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ORIGINAL REPORT

Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial

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ABSTRACT

Purpose
Three-year disease-free survival (DFS) was significantly improved in patients who had undergone resection with curative intent for stage II or III colon cancer who received bolus plus continuous-infusion fluorouracil plus leucovorin (LV5FU2) with the addition of oxaliplatin (FOLFOX4). Final results of the study, including 6-year overall survival (OS) and 5-year updated DFS, are reported.

Patients and Methods
A total of 2,246 patients were randomly assigned to receive LV5FU2 or FOLFOX4 for 6 months. The primary end point was DFS. Secondary end points were OS and safety.

Results
Five-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups, respectively (hazard ratio [HR] = 0.80; 95% CI, 0.68 to 0.93; $P = .003$). Six-year OS rates were 78.5% and 76.0% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.84; 95% CI, 0.71 to 1.00; $P = .046$); corresponding 6-year OS rates for patients with stage III disease were 72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97; $P = .023$). No difference in OS was seen in the stage II population. The incidence of second noncolorectal cancers was 5.5% and 6.1% in the FOLFOX4 and LV5FU2 groups, respectively. Among patients receiving oxaliplatin, the frequency of grade 3 peripheral sensory neuropathy was 1.3% 12 months after treatment and 0.7% at 48 months.

Conclusion
Adding oxaliplatin to LV5FU2 significantly improved 5-year DFS and 6-year OS in the adjuvant treatment of stage II or III colon cancer and should be considered after surgery for patients with stage III disease.

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer death in Western countries.[1] Worldwide, colon and rectum cancers accounted for approximately 1 million new cancer cases in 2002. The number of annual colorectal cancer deaths is approximately half the annual incidence.[2]

The benefits of fluorouracil (FU)–based adjuvant chemotherapy in reducing recurrence and prolonging survival are well established, especially for stage III but not for stage II disease. The Intergroup Trial INT-0035 was the first large-scale study to demonstrate a significant reduction (33%) in the risk of death with adjuvant FU plus levamisole in patients with stage III colon cancer.[3] Subsequently, the FU plus leucovorin combination (FL) became the standard of care in this patient setting.[4-6] In metastatic colorectal cancer (stage IV), regimens combining oxaliplatin with FL have shown improved efficacy (in terms of response rate and progression-free survival) compared with FL alone[7-8] and FL plus irinotecan.[9]

To determine whether the improved efficacy observed with oxaliplatin in the metastatic setting translates into benefits in earlier stage disease, we conducted a large international phase III clinical trial in stage II or III colon cancer (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer [MOSAIC]). In this phase III study of 2,246 patients who had undergone resection with a curative intent for either stage II or III colon cancer, bolus plus continuous-infusion FU plus leucovorin (LV5FU2) plus oxaliplatin (FOLFOX4) improved 3-year disease-free survival (DFS) compared with

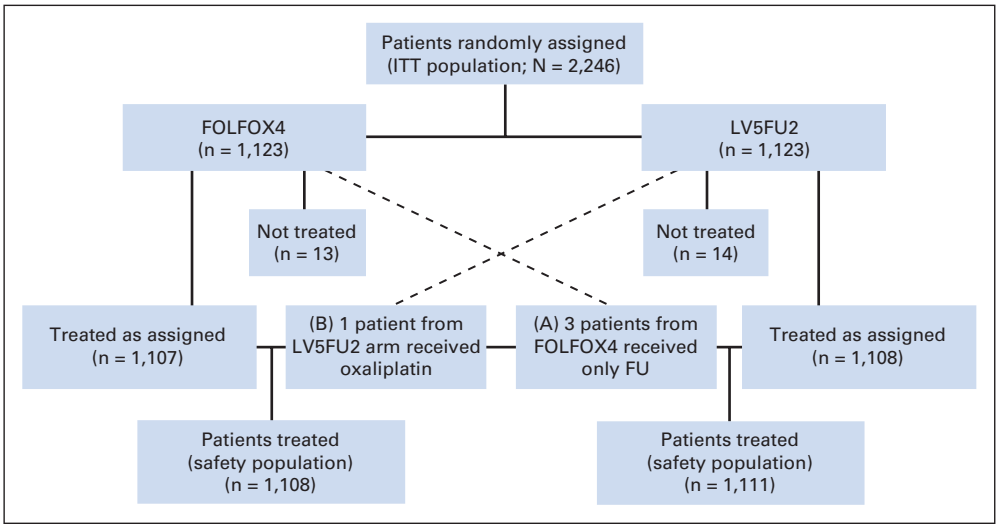

Fig 1. CONSORT diagram of patient flow. (A) Three patients were randomly assigned to the bolus plus continuous-infusion fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) arm but did not receive oxaliplatin. Therefore, these patients were considered in the FOLFOX4 arm for intent-to-treat (ITT) efficacy analysis and in the bolus plus continuous-infusion fluorouracil plus leucovorin (LV5FU2) arm for safety analysis. (B) One patient was randomly assigned to the LV5FU2 arm but received oxaliplatin. Therefore, this patient was considered in the LV5FU2 arm for ITT efficacy analysis and in the FOLFOX4 arm for safety analysis. FU, fluorouracil.

LV5FU2 alone (FOLFOX4 = 78.2%; LV5FU2 = 72.9%; hazard ratio [HR] = 0.77; 95% CI, 0.65 to 0.91; $P = .002$).[10] Overall survival (OS) data were immature at that time. We report here the results for OS at 6 years together with the final 5-year DFS results.

PATIENTS AND METHODS

Patients and Treatment

Eligible patients were 18 to 75 years of age and had undergone complete resection of histologically proven stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) colon cancer. Stage II patients classified as high risk for the purposes of an exploratory analysis had at least one of the following: T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or less than 10 lymph nodes examined. Prior chemotherapy, immunotherapy, or radiotherapy was not permitted, and study treatment had to be started within 7 weeks of surgery. All patients provided written informed consent, and the study was approved by the ethics committees of the participating centers.

In this open-label study, patients were randomly assigned to receive 12 cycles of LV5FU2[11] or FOLFOX4.[12] Dose modifications were performed according to predefined guidelines based on toxicities, as previously described.[10] Oxaliplatin was discontinued if there was persistent paresthesia or functional impairment.

Follow-Up

Patients were evaluated before random assignment, every 2 weeks during treatment (12 cycles in total), and then every 6 months up to 5 years after completion of study. In line with a postmarketing commitment related to the US Food and Drug Administration approval letter for oxaliplatin (November 2004), follow-up for OS was extended to 6 years after completion of study treatment. Assessments were made for relapse, second cancers, late toxicity, and death. The cutoff dates for final analyses were June 1, 2006 for DFS and January 16, 2007 for OS. Adverse events were graded according to National Cancer Institute's Common Toxicity Criteria, version 1.

Statistical Analysis

Random assignment was performed centrally; the minimization method was used to balance treatment allocation according to TNM stage (T2 or T3 *v* T4 and N0 *v* N1 *v* N2), the presence or absence of bowel obstruction or tumor perforation, and the medical center. The original planned sample size was 1,500 patients. After a protocol amendment (June 2000), this was increased to 2,200 patients, which provided a power of more than 90% to detect a difference in DFS (with a two-sided $\alpha = .05$ derived with the use of the log-rank test),[10] assuming 3-year DFS rates of 73% in the control group and 79% in the group receiving FOLFOX4, a ratio of stage II to stage III disease of 2:3, an enrollment period and follow-up period of 3 years, and a decrease in the risk of relapse after 3 years.

The primary efficacy variable was DFS, which was defined as the time from random assignment to relapse or death, whichever occurred first. The duration of follow-up was defined as the number of months from random

Table 1. Patient Demographics and Baseline Characteristics (intent-to-treat population)

Patient Demographics and Clinical Characteristics	% of Patients	
	Arm A: FOLFOX4 (n = 1,123)	Arm B: LV5FU2 (n = 1,123)
Median age, years	61.0	60.0
Age category, years		
< 65	64.4	66.2
≥ 65	35.6	33.8
Sex		
Male	56.1	52.4
Female	43.9	47.6
Disease stage		
Stage II	40.2	39.9
Stage III	59.8	60.1
Depth of invasion		
T2	4.5	4.8
T3	76	75.9
T4	19	18.5
No. of nodes involved, for stage III		
1-4 positive nodes	44.4	45.7
> 4 positive nodes	15.1	15.2
Perforation present	6.9	6.9
Bowel obstruction present	17.9	19.3
Histology		
Differentiated	83.2	81.4
Poorly differentiated	12.6	13.2
Unknown	4.2	5.4

Abbreviations: FOLFOX4, bolus plus continuous-infusion fluorouracil plus leucovorin plus oxaliplatin; LV5FU2, bolus plus continuous-infusion fluorouracil plus leucovorin.

assignment until the last follow-up visit or data cutoff. Second colorectal cancers were considered relapses, whereas noncolorectal tumors were disregarded in the analyses. OS was measured from the time of random assignment until death from any cause.

Comparisons of DFS and OS between groups according to the intent-to-treat (ITT) principle were performed using a two-sided stratified log-rank test based on the primary tumor site. Analyses adjusted by disease stage were performed using Cox regression modeling. HRs with 95% CIs were calculated using the Cox proportional hazards model. Survival curves were presented according to Kaplan-Meier methods. Subgroups used to identify prognostic factors for survival within the stage III population included age ($< v \geq 65$ years), sex, T stage (T1, T2, or T3 *v* T4), baseline carcinoembryonic antigen ($< v \geq 5$ ng/mL), nodal stage (one to three *v* four or more nodes), perforation (yes *v* no), occlusion (yes *v* no), venous invasion (yes *v* no), and differentiation (poor *v* well or moderate).

The final DFS analysis was performed as per the initial protocol when the last patient included had 5 years of follow-up. The final OS analysis was performed when the last patient included had 6 years of follow-up, as

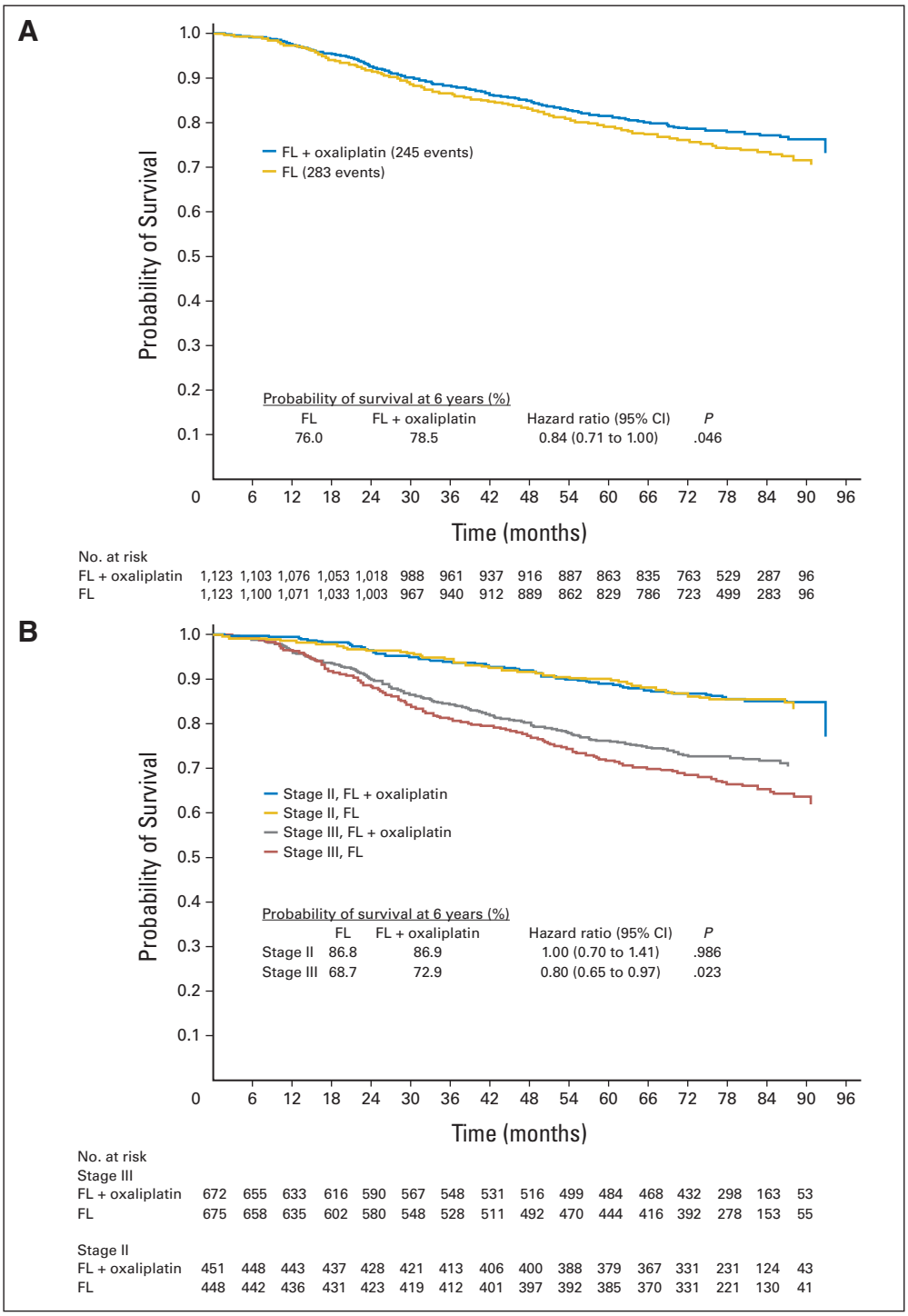

Fig 2. Kaplan-Meier estimates of overall survival (A) by treatment arm and (B) by treatment arm and by stage (intent-to-treat population). FL, fluorouracil and leucovorin.

requested by the US Food and Drug Administration. The cutoff dates for this analysis were June 1, 2006 for DFS and January 16, 2007 for OS. Safety was analyzed in all patients who received at least one dose of protocol-specified treatment (safety population).

RESULTS

Patients and Treatment

Between October 27, 1998 and January 16, 2001, 2,246 patients were enrolled, 1,123 in each treatment arm (ITT population; Fig 1). Patient characteristics were well matched between the two treatment groups (Table 1).[10] In both groups, 60% and 40% of patients had stage III and stage II disease, respectively. At least one cycle of study treatment was received by 1,111 patients in the LV5FU2 group and 1,108 patients in the FOLFOX4 group. The planned 12 cycles of chemotherapy were received by 74.7% and 86.5% of patients in the groups administered FOLFOX4 and LV5FU2, respectively. The median oxaliplatin dose received per patient in the FOLFOX4 group was 810 mg/m^2 (compared with the per-protocol 12-cycle dose of 1,020 mg/m^2). Chemotherapy after relapse was received by 73.6% of patients in the FOLFOX4 treatment arm and 77.2% of patients in the LV5FU2 arm.

OS in all Patients (ITT Population)

After a median follow-up time of 81.9 months, the probabilities of surviving at 6 years were 78.5% and 76.0% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.84; 95% CI, 0.71 to 1.00; $P = .046$; Fig 2A), corresponding to a 16% reduction in the risk of death in favor of FOLFOX4. Because the disease stage was the main prognostic factor for OS (HR = 1.85; 95% CI, 1.47 to 2.34; $P < .0001$), additional independent OS analyses were performed for patients with stage II and stage III tumors. However, the interaction between stage of disease and treatment was not statistically significant (DFS, $P = .703$; OS, $P = .275$). Overall, there were 245 deaths (21.8%) in the FOLFOX4 group and 283 deaths (25.2%) in the LV5FU2 group. The vast majority of deaths were a result of relapse or recurrence (180 of 245 and 234 of 283 deaths), with six deaths in each group being a result of adverse events. The median time from relapse to death was 21 months for the FOLFOX4 group and 24 months for the LV5FU2 group.

OS in Stage III and Stage II

Among patients with stage III disease (n = 672 and n = 675 in the FOLFOX4 and LV5FU2 groups, respectively), the probabilities of surviving at 6 years were 72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97; $P = .023$), corresponding to a 20% reduction in the risk of death in favor of FOLFOX4 (Fig 2B). Among patients with stage II disease (n = 451 and n = 448 in the FOLFOX4 and LV5FU2 groups, respectively), the probabilities of surviving at 6 years were 86.9% and 86.8%, respectively (HR = 1.00; 95% CI, 0.70 to 1.41; $P = .986$; Fig 2B). In an exploratory analysis, the probabilities of OS at 6 years in high-risk stage II patients were 85.0% and 83.3% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.91; 95% CI, 0.61 to 1.36; $P = .648$).

Subgroup analyses were performed to identify prognostic factors for OS within the stage III population (Fig 3). Calculation of HRs and 95% CIs showed that the potential benefit from oxaliplatin-based chemotherapy could not be excluded in any subgroup defined on the basis of prognostic factors at baseline, whereas a significant benefit from oxaliplatin was confirmed in several subgroups. In a multivariate analysis, the following factors remained statistically significant prognostic factors in the model: age, lymph node involvement, T stage, tumor obstruction, and differentiation. The treatment effects regarding these factors were consistent because none of the factor by treatment interactions was statistically significant. Prognosis analysis (univariate and multivariate analyses) for the whole population and for stage III and stage II patients will be submitted in another publication.

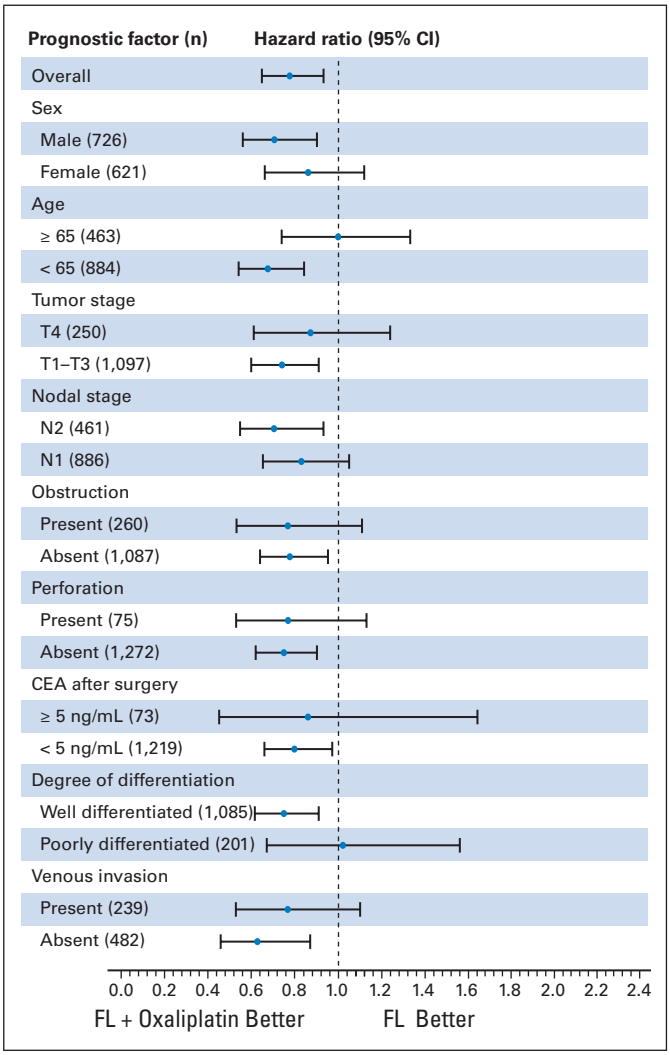

Fig 3. Hazard ratios and 95% CIs for death in stage III patients administered oxaliplatin plus fluorouracil and leucovorin compared with stage III patients administered fluorouracil and leucovorin (FL) according to baseline prognostic factors (intent-to-treat population). Analyses were conducted using Cox regression modeling. CEA, carcinoembryonic antigen.

DFS in All Patients (ITT Population)

After a median follow-up time of 73.5 months in the FOLFOX group and 73.4 months in the LV5FU2 group, the number of patients who had an event was 304 (27.1%) in the FOLFOX4 group and 360

(32.1%) in the LV5FU2 group (Table 2); the corresponding probabilities of survival without disease at 5 years were 73.3% and 67.4%, respectively. The HR for DFS was 0.80 (95% CI, 0.68 to 0.93; $P = .003$), corresponding to a 20% reduction in the risk of relapse in favor of FOLFOX4 (Table 2; Fig 4A).

Five-Year DFS in Stage III and Stage II

Among patients with stage III disease, the probabilities of DFS events at 5 years were 66.4% and 58.9% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.78; 95% CI, 0.65 to 0.93; $P = .005$; Fig 4B). Among stage II patients, the probabilities of DFS events at 5 years were 83.7% and 79.9% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.84; 95% CI, 0.62 to 1.14; $P = .258$; Fig 4B). In an exploratory analysis, the probabilities of DFS at 5 years in high-risk stage II patients were 82.3% and 74.6% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.72; 95% CI, 0.50 to 1.02).

Safety

The safety analysis, as originally reported for patients on treatment, included all patients who received at least one cycle of treatment.[10] Grade 3 peripheral sensory neuropathy (PSN) during treatment was reported in 138 patients (12.5%) in the FOLFOX4 group and 0.2% of the patients in the LV5FU2 group. The frequency of PSN among patients in the FOLFOX4 group declined during the follow-up period (Fig 5). Among 976 patients who were assessed for PSN 18 months after the end of treatment, 235 (24.1%) had symptoms of any grade, with seven patients (0.7%) reporting grade 3 symptoms. At 48 months, grade 1, 2, and 3 PSN was observed in 11.9%, 2.8%, and 0.7% of the patients examined, respectively.

Second Cancers

Second cancers were reported in 5.5% of patients in the FOLFOX4 group (n = 62: breast, n = 9; other gynecologic, n = 4; urologic, n = 18; cutaneous, n = 9; lung and pleura, n = 7; digestive tract other than colorectal, n = 6; hematologic, n = 6 [five lymphomas and one myeloma]; CNS, n = 1; hypopharynx, n = 1; and thyroid, n = 1), and 6.1% of the patients in the LV5FU2 group (n = 68: breast, n = 17; other gynecologic, n = 2; urologic, n = 20; cutaneous, n = 9; lung and pleura, n = 9; digestive tract other than colorectal, n = 5; hematologic, n = 2 [one acute leukemia and one myelodysplasia]; CNS, n = 1; larynx, n = 2; and fallopian tube, n = 1).

DISCUSSION

On the basis of the 3-year DFS improvement that was previously reported from this trial,[10] adjuvant FOLFOX4 should be considered after surgery for patients with stage II or III colon cancer. This final analysis with extended 5-year DFS and 6-year OS follow-up of patients in the MOSAIC trial showed statistically significant overall relative risk reductions of 20% for recurrence and 16% for death in favor of oxaliplatin, confirming the benefit in 3-year DFS already observed and demonstrating that the DFS benefit translates into an OS benefit.

In the MOSAIC trial, the significant DFS and OS benefits observed with the addition of oxaliplatin to FL in the overall population were driven entirely by the favorable effect in the subgroup of patients with stage III disease. The clinical benefit of FOLFOX4 compared with LV5FU2 in terms of 6-year OS and 5-year DFS reached statistical significance and clinical relevance only among stage III patients. For stage II patients, there was no statistically significant improved 5-year DFS and 6-year OS. Although chemotherapy after surgery is standard for patients with stage III colon cancer, the role of adjuvant therapy for stage II colon cancer remains controversial.[12] A recent publication[13] demonstrated that, for patients with stage II disease, FL improved survival at 5 years by 3.6%. In this study, we found in an exploratory analysis a trend toward improved DFS at 5 years in patients with high-risk stage II disease treated by FOLFOX4 compared with LV5FU2. Future studies will look to identify high-risk stage II disease patients and will evaluate oxaliplatin-based adjuvant chemotherapy in this subgroup of patients.

The traditional end point for clinical trials of adjuvant colon cancer treatment was 5-year OS. The Adjuvant Colon Cancer Endpoints (ACCENT) meta-analysis of adjuvant studies, which was carried out before the approval of oxaliplatin and irinotecan for advanced disease, demonstrated that 3-year DFS was an excellent predictor of 5-year OS results[14] and could be an appropriate primary end point for

Table 2. Events for DFS (median follow-up, 73.4 months) and Overall Survival (median follow-up, 81.9 months) and Patients Alive With Relapse (median follow-up, 73.4 months)

Population	No. of Patients	DFS Events		Deaths		Patients Alive With Relapse	
		No.	%	No.	%	No.	%
Overall population							
FOLFOX4	1,123	304	27.1	245	21.8	67	6.0
LV5FU2	1,123	360	32.1	283	25.2	96	8.5
Stage III							
LV5FU2	675	271	40.1	220	32.6	55	8.1
FOLFOX4	672	226	33.6	182	27.1	47	7.0
Stage II							
FOLFOX4	451	78	17.3	63	14.0	20	4.4
LV5FU2	448	89	19.9	63	14.1	31	6.9

Abbreviations: DFS, disease-free survival; FOLFOX4, bolus plus continuous-infusion fluorouracil plus leucovorin plus oxaliplatin; LV5FU2, bolus plus continuous-infusion fluorouracil plus leucovorin.

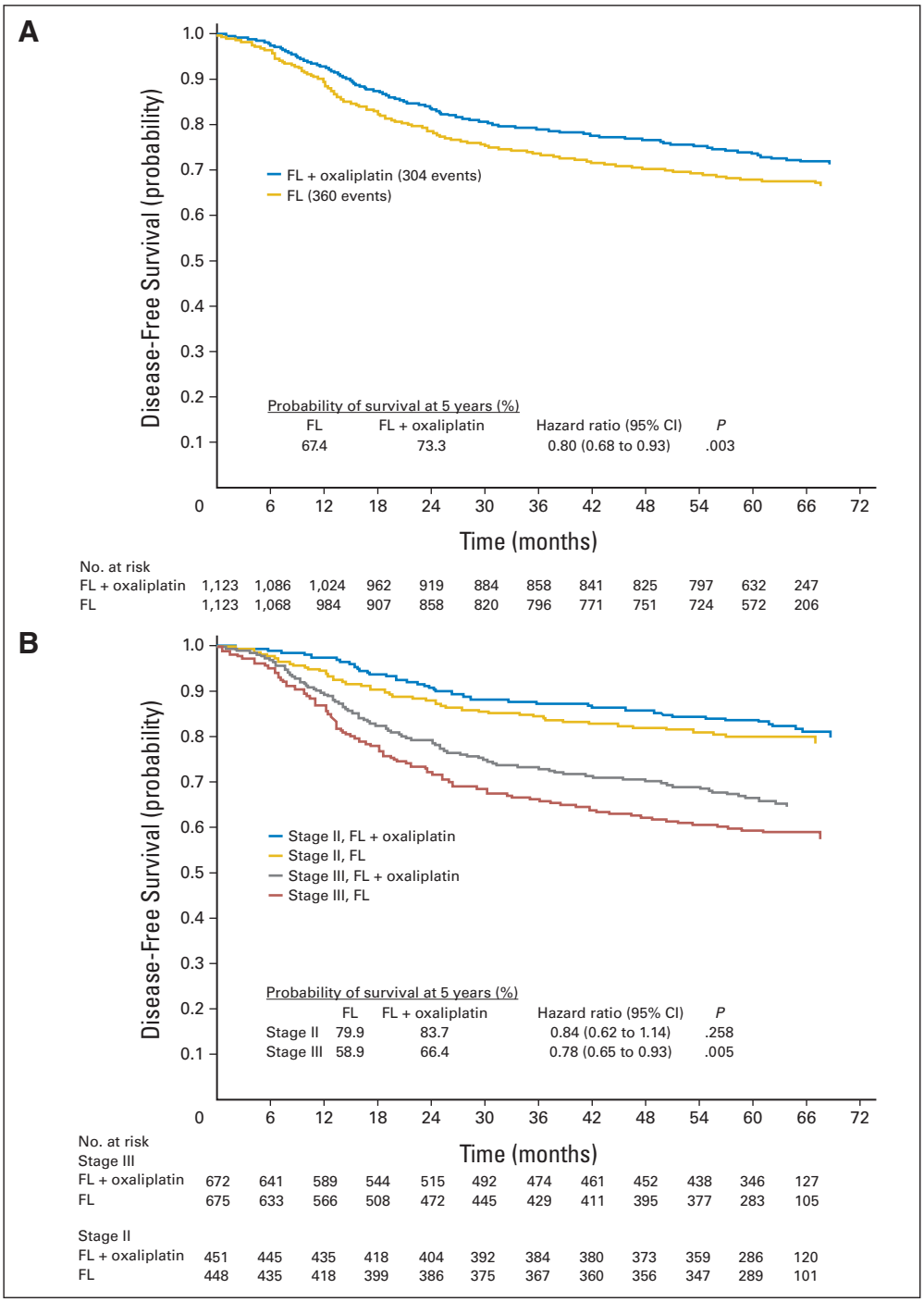

Fig 4. Kaplan-Meier estimates of disease-free survival (A) by treatment arm and (B) by treatment arm and by stage (intent-to-treat population). FL, fluorouracil and leucovorin.

adjuvant studies in colon cancer. These findings led to the approval by the US Food and Drug Administration of 3-year DFS as a primary end point for adjuvant colon cancer studies. Further analysis of ACCENT indicated that there was no association between time to recurrence and OS in patients with stage II disease,[15] findings that may explain why, although there was a trend toward improved DFS in stage II patients in this study, this was not translated into an OS benefit. Prolonged survival after recurrence reduces the association between 3-year DFS and 5-year OS.[16] Of note, patients in the ACCENT database were enrolled between 1977 and 1999, when median time between metastatic recurrence and death was only 13.3 months.[15] In the MOSAIC study, as in other recently reported adjuvant studies,[17,18] the availability of new therapies after relapse (oxaliplatin, irinotecan, bevacizumab, cetuximab, and surgery of metastases) may have also contributed to improvements in median survival. The extended follow-up required to observe OS improvements further supports the use of DFS not only as a surrogate end point for survival, but also as a full end point in the colon cancer adjuvant studies.[16]

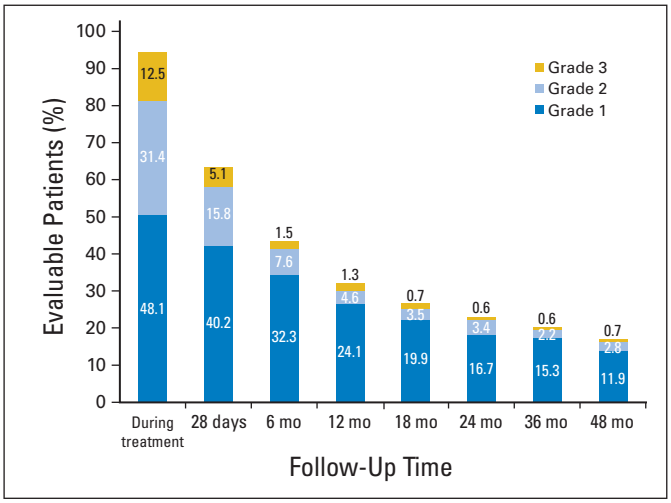

Fig 5. Proportion of patients treated with oxaliplatin plus fluorouracil and leucovorin with grade 1, 2, or 3 peripheral sensory neuropathy during treatment and after follow-up to 4 years.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial also evaluated the addition of oxaliplatin to an alternative FL schedule (weekly Roswell Park regimen of bolus FL) as adjuvant therapy after surgery in a similar population of patients with stage II or III colon cancer.[19] As in MOSAIC, the addition of oxaliplatin was associated with a significant benefit in DFS. With longer follow-up, this DFS advantage in favor of the addition of oxaliplatin remained, and a favorable trend seems to be emerging for OS.[20]

With the exception of PSN, we have not identified any other long-term adverse effects of FOLFOX4. Although 92.0% of patients treated with FOLFOX4 developed PSN of any grade during treatment, in most cases, the symptoms resolved or improved over time. Four years after completion of therapy, 15.5% of patients had residual PSN, but less than 1% of patients had symptoms that were graded as severe. Because we did not perform long-term neurologic assessments on patients randomly assigned to the control arm, we cannot exclude the possibility that some cases of long-term sensory neuropathy observed in the FOLFOX4 group could be linked to other causes. Various techniques have been used in attempt to decrease the risk of oxaliplatin-induced PSN. These include dosing and scheduling modifications and adjustments during chemotherapy administration and coadministration of various neuroprotectants.[21-23] Preliminary patient-reported outcome data from the NSABP C-07 trial suggest that symptoms of oxaliplatin-associated neurotoxicity persisting for 6 years after treatment fail to reach clinical significance.[24] It should be noted, however, that the cumulative oxaliplatin exposure in this trial was less than in MOSAIC; the per-protocol planned oxaliplatin dose was 1,020 mg/m^2 (12 cycles) in MOSAIC and 765 mg/m^2 (nine cycles) in NSABP C-07, whereas the median oxaliplatin dose received per patient was 810 mg/m^2 (9.5 cycles) in MOSAIC and 667 mg/m^2 (7.8 cycles) in NSABP C-07. On the basis of the neurotoxicity data in MOSAIC[10] and C-07,[19] guidance concerning oxaliplatin administration should be not to administer oxaliplatin in patients with persistent paresthesia or functional impairment persisting between cycles. In the future, an important question will be how many cycles of oxaliplatin should be administered. This question is currently being addressed by the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Colon Cancer Prospective Pooled Analysis, which aims to demonstrate that 3 months of oxaliplatin-based adjuvant therapy is not inferior to 6 months of the identical therapy in terms of DFS in patients with stage III colon cancer.

Long-term follow-up of the MOSAIC trial allowed us to confirm the DFS benefit of adding oxaliplatin to a regimen of FU and leucovorin in the adjuvant treatment of colon cancer and to show that this effect translates into an OS benefit. These results suggest that adjuvant oxaliplatin plus FU and leucovorin is useful after surgery for patients undergoing treatment with a curative intent for stage III colon cancer. A similar conclusion cannot be drawn for stage II disease as a whole, although there is some evidence from our results that patients classified as having high-risk stage II disease may also benefit from such treatment. Critical issues for the future include duration of therapy, the use of new agents, and optimizing combinations of targeted therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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