,000 patients, for the relative and absolute benefits of 6 vs 3 months of oxaliplatin-based therapy. In the overall cohort, despite the failure to confirm noninferiority of 3 months to 6 months, the absolute improvement of 0.9% in 3-year DFS between 6 vs 3 months is of questionable clinical significance, particularly considering the 30% absolute increase in grade 2 or higher symptomatic neuropathy seen with 6 months of therapy. The varied 3-year DFS rates between the low-risk and high-risk subgroups, as well as the FOLFOX and CAPOX subgroups, appear to be most clinically relevant to help guide clinicians when discussing adjuvant therapy (Figures 1-3). Given the clear increase in neurotoxicity with extended duration oxaliplatin, it is imperative that patient preferences be carefully considered when discussing adjuvant therapy.

Disclosures

None of the authors have any conflicts of interest to disclose.

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payments to companies; they are less concerned about the benefit of the treatment. If a drug meets a threshold for benefit, Australia then cuts a creative deal with the manufacturer. For example, price-volume arrangements can provide good access.

H&O Do you foresee a way to standardize value assessment across institutions and/or nationwide?

PB It would be possible to use a value framework like the one from ICER (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework). The barriers are not technical; they are political.

Disclosure

Dr Bach reports grants from Kaiser Permanente, the Laura and John Arnold Foundation, and an NIH Core Grant P30 CA 008748 received during the conduct of a study. He has received personal fees from the American Society of Health-System Pharmacists, Gilead Sciences, WebMD, Goldman Sachs, Defined Health, Vizient, Anthem, Excellus Health Plan, Hematology/Oncology Pharmacy Association, Novartis Pharmaceuticals, Janssen Pharmaceuticals, Third Rock Ventures, JMP Securities, Genentech, Mercer, and United Rheumatology. He has received consulting fees from Foundation Medicine and Grail, outside the submitted work.

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