original reports

Oxaliplatin (3 months *v* 6 months) With 6 Months of Fluoropyrimidine as Adjuvant Therapy in Patients With Stage II/III Colon Cancer: KCSG CO09-07

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abstract

PURPOSE The combination of oxaliplatin and fluoropyrimidine for 6 months is one of the standard options for adjuvant therapy for high-risk stage II and III colorectal cancers (CRCs). The optimal duration of oxaliplatin to diminish neurotoxicity without compromising efficacy needs to be clarified.

PATIENTS AND METHODS This open-label, randomized, phase III, noninferiority trial randomly assigned patients with high-risk stage II and III CRC to 3 and 6 months of oxaliplatin with 6 months of fluoropyrimidine groups (3- and 6-month arms, respectively). The primary end point was disease-free survival (DFS), and the noninferiority margin was a hazard ratio (HR) of 1.25.

RESULTS In total, 1,788 patients were randomly assigned to the 6-month (n = 895) and 3-month (n = 893) arms, and 83.6% in the 6-month arm and 85.7% in the 3-month arm completed the treatment. The neuropathy rates with any grade were higher in the 6-month arm than in the 3-month arm (69.5% *v* 58.3%; $P < .0001$). The 3-year DFS rates were 83.7% and 84.7% in the 6-month and 3-month arms, respectively, with an HR of 0.953 (95% CI, 0.769 to 1.180; test for noninferiority, $P = .0065$) within the noninferiority margin. Among patients with stage III CRC treated by capecitabine plus oxaliplatin, the 3-year DFS of the 3-month arm was noninferior as compared with that of the 6-month arm with an HR of 0.713 (95% CI, 0.530 to 0.959; $P = .0009$). However, among patients with high-risk stage II and stage III CRC treated by infusional fluorouracil, leucovorin, and oxaliplatin, the noninferiority of the 3-month arm compared with the 6-month arm was not proven.

CONCLUSION This study suggests that adding 3 months of oxaliplatin to 6 months of capecitabine could be considered an alternative adjuvant treatment for stage III CRC (ClinicalTrials.gov identifier: NCT01092481).

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INTRODUCTION

The benefit of adjuvant fluoropyrimidine therapy was first documented in patients with stage III colorectal cancer (CRC).[1] Subsequently, studies showed that adding oxaliplatin to fluoropyrimidine therapy prolonged disease-free survival (DFS) in patients with high-risk stage II or III CRC.[2-5] On the basis of these data, the combination of oxaliplatin and fluoropyrimidine for 6 months is one of the standard options for adjuvant therapy for high-risk stage II or III CRC. Although the inclusion of oxaliplatin in adjuvant therapy brings an additional benefit to outcomes of CRC, simultaneously, this leads to some drawbacks, such as cost and toxicity.[6,7] In particular, peripheral sensory neuropathy caused by oxaliplatin has a critical effect on the quality of life of patients. Peripheral sensory neuropathy is known to be dependent on cumulative doses of oxaliplatin.[6,8] Notably, different cumulative doses of oxaliplatin were used in the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (1,020 mg/m^2)[2] and the National Surgical Adjuvant Breast and Bowel Project C-07 study[3] (765 mg/m^2); however, the efficacies reported in these two studies were similar.

In a metastatic setting, the use of oxaliplatin discontinuation and reintroduction strategy showed oxaliplatin can be safely stopped (oxaliplatin-free interval) after six cycles in a infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen in the OPTIMOX1 study.[9] However, the planned complete discontinuation of

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The present study was designed to clarify the optimal duration (3 *v* 6 months) of oxaliplatin with standard 6 months of fluoropyrimidine therapy to diminish the neurotoxicity without compromising the efficacy of adjuvant therapy in patients with high-risk stage II or III colorectal cancer (CRC).

Knowledge Generated

(1) Decreased neuropathy of 3 months of oxaliplatin with 6 months of fluorouracil (FU) compared with 6 months of oxaliplatin and FU. (2) Adding 3 months of oxaliplatin to 6 months of capecitabine is an alternative adjuvant treatment for stage III CRC.

Relevance

For patients with stage III CRC treated with capecitabine plus oxaliplatin, adding 3 months of oxaliplatin to 6 months of FU therapy could be strongly supported.

chemotherapy (chemotherapy-free interval) had a negative impact on progression-free survival compared with the maintenance therapy strategy. These results suggest that chemotherapy discontinuation cannot be decided before therapy is initiated in patients with advanced CRC in the GERCOR OPTIMOX2 study.[10]

These findings suggest that the shorter duration of oxaliplatin within the standard 6 months of fluoropyrimidine treatment might diminish the neurotoxicity without compromising the efficacy of adjuvant therapy in patients with high-risk stage II or III CRC.

Accordingly, the present study was designed to clarify the optimal duration (3 *v* 6 months) of oxaliplatin with standard 6 months of fluoropyrimidine therapy to diminish the neurotoxicity without compromising the efficacy of adjuvant therapy in patients with high-risk stage II or III CRC.

PATIENTS AND METHODS

Design and Participants

This open-label, phase III, randomized, multicenter, open, noninferiority trial was conducted in 21 Korean centers (ClinicalTrials.gov identifier: NCT01092481). Eligible patients had high-risk stage II (fulfilling at least one of the following criteria: T4 tumor, grade > 3, clinical features of bowel obstruction or perforation, and histologic signs of vascular, lymphatic, or perineural invasion) or III, histologically confirmed colon adenocarcinoma and underwent curative-intent resection for tumors without microscopic residual diseases (starting the study within 42 days after surgery). Additional eligibility criteria were as follows: age > 18 years, Eastern Cooperative Oncology Group performance status of 0-1, and signed written informed consent before any specific procedure.

The trial was conducted in accordance with the Declaration of Helsinki and the guidelines for good clinical practice. The trial protocol () was approved by the local ethics committee of each participating site (Korea), and all patients provided written informed consent before enrollment.

Random Assignment and Masking

Patients eligible for this study were randomly assigned to 3 months or 6 months of oxaliplatin with 6 months of fluoropyrimidine therapy in a 1:1 ratio. Allocation was performed centrally using a web-based random assignment procedure. Patients who fulfilled all the eligibility criteria were prospectively stratified according to the stage (high-risk II *v* IIIA *v* IIIB *v* IIIC) and age (younger than 65 *v* 65 years and older). A random permutated block design was used within the strata.

Procedures

The dose and delivery schedules of adjuvant therapy used in the present study were on the basis of modified FOLFOX6 (mFOLFOX: infusional fluorouracil, leucovorin, and oxaliplatin; 12 cycles) or capecitabine plus oxaliplatin (CAPOX; eight cycles), as described previously.[11-13] For high-risk stage II CRC, only mFOLFOX6 can be used. For stage III CRC, mFOLFOX6 or CAPOX can be used on the basis of the investigator's decision. CAPOX was not allowed at the start of the study and was then allowed from January 2012. In terms of adjuvant therapy, CAPOX has been available only for patients with stage III CRC in South Korea since December 2011. Oxaliplatin was applied differently to the 3-month and 6-month arms.

Physical examinations included weight, Eastern Cooperative Oncology Group performance status, vital signs, existing signs and symptoms, and adverse events with the National Cancer Institute Common Terminology Criteria (NCI-CTC) Adverse Events (version 4.02). Laboratory tests were performed at each chemotherapy cycle. Imaging and CEA tests were conducted in both the 3- and 6-month arms at 7 months after chemotherapy. Disease evaluation, including a thorax plus abdominal and pelvic computed tomography scan, was planned every 6 months for 5 years.

Follow-up visits after the treatment were performed every 3 months during the first 1 year and every 6 months thereafter.

Outcomes

The primary end point was DFS, which was defined as the time from the date of operation to the time of disease recurrence (as assessed by the investigators) or death due to any cause. DFS was assessed in the intent-to-treat (ITT) population.

The secondary end points were overall survival (OS) and safety according to the NCI-CTC Adverse Events, version 4.02.

Statistical Analysis

In the present study, a sample size of 2,660 patients, including patients with high-risk stage II and III CRC, was expected to observe 497 events required to reach 90% power to declare noninferiority of the 3-month arm when the true hazard ratio (HR) between arms was 1.0. This study had a type 1 error rate of 0.025 if the true HR between the arms was 1.25. An expected 3-year DFS rate of 78% in the 6-month arm was established, and a dropout rate of 15% was assumed. We roughly expected that 1,000 patients could be enrolled every year, the total duration of patient enrollment was 3 years, and the additional follow-up/analysis duration would be 4 years. In the MOSAIC trial and the NSABP C-07 trial, the 3-year disease-free survival in the FOLFOX group was 78% as compared with 73% with fluorouracil and leucovorin.[2,3] In this study, the 3-month arm was defined as 3 months of oxaliplatin with 6 months of fluoropyrimidine therapy. Therefore, to confirm noninferiority for the 3-month arm, we would to be confident that this benefit (about 5%, 78% *v* 73%) was retained. Originally, we planned to recruit 2,660 patients consisting of 1,330 patients for each arm. We expected that approximately 1,000 patients could be enrolled every year, but the enrollment rate of patients was too low. Thus, when 1,815 patients were recruited in this study, we decided to stop recruiting additional patients in January 2016. Although this study did not recruit the planned target number of patients, the findings of the present study added scientific evidence for the regimen and duration of adjuvant treatment in CRC.

This trial used a modified intention-to-treat design (all randomly assigned patients who received at least one dose of protocol therapy). Patients who were randomly assigned to one of the two arms and received at least one dose of the study drug were included in the ITT population. The ITT population was used for the analysis in this study. Descriptive statistics were used to summarize patient characteristics. Categorical variables are presented as frequencies, and continuous variables are summarized by medians. Patient characteristics were compared between the two arms using the chi-square test and the Wilcoxon-Mann-Whitney test. All efficacy analyses were descriptive. The Kaplan-Meier method was used to plot both DFS and OS. Survival curves were compared between the two arms using a one-sided log-rank test. HRs of the 3-month arm to the 6-month arm and 95% CIs were estimated using Cox proportional hazards assumption for each subgroup. Associations between clinical features and DFS were assessed with a forest plot using HRs in each subgroup. At the time of analyzing the

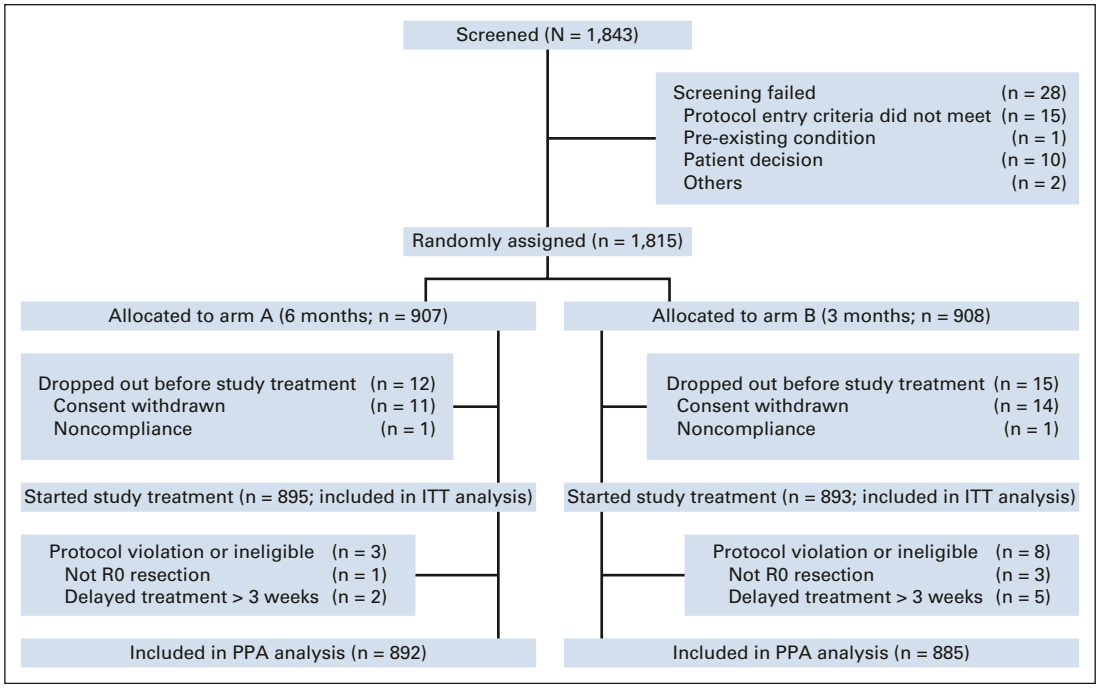


FIG 1. CONSORT diagram. ITT, intention-to-treat; PPA, per-protocol population analysis.

TABLE 1. Baseline Patients' Characteristics per Each Arm

Characteristic	Treatment Arm		
	6 Months (n = 895)	3 Months (n = 893)	Total (N = 1,788)
Age, years. median	58 (52-65)	58 (52-65)	
Sex, No. (%)			
Female	360 (40.2)	378 (42.3)	738
Male	535 (59.8)	515 (57.7)	1,050
ECOG PS, No. (%)			
0	489 (54.6)	501 (56.1)	990
1	406 (45.4)	392 (43.9)	798
Tumor site side, No. (%)			
Right	292 (32.6)	274 (30.7)	566
Left	597 (66.7)	611 (68.4)	1,208
Both	6 (0.7)	8 (0.9)	14
T stage, No. (%)			
TX	1 (0.1)		1
T1	44 (4.9)	43 (4.8)	87
T2	59 (6.6)	67 (7.5)	126
T3	630 (70.4)	635 (71.1)	1,265
T4	161 (18.0)	148 (16.6)	309
N stage, No. (%)			
N0	196 (21.9)	196 (22.0)	392
N1	540 (60.3)	533 (56.6)	1,073
N2	159 (17.8)	164 (18.4)	323
Nodes examined, No. (%)			
Median	23 (17-33)	23 (16-32)	
Stage, No. (%)			
High-risk stage II	196 (21.9)	196 (22.0)	392
Stage III	699 (78.1)	697 (78.0)	1,396
Extended stage, No. (%)			
High-risk stage II	196 (21.9)	196 (22.0)	392
Stage III (T1-3 and N1)	456 (51.0)	476 (53.3)	932
Stage III (T4 and/or N2)	243 (27.2)	221 (24.8)	464
Histologic differentiation, No. (%)			
Well	111 (12.4)	106 (11.9)	217
Moderate	704 (78.7)	717 (80.3)	1,421
Poorly	46 (5.1)	45 (5.0)	91
Others	39 (4.4)	28 (3.1)	67

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; N, node; T, tumor.

data, we also decided to perform additional examines for significant factors discovered in the previous studies.[14,15]

RESULTS

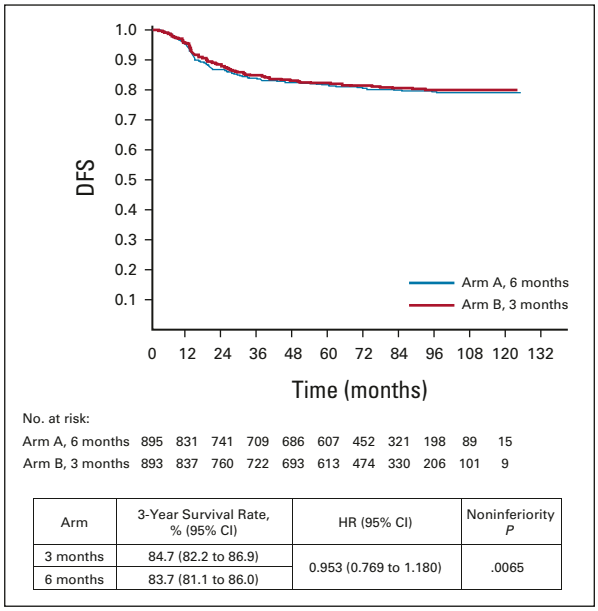
From January 2010 to January 2016, 1,815 patients were randomly selected from 21 Korean sites. The CONSORT diagram showed that 1.5% of screened patients were excluded from the random assignment of the study. Twenty-seven patients of the random assignment did not receive the study treatment because of consent withdrawn (n = 25) and noncompliance (n = 2). The ITT population comprised 1,788 patients (98.5%), including 895 in the 6-month arm and 893 in the 3-month arm (Fig 1). Patients enrolled in this study commonly received

TABLE 2. Neuropathic Toxicity in Intention-to-Treat Population (3-month arm *v* 6-month arm)

Toxicity	6 Months	3 Months	*P*
Neuropathy, No. (%)			
Yes	621 (69.46)	521 (58.34)	.000
No	273 (30.54)	372 (41.66)	
Neuropathy, grade, No. (%)			
1	393 (63.29)	395 (75.82)	.000
2	196 (31.56)	105 (20.15)	
3	30 (4.83)	21 (4.03)	
4	2 (0.32)		
Neuropathy with grade 3-4, No. (%)			
Yes	32 (3.58)	21 (2.35)	.1261
No	862 (96.42)	872 (97.65)	

fluoropyrimidine for 6 months. For the 6-month arm, 6 months of oxaliplatin treatment was planned, and for the 3-month arm, 3 months of oxaliplatin treatment was planned. A total of 1,396 (78.1%) patients had stage III CRC.

Baseline patient characteristics are presented in Table 1. There was no difference between the two arms in clinical and pathologic features. No significant difference was observed between the two arms in the sidedness of the primary tumor (right *v* left) or stage (high-risk stage II *v* stage III) that might potentially affect the outcomes. Particularly, when patients with stage III CRC were divided according to low and high risks that were previously defined, there was no difference between the two arms. The median number of nodes examined in the 6-month and 3-month arms was 23 (range, 17-33) and 23 (range, 16-32), respectively. This finding suggests that qualified surgery was performed in both arms.



Arm	3-Year Survival Rate, % (95% CI)	HR (95% CI)	Noninferiority *P*
3 months	84.7 (82.2 to 86.9)	0.953 (0.769 to 1.180)	.0065
6 months	83.7 (81.1 to 86.0)		

FIG 2. DFS by study group. DFS, disease-free survival; HR, hazard ratio.

Treatment Completion and Peripheral Sensory Neuropathy

Treatment compliance with the combination of oxaliplatin and fluoropyrimidine has already been reported in many previous studies. Herein, we report important and interesting points between the two arms. The treatment completion rate was 83.6% (748 of 895) in the 6-month arm and 85.7% (765 of 893) in the 3-month arm. The neuropathy rates with any grade were higher in the 6-month arm than in the 3-month arm (69.5% *v* 58.3%, $P < .0001$; Table 2). However, there was no difference in neuropathy of ≥ grade 3 between the two arms ($P = .1261$). We also analyzed the treatment adherence according to the study arm and treatment regimen. For fluorouracil and capecitabine, the relative dose intensity (RDI) that were delivered was 0.870 and 0.875, respectively, in the 3-month arm, as compared with 0.867 and 0.844 in the 6-month arm ($P > .05$). For oxaliplatin, the RDI in FOLFOX and CAPOX was 0.942 and 0.917, respectively, in the 3-month arm as compared with 0.835 and 0.810, respectively, in the 6-month arm ($P < .05$). For FOLFOX regimen, the RDI of oxaliplatin and fluorouracil was 0.871 and 0.868, respectively. For CAPOX regimen, the RDI of oxaliplatin and capecitabine was 0.845 and 0.859, respectively. There was no significant difference of the RDI for each drug between two regimens ($P > .05$).

DFS

The median follow-up duration was 78.7 months, and there were 336 DFS events. The 3-year DFS rates were 83.7% (95% CI, 81.1 to 86.0) in the 6-month arm and 84.7% (95% CI, 82.2 to 87.0) in the 3-month arm. The 5-year DFS rates were 81.6% (95% CI, 78.9 to 84.1) in the 6-month arm and 82.2% (95% CI, 79.5 to 84.6) in the 3-month arm. The HR for DFS of the 6-month arm versus the 3-month arm was 0.953 (95% CI, 0.769 to 1.180; test for noninferiority, $P = .0065$) within the noninferiority margin (Fig 2).

Next, we analyzed the DFS between the two arms according to subgroups of the stage (Fig 3). In patients with high-risk stage II CRC, the 3-year DFS rates were 93.1% (95% CI, 88.4 to 95.9) in the 6-month arm and 88.9% (95% CI, 83.5 to 92.6) in the 3-month arm, with an HR of 1.192 (95% CI, 0.698 to 2.036; test for noninferiority, $P = .4313$), which did not meet the criteria for noninferiority (Fig 3A). Furthermore, we divided patients with stage III CRC into two subgroups (high-risk stage III: T4 and/or N2; low-risk stage III: T1-3N1) on the basis of prognosis. The noninferiority of the 3-month arm compared with the 6-month arm was not proven in both the T1-3N1 population (HR, 0.900; 95% CI, 0.640 to 1.266; test for noninferiority, $P = .0296$; Fig 3B) and the T4 and/or N2

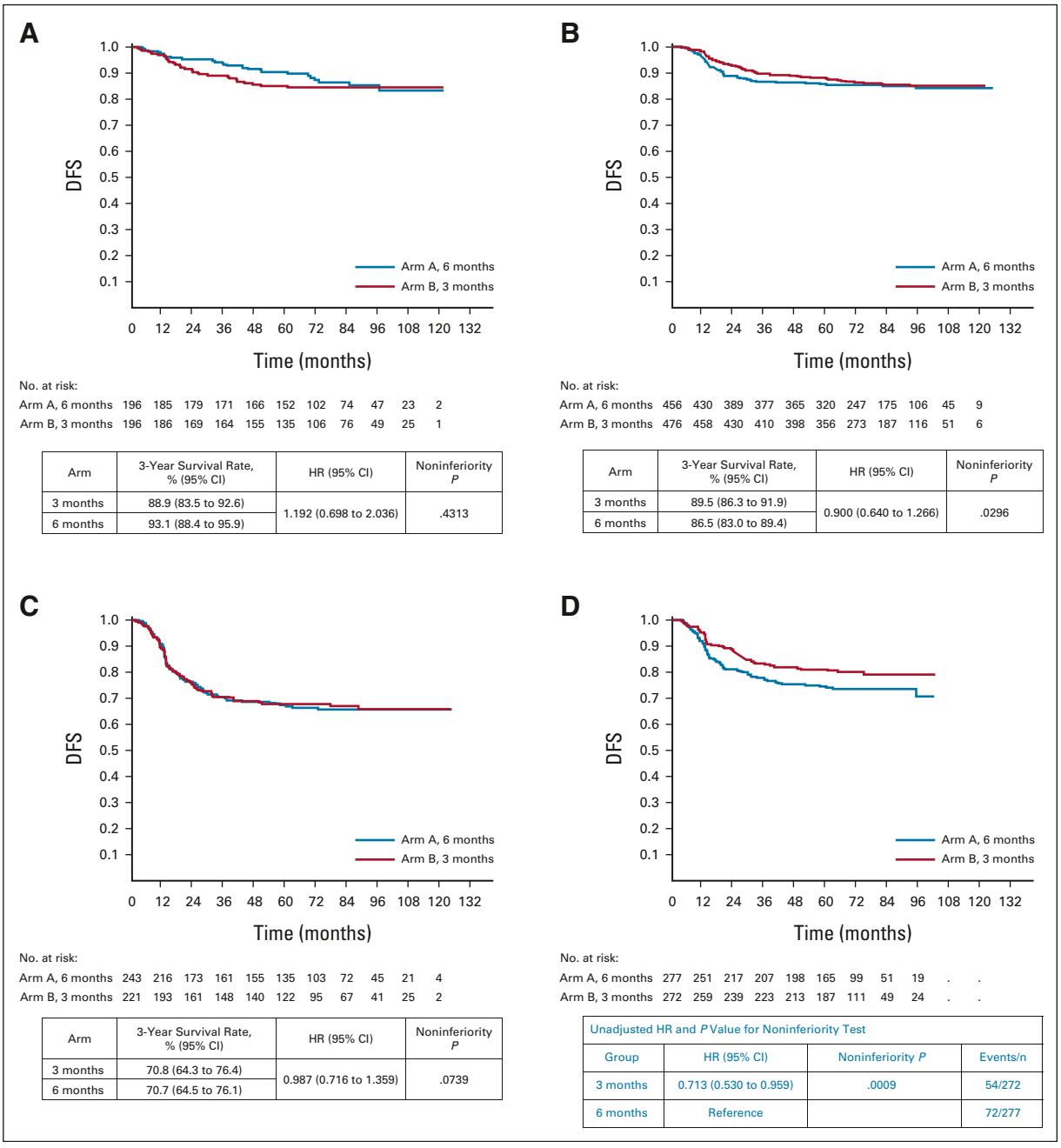
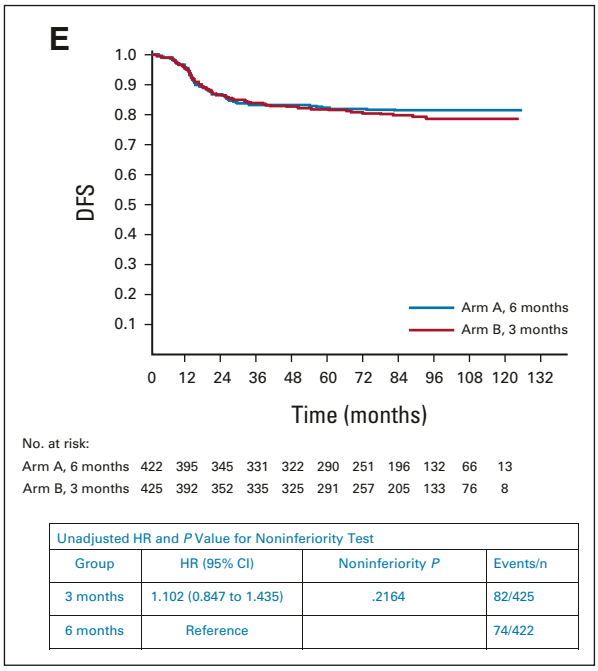


FIG 3. DFS by study group, stage group, and regimen: (A) stage II high risk, (B) stage III low risk, (C) stage III high risk, (D) CAPOX, and (E) FOLFOX. CAPOX, capecitabine plus oxaliplatin; DFS, disease-free survival; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio. (continued on next page)

population (HR, 0.987; 95% CI, 0.716 to 1.359; test for noninferiority, $P = .0739$; Fig 3C).

We also evaluated the DFS between the two arms according to subgroups of regimens. The clinicopathologic characteristics between patients receiving FOLFOX and CAPEOX are presented in Appendix Table A1 (online only). For patients with stage III CRC receiving CAPOX, the 3-year DFS of the 3-month arm was noninferior as compared with that of the 6-month arm with an HR of 0.713 (95% CI, 0.501 to 1.015; test for noninferiority, $P = .0009$; Fig 3D). However, among patients with high-risk stage II and/or stage III CRC receiving FOLFOX, the noninferiority of the 3-month arm compared with the 6-month arm was not proven (Fig 3E).

The forest plot (Fig 4) showed that the noninferiority of the 3-month arm was demonstrated only in the subgroup of



Unadjusted HR and *P* Value for Noninferiority Test			
Group	HR (95% CI)	Noninferiority *P*	Events/n
3 months	1.102 (0.847 to 1.435)	.2164	82/425
6 months	Reference		74/422

FIG 3. (Continued).

the CAPOX regimen ($P = .0441$). Among 1,788 patients in the ITT population, 551 patients received CAPOX, including 278 in the 6-month arm and 273 in the 3-month arm. The HR for OS of the 6-month arm versus the 3-month arm was 0.86 (95% CI, 0.635 to 1.165; $P = .3304$; Fig 5).

DISCUSSION

This study showed the noninferiority of 3 months of oxaliplatin in combination with 6 months of fluorouracil (FU) therapy (3-month arm) compared with 6 months of oxaliplatin and FU therapy (6-month arm) in patients with high-risk stage II and III CRC. On the basis of subset analysis, in the subgroups of high-risk stage II, T1-3N1, and T4 and/or N2, the noninferiority of the 3-month arm compared with the 6-month arm was not proven. Among patients with stage III CRC treated by CAPOX, the 3-year DFS of the 3-month arm was noninferior as compared with that of the 6-month arm with an HR of 0.713 (95% CI, 0.530 to 0.959; test for noninferiority, $P = .0009$). However, among patients with high-risk stage II and stage III CRC treated by FOLFOX, the noninferiority of the 3-month arm compared with the 6-month arm was not proven. In terms of neurotoxicity, as expected, 3 months of oxaliplatin treatment showed a significantly lower neuropathy rate with any grade (58.3%) compared with 6 months of oxaliplatin treatment (69.5%). These findings suggest that adding 3 months of oxaliplatin to 6 months of capecitabine (CAPOX) could be considered an alternative adjuvant treatment for stage III CRC.

We also compared DFS in the 3-month arm with that of patients in the 6-month arm who received oxaliplatin of at least 5 months, to evaluate more accurately the influence of the duration of oxaliplatin on DFS. This analysis presented that the noninferiority of the 3-month arm compared with the 6-month arm was not proven (Appendix Fig A1, online only).

In the present study, only mFOLFOX6 could be used for high-risk stage II CRC. Thus, whether 3 months of oxaliplatin treatment on the basis of the CAPOX regimen is sufficient in high-risk stage II diseases is not known in this study. For stage III CRC, mFOLFOX6 or CAPOX could be used by the investigator's decision. This study included 1,396 stage III patients (78.1%) among the ITT population (1,788 patients). Of the 1,396 stage III patients, 551 (39.5%) received CAPOX, including 278 in the 6-month arm and 273 in the 3-month arm. In this study, noninferiority between the 3- and 6-month arms was seen only among patients receiving CAPOX and not FOLFOX. The forest plot for DFS showed that the noninferiority of the 3-month arm was demonstrated only in the subgroup of the CAPOX regimen ($P = .0441$). This finding is consistent across the trials including the IDEA consortium. The findings suggest that on the basis of the CAPOX regimen, 3 months of oxaliplatin might be substituted for 6 months of oxaliplatin, irrespective of the risk of stage III disease. However, since all trials did not conduct the random assignment according to regimens (CAPOX *v* FOLFOX), any definite answer could not be made about whether either adjuvant regimen was better. Some hypotheses have been proposed as follows: the difference of dosing schedule of oxaliplatin and FU and the delivery of FU between two regimens.

The current guidelines on the basis of phase III studies recommend that adjuvant oxaliplatin-based chemotherapy should be offered for a duration of 6 months for patients with T4 and/or N2 stage III CRC.[7] For patients with T1-3N1 stage III CRC, adjuvant oxaliplatin-based chemotherapy may be offered for a duration of 3 or 6 months after a discussion with patients. The present study supports the recommendations of current guidelines in patients with stage III CRC receiving CAPOX. In this study, FU was used for 6 months in both the 3- and 6-month arms of oxaliplatin. However, other phase III studies for 3 versus 6 months of adjuvant therapy in CRC used the same treatment duration for FU and oxaliplatin.[15-18] Considering similar findings between the present study and previous phase III studies, 3 months of FU might be sufficient as the counterpart of 3 months of oxaliplatin.

For patients with low-risk stage III CRC, this study showed that 3-year DFS in 3- and 6 month arms was 89.5% and 86.5%, respectively. Among patients with high-risk stage III CRC, DFS in 3- and 6-month arms was 70.8% and 70.7%, respectively. Meanwhile, in the IDEA consortium, 3-year DFS for 3- and 6-month arms in low risk was 83.1% and 83.3%, respectively, and

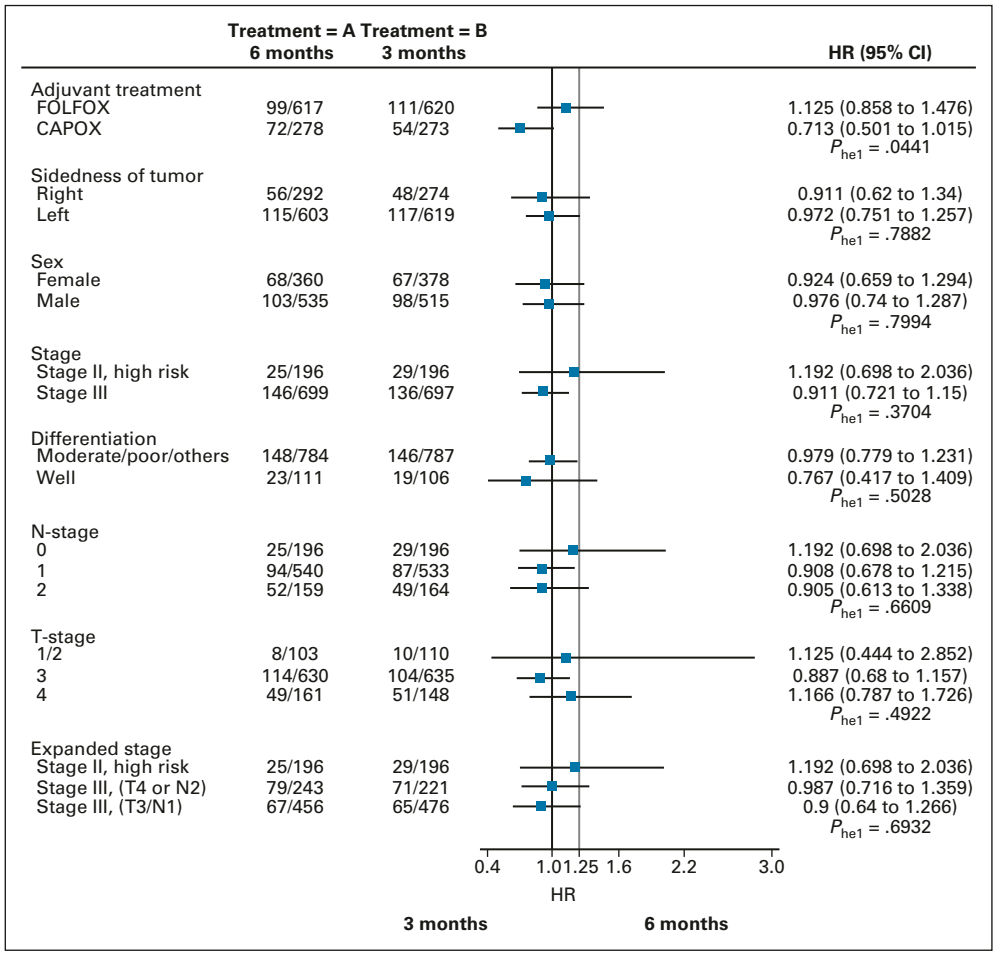
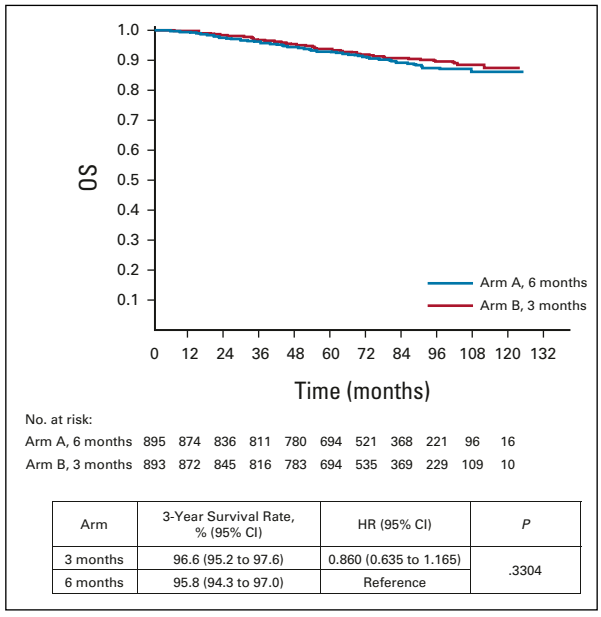


FIG 4. Forest plot for disease-free survival. FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; CAPOX, capecitabine plus oxaliplatin; Het, heterogeneity; HR, hazard ratio; N, node; T, tumor.



Arm	3-Year Survival Rate, % (95% CI)	HR (95% CI)	*P*
3 months	96.6 (95.2 to 97.6)	0.860 (0.635 to 1.165)	.3304
6 months	95.8 (94.3 to 97.0)	Reference	

FIG 5. OS by study group. HR, hazard ratio; OS, overall survival.

in high risk was 62.7% and 64.4%, respectively.[14] As compared with the IDEA consortium, 3-year DFS for the 3-month arm in this study commonly showed favorable trends commonly irrespective of the risk in stage III. This finding might suggest that the strategy of the discontinuation of oxaliplatin at 3 months while continuing a FU is better than that of the discontinuation of both oxaliplatin and FU at 3 months. Additionally, in subgroup analyses, although statistical noninferiority was not proven among patients with T4 N2, the DFS curve essentially was overlapped between the 3- and 6-month arms. This finding might also support the discontinuation of oxaliplatin at 3 months while continuing a FU, a common clinical practice.

In this study, the 3-year DFS rates for high-risk stage II and III CRCs were 83.7% (95% CI, 81.1 to 86.0) in the 6-month arm and 84.7% (95% CI, 82.2 to 87.0) in the 3-month arm. The 3-DFS rate in the control arm was observed as 83.7%. This rate is much higher than the hypothesized rate (78%) and the rate of the control arm in the IDEA trial (75.5%). This discrepancy may be caused by heterogeneous risks of diseases among studies. In the present study, patients with high-risk stage II and low-risk stage III CRC occupied 73.9% of overall study population. However, in the IDEA

trial, patients of the same stage held 58.7% of overall study population. The different proportion of stages among studies affected the 3-year DFS rates in the control arm as well as in the experimental arm. Thus, although studies had the different 3-year DFS rates in the control and the experimental arms, studies had the similar statistical power and noninferior margin.

Stage II disease is known to be biologically different from stage III disease, with different sensitivities to chemotherapy. The molecular biology of cancers that move directly from the primary site to distant metastasis without going through the lymph node route is different from that with going through the lymph node route. The present study included a small proportion of patients with high-risk stage II CRC (392 of 1,788, 21.9%), and all patients with stage II tumors received treatment with mFOLFOX6; the two DFS curves for high-risk stage II differed substantially, with a 4.2% absolute difference at 3 years in favor of the 6-month arm. This finding is similar to that of the Three or Six Colon Adjuvant trial.[16] However, in the SCOT study, 3 months of treatment showed a favorable trend for DFS in high-risk stage II disease.[15] These discordant findings in high-risk stage II disease may be due to different sample sizes and chemotherapy regimens among studies. Especially, in this study, what all patients with high-risk stage II CRC received only FOLFOX might affect the difference of the 3-year DFS between the 3- and 6-month arms.

In conclusion, 3 months of oxaliplatin in combination with 6 months of FU therapy was not inferior to 6 months of oxaliplatin in combination with 6 months of FU therapy for patients with high-risk stage II and III CRC. In particular, for patients with stage III CRC treated with CAPOX, adding 3 months of oxaliplatin to 6 months of FU therapy could be strongly supported.

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REFERENCES

1. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 322:352-358, 1990
2. Andre 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
3. 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
4. Haller DG, Tabernero J, Maroun J, et al: Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 29:1465-1471, 2011

5. Schmoll HJ, Van Cutsem E, Stein A, et al: ESMO consensus guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 23:2479-2516, 2012
6. Land SR, Kopec JA, Cecchini RS, et al: Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J Clin Oncol 25:2205-2211, 2007
7. Lieu C, Kennedy EB, Bergsland E, et al: Duration of oxaliplatin-containing adjuvant therapy for stage III colon cancer: ASCO clinical practice guideline. J Clin Oncol 37:1436-1447, 2019
8. Pachman DR, Qin R, Seisler DK, et al: Clinical course of oxaliplatin-induced neuropathy: Results from the randomized phase III trial N08CB (Alliance). J Clin Oncol 33:3416-3422, 2015
9. Tournigand C, Cervantes A, Figer A, et al: OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer—A GERCOR study. J Clin Oncol 24:394-400, 2006
10. Chibaudel B, Maindrault-Goebel F, Lledo G, et al: Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. J Clin Oncol 27:5727-5733, 2009
11. Andre T, de Gramont A, Vernerey D, et al: Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: Updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol 33:4176-4187, 2015
12. Schmoll HJ, Cartwright T, Tabernero J, et al: Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: A planned safety analysis in 1, 864 patients. J Clin Oncol 25:102-109, 2007
13. Matsumoto S, Nishimura T, Kanai M, et al: Safety and efficacy of modified FOLFOX6 for treatment of metastatic or locally advanced colorectal cancer. A single-institution outcome study. Chemotherapy 54:395-403, 2008
14. Andre T, Meyerhardt J, Iveson T, et al: Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): Final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol 21:1620-1629, 2020
15. Iveson TJ, Kerr RS, Saunders MP, et al: 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): An international, randomised, phase 3, non-inferiority trial. Lancet Oncol 19:562-578, 2018
16. Sobrero A, Lonardi S, Rosati G, et al: FOLFOX or CAPOX in stage II to III colon cancer: Efficacy results of the Italian three or six colon adjuvant trial. J Clin Oncol 36:1478-1485, 2018
17. Andre T, Vernerey D, Mineur L, et al: 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. J Clin Oncol 36:1469-1477, 2018
18. Grothey A, Sobrero AF, Shields AF, et al: Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 378:1177-1188, 2018

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Oxaliplatin (3 months *v* 6 months) With 6 Months of Fluoropyrimidine as Adjuvant Therapy in Patients With Stage II/III Colon Cancer: KCSG CO09-07

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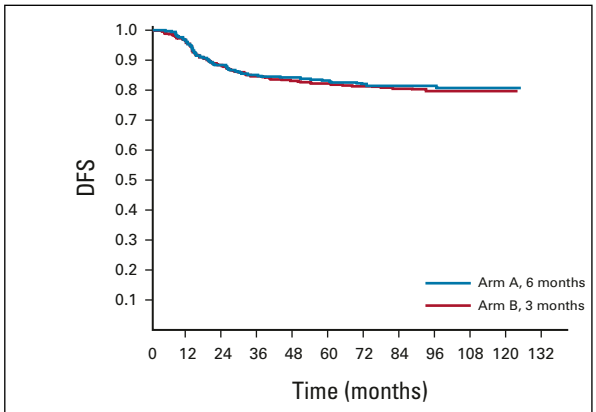
APPENDIX

TABLE A1. Baseline Patients' Characteristic per Treatment Regimen

Characteristic	Treatment Regimen		*P*
	FOLFOX (n = 1,237)	CAPOX (n = 551)	
Sex, No. (%)			
Female	525 (42.4)	213 (38.7)	.1334
Male	712 (57.6)	338 (61.3)	
Tumor site side, No. (%)			
Right	396 (32.0)	170 (30.8)	.6263
Nonright	841 (68.0)	381 (69.2)	
T stage, No. (%)			
TX/1/2	129 (10.4)	85 (15.3)	.0107
T3	885 (71.5)	380 (69.1)	
T4	223 (18.0)	86 (15.6)	
N stage, No. (%)			
N0	390 (31.5)	2 (0.4)	.0000
N1	654 (52.9)	419 (76.0)	
N2	193 (5.6)	130 (23.6)	
Stage, No. (%)			
High-risk stage II	390 (31.5)	2 (0.4)	.0000
Stage III	847 (68.5)	549 (99.6)	
Extended stage, No. (%)			
High-risk stage II	390 (31.5)	2 (0.4)	.0000
Stage III (T1-3 and N1)	567 (45.8)	365 (66.2)	
Stage III (T4 and/or N2)	280 (22.6)	184 (33.4)	
Histologic differentiation, No. (%)			
Well	146 (11.8)	71 (12.9)	.5173
Moderate/poorly/others	1,091 (88.2)	480 (87.1)	

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; N, node; T, tumor.



No. at risk:

Arm A, 6 months	565	535	479	458	447	403	311	232	151	69	10
Arm B, 3 months	893	837	760	722	693	613	474	330	206	101	9

Group	3-Year Survival Rate, % (95% CI)	HR (90% CI)	Noninferiority *P*
3 months	84.7 (82.2 to 86.9)	1.047 (0.851 to 1.289)	.0806
6 months	84.8 (81.5 to 87.5)	Reference	

FIG A1. Comparison of DFS in the 3-month arm with that of patients in the 6-month arm who received oxaliplatin of at least 5 months. DFS, disease-free survival; HR, hazard ratio.