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% vs 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 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).
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 (1) 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 permuted 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, 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.](image-url)
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

| Characteristic           | Treatment Arm |            | Total (N = 1,788) |
|--------------------------|---------------|-----------|-------------------|
|                          | 6 Months (n = 895) | 3 Months (n = 893) |                |
| 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.
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 vs left) or stage (high-risk stage II vs 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.

### 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% vs 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 population (HR, 0.871; 95% CI, 0.698 to 1.087; test for noninferiority, P = .1539).
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, 0.530 to 0.959; 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
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 vs 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. 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. 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

| Group | HR (95% CI) | P Noninferiority | Events/n |
|-------|------------|------------------|----------|
| 3 months | 1.142 (0.847 to 1.539) | .2164 | 82/425 |
| 6 months | Reference | .3304 | 74/422 |

![FIG 3. (Continued).](image-url)

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.
in high risk was 62.7% and 64.4%, respectively.\textsuperscript{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

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Treatment & A & B & HR (95% CI) \\
\hline
Adjuvant treatment & & & \\
FOLFOX & 99/617 & 111/620 & 1.125 (0.858 to 1.476) \\
CAPOX & 72/278 & 54/273 & 0.713 (0.501 to 1.015) \\
Sidedness of tumor & & & \\
Right & 56/292 & 48/274 & 0.911 (0.62 to 1.34) \\
Left & 115/603 & 117/619 & 0.972 (0.751 to 1.257) \\
Sex & & & \\
Female & 68/360 & 67/378 & 0.924 (0.659 to 1.294) \\
Male & 103/535 & 98/515 & 0.976 (0.74 to 1.287) \\
Stage & & & \\
Stage II, high risk & 25/196 & 29/196 & 1.192 (0.698 to 2.036) \\
Stage III & 146/699 & 136/697 & 0.911 (0.721 to 1.15) \\
Differentiation & & & \\
Moderate/poor/others & 148/784 & 146/787 & 0.979 (0.779 to 1.231) \\
Well & 23/111 & 19/106 & 0.767 (0.417 to 1.409) \\
N-stage & & & \\
0 & 25/196 & 29/196 & 1.192 (0.698 to 2.036) \\
1 & 94/540 & 87/533 & 0.906 (0.678 to 1.215) \\
2 & 52/159 & 49/154 & 0.905 (0.613 to 1.338) \\
T-stage & & & \\
1/2 & 8/103 & 10/110 & 1.125 (0.444 to 2.852) \\
3 & 114/630 & 104/635 & 0.887 (0.68 to 1.157) \\
4 & 49/161 & 51/148 & 1.166 (0.787 to 1.726) \\
Expanded stage & & & \\
Stage II, high risk & 25/196 & 29/196 & 1.192 (0.698 to 2.036) \\
Stage III, (T4 or N2) & 79/243 & 71/221 & 0.987 (0.716 to 1.359) \\
Stage III, (T3/N1) & 67/456 & 65/476 & 0.9 (0.64 to 1.266) \\
\hline
\end{tabular}
\caption{OS by study group. HR, hazard ratio; OS, overall survival.}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{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.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{OS by study group. HR, hazard ratio; OS, overall survival.}
\end{figure}
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. However, in the SCOT study, 3 months of treatment showed a favorable trend for DFS in high-risk stage II disease. 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.

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

AFFILIATIONS

1Sungkyunkwan University School of Medicine, Samsung Medical Centre, Seoul, South Korea
2Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
3Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Korea
4Yonsei University College of Medicine, Seoul, Korea
5Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
6Good Gangan Hospital Cancer Center, Pusan, South Korea
7Ajou University School of Medicine, Suwon, South Korea
8Gachon University Gil Hospital, Incheon, Korea
9Hallym University Medical Center, Hallym University, Anyang, Korea, South Korea
10Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
11Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea
12Gyeongsang National University, Jinju, Korea
13Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, South Korea
14Goyang Good Clinic, Goyang, Korea
15Center for Colorectal Cancer, Southwest Centre, Seoul, South Korea
16Hallym University Pusan College of Medicine, Goyang, Korea
17Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea
18Samsung Medical Center, Seoul, South Korea
19Yonsei University College of Medicine, Seoul, Korea
20Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
21Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea
22Hospital Group (KCSG CO09-07) and Sano-Aventis (including investigational product supply).

CLINICAL TRIAL INFORMATION

NCT01092481

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02962.

AUTHOR CONTRIBUTIONS

Conception and design: Sun Young Kim, Seong Hyeon Yun, Ji Yeon Baek, Seong Geun Kim, Sun Jin Sym, Dae Young Zang, Yeul Hong Kim, Min-Ji Kim, Young Suk Park
Administrative support: Seong Hyeon Yun
Provision of study materials or patients: Sun Young Kim, Seong Hyeon Yun, Seek-Byung Lim, Jae Hwan Oh, Joong Bae Ahn, Seong Geun Kim, Sun Jin Sym
Collection and assembly of data: Seung Tae Kim, Sun Young Kim, Seong Hyeon Yun, Hee Cheol Kim, Woo Yong Lee, Tae Won Kim, Yong Sang Hong, Seok-Byung Lim, Ji Yeon Baek, Jae Hwan Oh, Joong Bae Ahn, Sang Joon Shin, Sae-Won Han, Seong Geun Kim, Seok Yun Kang, Sun Jin Sym, Dae Young Zang, Yeul Hong Kim, In Sil Choi, Jung Hun Kang, Min-Ji Kim, Young Suk Park
Data analysis and interpretation: Seung Tae Kim, Sun Young Kim, Jeeyun Lee, Tae Won Kim, Sang Joon Shin, Dae Young Zang, Yeul Hong Kim, Min-Ji Kim, Young Suk Park
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02962.
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, Kopech 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

---

Adjuvant Chemotherapy in Colon Cancer
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sun Young Kim
Consulting or Advisory Role: Ono Korea Co, Ltd
Research Funding: Roche/Genentech (Inst)

Jeeyun Lee
Consulting or Advisory Role: Oncologie, Mirati Therapeutics
Research Funding: AstraZeneca, Merck Sharp & Dohme

Tae Won Kim
Employment: Asan Medical Center
Consulting or Advisory Role: Pfizer (Inst)
Research Funding: Sanofi (Inst), AstraZeneca (Inst), Roche/Genentech (Inst)

Yeul Hong Kim
Stock and Other Ownership Interests: OncoMaster
Research Funding: MSD Oncology (Inst), Ono Pharmaceutical (Inst), Macrogenics (Inst), Korea Astellas (Inst), Zymeworks (Inst)

No other potential conflicts of interest were reported.

© 2022 by American Society of Clinical Oncology Volume 40, Issue 33
## APPENDIX

### TABLE A1. Baseline Patients’ Characteristic per Treatment Regimen

| Characteristic               | FOLFOX (n = 1,237) | CAPOX (n = 551) | P      |
|-----------------------------|--------------------|----------------|--------|
| 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.
Arm B, 3 months
Arm A, 6 months

| 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 (87.0 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.