VOLUME 29 · NUMBER 28 · OCTOBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Oxaliplatin As Adjuvant Therapy for Colon Cancer: Updated Results of NSABP C-07 Trial, Including Survival and Subset Analyses

Greg Yothers, Michael J. O'Connell, Carmen J. Allegra, J. Philip Kuebler, Linda H. Colangelo, Nicholas J. Petrelli, and Norman Wolmark

Greg Yothers, Michael J. O'Connell, Carmen J. Allegra, J. Philip Kuebler, Linda H. Colangelo, Nicholas J. Petrelli, and Norman Wolmark, National Surgical Adjuvant Breast and Bowel Project Operations and Biostatistical Center; Greg Yothers and Linda H. Colangelo, Graduate School of Public Health, University of Pittsburgh; Norman Wolmark, Allegheny General Hospital, Pittsburgh, PA; Carmen J. Allegra, University of Florida, Gainesville, FL; J. Philip Kuebler, Columbus Community Clinical Oncology Program, Columbus, OH; and Nicholas J. Petrelli, Helen F. Graham Cancer Center at Christiana Care, Newark, DE.

Submitted April 8, 2011; accepted June 16, 2011; published online ahead of print at www.jco.org on August 22, 2011.

Supported by Public Health Service Grants No. U10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Greg Yothers, PhD, NSABP Biostatistical Center, One Sterling Plaza, 201 N Craig St, Ste 350, Pittsburgh, PA 15213; e-mail: yothers@nsabp.pitt.edu.

0732-183X/11/2928-3768/$20.00

DOI: 10.1200/JCO.2011.36.4539

ABSTRACT

Purpose
The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial demonstrated that the addition of oxaliplatin to fluorouracil plus leucovorin (FULV) improved disease-free survival (DFS) in patients with stage II or III colon cancer. This analysis is the first publication of overall survival (OS) for the NSABP C-07 study. We updated DFS and examined both end points in clinically relevant patient subsets.

Patients and Methods
Other studies have identified patients age 70 or older and those with stage II disease as patient subsets in which oxaliplatin may not be effective. We investigated toxicity as a driver of divergent outcomes in these subsets.

Results
In all, 2,409 eligible patients with follow-up were randomly assigned to either FULV (FU 500 mg/m^2 by intravenous [IV] bolus weekly for 6 weeks; leucovorin 500 mg/m^2 IV weekly for 6 weeks of each 8-week cycle for three cycles) or FLOX (FULV plus oxaliplatin 85 mg/m^2 IV on days 1, 15, and 29 of each cycle). With 8 years median follow-up, OS was similar between treatment groups (hazard ratio [HR], 0.88; 95% CI, 0.75 to 1.02; $P = .08$). FLOX remained superior for DFS (HR, 0.82; 95% CI, 0.72 to 0.93; $P = .002$). The effect of oxaliplatin on OS did not differ by stage of disease (interaction $P = .38$ for OS; interaction $P = 0.37$ for DFS) but did vary by age for OS (younger than age 70 *v* 70+ interaction $P = .039$). There was a similar trend for DFS (interaction $P = .073$). Oxaliplatin significantly improved OS in patients younger than age 70 (HR, 0.80; 95% CI, 0.68 to 0.95; $P = .013$), but no positive effect was evident in older patients.

Conclusion
Overall, the addition of oxaliplatin to FULV has not been proven to extend OS in this trial, but the DFS effect remained strong. Unplanned subset analyses suggest a significant OS effect of oxaliplatin in patients younger than age 70.

J Clin Oncol 29:3768-3774. © 2011 by American Society of Clinical Oncology

INTRODUCTION

The results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial,[1] along with the initial report of National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07,[2] showed that oxaliplatin added to fluorouracil (FU) and leucovorin (LV) significantly improved disease-free survival (DFS) and established oxaliplatin as part of the standard of care for the adjuvant treatment of early-stage colon cancer. Controversy remains over whether all patients with stage II or III colon cancer should receive oxaliplatin as part of their adjuvant therapy. The overall survival (OS) results of the MOSAIC trial[3] showed a survival benefit for all stage II and III patients combined, but the authors concluded that this effect was restricted to patients with stage III disease. A pooled analysis by the Adjuvant Colon Cancer Endpoints (ACCENT) Group of recent trials of adjuvant therapy for colon cancer, including MOSAIC and NSABP C-07,[4] suggested that the benefit of oxaliplatin for OS and DFS may be restricted to patients younger than age 70.

The purpose of this analysis was to present the OS results of NSABP C-07, to update our DFS results, and to perform exploratory analyses to determine whether the effect of oxaliplatin on these end points appears to vary in selected patient subsets. We also explore toxicity as a possible driver of divergent

outcomes in patient subsets. DFS findings were previously reported with a median of 3.5 years follow-up.[2]

PATIENTS AND METHODS

NSABP C-07 was approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services. Written informed consent was required for participation in the trial.

Eligibility

Patients eligible for this trial had either stage II (T3-4, N0, M0) or stage III (T1-4, N1-2, M0) colon cancer and had undergone potentially curative surgical resection with no evidence of residual malignant disease. Patients were randomly assigned to one of the treatments described below within 42 days after curative resection. Additional details were provided by Kuebler et al.[2]

Random Assignment Procedures

Patients were stratified according to main member institution and number of metastatic regional lymph nodes (0, 1 to 3, 4 or more). They were then randomly assigned to one of the regimens described below in the Treatment section.

Treatment

Fluorouracil plus leucovorin (FULV) regimen. LV was given as a 2-hour intravenous infusion in a dose of 500 mg/m^2 weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle) followed by a 2-week rest period. FU was administered as an intravenous bolus 1 hour after the LV infusion was begun at a dose of 500 mg/m^2 weekly for 6 weeks (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle) followed by a 2-week rest period. Patients were to receive three 8-week cycles of therapy for a total treatment duration of 24 weeks (6 months).

FULV plus oxaliplatin (FLOX) regimen. FU and LV were given exactly as described in the previous paragraph. In addition, oxaliplatin was administered as a 2-hour infusion at a dose of 85 mg/m^2 before FULV on days 1, 15, and 29 of the treatment cycle. Patients were to receive three cycles of therapy for a total treatment duration of 6 months.

Statistical Methods

DFS was the primary end point of NSABP C-07 (time from random assignment to recurrence, death, or second primary cancer, whichever occurred first). OS was a secondary end point (time from random assignment to death from any cause). The protocol specified that the definitive analysis of OS would take place 5 years after completion of accrual, by which time 700 deaths were expected. That number of deaths provides power of 0.89 to detect an absolute improvement in the 5-year OS rate of 5%, or equivalently, a hazard ratio (HR) for death of 0.786 for patients treated with FLOX relative to FULV.

Log-rank tests[5] (stratifying for number of positive nodes of 0, 1 to 3, 4 or more) were used to test for treatment differences overall. Cox models[6] were used to estimate HRs, to examine the effect of other potentially prognostic covariates, and to test for treatment-covariate interaction. All *P* values are two-sided and are considered significant if they are less than .05. All CIs are 95%. Multivariate Cox models began with all suspected prognostic variables and treatment interaction terms for all variables in the model. Nonsignificant terms were dropped one at a time, beginning with the least significant. Whenever an interaction term was in the model, the main effect terms remained in, regardless of significance. Patients were analyzed according to their randomly assigned treatment, regardless of treatment actually received. Only ineligible patients and patients without follow-up were excluded from analysis, in accordance with the study protocol.

RESULTS

Patient Disposition and Characteristics

The study accrued 2,492 patients (1,245 to the FULV arm and 1,247 to the FLOX arm) between February 1, 2000, and November 15, 2002. Fifty-eight patients (2.3%) were deemed ineligible (23 assigned to the FULV arm and 35 assigned to the FLOX arm). Twenty-five other patients (13 assigned to the FULV arm and 12 assigned to the FLOX arm) had no follow-up data (all were consent withdrawals) and were not included in the analyses. Thus, 2,409 patients (96.7% of those randomly assigned) were included in the analyses: 1,209 on the FULV arm and 1,200 on the FLOX arm. The demographics and disease characteristics were well balanced across treatment arms.[2] Twenty-nine percent of patients were stage II and these patients had a median of 13 nodes examined. Median follow-up by reverse censoring[7] was 8 years. Cutoff date for this analysis was June 30, 2010.

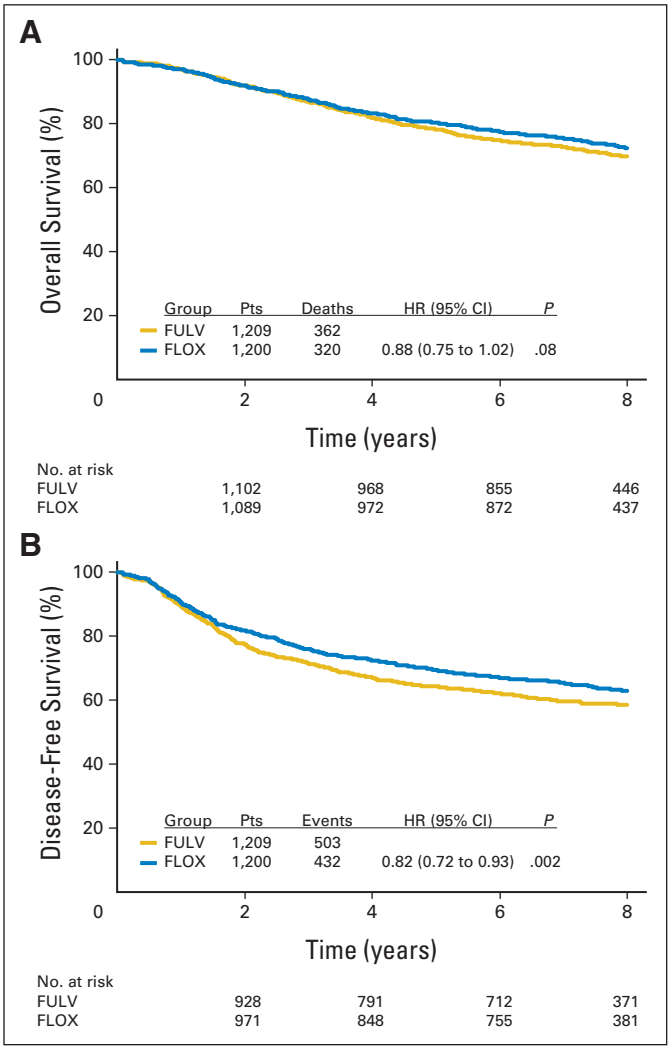

Fig 1. Overall survival (A) and disease-free survival (B) in the National Surgical Adjuvant Breast and Bowel Project C-07 trial. FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FULV, fluorouracil plus leucovorin; HR, hazard ratio; Pts, patients.

Table 1. Kaplan-Meier Estimates of Disease-Free Survival and Overall Survival at 5 Years, by Subset

Subset	Overall Survival (%)			Disease-Free Survival (%)		
	FULV	FLOX	Increase With FLOX	FULV	FLOX	Increase With FLOX
Stage						
II	89.6	89.7	0.1	80.1	82.1	2.0
III	73.8	76.5	2.7	57.8	64.4	6.6
III (1-3 nodes)	79.6	83.3	3.8	65.5	71.4	5.9
III (4+ nodes)	63.2	64.5	1.3	43.7	52.3	8.6
Age, years						
< 70	78.8	81.8	3.1	64.7	70.7	6.0
70+	76.3	71.6	−4.7	62.0	62.8	0.8
All patients	78.4	80.2	1.8	64.2	69.4	5.2

Abbreviations: FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FULV, fluorouracil plus leucovorin.

Survival

The Kaplan-Meier curves for OS are shown by treatment in Figure 1A. There were 682 deaths among these 2,409 patients (362 on FULV and 320 on FLOX). With a *P* value of .08, OS did not differ significantly by treatment in the full cohort of this study. The HR for FLOX versus FULV was 0.88 (95% CI, 0.75 to 1.02), corresponding to a 12% relative reduction in the risk of death. The overall OS estimates at 5 years were 78.4% for FULV and 80.2% for FLOX, an absolute difference of 1.8%, favoring FLOX. Kaplan-Meier estimates of OS and DFS at 5 years are presented in Table 1 for the full cohort and by subsets based on tumor stage and patient age.

DFS

The Kaplan-Meier curves for DFS are shown by treatment in Figure 1B. There were 935 DFS events (503 on FULV and 432 on FLOX) in these 2,409 patients. With a *P* value of .002, DFS remained significantly different by treatment in the full cohort of this study, which is consistent with the original report of this study.[2] The HR for FLOX versus FULV was 0.82 (95% CI, 0.72 to 0.93), corresponding to an 18% relative reduction in the risk of a DFS event. The overall DFS estimates at 5 years were 64.2% for FULV and 69.4% for FLOX, an absolute difference of 5.2% favoring FLOX (Table 1).

Multivariate Modeling

Modeling began with the following factors included: treatment (FULV, FLOX), age (< 70, 70+ years), sex (female, male), positive nodes (0, 1 to 3, 4 or more), depth of tumor penetration (T1 and T2 combined formed the first level, T3, T4), location of tumor (left, right including other/unknown, sigmoid), and treatment interaction terms for age, sex, tumor penetration, and positive nodes. The age 70 years cutoff was chosen for consistency with a prior pooled analysis.[4] The model was developed on the OS end point because OS data are now mature. The final model is given in Table 2. Notably, the only treatment interaction term remaining is with age, suggesting that the effect of oxaliplatin in patients younger than age 70 is different from the effect in patients age 70 or older ($P = .039$). DFS results by using the same model are presented in Table 2 for comparison, although the treatment-age interaction is not significant at $P < .05$ for this end point.

The interaction of treatment and positive nodes was not significant in our model, which suggests that the relative effect of treatment was similar in all three categories. To directly test for a difference in the effect of oxaliplatin by stage of disease (II, III), we began with the model in Table 2 that best described OS, added terms for stage and the treatment-stage interaction, and dropped terms that could confound stage (positive nodes and depth of tumor penetration). The treatment-stage interaction term in this model was not significant (OS interaction $P = .38$; DFS interaction $P = 0.37$), suggesting that the relative effect of treatment was similar in stage II and stage III disease.

Exploratory Subset Analysis by Age

The significant interaction of treatment and age justifies the examination of outcomes separately by age group. Figure 2A shows OS for patients younger than age 70 in the left panel and patients at least age 70 in the right panel. OS is significantly improved with FLOX

Table 2. Multivariate Cox Models

Variable	Overall Survival			Disease-Free Survival*		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment-age interaction	1.46	1.02 to 2.09	.0391	1.34	0.97 to 1.84	.0733
Treatment			.0127			< .001
FULV	Referent group			Referent group		
FLOX	0.80	0.68 to 0.96		0.76	0.66 to 0.88	
Age, years			.0307			.1580
< 70	Referent group			Referent group		
70+	1.32	1.03 to 1.70		1.17	0.94 to 1.46	
No. of positive nodes			< .001			< .001
0	0.51	0.41 to 0.64		0.56	0.47 to 0.67	
1-3	Referent group			Referent group		
4+	2.04	1.73 to 2.40		1.79	1.55 to 2.07	
Tumor penetration			< .001			< .001
T1 or T2	0.42	0.31 to 0.58		0.49	0.38 to 0.62	
T3	Referent group			Referent group		
T4	1.66	1.28 to 2.15		1.56	1.24 to 1.96	

Abbreviations: FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FULV, fluorouracil plus leucovorin; HR, hazard ratio.
*Test for treatment-age interaction not significant for disease-free survival; a model consistent with the overall survival model is presented for comparison.

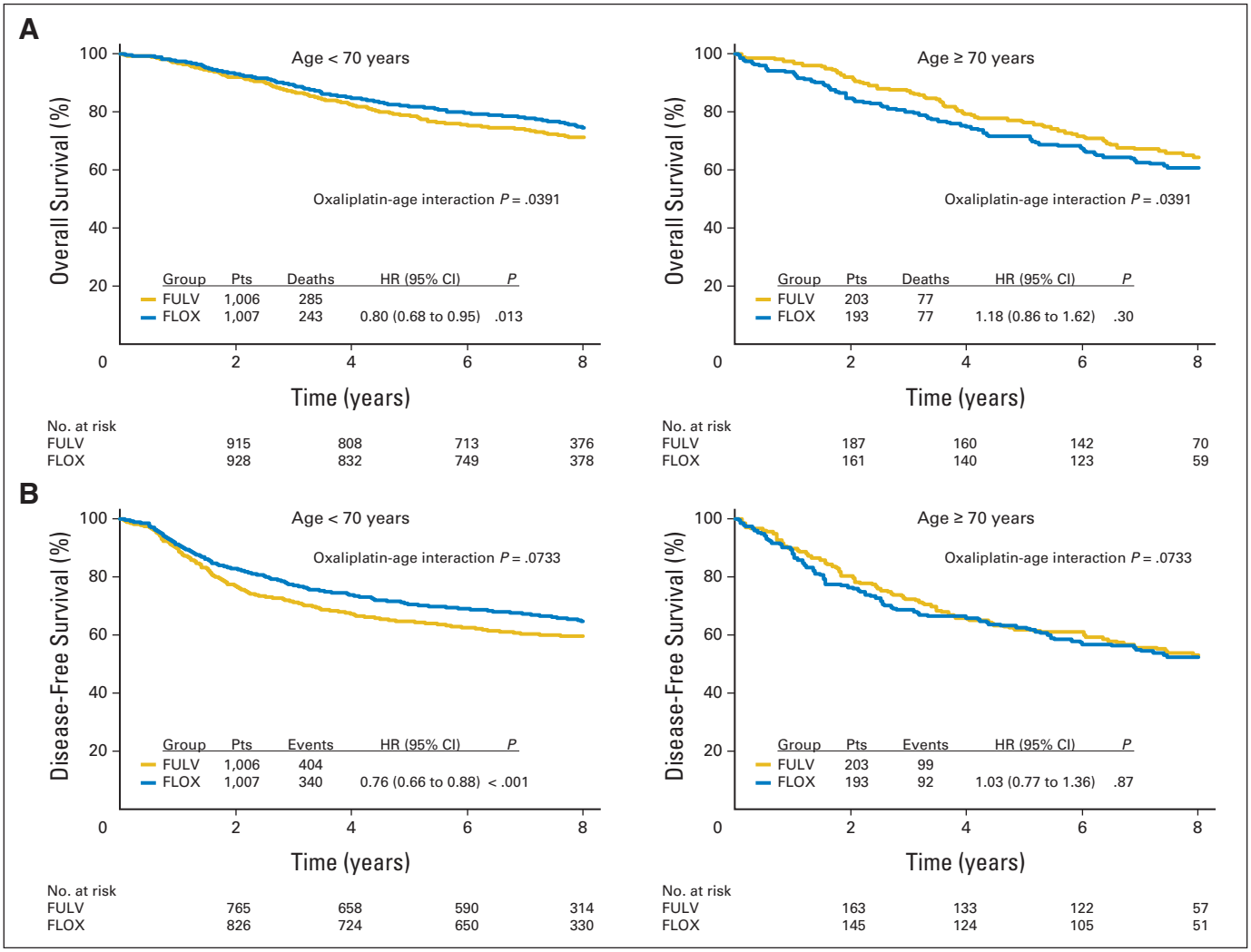

Fig 2. Overall survival (A) and disease-free survival (B) by age in years (< 70, 70+) in the National Surgical Adjuvant Breast and Bowel Project C-07 trial. FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FULV, fluorouracil plus leucovorin; HR, hazard ratio; Pts, patients.

compared with FULV for patients younger than age 70 (HR, 0.80; 95% CI, 0.68 to 0.95; $P = .013$). The 5-year OS estimates were 78.8% for FULV and 81.8% for FLOX, a 3.1% improvement in patients younger than age 70 years (Table 1). OS did not vary significantly by treatment in patients at least age 70 years ($P = .30$), but nominal OS at 5 years was 4.7% worse for patients treated with FLOX (71.6%) compared with that for patients treated with FULV (76.3%) among these older patients. DFS outcomes by age show a similar pattern (Fig 2B).

Toxicity, Dose Delivered, and Performance Score by Age and Treatment

Selected toxicities and dose of treatment delivered are presented in Table 3 by age group and treatment arm. Patients age 70 years or older assigned to FULV experienced grade 4 or 5 toxicity at a rate of 13%, and those assigned to FLOX had a rate of 20% (odds ratio, 1.59; 95% CI, 0.93 to 2.73). The corresponding rates in younger patients were lower on both arms (9% and 10%) with an odds ratio of 1.13 (95% CI, 0.84 to 1.51). Younger patients received higher cumulative doses of FU than did older patients, but FLOX patients received approximately 91% as much FU as did FULV patients, regardless of age. FU dose intensity was also slightly increased in younger patients and showed a similar odds ratio by treatment arm regardless of age (approximately 92%). Cumulative dose of oxaliplatin was reduced by approximately 25% in patients age 70 years or more compared with younger patients (512 *v* 680 mg/m^2), but dose intensity was similar (4.4 *v* 4.5 mg/m^2/d), which suggests that older patients were more likely to discontinue oxaliplatin early. Of NSABP C-07 patients older than age 70 years, 18% had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 or 2 compared with 16% of patients younger than age 70.

Exploratory Subset Analysis by Stage

Our analysis did not find significant interaction between treatment and stage of disease. However, for comparison with findings from the MOSAIC trial, we present outcomes separately by stage. Figure 3A shows OS for stage III patients in the left panel and stage II patients in the right panel. OS improvement with FLOX compared with FULV borders on significant for stage III patients (HR, 0.85; 95% CI, 0.72 to 1.00; $P = .052$). The 5-year OS estimates were 73.8% for

Table 3. Toxicity and Dose Delivered by Age and Treatment

Treatment End Point	Age (years) < 70	70+	All Ages
FULV			
Grade 5 toxicity (death), %	1.1	1.4	1.1
Any grade 4 to 5 toxicity, %	9.3	13.0	9.9
Grade 3 + diarrhea, %	31.1	38.6	32.4
Grade 3 + nausea, %	10.4	14.0	11.0
Grade 3 + vomiting, %	7.5	9.7	7.9
Grade 2 + neurosensory function, %	3.4	4.3	3.6
Median FU dose delivered, mg/m^2	8,000	6,872	7,800
Median FU dose intensity, mg/m^2/d	52.9	49.7	52.6
Median oxaliplatin dose delivered, mg/m^2	—	—	—
Median oxaliplatin dose intensity, mg/m^2/d	—	—	—
FLOX			
Grade 5 toxicity (death), %	0.9	3.6	1.3
Any grade 4 to 5 toxicity, %	10.4	19.3	11.8
Grade 3 + diarrhea, %	36.3	47.9	38.1
Grade 3 + nausea, %	14.4	21.9	15.6
Grade 3 + vomiting, %	11.1	17.2	12.1
Grade 2 + neurosensory function, %	32.1	20.9	30.4
Median FU dose delivered, mg/m^2	7,239	6,275	7,062
Median FU dose intensity, mg/m^2/d	48.2	47.1	48.1
Median oxaliplatin dose delivered, mg/m^2	680	512	676
Median oxaliplatin dose intensity, mg/m^2/d	4.5	4.4	4.4

Abbreviations: FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FU, fluorouracil; FULV, fluorouracil plus leucovorin.

FULV and 76.5% for FLOX, a 2.7% improvement in stage III patients (Table 2). OS did not vary significantly by treatment in stage II patients ($P = .84$), and nominal OS at 5 years was similar by treatment in stage II, differing by only 0.1%. DFS outcomes by stage show a similar pattern (Fig 3B), except that the treatment differences for DFS are significant in stage III and there is a hint of benefit in stage II (2% increased 5-year OS with FLOX).

DISCUSSION

NSABP C-07 did not demonstrate a significant benefit for OS with the addition of oxaliplatin to FULV according to our prespecified analysis plan. However, our results do show a trend for benefit with an HR of 0.88 (95% CI, 0.75 to 1.02; $P = .08$). Our results are consistent with those from the MOSAIC trial, which showed an HR of 0.84 (95% CI, 0.71 to 1.00; $P = .046$).[3] Taken together, these two trials show an OS benefit for oxaliplatin added to fluoropyrimidine therapy for adjuvant treatment of early-stage colon cancer. The magnitude of benefit is approximately a 15% reduction in the hazard of death for all stage II and III patients participating in these two trials.

With 8 years median follow-up, NSABP C-07 continues to show a strong overall benefit from oxaliplatin for DFS (HR, 0.82; 95% CI, 0.72 to 0.93; $P = .002$). Again, our result is consistent with that from the MOSAIC trial, which reported an HR of 0.80 (95% CI, 0.68 to 0.93) and $P = .003$ with minimum 5-year follow-up.[3]

Our finding that the effect of oxaliplatin differs by age group is provocative. Certainly any true difference in the biologic effect of oxaliplatin on colon cancer is not dependent on chronologic age being on one side or the other of the age 70 years threshold. Rather, chronologic age is tightly correlated with real changes in biology related to the aging process, and a chronologic age of 70 years or more seems to identify a group of patients not deriving survival benefit from oxaliplatin. The OS Kaplan-Meier estimates from NSABP C-07 for older patients in the right panel of Figure 2A shows poorer OS in the FLOX arm. The curves separate early (before 1 year), possibly suggesting consequences of toxicity related to therapy. In patients age 70 years or older, FLOX patients were more likely to experience grade 4 or 5 toxicity (odds ratio, 1.59; 95% CI, 0.93 to 2.73; FLOX/FULV). In younger patients, the rates of these toxicities were similar by treatment (odds ratio, 1.13; 95% CI, 0.84 to 1.51). These differences in toxicity are not conclusive, but they do suggest that older patients may be more likely to have adverse outcomes related to treatment with oxaliplatin. ECOG performance score does not seem to be a sensitive marker of the types of age-related changes that may influence outcomes with oxaliplatin. Of NSABP C-07 patients older than age 70, 18% had a score of 1 or 2 compared with 16% of patients younger than age 70. Younger patients received higher cumulative doses of FU than did older patients, but FLOX patients received approximately 91% as much FU as did FULV patients, regardless of age. FU dose intensity was similarly slightly increased in younger patients, but the ratio of dose intensity (FLOX/FULV) did not vary by age. Patients age 70 years or older received approximately 25% less oxaliplatin overall compared with younger patients, but dose intensities were similar, which suggests that older patients received fewer cycles.

Our results showing that the OS effect of oxaliplatin is different by age group is somewhat inconsistent with the MOSAIC results (Tournigand et al, manuscript submitted for publication).[8] They did not find a significant age-treatment interaction for OS ($P = .18$), but they did find poorer OS outcomes with oxaliplatin in patients age 70 and older (OS HR, 1.10; 95% CI, 0.73 to 1.65; $P = .661$), similar to the results from this report of NSABP C-07 (OS HR, 1.18; 95% CI, 0.86 to 1.62; $P = .30$). The bolus FLOX regimen used in NSABP C-07 is associated with increased GI toxicity[9,10] compared with the infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen used in MOSAIC (grade 3 to 4 GI toxicity, 38% FLOX *v* 11% FOLFOX). The less toxic regimen in MOSAIC may have attenuated the adverse effect of oxaliplatin in older patients. Some evidence was found in the MOSAIC results (Tournigand et al, manuscript submitted for publication)[8] that recurrent disease was managed more aggressively for patients on the control arm compared with patients who were treated with oxaliplatin; such data are not available for NSABP C-07. There was an imbalance of deaths caused by second primary cancer in the MOSAIC trial among patients at least 70 years old, with only one death in the control arm and nine deaths in the oxaliplatin arm. No such imbalance was observed in NSABP C-07, in which there were three deaths from second cancer in the control arm and five deaths in the oxaliplatin arm among those older than age 70 years. The similarity of OS results between these studies in the subset of older patients warrants caution in using oxaliplatin in this subset, even with infusional regimens.

There appear to be real age-related differences in response to oxaliplatin that have affected survival outcomes in this study. Older patients in NSABP C-07 did not have improved survival with FLOX, but younger patients did have improved survival. Although

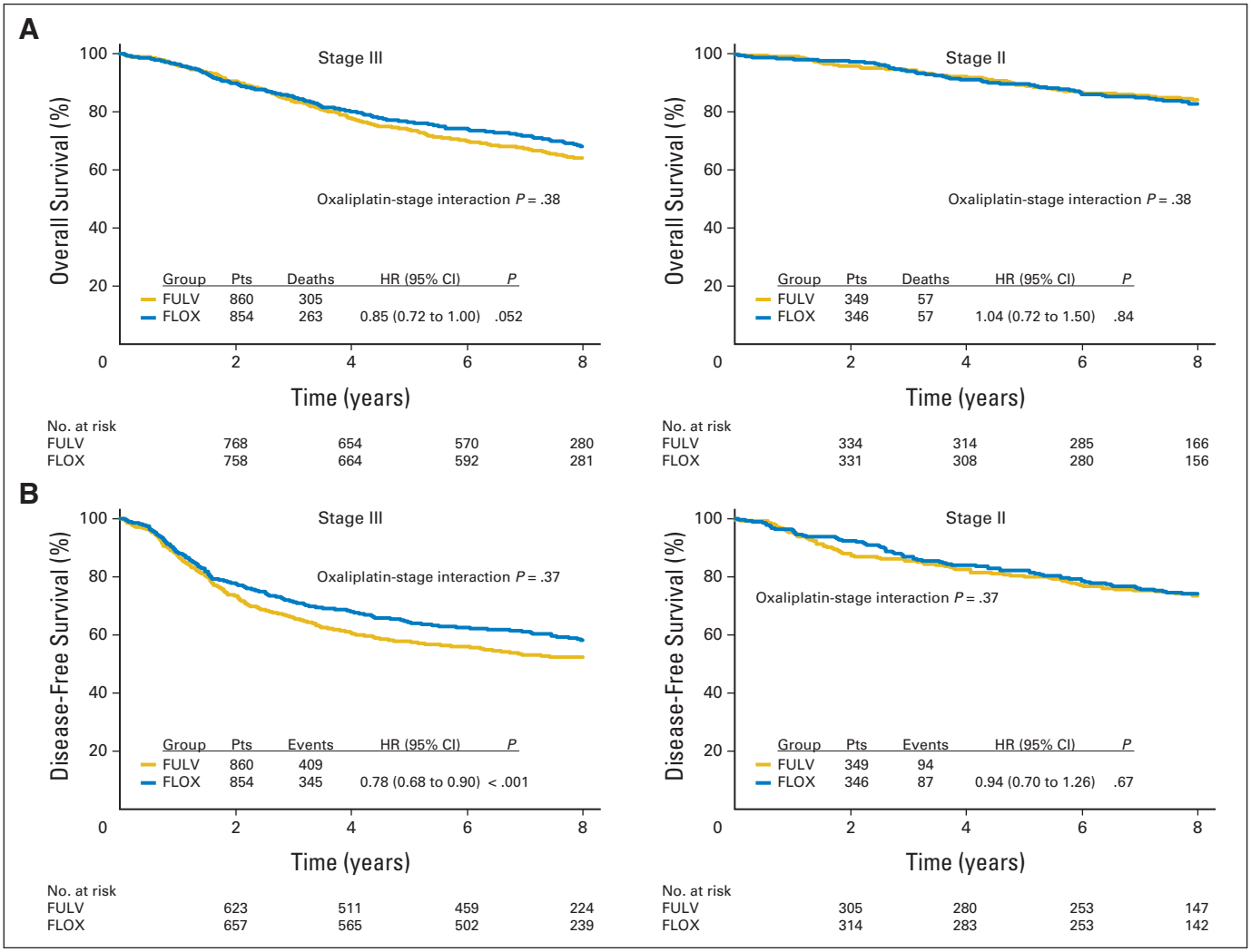

Fig 3. Overall survival (A) and disease-free survival (B) by disease stage (II or III) in the National Surgical Adjuvant Breast and Bowel Project C-07 trial. FLOX, fluorouracil plus leucovorin with the addition of oxaliplatin; FULV, fluorouracil plus leucovorin; HR, hazard ratio; Pts, patients.

a chronologic age of at least 70 years may not be an ideal marker for the true cause of differences in outcome, it appears to be the best marker currently available. In making treatment decisions for individual patients, we suggest that advanced age be one factor taken into account when oxaliplatin is being considered. We do not favor a rigid rule using chronologic age of older than 70 years to determine the use of oxaliplatin. The question here is only about the addition of oxaliplatin to fluoropyrimidine chemotherapy; Sargent et al[11] have demonstrated that elderly patients do benefit from fluoropyrimidine therapy without oxaliplatin. North Central Cancer Treatment Group (NCCTG) N0949 is a currently accruing prospective randomized phase III trial evaluating the worth of oxaliplatin as part of first-line therapy for metastatic colon cancer in patients at least 70 years of age, which should provide additional insight.

We were not able to demonstrate conclusively that outcomes differed by stage of disease in NSABP C-07. Our data are consistent with the MOSAIC data in showing no evidence for a difference in survival within the stage II cohorts, although both these analyses are underpowered to detect the relative differences observed in stage III. Even though one cannot rule out beyond a reasonable doubt the possibility of a positive effect for oxaliplatin on OS in stage II colon cancer, one could reasonably conclude that a preponderance of the evidence suggests that the relative effect of oxaliplatin in stage II colon cancer is smaller than that in stage III. A smaller relative effect (HR closer to 1) combined with the lower absolute rate of death in patients treated without oxaliplatin in stage II implies that any favorable absolute difference in outcome with oxaliplatin would be small. NSABP C-07 shows a 0.1% improvement in 5-year OS with oxaliplatin, and MOSAIC shows a 0.1% improvement in 6-year OS.[3] Considering the added toxicity associated with oxaliplatin treatment, the risk:benefit ratio with this agent is likely unfavorable for most patients with stage II colon cancer.

The use of oxaliplatin with fluoropyrimidine therapy is appropriate for most patients with stage III colon cancer and perhaps selected patients with high-risk stage II colon cancer. In patients of advanced age, caution is warranted in selecting patients for oxaliplatin therapy. Consideration should be given to the patient's overall state of health and potential for tolerating adverse events.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Michael J. O'Connell, sanofi-aventis (U), Hoffman-La Roche (U); Carmen J. Allegra, sanofi-aventis; Nicholas J. Petrelli, Genentech (C); Norman Wolmark, Genentech (U), sanofi-aventis (U) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Greg Yothers, J. Philip Kuebler, Linda H. Colangelo, Nicholas J. Petrelli, Norman Wolmark
Administrative support: Greg Yothers, Norman Wolmark
Provision of study materials or patients: J. Philip Kuebler, Nicholas J. Petrelli
Collection and assembly of data: Greg Yothers, Linda H. Colangelo
Data analysis and interpretation: Greg Yothers, Michael J. O'Connell, Carmen J. Allegra, J. Philip Kuebler, Linda H. Colangelo, Norman Wolmark
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-2351, 2004

2. Kuebler JP, Wieand HS, O'Connell MJ, et al: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. J Clin Oncol 25:2198-2204, 2007

3. André T, Boni C, Navarro M, et al: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC Trial. J Clin Oncol 27:3109-3116, 2009

4. Jackson McCleary NA, Meyerhardt J, Green E, et al: Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: Findings from the ACCENT Database. J Clin Oncol 27:170s, 2009 (suppl; abstr 4010)

5. Schoenfeld D: The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika 68:316-319, 1981

6. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

7. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996

8. Reference deleted

9. Kuebler JP, Colangelo L, O'Connell MJ, et al: Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: A prospective analysis. Cancer 110:1945-1950, 2007

10. Sharif S, O'Connell MJ, Yothers G, et al: FOLFOX and FLOX regimens for the adjuvant treatment of resected stage II and III colon cancer. Cancer Invest 26:956-963, 2008

11. Sargent DJ, Goldberg RM, Jacobson SD, et al: A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 345:1091-1097, 2001

