VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Therapy With Fluorouracil and Oxaliplatin in Stage II and Elderly Patients (between ages 70 and 75 years) With Colon Cancer: Subgroup Analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer Trial

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Submitted February 23, 2012; accepted June 13, 2012; published online ahead of print at www.jco.org on August 20, 2012.

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

Clinical trial information: NCT00275210.

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0732-183X/12/3027-3353/$20.00

DOI: 10.1200/JCO.2012.42.5645

ABSTRACT

Purpose
Oxaliplatin combined with fluoropyrimidine improves survival in patients with stage III colon cancer. However, adjuvant chemotherapy with oxaliplatin is controversial in stage II and elderly patients.

Patients and Methods
We performed subgroup analyses of stage II and elderly patients randomly assigned fluorouracil with leucovorin (FL) ± oxaliplatin (FOLFOX4) in the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer study. Comorbidities, severe adverse events, second cancers, management of relapse and death as a result of causes than other colon cancer were studied.

Results
Two thousand two hundred forty-six patients were enrolled. Overall, 899 patients had stage II disease, including 330 low-risk and 569 high-risk patients. A total of 315 patients were ages 70 to 75 years. For stage II patients, the hazard ratio (HR) for comparing FOLFOX4 with FL was 0.84 (95% CI, 0.62 to 01.14) for disease-free survival (DFS), 0.70 (95% CI, 0.49 to 0.99) for time to recurrence (TTR), and 1.00 (95% CI, 0.70 to 1.41) for overall survival (OS). There was no interaction between treatment and stage or age. Low-risk stage II patients did not benefit from oxaliplatin. In high-risk stage II patients, the HR comparing FOLFOX4 with FL was 0.72 (95% CI, 0.51 to 1.01) for DFS, 0.62 (95% CI, 0.41 to 0.92) for TTR, and 0.91 (95% CI, 0.61 to 1.36) for OS. In elderly patients, the HR comparing FOLFOX4 with FL was 0.93 (95% CI, 0.64 to 1.35) for DFS, 0.72 (95% CI, 0.47 to 1.11) for TTR, and 1.10 (95% CI, 0.73 to 1.65) for OS.

Conclusion
The results of these subset analyses show no statistically significant benefit (OS and DFS) for the addition of oxaliplatin to FL as adjuvant treatment for either stage II and elderly patients.

J Clin Oncol 30:3353-3360. © 2012 by American Society of Clinical Oncology

INTRODUCTION

The estimated worldwide incidence of colorectal cancer (CRC) is 1.2 million per year.[1] The median age at diagnosis is 71 years and one third of all colon cancers (CC) are diagnosed at stage II in western countries.[2]

On the basis of three positive adjuvant studies, the use of oxaliplatin in adjuvant chemotherapy, in combination with fluorouracil (FU) modulated by leucovorin (LV) or capecitabine, is a standard of care for nonmetastatic CC patients with positive lymph nodes (stage III).[3-7] However, the use of adjuvant therapy for stage II patients remains controversial. Current NCCN recommendations are against the routine use of adjuvant therapy for stage II CC.[8] The efficacy of FU and LV in adjuvant therapy for stage II patients was investigated by the Quick and Simple and Reliable study.[9] The benefit in overall survival (OS) was small (3%) and statistically significant but not enough to support the routine use of FU/LV for all patients with stage II CC. Among Medicare patients with stage II CC (age ≥ 65 years), adjuvant chemotherapy did not substantially improve overall

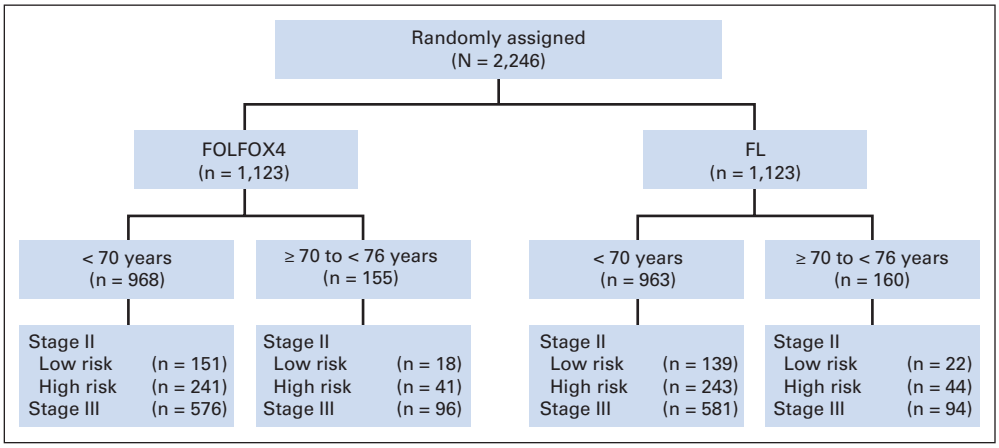

Fig 1. CONSORT diagram. FL, fluorouracil with leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.

survival.[10] A second unresolved issue in adjuvant chemotherapy for CRC concerns its use in elderly patients. In pivotal clinical trials, the average age of patients was approximately 10 years younger than in the whole population of CC patients.[2,3,5,11] Two studies, a pooled analysis in resected, stage II and III CC patients[11] and a population-based cohort study according to the Surveillance, Epidemiology and End Results registry,[12] reported that selected patients older than 70 years did indeed receive the same benefit from FU-based adjuvant therapy as their younger counterparts. In contrast, a meta-analysis concluded that elderly patients did not benefit from oxaliplatin-based adjuvant chemotherapy.[13]

The Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial was a pivotal trial for the regulatory approval of oxaliplatin in the adjuvant setting. We performed a posthoc exploratory study of stage II and elderly patients to deeper explore the role of oxaliplatin-based chemotherapy these subgroups.

PATIENTS AND METHODS

The MOSAIC trial was a randomized trial comparing LV followed by bolus and 22-hour infusional FU for 2 consecutive days (FL) or the same regimen plus oxaliplatin (FOLFOX4) in stage II and III CC. In this open-label study, 2,246 patients were randomly assigned using the minimization method between 12 fortnightly cycles of FL or FOLFOX4.[3] Eligible patients were 18 to 75 years of age and had undergone complete resection of stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) CC. Stage II patients were classified as high risk when they had at least one of the following: T4 staging, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes examined. Patients with none of these prognostic factors were classified as low-risk stage II patients (Fig 1).

Comorbidities were registered at inclusion and classified according to the Adult Comorbidity Evaluation-27.[14] Management of recurrence was extracted from the database, including surgery for metastases and chemotherapy at recurrence.

The primary end point was disease-free survival (DFS), which was defined as the time from randomization to recurrence or death as a result of any cause. Second CRCs were considered recurrence, whereas non-CRC disease was disregarded in the analyses. Time to recurrence (TTR) was defined as the time from randomization to recurrence related to the same cancer. For TTR, a second primary CRC was considered recurrence, but other primary cancers were ignored, and deaths unrelated to CRC were censored observations. OS was measured as the time from randomization until death as a result of any cause. A post-DFS event was measured from the date of recurrence until death as a result of any cause (death was considered an event at time 0). Patients who were still alive and had never relapsed were excluded from this analysis.

Clinical characteristics, comorbidities, severe adverse events (SAEs), incidence of second cancers during follow-up, and cause of death were described using frequency and compared using χ^2 tests.

Follow-up was calculated using the reverse Kaplan-Meier method. The cutoff dates were June 1, 2006 for DFS and TTR and January 16, 2007 for OS. Median follow-up for DFS and TTR was 63 months and for OS was 80 months.

DFS, TTR, and OS were estimated using the Kaplan-Meier method. Interaction tests were performed between allocated chemotherapy and stage II (low- *v* high-risk) or age (< 70 *v* ≥ 70 years), respectively, using the Cox proportional hazards model to calculate hazard ratios (HRs) with 95% CIs. These analyses aimed to investigate whether efficacy for investigated treatments differed according to age or risk in stage II patients. Posthoc power for interaction test was calculated.

Exploratory subgroup analyses for patients ages ≥ 70 years and stage II patients (overall, high and low risk) were done to compare FOLFOX4 with FL.

All tests were two sided at the 5% error level. STATA XI software was used for the analyses and GraphPad for the survival curves.

RESULTS

At the cutoff dates, 528 patients died, 628 patients experienced an event for DFS, and 573 patients experienced an event for TTR. Overall results in OS and DFS have previously been reported for the whole population.[3,4] Table 1 lists patient characteristics. Table 2 and Table 3 list the survival results.

Stage II Patients

Overall, 899 patients with stage II disease were included, 451 in the FOLFOX4 arm and 448 in the FL arm. Of these patients, 569 were classified as high-risk, including 282 in the FOLFOX4 arm and 287 in the FL arm. No imbalance of initial characteristics or incidence of comorbidities was observed between the two arms. Thirty-eight patients had an SAE in the FOLFOX4 group and 30 in the FL group ($P = .26$). No survival benefit for oxaliplatin was observed in low-risk stage II patients (Table 2).

DFS. For the whole population of stage II patients, the HR for comparing FOLFOX4 with FL was 0.84 (95% CI, 0.62 to 01.14; $P = .258$). The interaction test between treatment and risk in stage II for

Table 1. Population and Tumor Characteristics in Patients With High-Risk Stage II Colon Cancer and Patients Older Than 70 Years Treated With Leucovorin and Fluorouracil With or Without Oxaliplatin

	High-Risk Stage II				Patients > 70 Years			
	FOLFOX4 (n = 282)		FL (n = 287)		FOLFOX4 (n = 155)		FL (n = 160)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Median	61		61		72		72	
< 70	241	85	243	85	0	0	0	0
≥ 70	41	15	44	15	155	100	160	100
Sex								
Men	154	55	148	52	98	63	86	54
Women	128		139		57		74	
Karnofsky index								
> 80	233	83	249	87	109	70	124	77
≤ 80	49	17	38	13	46	30	36	23
Stage II								
Low risk	NA		NA		21	14	24	15
High risk	NA		NA		38	25	42	26
< 10 nodes evaluated	152	54	149	52	27		21	
Perforation	38	13	43	15	1		7	
Obstruction	71	25	87	30	7		17	
Venous invasion	35	12	45	16	2		6	
Poorly differentiated	47	17	42	15	1		5	
T4a*	84	30	87	30	5		3	
T4b†	29	10	33	11	4		11	
Stage III								
T2N1	NA		NA		8	5	3	2
T3-4N1	NA		NA		64	41	62	39
Any TN2	NA		NA		24	15	29	18
Comorbidities‡	129		113		85		93	
Cardiovascular	98		84		74		75	
Other malignancy	3		2		1		1	
Endocrine	33		19		12		13	
Grade 1	110		101		76		81	
Grade 2	19		12		9		12	
Multiple	34		21		19		18	
Score								
1	84		82		63		64	
2	37		31		15		27	
3	8		1		6		2	
4	1		0		1		0	

Abbreviations: FL, fluorouracil with leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; NA, not applicable.
*T4a invades through serosa into free peritoneal cavity.
†T4b invades through serosa into a contiguous organ or tumor directly invades other organs or structures.
‡Adult Comorbidity Evaluation-27. Index for each important medical comorbidy: grade 1, mild decompensation; grade 2, moderate decompensation. Overall comorbidity score is defined according to the highest ranked single ailment, except in the case where two or more grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score is designated as grade 3.

DFS was not significant ($P = .066$). Compared with the FL and low-risk subgroup (n = 161), HRs were 2.50 (95% CI, 1.51 to 4.14) for FL and the high-risk subgroup (n = 287), 1.36 (95% CI, 0.76 to 2.45) for the FOLFOX4 and low-risk subgroup (n = 169), and 1.8 (95% CI, 1.07 to 3.02) for the FOLFOX4 and high-risk subgroup (n = 282), respectively. Calculated posthoc power for interaction test was 53%.

In high-risk patients, as compared with FL, FOLFOX4 did not significantly improve DFS (HR = 0.72; 95% CI, 0.51 to 1.02; $P = .063$). Five-year DFS rates in high-risk stage II patients were 82.3% (95% CI, 77.2% to 86.28%) in the FOLFOX4 arm and 74.6% (95% CI, 69.1% to 79.34%) in the FL arm (Fig 2).

TTR. For the whole population of stage II patients, the HR for comparing FOLFOX4 with FL was 0.70 (95% CI, 0.49 to 0.99; $P = .045$). The interaction test between treatment and risk in stage II patients for TTR was not significant ($P = .235$). Comparing with the FL and low-risk subgroup, HRs were 2.45 (95% CI, 1.39 to 4.32) for the FL and high-risk subgroup, 1.01 (95% CI, 0.50 to 2.05) for the FOLFOX4 and low-risk subgroup, and 1.52 (95% CI, 0.84 to 2.76) for the FOLFOX4 and high-risk subgroup, respectively. Calculated post-hoc power for interaction test was 28%.

In high-risk patients, as compared with FL, FOLFOX4 improved TTR (HR, 0.62; 95% CI, 0.41 to 0.93; $P = .020$). The 5-year TTR rates in high-risk patients were 86.8% in the FOLFOX4 arm (95% CI, 82.2% to 90.3%) versus 78.8% in the FL arm (95% CI, 73.4% to 83.2%).

OS. For the whole population of stage II patients, the HR for comparing FOLFOX4 with FL was 1.00 (95% CI, 0.70 to 1.41; $P =$

Table 2. Survival in Low-Risk Stage II Colon Cancer Patients

	FOLFOX4		FL		HR		
Survival Rate	Patients (%)	95% CI	Patients (%)	95% CI	Rate	95% CI	*P*
5-year DFS	86.0	79.7% to 90.5%	89.3	83.3% to 93.2%	1.36	0.76 to 2.45	.305
5-year TTR	90.8	85.2% to 94.4%	90.5	84.7% to 94.2%	1.01	0.50 to 2.05	.972
6-year OS	90.2	84.4% to 93.9%	93.0	87.6% to 96.0%	1.36	0.67 to 2.78	.399

Abbreviations: DFS, disease-free survival; FL, fluorouracil with leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; OS, overall survival; TTR, time to recurrence.

.986). The interaction test between treatment and risk in stage II patients for OS was not significant ($P = .343$). Compared with the FL and low-risk subgroup, HRs were 2.36 (95% CI, 1.28 to 4.34), for the FL and high-risk subgroup, 1.35 (95% CI, 0.66 to 2.76) for the FOLFOX4 and low-risk subgroup (n = 169), and 2.14 (95% CI, 1.16 to 3.98) for the FOLFOX4 and high-risk subgroup, respectively. Calculated posthoc power for the interaction test was 20%.

In high-risk patients, as compared with FL, treatment with FOLFOX4 did not improve OS (HR, 0.91; 95% CI, 0.61 to 1.36; $P = .648$). The 6-year OS rates were 85.0% (95% CI, 80.2% to 88.7%) and 83.3% (95% CI, 78.4% to 87.2%) in the FOLFOX4 and FL arms, respectively (HR, 0.91; 95% CI, 0.61 to 1.36; $P = .48$).

Post-DFS survival. Median OS after reaching the DFS end point was 13.4 months in the FOLFOX4 group as compared with 28.6 months in the FL group (HR, 1.61; 95% CI, 1.06 to 2.46; $P = .045$).

Elderly Patients

Overall, 315 patients ages 70 to 75 years were included in this analysis, with 155 in the FOLFOX4 arm and 160 in the FL arm. The mean age was 72 years. No imbalance of initial characteristics was observed between the two groups. The incidence of comorbidities was similar in the two groups. Thirty patients had an SAE in the FOLFOX4 arm compared with 15 patients in the FL arm ($P = .018$). The tolerance of FOLFOX4 and the dose intensity of FU and oxaliplatin in patients older than 70 years were similar to those observed in younger patients.[15]

DFS. The interaction test between treatment and age for DFS was not significant ($P = .418$). Compared with the FL and age younger than 70 years subgroup (n = 963), HRs were 1.16 (95% CI, 0.87 to 1.54) for the FL and age ≥ 70 years subgroup (n = 160), 0.78 (95% CI, 0.66 to 0.92) for the FOLFOX4 and age younger than 70 years subgroup (n = 968), and 1.06 (95% CI, 0.80 to 1.42) for the FOLFOX4 and age ≥ 70 years subgroup (n = 155), respectively. Calculated posthoc power for interaction test was 19%.

In patients ages ≥ 70 years, as compared with FL, treatment with FOLFOX4 did not improve DFS (HR, 0.93; 95% CI, 0.64 to 1.35; $P = .71$). Five-year DFS in patients ≥ 70 years were 69.1% (95% CI, 61.3 to 75.8) for the FOLFOX4 subgroup and 65.8% (95% CI, 57.8 to 72.7) for the FL subgroup, respectively (Table 3 and Fig 3). In men who died as a result of causes unrelated to CC, HR was 1.20 (95% CI, 0.73 to 1.98), whereas in similar women, the HR was 0.71 (95% CI, 0.41 to 1.25). In stage III patients, HR was 0.98 (95% CI, 0.62 to 1.56).

TTR. The interaction test between treatment and age for TTR was not significant ($P = .719$). Compared with the FL and age younger than 70 years subgroup, the HRs were 1.05 (95% CI, 0.77 to 1.44) for the FL and age ≥ 70 years subgroup (n = 160), 0.74 (95% CI, 0.62 to 0.88) for the FOLFOX4 and age younger than 70 years subgroup, and 0.71 (95% CI, 0.50 to 1.02) for the FOLFOX4 and age ≥ 70 years subgroup, respectively. The calculated posthoc power for the interaction test was 6%.

In patients ages ≥ 70 years, as compared with FL, treatment with FOLFOX4 did not improve TTR (HR, 0.68; 95% CI, 0.43 to 1.06; $P = .089$; Fig 3). The probability of TTR at 5 years was 78.8% (95% CI, 71.2 to 84.6) for FOLFOX4 (and age ≥ 70 years) and 69.9% (95% CI, 61.9 to 76.5) for FL (and age ≥ 70 years).

OS. The interaction test between treatment and age for OS was not significant ($P = .180$). Compared with the FL and age younger than 70 years subgroup, HRs were 1.17 (95% CI, 0.85 to 1.61) for the FL and age ≥ 70 years subgroup, 0.80 (95% CI, 0.66 to 0.97) for the FOLFOX4 and age younger than 70 years subgroup, and 1.27 (95% CI, 0.93 to 1.74) for the FOLFOX4 and age ≥ 70

Table 3. Cox Analysis HR for DFS, TTR, and OS According to Stage and Age

FOLFOX4 *v* FL by Subgroup	No. of Patients	Five-Year DFS			Five-Year TTR			Six-Year OS		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Stage III	1,347	0.78	0.65 to 0.93	.005	0.74	0.61 to 0.89	.001	0.80	0.65 to 0.97	.023
Stage II	899	0.84	0.62 to 1.14	.258	0.70	0.49 to 0.99	.045	1.00	0.7 to 1.41	.986
High risk	569	0.72	0.51 to 1.01	.062	0.62	0.41 to 0.92	.002	0.91	0.61 to 1.36	.648
Low risk	330	1.36	0.76 to 2.45	.305	1.01	0.5 to 2.05	.972	1.36	0.67 to 2.5	.399
Age < 70 years, all stages	1,931	0.78	0.66 to 0.92	.003	0.74	0.62 to 0.88	.001	0.80	0.66 to 0.97	.020
Age 70-75 years, all stages	315	0.93	0.64 to 1.35	.710	0.72	0.47 to 1.11	.140	1.10	0.73 to 1.65	.661

Abbreviations: DFS, disease-free survival; FL, fluorouracil with leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; OS, overall survival; TTR, time to recurrence.

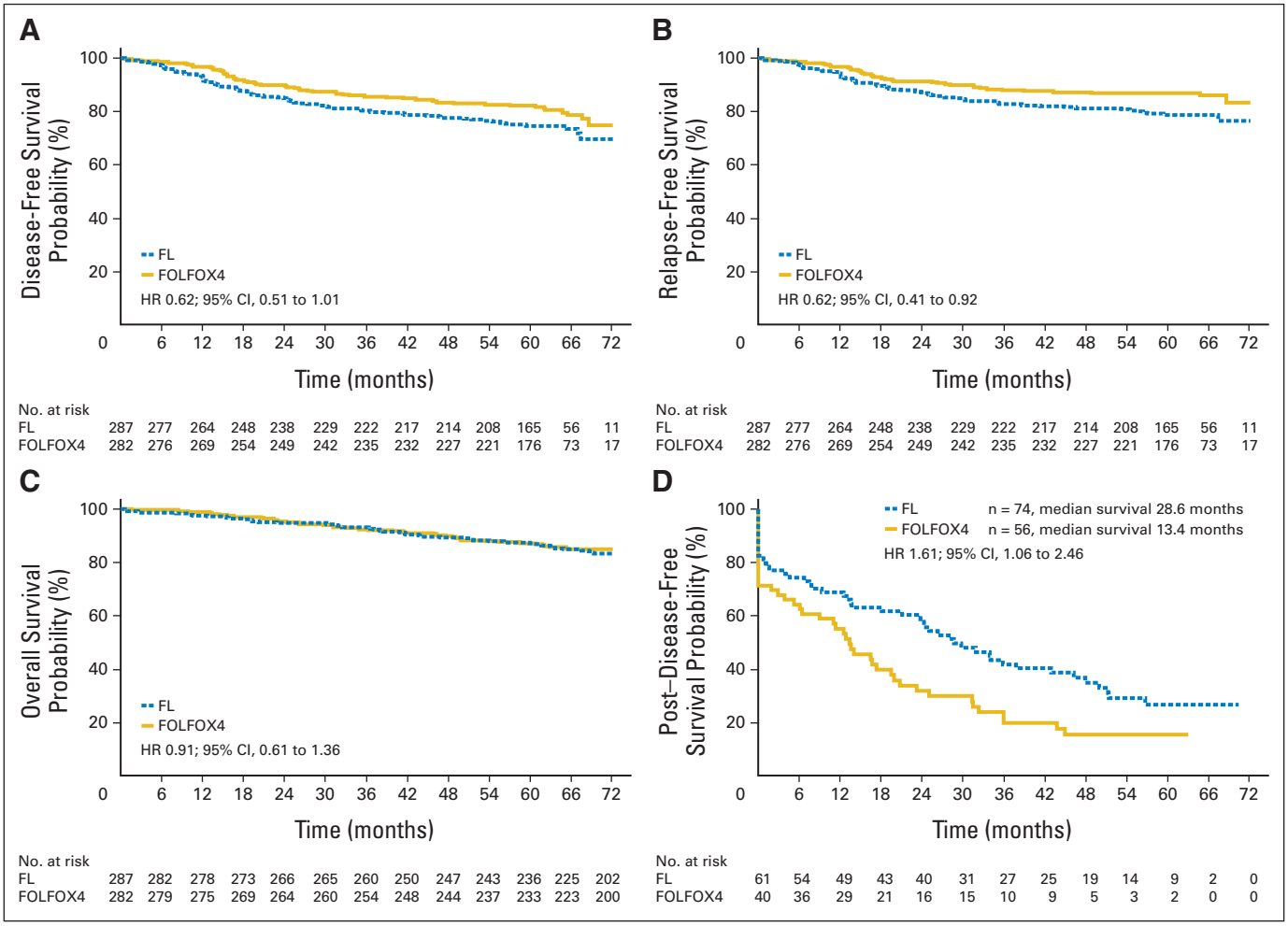

Fig 2. Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in patients with high-risk stage II colon cancer treated with leucovorin and fluorouracil with oxaliplatin (FOLFOX4) or without (FL). DFS, disease-free survival; HR, hazard ratio.

years subgroup, respectively. The calculated posthoc power for the interaction test was 35%.

In patients ages ≥ 70 years, as compared with FL, treatment with FOLFOX4 did not improve OS (HR, 1.10; 95% CI, 0.73 to 1.65; $P = .661$). The probability of OS at 5 years was 75.8% (95% CI, 68.2 to 81.8) for FOLFOX4 and 76.1% (95% CI, 68.6 to 82.1) for FL.

Interestingly, in elderly patients, the HR comparing FOLFOX4 and FL increased over time for DFS and OS but not for TTR (Appendix Fig A1 [online-only]). HRs for these end points in older and younger patients are listed in Table 2.

Post-DFS events. In elderly patients treated with FOLFOX4, the median OS after the DFS end point was 3.6 months, compared with 13.7 months in patients treated with FL (HR, 1.52; 95% CI, 1.04 to 2.49; $P = .033$; Fig 2). The number of DFS events unrelated to colon cancer was higher in the patients treated with FOLFOX4 (n = 19; 17 were men and two were women) than in those treated with FL (n = 11; six were men and five were women).

Management of Relapse

Following relapse, more patients received chemotherapy or had surgery of metastases in the FL versus the FOLFOX4 arm (Table 4). The difference was statistically significant for oxaliplatin- or irinotecan-based chemotherapy in elderly patients (30 *v* 16 patients; $P = .01$) and for surgery in both high-risk stage II patients (26 *v* 11 patients; $P = .01$) and elderly patients (22 *v* 9 patients; $P = .01$).

Second Cancers

The incidence of second cancers was similar between the two arms of the trial and among the high-risk stage II patients. Among elderly patients, 10 patients (6.2%) had a second cancer in the FL arm and 17 patients (11.0%) in the FOLFOX4 arm. In the oxaliplatin arm, the incidence of second cancers was significantly different between the elderly and the younger patients (11.0% *v* 4.0%; $P = .001$) but not in the FL arm (6.3% *v* 5.3%; $P = .16$). At the cutoff date, more elderly patients had died of second cancer in the FOLFOX4 arm than in the FL arm (9 *v* 1 patients; $P = .02$; Table 4 and Appendix Table A1).

DISCUSSION

The results of this article show that patients with low-risk stage II CRC do not benefit from oxaliplatin; in high-risk stage II patients, oxaliplatin significantly improved TTR without benefit in DFS or OS. However, these subgroups analyses should be cautiously considered as

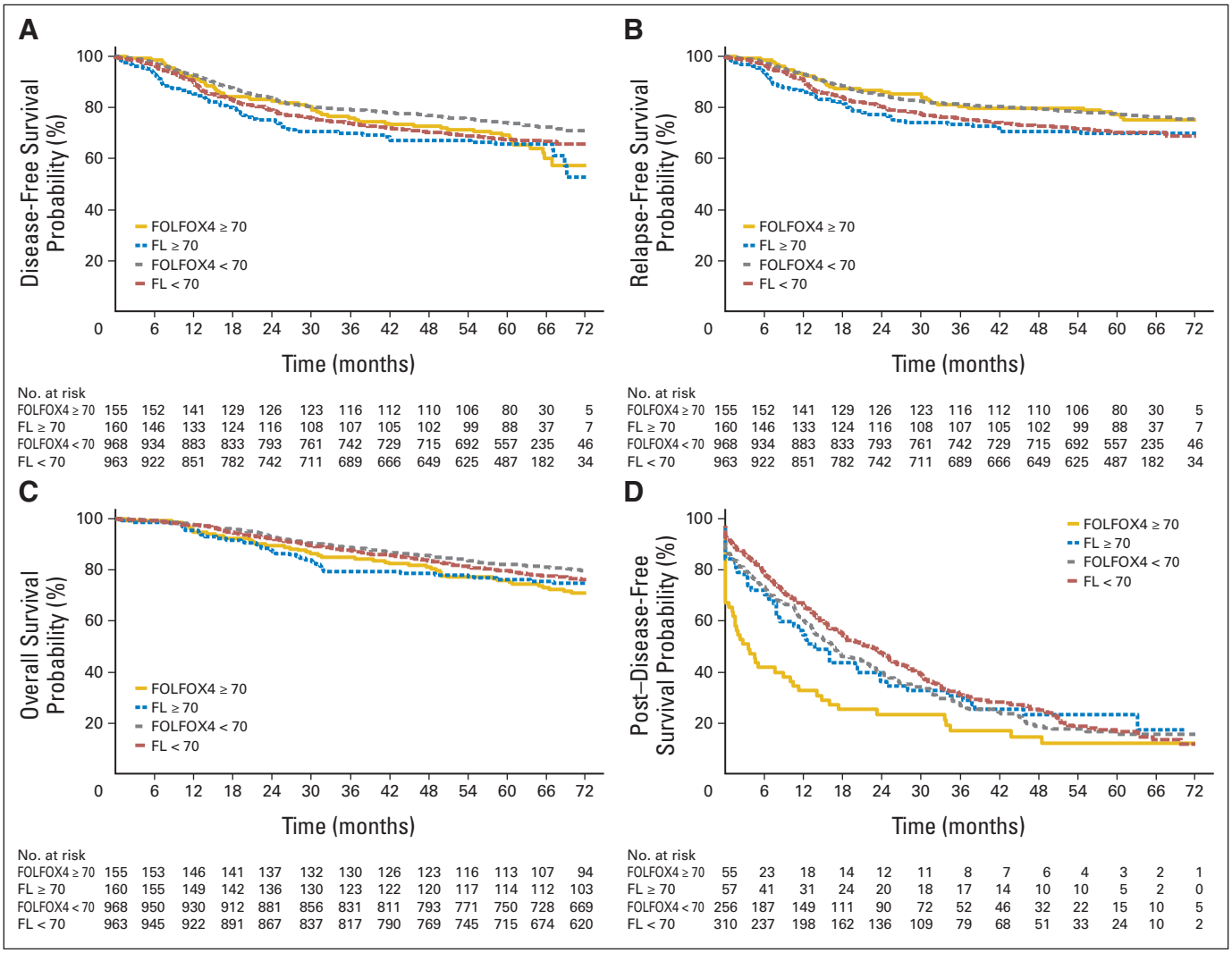

Fig 3. Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in patients older than 70 years treated with leucovorin and fluorouracil with oxaliplatin (FOLFOX4) or without (FL).

exploratory results only. In elderly patients, there was no benefit from oxaliplatin for TTR, DFS, or OS, but the subgroup was small and restricted to patients younger than 76 years. The lack of interaction between treatment and stage or age suggests that the effect of FOLFOX4 compared with FL does not differ according to high versus low risk in stage II patients or according to age. The benefit of oxaliplatin seems to be reduced as compared with stage III or younger patients in terms of DFS and OS, while maintained in TTR. Survival estimation of high-risk stage II and elderly patient subgroups in the MOSAIC study shows similarities that are in part explained by the overlap in the subgroups: 40% of the elderly were stage II and 15% of the stage II patients were older than 70 years.

Differences in comorbidities, dose intensity, and toxicity, or even serious adverse events, although more frequently observed in the oxaliplatin arm, do not explain these results. We did, however, observe imbalances between the treatment arms in the occurrence of deaths from second cancers other than CRC and from deaths after relapse, both of which favored FL. The worst prognosis following relapses after FOLFOX4 than FL therapy may be as a result of worse prognostic factors at relapse or less intense management, including chemotherapy and surgery of metastases.

At this time, no formal consensus exists for the definition of DFS in CRC. In National Surgical Adjuvant Breast and Bowel Project (NSABP)[5,6] studies and for Punt et al,[16] other primary cancer (CRC or other cancer) are considered events for DFS[5,6] but not in the MOSAIC study. A recent study[17] underlined that inclusion of second primary other cancers as an event in DFS definition significantly alters DFS. Evaluation of chemotherapy efficacy using OS and DFS is difficult in the elderly population who face the confounding effects of death as a result of causes other than CRC. This study also showed that the inclusion of second primary other cancers had a more detrimental effect on DFS in stage II patients than in stage III because stage II patients had fewer distant metastases and death as a result of CRC.[17] TTR, which is not affected by death of causes other than CC, could be a more appropriate end point in this population.

The definition of high-risk stage II disease was based on consensual prognostic factors (T4, perforation and number of examined lymph nodes) and prognostic factors that are still debated (poorly

Table 4. Number of Events Observed in Patients With High-Risk Stage II Colon Cancer and Patients Older Than 70 Years Treated With Leucovorin and Fluorouracil With or Without Oxaliplatin

	High-Risk Stage II				Patients ≥70 Years			
	FOLFOX4 (n = 282)		FL (n = 287)		FOLFOX4 (n = 155)		FL (n = 160)	
Event Type	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Relapse	38	13	59	20	38	24	48	18
Alive with relapse	11	4	27	9	7	4	13	8
Chemotherapy	33	12	46	16	23	15	34	21
Oxaliplatin/irinotecan	20	7	33	11	16*	10	30*	19
Surgery of metastases	11*	4	26*	9	9*	6	22*	14
Deaths	45	16	50	17	48	31	44	28
Colon cancer	27	10	32	11	31	20	35	22
Ex colon†	18	6	18	6	17	11	9	6
Adverse event	1		3		0		1	
Second cancer	5		3		9		1	
Cardiovascular	6		5		6		3	
Other	6		7		2		4	
Second cancer	13	5	16	6	17	11	10	4
Alive with second cancer	8		13		8		9	

Abbreviations: FL, fluorouracil with leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.
*Significant difference between FOLFOX4 and FL.
†Total of deaths as a result of adverse event, second cancer, cardiovascular cause, or other.

differentiated tumor, obstruction, lymphatic, venous, or perineural invasion).[18-20] Some stage II disease, such as T4b, have a poor prognosis with a 5-year OS rate of 46%, whereas the 5-year OS rate reaches 80% in the global stage II population,[21] underlining the fact that the prognosis is not only a question of stage. Although the Quick and Simple and Reliable study was positive,[9] a recent retrospective study of patients older than 65 years with stage II CRC[10] reported that adjuvant chemotherapy without oxaliplatin did not improve OS even in high-risk patients, although the conclusions were questioned.[22] Today, the decision to administer chemotherapy to stage II patients is still based on clinical and pathologic markers of risk that are inadequately informative in most patients. For high-risk stage II patients, despite a nonsignificant increase in DFS and OS by 7.7% and 1.7%, respectively, our study suggests that translational research is urgently needed to better define patients who can benefit from oxaliplatin.[23-25] This translational collaborative work (predictive factor of oxaliplatin benefit on tumor blocks collected in the MOSAIC and C07 study) is ongoing.

A benefit of FU adjuvant therapy in elderly patients was reported in a meta-analysis by Sargent et al.[11] Combination chemotherapy with oxaliplatin achieved similar survival benefit and toxicity in young and elderly patients with metastatic CRC.[14] However, a combined analysis of the two pivotal adjuvant trials evaluating oxaliplatin-FU versus FU, MOSAIC, and NSABP C-07, failed to demonstrate a DFS or OS benefit in elderly patients despite a positive trend for TTR.[13] In the NSABP C-07 study, in contrast with the MOSAIC study, there was an interaction between treatment and age, and a benefit in DFS was not observed.[6] This might be explained by the toxicity of the bolus FU/leucovorin and oxaliplatin regimen used in NSABP C-07, including diarrhea, dehydration, and bowel wall injury.[5] The results of the NO16968 trial in the elderly population, comparing FU/LV and Xeloda plus oxaliplatin, have shown comparable results in young and elderly populations.[7,26]

In any case, the majority of the patients receiving the adjuvant treatment will have no benefit of oxaliplatin. The potential benefit of treatment must be put in balance with the cost and the risk of neuropathy. Our study has limitations. The primary objective of the trial was DFS for the whole population, such that MOSAIC was underpowered for subgroup analyses. The posthoc analyses reported in our article should be considered as exploratory only. Patients ages older than 75 years were not included in MOSAIC trial, restricting our conclusions in the elderly population to patients between 70 and 75 years.

The administration of fluoropyrimidines alone remains the standard option for both elderly and selected high-risk stage II patients. According to the MOSAIC subgroup analyses reported in our article, the addition of oxaliplatin to infusional FU/leucovorin has not been shown to be beneficial in low-risk or high-risk stage II patients or for patients between 70 and 75 years. The identification of a patient population for which adjuvant therapy is necessary, safe, and effective continues to be challenging especially for high-risk stage II patients and for elderly patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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:** Josep Tabernero, sanofi-aventis (C); Aimery de Gramont, sanofi-aventis (C) **Stock Ownership:** None **Honoraria:** Christophe Tournigand, sanofi-aventis; Thierry André, Baxter, sanofi-aventis; Gérard Lledo, sanofi-aventis; Tamas Hickish, sanofi-aventis; Corrado Boni, sanofi-aventis **Research Funding:** Josep Tabernero, sanofi-aventis **Expert Testimony:** None **Other Remuneration:** None

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Final approval of manuscript: All authors

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