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ORIGINAL REPORT

Three Versus 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Disease-Free Survival Results From a Randomized, Open-Label, International Duration Evaluation of Adjuvant (IDEA) France, Phase III Trial

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ABSTRACT

Purpose

Reduction of adjuvant treatment duration may decrease toxicities without loss of efficacy in stage III colon cancer. This could offer clear advantages to patients and health care providers.

Methods

In International Duration Evaluation of Adjuvant Chemotherapy (IDEA) France, as part of the IDEA international collaboration, patient with colon cancer patients were randomly assigned to 3 and 6 months of modified FOLFOX6 (mFOLFOX6: infusional fluorouracil, leucovorin, and oxaliplatin) or capecitabine plus oxaliplatin (CAPOX) by physician choice. The primary end point was disease-free survival (DFS), and analyses were descriptive.

Results

A total of 2,010 eligible patients received either 3 or 6 months of chemotherapy (modified intention-to-treat population); 2,000 (99%) had stage III colon cancer (N1: 75%, N2: 25%); 1,809 (90%) received mFOLFOX6, and 201 (10%) received CAPOX. The median age was 64 years, and the median follow-up time was 4.3 years. Overall, 94% (3 months) and 78% (6 months) of patients completed treatment (fluoropyrimidines ± oxaliplatin). Maximal grade 2 and 3 neuropathy rates were 28% and 8% in the 3-month arm and 41% and 25% in the 6-month arm ($P < .001$). Final rates of residual neuropathy greater than grade 1 were 3% in the 3-month arm and 7% in the 6-month arm ($P < .001$). There were 578 DFS events: 314 and 264 in the 3- and 6-month arms, respectively. The 3-year DFS rates were 72% and 76% in the 3- and 6-month arms, respectively (hazard ratio [HR], 1.24; 95% CI, 1.05 to 1.46; $P = .0112$). In the 3 and 6-month arms, respectively, for patients who received mFOLFOX6, the 3-year DFS rates were 72% and 76% (HR, 1.27; 95% CI, 1.07 to 1.51); for the T4 and/or N2 population, they were 58% and 66% (HR, 1.44; 95% CI, 1.14 to 1.82); and for the T1-3N1 population, they were 81% and 83% (HR, 1.15; 95% CI, 0.89 to 1.49).

Conclusion

IDEA France, in which 90% of patients received mFOLFOX6, shows superiority of 6 months of adjuvant chemotherapy compared with 3 months, especially in the T4 and/or N2 subgroups. These results should be considered alongside the international IDEA collaboration data.

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ASSOCIATED CONTENT

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Data Supplements

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INTRODUCTION

On the basis of positive findings from three large phase III trials, 6 months of adjuvant chemotherapy with fluoropyrimidines and oxaliplatin is the current worldwide standard of care for patients with stage III colon cancer.[1-8] Multiple trials in the 1990s demonstrated that the previous 12-month standard of fluoropyrimidines-based chemotherapy could be

reduced to 6 months,[9-11] and a single underpowered trial with fluorouracil alone showed similar outcomes for 3 and 6 months of therapy.[12]

Despite the efficacy of fluoropyrimidines and oxaliplatin-based chemotherapy in patients with stage III colon cancer, this treatment leads to significant costs and toxicities. In particular, the oxaliplatin-induced cumulative dose-dependent peripheral sensory neuropathy (PSN) is a clinically relevant issue. The ability to reduce treatment duration without loss of the efficacy would offer a clear advantage of decreased toxicities, especially persistent PSN, to patients and would decrease costs to health care providers.

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was established to prospectively pool and analyze data from six randomized trials to compare whether a 3-month course of oxaliplatin-based adjuvant therapy is at least noninferior to the current 6-month standard treatment in patients with stage III colon cancer. Three-year disease-free survival (DFS) was the primary end point.[13]

In accordance with the international rules of participation to IDEA, the accrual goal for the IDEA France study was to include 2,000 patients. IDEA France, like other studies in the international IDEA initiative, will not report its primary findings until the international IDEA data are published.[14] We report here the IDEA France study results for DFS, treatment compliance, and safety.

PATIENTS AND METHODS

Design and Participants

IDEA France is a multicenter, two-arm, open-label, randomized phase III trial conducted at 129 French centers. Eligible patients were age 18 years or older; had stage III (according to TNM staging defined by the American Joint Cancer Committee[14a]), histologically confirmed colon cancer; and had undergone curative intent surgery—defined as a tumor location greater than 12 cm from the anal verge by endoscopy and/or above the peritoneal reflection at surgery (high rectum), without microscopic evidence of residual disease—no more than 8 weeks before random assignment; had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; had postoperative carcinoembryonic antigen (CEA) levels $\leq$ 10 ng/mL (2$\times$ normal value); and had signed written informed consent obtained before any study-specific procedures occurred.

The study was done in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. Approval of the protocol was obtained from an independent ethics committee.

Random Assignment and Masking

After informed consent was obtained, eligible patients were randomly assigned (1:1) to receive 3 or 6 months of chemotherapy with modified FOLFOX6 (mFOLFOX: infusional fluorouracil, leucovorin, and oxaliplatin; six or 12 cycles) or capecitabine plus oxaliplatin (CAPOX; four or eight cycles). Allocation was done centrally with a randomization procedure and a minimization technique stratified by center T stage (1 or 2 *v* 3 *v* 4), N stage (1 *v* 2), ECOG PS (0 *v* 1 *v* 2), and age ($<$ 70 years *v* $\geq$ 70 years). The choice between mFOLFOX6 and CAPOX was left to the patient and investigator decision.

Procedures

Dose and delivery schedules of the oxaliplatin-based adjuvant treatment options (mFOLFOX6 and CAPOX) were detailed previously.[3] Physical examination, which included weight, height, ECOG PS, existing signs and symptoms, and concomitant medications, was recorded at each chemotherapy cycle. Adverse events were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) at every cycle. An imaging assessment and a CEA test were mandatory in both treatment arms at 4 and 7 months after the first day of chemotherapy. Follow-up visits were scheduled every 6 months during the first 5 years and were preceded by a white complete blood count, a CEA test, abdominal ultrasounds and a chest x-ray, or a thorax plus abdominal and pelvis computed tomography scan. Colonoscopy was done within the first year after surgery and then (if negative) every 3 to 5 years, or more often if polyposis was diagnosed.

Outcomes

The primary end point of the trial was DFS, defined as the time from random assignment to relapse or death, whichever occurred first. Secondary colorectal cancers were regarded as DFS events, whereas noncolorectal cancers were disregarded in the analysis. Data for patients lost to follow-up were censored.

Secondary end points were overall survival (OS), the treatment compliance (duration, dose intensity, and dose in mg/m^2), the toxicities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (specifically the worst grade toxicity experienced during the on-study period and up to the first month after last administration of chemotherapy), and a PSN-specific longitudinal measurement during the whole follow-up period. Residual PSN was considered as the last available measurement for neuropathy toxicity, and maximal neuropathy at any time was defined as the maximum grade observed during the study period and the follow-up period.

Statistical Analysis

IDEA France was a phase III randomized study with an accrual goal of 2,000 patients with stage III colon cancer within the IDEA international collaboration initiated to answer the single primary hypothesis of the international project: that 3 months of adjuvant fluoropyrimidine and oxaliplatin after surgery for stage III colon cancer is noninferior, in terms of DFS, to 6 months. IDEA France did not have its own sample size/power calculation.

In the IDEA collaboration study, a sample size of 10,500 patients—on the basis of an expected accrual duration of 4.5 years, an expected minimum follow-up time of 1.5 years, and an expected 3-year DFS rate of 72% in the control group (6 months)—was expected to provide the 3,390 DFS events required to reach 90% power to declare noninferiority of the 3-month arm when a true hazard ratio (HR) between arms was 1.0. This design had a type-1error rate of .025 if the true HR between arms was 1.12.[13]

Because of the lack of the French database power for noninferiority, the main objective of this analysis was to compare DFS between 3 and 6 months of chemotherapy as a superiority trial with a descriptive, not prespecified, approach. IDEA France analysis was conducted concomitant with the IDEA international collaboration analysis (data cutoff of February 2017 for both analyses). Analysis of the primary and secondary efficacy end points was performed on the basis of the modified intention-to-treat (mITT) population (ie, only patients who did not receive any therapy whatsoever were excluded from the analysis). Follow-up duration was calculated with a reverse Kaplan-Meier estimation.[15] All efficacy analyses were descriptive. The assumption of proportionality was checked by plotting log–minus-log survival curves and with cumulative martingale process plots.

Patient compliance to treatment was reported for the mITT population by duration group and/or by treatment regimen with mean (standard deviation) and median (interquartile range [IQR]) data for the numbers of cycle and doses (received *v* expected), treatment duration, and dose intensity (defined separately for each agent). Patient compliance between arms was compared with the Student *t* test and the Wilcoxon-Mann-Whitney test for mean and median parameters, respectively. All

analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC) and R software, version 2.15.2 (R Development Core Team, Vienna, Austria; http://www.r-project.org).

RESULTS

Between May 12, 2009, and May 21, 2014, 2,022 patients were randomly assigned. The mITT population resulted in 2,010 (99%) patients; 1,002 were in the 3-month arm, and 1,008 were in the 6-month arm. The proportions of mFOLFOX6- and CAPOX-treated patients were 90% and 10%, respectively (Fig 1). Baseline patient and tumor characteristics were similar between treatment durations (Table 1). CAPOX-treated patients (n = 201; 10%) were younger than those treated with mFOLFOX6; fewer had N2 status, but they had a greater number of lymph nodes examined (Data Supplement). By mFOLFOX6 or CAPOX regimen, baseline patient and tumor characteristics also were similar between treatment durations (Data Supplement).

In the overall mITT population at the time of data cutoff, the median follow-up was 4.3 years (IQR, 3.3 to 5.3 years). There were 578 DFS events (3-month arm: n = 314; 6-month arm: n = 264) that led to 3-year DFS rates of 72% and 76% (HR, 1.24; 95% CI, 1.05 to1.46; P = .0112; Fig 2A) in the 3- and 6-month arms, respectively.

The DFS advantage was confirmed in 1,809 (90%) patients treated with mFOLFOX6; the 3-year DFS rates were 72% and 76% (HR, 1.27; 95% CI, 1.07 to 1.51; Fig 2B) in the 3- and 6-month arms, respectively. However, the 3-year DFS rate was similar for the two treatment durations in the 201 (10%) CAPOX-treated patients (72% *v* 71%; HR, 0.97; 95% CI, 0.59 to 1.59; Fig 2C).

Subgroup analyses of DFS showed a tendency for greater benefit from 6 months of treatment compared with 3 months in all subgroups except CAPOX (Fig 3A). A similar result was observed for the mFOLFOX6 population (Fig 3B). Kaplan-Meier estimates of DFS for the T and N subgroups in the mITT overall, mITT mFOLFOX6, and mITT CAPOX populations are shown in Data Supplement. In the mITT population, the overall 3-year DFS rate for 3 versus 6 months of treatment was 59% versus 65% (HR, 1.38; 95% CI, 1.10 to 1.73) in the T4N2 population and was 80% versus 83% (HR, 1.15; 95% CI, 0.91 to 1.47) in the T1-3N1 population. In the mFOLFOX6 subgroups, the 3-year DFS rate for 3 versus 6 months of treatment with mITT mFOLFOX6 was 58% versus 66% (HR, 1.44; 95% CI, 1.14 to 1.82) in the T4 and/or N2 population and was 81% versus 83% (HR, 1.15; 95% CI, 0.89 to 1.49) in the T1-3N1 population.

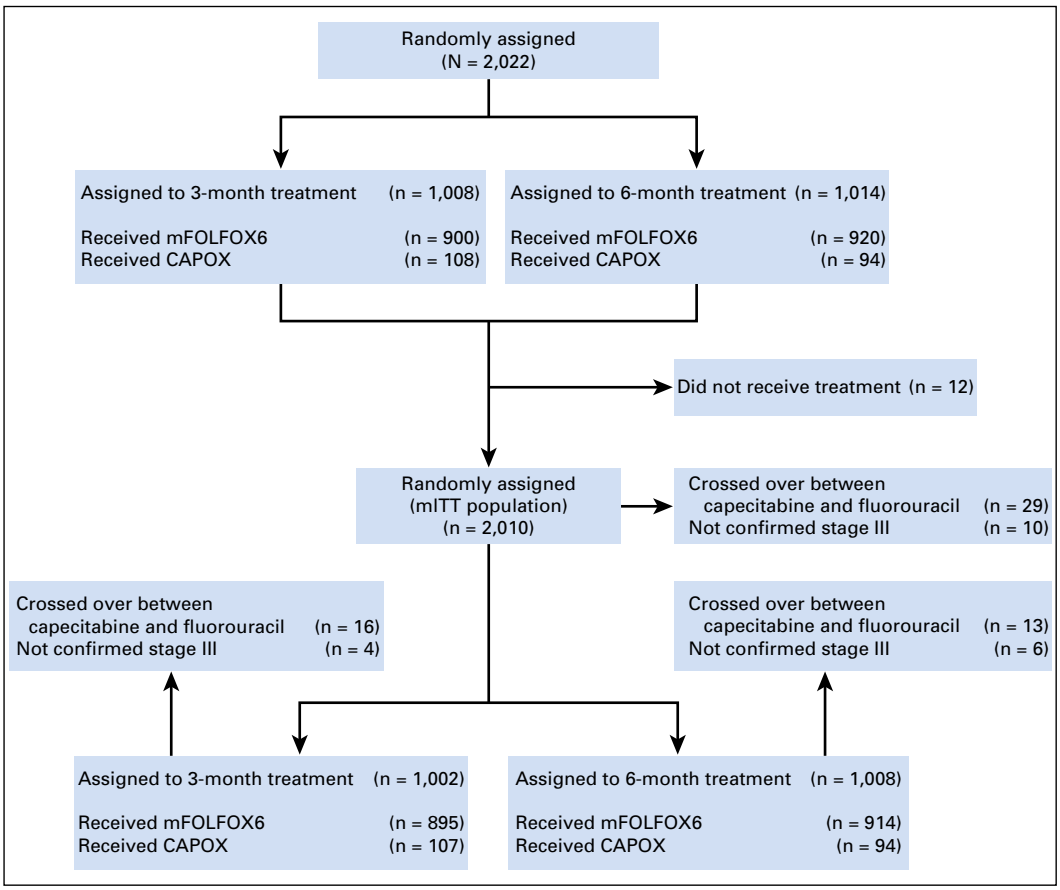

Fig 1. CONSORT diagram. Of the 12 patients who did not receive treatment, six were randomly assigned to the 3-month treatment arm (n = 1 CAPOX; n = 5 FOLFOX), and six were randomly assigned to the 6-month treatment arm (n = 6 FOLFOX). Of the 29 patients who crossed over between capecitabine and fluorouracil, 16 were randomly assigned to the 3-month treatment arm (n = 7 CAPOX, n = 9 FOLFOX), and 13 were randomly assigned to the 6-month treatment arm (n = 3 CAPOX; n = 10 FOLFOX). CAPOX, capecitabine plus oxaliplatin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; mITT, modified intention-to-treat.

Table 1. Baseline Demographic and Clinical Characteristics of the Modified Intention-to-Treat Population by Randomized Arms

Characteristic	Patients by Arm		
	Overall mITT Population (N = 2,010)	3-Month Arm (n = 1,002)	6-Month Arm (n = 1,008)
Age (years)			
Mean (SD)	63.9 (9.4)	63.9 (9.4)	63.9 (9.3)
Median (IQR)	64.7 (58.1-70.8)	64.8 (58.1-70.9)	64.7 (58.1-70.7)
Sex*			
Female	866 (43)	439 (44)	427 (42)
Male	1,144 (57)	563 (56)	581 (58)
ECOG performance status*			
0	1,479 (74)	739 (74)	740 (73)
1	502 (25)	249 (25)	253 (25)
2	29 (1)	14 (1)	15 (1)
Tumor stage*			
T1	78 (4)	45 (4)	33 (3)
T2	161 (8)	76 (8)	85 (8)
T3	1,399 (70)	711 (71)	688 (68)
T4	372 (18)	170 (17)	202 (20)
T4a	289 (78)	127 (75)	162 (80)
T4b	83 (22)	43 (25)	40 (20)
Node stage*			
N0 (0)	3 (0.1)	1 (0.1)	2 (0.2)
N1 (1-3)	1,501 (75)	748 (75)	753 (75)
N2 (≥ 4)	506 (25)	253 (25)	253 (25)
Tumor and node stage			
T1-3 and N1	1,245 (62)	633 (63)	612 (61)
T4 and/or N2	764 (38)	368 (37)	396 (39)
Obstruction			
No	1,707 (85)	845 (84)	862 (86)
Yes	301 (15)	156 (16)	145 (14)
Missing	2	1	1
Perforation			
No	1,914 (95)	961 (96)	953 (95)
Yes	95 (5)	41 (4)	54 (5)
Missing	1	0	1
Median (IQR) No. of lymph nodes examined*	20.0 (14.0-27.0)	19.0 (14.0-26.0)	20.0 (14.0-27.0)
Colon			
Left	1,161 (60)	569 (60)	592 (61)
Right	746 (39)	377 (39)	369 (38)
Both	16 (1)	8 (1)	8 (1)
Missing	87	48	39
Histologic grade			
Well or moderately differentiated	1,764 (92)	880 (91)	884 (92)
Slightly or not differentiated	159 (8)	82 (8)	77 (8)
Missing	87	40	47
Median (IQR) time from surgery to random assginment, weeks	5.9 (4.9-7.0)	5.9 (4.9-7.0)	5.9 (4.9-7.0)

NOTE. Data are given as No. (%) except where otherwise noted.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, Interquartile range; mITT, modified intention-to-treat; PS, performance status; SD, standard deviation.
*No missing data.

In the overall mITT population, there were 274 OS events (3-month arm: n = 145, 6-month arm: n = 129), which yielded 3-year OS rates of 92% and 92%, respectively (HR, 1.15; 95% CI, 0.91 to 1.46; Data Supplement). In the 3-month and 6-month arms, respectively, the 3-year OS rates in the mFOLFOX6 population were 91% and 93%; (HR, 1.16; 95% CI, 0.90 to 1.48) and in the CAPOX population were 92% and 89% (HR, 1.08; 95% CI, 0.49 to 2.37; Data Supplement).

Patient treatment compliance according to treatment duration is listed in Table 2. The median oxaliplatin dose intensity was 97% in the 3-month arm and was 72% in the 6-month arm. Overall, 94% and 78% of patients completed 3 and 6 months of chemotherapy, respectively. The median and mean numbers of mFOLFOX6 cycles were 6.0 and 5.9, in the 3-month arm and 12 and 10.9 in the 6-month arm. The median and mean numbers of CAPOX cycles were 4.0 and 4.0 in the 3-month arm, and 8.0 and 7.1 in the 6-month arm, respectively. The Data Supplement provides details about treatment compliance by chemotherapy regimen and by treatment duration.

In the mITT population during a 6-month post–random assignment period, 12 deaths were recorded: seven (1%) in the 3-month arm (n = 1 each of febrile neutropenia, sepsis, infarct, and glioblastoma; n = 3 related to colon cancer) and five (0.5%) in the 6-month arm (n = 1 each of pulmonary fibrosis, pulmonary embolism, colonic perforation, cerebral hemorrhage, and unknown cause). A total of 295 patients (29%) experienced grade 3 or greater toxicities in the 3-month arm compared with 467 (46%) in the 6-month arm ($P < .001$). The most frequent maximal toxicities in the -3 and 6-month arms during the on-study period (up to the first month after last administration of chemotherapy) were as follows: overall grade 3 to 4 toxicity (29% *v* 56%; $P < .001$), grade 2 to 4 PSN (29% *v* 59%; $P < .001$), grade 3 to 4 neutropenia (12% *v* 17%; $P = .0050$), and grade 3 to 4 diarrhea (5% *v* 6%; $P = .3753$). All toxicities are summarized in the Data Supplement. Grade 2 or greater adverse events occurred in similar proportions of mFOLFOX6- and CAPOX-treated patients (38% and 38%); there was more grade 3 to 4 neutropenia with mFOLFOX6 (15% *v* 8%; $P = .01$) and more grade 3 to 4 diarrhea (9% *v* 5%; $P = .0046$) and more vomiting (5% *v* 2%; $P = .0068$) with CAPOX. The incidence of grade 3 to 4 neutropenia was higher in mFOLFOX6-treated than in CAPOX-treated patients (15% and 8%; $P = .0116$). Patients treated with mFOLFOX6 experienced less grade 3 to 4 diarrhea and vomiting than those treated with CAPOX (diarrhea: 5% and 19%; $P = .0046$; vomiting: 2% and 5%; $P = .0068$). Overall, maximal grade 0 to 1, 2, and 3 to 4 PSN were reported in, respectively, 64%, 28%, and 8% of patients in the 3-month arm and 33%, 41%, and 25% of patients in the 6-month arm ($P < .001$). After a median follow-up time of 3.6 years (IQR, 2.6 to 4.8 years) from random assignment, the final residual grade 2 and 3 to 4 neuropathy rates were 2% and 0.5% in the 3-month arm and were 6% and 2% in the 6-month arm ($P < .001$; Table 3).

DISCUSSION

We found that, after a median follow-up time of 4.3 years, patients with stage III colon cancer treated with 3 months of oxaliplatin-based adjuvant chemotherapy had a decreased 3-year DFS rate compared with those treated with 6 months (72% *v* 76%). In the mFOLFOX6 subgroup (90% of patients enrolled), 3 months of chemotherapy also was associated with a decreased 3-year DFS rate (72% *v* 76%), with a difference noted especially in the T4 and/or

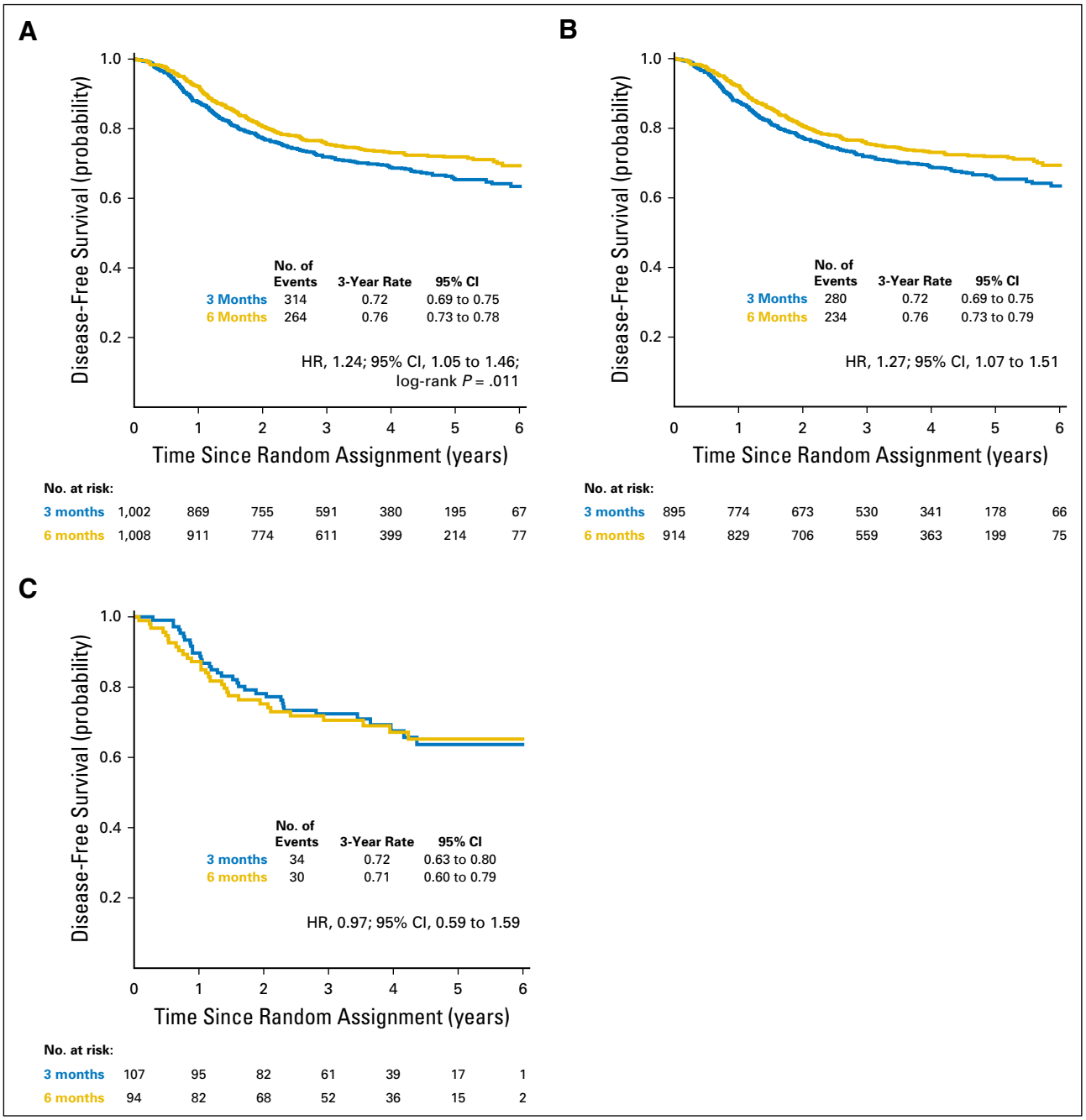

Fig 2. Kaplan-Meier estimates of disease-free survival from random assignment in the (A) overall modified intention-to-treat (mITT), (B) mITT modified FOLFOX6 (mFOLFOX6: fluorouracil, leucovorin, and oxaliplatin), and (C) mITT capecitabine plus oxaliplatin (CAPOX) populations.

N2 population (58% *v* 66%), and, though less clinically relevant, in the T1-3N1 population (81% *v* 83%).

FOLFOX regimens were initiated in France[16-18] and emerged as the preferred drugs of French medical oncology for adjuvant chemotherapy of stage III colon cancer. Patients received either mFOLFOX6 or CAPOX according to investigator choice. Despite the advantages of the oral route of administration for fluoropyrimidines and the every-3-week schedule for oxaliplatin with the CAPOX regimen, French investigators preferred mFOLFOX6. In a previous large, phase III study for metastatic colorectal cancer that evaluated FOLFOX4 versus CAPOX, the CAPOX regimen caused less myelosuppression and stomatitis but more hand-foot syndrome and diarrhea than FOLFOX.[19] As a result, 90% of patients were treated with the mFOLFOX6 regimen in our study. This observation demonstrates how physician tendencies influence clinical practice.

The 10-year update of the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) data confirmed a significant DFS improvement of FOLFOX4, which translated into a long-term OS benefit.[3] After 6 months of chemotherapy and a median number of 9.5 oxaliplatin cycles (oxaliplatin median dose, 810 mg/m^2) the

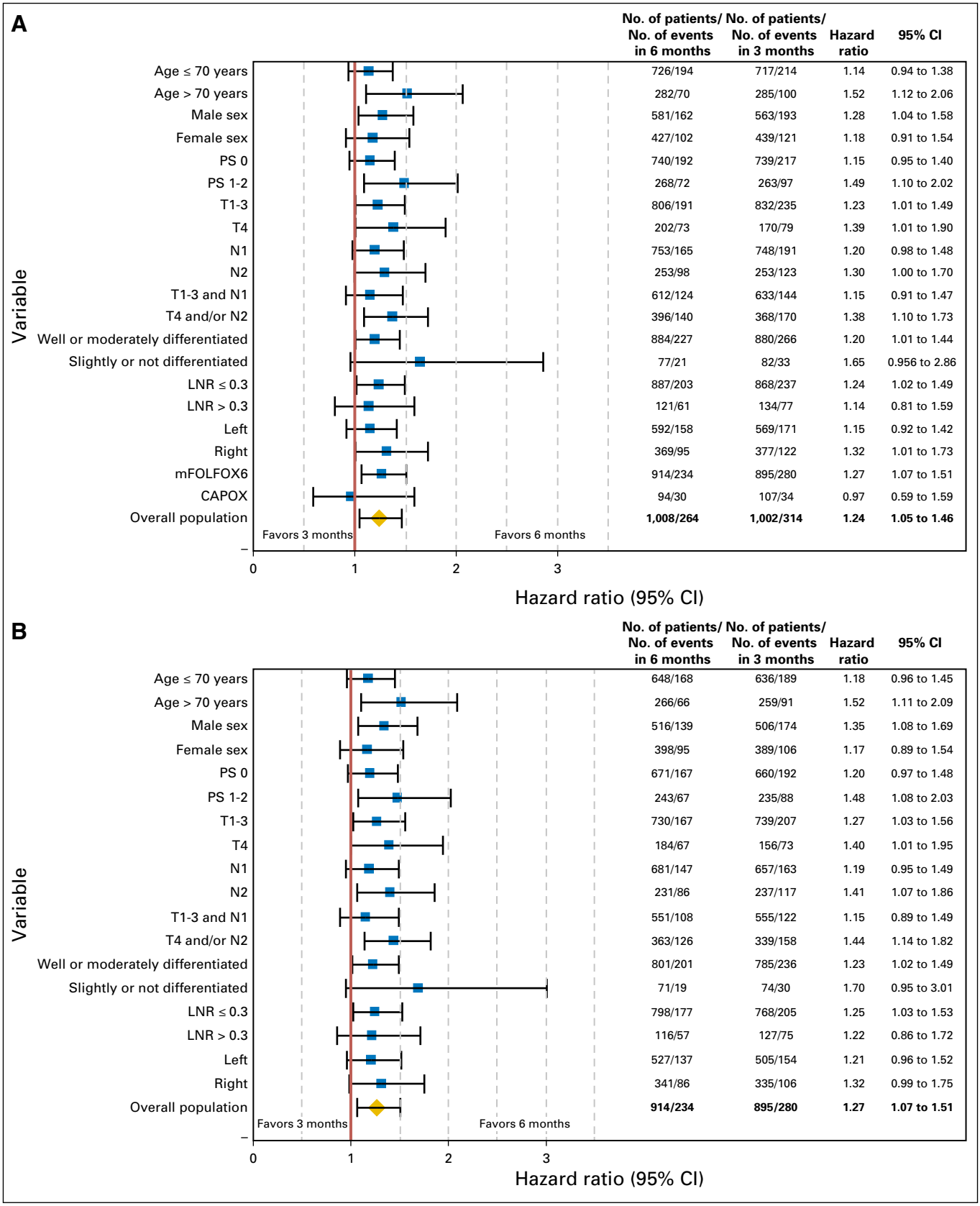

Fig 3. Forest plot for disease-free survival in (A) overall modified intention-to-treat (mITT) population and (B) mITT modified FOLFOX6 (mFOLFOX6: fluorouracil, leucovorin, and oxaliplatin) population. CAPOX, capecitabine plus oxaliplatin; HR, hazard ratio; LNR, lymph node ratio; PS, performance status.

Table 2. Patients' treatment compliance by randomized arm in the modified intention-to-treat population

Variable	mITT Population (N = 2,010)		
	3-Month Arm (n = 1,002)	6-Month Arm (n = 1,008)	*P*
Treatment duration			
Received treatment, weeks*			
Mean (SD)	11.8 (1.8)	21.7 (5.2)	
Median (IQR)	12.0 (12.0-12.0)	24.0 (24.0-24.0)	
Range (min-max)	2.0-24.0	2.0-36.0	
Full length of treatment, %			
Yes†	930 (94)	780 (78)	
No‡	56 (6)	215 (22)	
Missing	16	13	
Dose intensity			
5-fluorouracil§			
Mean (SD)	0.93 (0.15)	0.84 (0.21)	< .001
Median (IQR)	0.97 (0.90-1.0)	0.92 (0.80-0.99)	< .001
Range (min-max)	0.14-2.15	0.01-1.16	
Missing	9	10	
Capecitabine			
Mean (SD)	0.85 (0.17)	0.73 (0.27)	< .001
Median (IQR)	0.90 (0.82-0.94)	0.83 (0.67-0.92)	.0015
Range (min-max)	0.23-1.39	0.004-1.11	
Missing	7	3	
Oxaliplatin*			
Mean (SD)	0.91 (0.17)	0.70 (0.27)	< .001
Median (IQR)	0.97 (0.90-1.0)	0.72 (0.52-0.89)	< .001
Range (min-max)	0.14–2.17	0.06–5.24	
Oxaliplatin dose received, mg/m^2			
mFOLFOX6			
Mean (SD)	466.54 (85.15)	710.65 (280.52)	< .001
Median (IQR)	494.22 (459.52-506.95)	732.39 (530.31-902.21)	< .001
Range	72.42-110.50	64.33–5,345.54	
CAPOX			
Mean (SD)	473.37 (96.81)	709.52 (260.05)	< .001
Median (IQR)	504.44 (453.89-521.10)	760.04 (579.59-894.29)	< .001
Range	129.10-780.13	110.36-1,328.16	

NOTE. Oxaliplatin theoretical doses were 510 mg/m^2 and 520 mg/m^2 in the 3-month arm for mFOLFOX6 and CAPOX treatment and 1,020 mg/m^2 and 1,040 mg/m^2 in the 6-month arm for mFOLFOX6 and CAPOX treatment, respectively.
Abbreviations: IQR, Interquartile range; max, maximum; min, minimum; mITT, modified intention-to-treat; SD, standard deviation.
*No missing data.
†A total of 12 or more weeks of treatment in 3 months or 24 or more weeks of treatment in 6 months.
‡Fewer than 12 weeks of treatment in 3 months or fewer than 24 weeks of treatment in 6 months.
§Infusional and bolus.

FOLFOX4 regimen was better in all subgroups of stage III colon cancer; the 10-year OS rates were 8% (P = .016) in the whole population, 13% (P = .013) in patients with stage III-N2 disease, and 6% (P = . 248) in patients with stage III-N1 disease.[3] This analysis showed that the added value of oxaliplatin was increased in patients with stage III-N2 disease. In a large, meta-analysis of the adjuvant colon cancer end points (ACCENT) group that used data pooled from five clinical trials to evaluate the effect of oxaliplatin in patients with colon cancer, oxaliplatin significantly reduced the risk of recurrence and death within the first 6 years after treatment, and the greatest benefit again was observed in patients with high-risk T4 and/or N2 disease.[20]

In this study, the forest plot for DFS in the overall mITT population suggests a homogeneous effect across all the subgroups: the HR is in favor of the 6-month treatment duration except in the CAPOX subgroup. These data are in line with the results of the IDEA international collaboration.[14] According to these data, if mFOLFOX6 is the selected regimen, patients with T4 and/or N2 colon cancer need 6 months of chemotherapy for a maximal relapse risk reduction. For the subgroups of patients with T1-3N1 colon cancer, the absolute difference in the 3-year DFS rate between 6 and 3 months of treatment was clinically less relevant (2%), and the benefit of oxaliplatin added to fluorouracil was less important in patients with T1-3N1 versus T4 and/or N2 colon cancer as it was in older studies.[3,20] For this T1-3N1 subgroup, the difference in outcome must be balanced against the known increased toxicity of a longer duration of therapy, which thus requires an informed discussion between patients and their oncologists about individualized treatment approaches. This would make us recommend, at least, that oxaliplatin should be stopped after six cycles in the T1-3N1 subgroup to avoid unnecessary persistent PSN if decision is to continue treatment of 6 months. In CAPOX-treated patients, there was no difference between 3 and 6 months of chemotherapy in terms of the 3-year DFS (72% *v* 71%) in the IDEA France study, although the low number of patients treated with CAPOX precludes from any robust conclusion. Nonetheless, this observation is in line with IDEA international collaboration. Interestingly, we showed in a previous publication the feasibility of

Table 3. Neuropathic Toxicity by Randomized Arm in the Modified Intention-to-Treat Population

Toxicity	No. (%) by Treatment Duration: 3-Month Arm (n = 1,002)	6-Month Arm (n = 1,008)	*P*
Maximal neuropathy during the 7 months after random assignment			
0-1	706 (71)	411 (41)	
2	235 (23)	388 (39)	
3-4	59 (6)	206 (20)	< .001
Missing	2	3	
Maximal neuropathy at any time (random assignment to last follow-up)			
0-1	637 (64)	336 (33)	
2	286 (28)	416 (41)	
3-4	79 (8)	255 (25)	< .001
Missing	0	1	
Residual neuropathy*			
0-1	974 (97)	933 (93)	
2	23 (2)	58 (6)	
3-4	5 (0.5)	16 (2)	< .001
Missing	0	1	

*Median follow-up, 3.6 years (interquartile range, 2.6 to 4.8 years) from random assignment.

the CAPOX regimen without a central venous access device for a large majority (81.2%) of patients with stage III colon cancer who were included in this study.[21]

In the mITT population, patient compliance to the full length of treatment was 94% and 78% in the 3- and 6-month arms, respectively; the mean duration of treatments received was 11.8 and 21.7 weeks, respectively. In case of grade 2 PSN (permanent dysesthesia persistent between cycles) or grade 3 PSN (paresthesia/dysesthesia with pain or with functional impairment that also interfered with daily living), oxaliplatin was stopped and fluoropyrimidines were continued for the planned duration. The median oxaliplatin (with mFOLFOX6) dose received per patient was 732.39 mg/m^2 (mean, 8.9 cycles) in the 6-month arm and was slightly inferior to the one received in the MOSAIC trial (810 mg/m^2; 9.5 cycles).[2] This was because of more stringent stoppage rules applied to oxaliplatin in the IDEA study. A shorter (3-month) duration of adjuvant oxaliplatin-based therapy was associated, unsurprisingly, with a lower incidence of principal and severe adverse effects—in particular, maximal PSN at any time of treatment; residual PSN with a median follow-up of 3.6 years from the first cycle; neutropenia; thrombocytopenia; fatigue; and allergy. Despite oxaliplatin median doses of 494.22 mg/m^2 (mFOLFOX6) and 504.44 mg/m^2 (CAPOX) in the 3-month arm, residual grade 2 to 3 PSN was still observed, which demonstrates the interpatient variability of this toxicity, possibly in relation to polymorphisms in oxaliplatin metabolism.[22]

In conclusion, the IDEA France study, in which the majority of patients (90%) were treated with the mFOLFOX6 regimen, shows the superior DFS of 6-month adjuvant treatment compared with 3 months, especially in patients with T4 and/or N2 colon cancer. This finding is in agreement with DFS HR data from the overall analysis of patients who received FOLFOX in the international IDEA collaboration.[14] Results about OS are not mature and will be updated with a longer follow-up time. These results should be integrated, discussed, and considered alongside the international IDEA collaboration data.

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Disclosures provided by the authors are available with this article at jco.org.

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Three Versus 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Disease-Free Survival Results From a Randomized, Open-Label, International Duration Evaluation of Adjuvant (IDEA) France, Phase III Trial

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