Introduction

In the 1980s, a large-scale randomized clinical study performed in the U.S.A. demonstrated the usefulness of combination therapy with 5-fluorouracil and levamisole (5-FU/LEV therapy) as adjuvant chemotherapy for patients with colon cancer. In the late 1980s, it was reported that 5-FU combined with leucovorin (5-FU/LV therapy) was more useful than lomustine, vincristine and 5-FU (MOF therapy) or surgery alone, after which 5-FU/LV therapy became a standard treatment option. Subsequently, 5-FU/LV was compared with 5-FU/LEV and the effect of adding LEV or interferon to 5-FU/LV therapy was investigated, demonstrating that 5-FU/LV was superior to 5-FU/LEV and there was no benefit of adding LEV or interferon to 5-FU/LV therapy. Based on these findings, 5-FU/LV therapy became standard adjuvant chemotherapy for colon cancer.

In the late 1990s, oral fluoropyrimidine formulations were investigated to improve the convenience of treatment. Lembersky et al. compared 5-FU/LV therapy (RPMI regimen) and tegafur uracil (UFT)/LV therapy in patients with stage II/III colon cancer, revealing non-inferiority of UFT/LV therapy to 5-FU/LV therapy based on disease-free survival (DFS) (hazard ratio [HR]: 1.004; 95% confidence interval [CI]: 0.847-1.190). Twelve et al. compared 5-FU/LV (Mayo regimen) and capecitabine in patients with stage III colon cancer and they demonstrated non-inferiority of capecitabine to 5-FU/LV, but not superiority, based on DFS (HR: 0.87; 95% CI: 0.75-1.00, P<0.001). Subsequently, both UFT/LV therapy and capecitabine became standard treatments.

In the 2000s, the effect of adding oxaliplatin was assessed by de Gramont et al. in a study comparing LV5FU2 with oxaliplatin + LV5FU2 (FOLFOX4 therapy) for stage II/III colon cancer, which showed the superiority of FOLFOX4 therapy based on 3-year DFS (78.2% vs. 72.9%; HR=0.77, P=0.002). These findings led to approval of FOLFOX as adjuvant chemotherapy for colon can-
cancer in Western countries. A follow-up study showed that FOLFOX4 therapy was significantly superior to LV5FU2 with respect to 5-year DFS (73.5% vs. 67.4%; HR=0.80, \( P=0.003 \)) and 6-year overall survival (OS) (78.5% vs. 76.0%; HR=0.84, \( P=0.046 \)), demonstrating the usefulness of FOLFOX for prolonging OS in addition to DFS. Stratified analysis showed that there was no difference between the two therapies in stage II patients (5-year DFS: 83.7% vs. 79.9%; HR=0.84, \( P=0.258 \) and 6-year survival rate: 86.9% vs. 86.8%; HR=1.00, \( P=0.986 \)), but FOLFOX4 therapy achieved better 5-year DFS and 6-year survival in stage III patients (5-year DFS: 66.4% vs. 58.9%; HR=0.78, \( P=0.005 \) and 6-year survival rate: 72.9% vs. 68.7%; HR=0.80, \( P=0.023 \)). Furthermore, Haller et al. compared 5-FU/LV therapy (RPMI or Mayo regimen) with oxaliplatin + capecitabine (XELOX therapy) for stage III colon cancer, and showed the superiority of XELOX therapy with respect to 3-year DFS (70.9% vs. 66.5%; HR=0.80, \( P=0.0045 \)). These results demonstrated the effectiveness of oxaliplatin with 5-FU derivatives, leading to approval of FOLFOX therapy in 2009 and XELOX therapy in 2011 in Japan.

The above-mentioned studies of oxaliplatin combined with 5-FU/LV performed in Western countries have demonstrated the usefulness of adjuvant chemotherapy with oxaliplatin for colon cancer. However, the efficacy and safety of oxaliplatin therapy have not been evaluated in Japan. Accordingly, we designed a phase II clinical study to determine whether oxaliplatin + 5-FU/LV (FOLFOX therapy) is effective adjuvant chemotherapy for Japanese patients with colon cancer, and to assess safety and adverse reactions during 12 courses of FOLFOX therapy. The primary endpoint of the study is DFS. Evaluation of DFS and OS in a database of 33,573 patients from 49 studies performed in Western countries revealed a moderate correlation between 3-year DFS and 6-year OS for stages II and III combined, while there were strong correlations between 3-year DFS and 5-year or 6-year OS in stage III patients. Moreover, the correlations between 2-year DFS and 5-year or 6-year OS were as strong as those between 3-year DFS and 5-year or 6-year OS. Based on these findings, we planned to evaluate 2-year and 3-year DFS in the present study. Because the Japanese national health insurance scheme accepted XELOX therapy for coverage in 2011 after this study had commenced, we added investigation of the efficacy and safety of XELOX to this study.

### Protocol Digests of the Study

**Objective**

The study is a phase II clinical study that is designed to demonstrate the efficacy of oxaliplatin + 5-FU/LV (FOLFOX therapy) and L-OHP + capecitabine (XELOX therapy) as adjuvant chemotherapy for Japanese patients with colon cancer, as well as the safety of FOLFOX therapy (12 cycles) and XELOX therapy (8 cycles) with a focus on the profile of adverse reactions.

**Endpoints**

The primary endpoint is 3-year DFS. The secondary endpoints are safety (adverse events [AEs]), the completion rate of study therapy, 2-year DFS, and 5-year OS.

**Eligibility Criteria**

**Inclusion Criteria**

1. Histologically confirmed stage III colon cancer (including rectosigmoid cancer).
2. D2- or D3-lymph node dissection according to the guidelines of the Japanese Society for Cancer of the Colon, Rectum, and Anus.
3. R0 resection of the primary tumor.
4. Age from 20 to 75 years at the time of giving informed consent.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
6. No prior chemotherapy or radiotherapy for colon cancer.
7. Adequate function of vital organs, as evidenced by the following data obtained within 7 days before registration (patients with the following levels of bone marrow, hepatic, and renal function based on the data obtained within 1 week before enrollment): 1) White blood cell count >4,000/mm\(^3\) and <12,000 mm\(^3\) 2) Neutrophil count >2,000/mm\(^3\) 3) Platelet count >100,000 mm\(^3\) 4) Hemoglobin >9.0 g/dL 5) Total bilirubin <2.0 mg/dL 6) Aspartate aminotransferase (AST) / glutamate oxaloacetate transaminase (GOT) <100 IU/L 7) Alanine aminotransferase (ALT) / glutamate pyruvate transaminase (GPT) <100 IU/L 8) Serum creatinine below the institutional upper limit of normal
9. Able to start the protocol treatment within 4 to 8 weeks after surgery.
10. Able to provide written informed consent before initiation of study-related procedures.

**Exclusion Criteria**

The exclusion criteria are:

- More than one synchronous cancer or more than one metachronous cancer separated by less than 5 years
- Serious postoperative complications, including
postoperative severe infection, anastomotic leakage, and gastrointestinal bleeding that have not resolved by enrollment.

3. Peripheral sensory neuropathy.
4. Uncontrolled hypertension.
5. Uncontrolled diabetes mellitus.
6. Significant electrocardiographic abnormalities or clinically problematic cardiac disease.
7. Severe pulmonary disease (including interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema, etc.).
8. Serious psychological or central nervous system disorders.
10. Ongoing systemic steroid therapy (oral or intravenous).
11. Women who are pregnant, possible pregnant, or breast-feeding, and women of childbearing potential who wish to become pregnant.
12. Patients for whom the study treatment is considered inappropriate by the investigator or subinvestigator.

Registration
An eligibility report form is sent to the registration center at the Department of Digestive and General Surgery of Saitama Medical Center (Saitama Medical University, Saitama, Japan). Information regarding the necessary follow-up tests is then sent to the investigator from the registration center. The registration period was from April 2010 to April 2014, and the ongoing follow-up period is 5 years from enrollment of the last subject.

Study Design
This study is being conducted in accordance with the Declaration of Helsinki (2008) and is registered with the University Hospital Medical Information Network Clinical Trial Registry [UMIN 000005427 (http://www.umin.ac.jp/ctr/indes.htm)].

Study Treatment
mFOLFOX6: Administration of l-LV (200 mg/m²) and oxaliplatin (85 mg/m²) by intravenous infusion over 2 hours, followed by rapid intravenous infusion of 5-FU (400 mg/m²) and then the slow infusion of 5-FU (2,400 mg/m² over 46 hours). This regimen is repeated every 2 weeks for 12 cycles.

XELOX: Intravenous infusion of oxaliplatin (130 mg/m² over 2 hours) on day 1 and oral administration of capecitabine (1,000 mg/m² twice daily) from the evening of day 1 to the morning of day 15. This regimen is repeated every 3 weeks for 8 cycles.

Dose Reduction and Withdrawal Criteria
The types and severities of AEs are evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0\textsuperscript{19}. In addition, peripheral neuropathy is assessed in accordance with the Neurotoxicity Criteria of Debiopharm (DEB-NTC)\textsuperscript{20-22}. Dose reduction for subsequent courses is based on AEs that occurred during the previous course, as detailed below. The dose may be reduced twice, after which protocol treatment is discontinued if a third dose reduction is required. The dose cannot be increased again after being reduced.

mFOLFOX6: If grade ≥3 AE (neutropenia, thrombocytopenia, other hematological toxicity, or diarrhea) occurs, the doses of oxaliplatin and 5-FU are reduced as follows: the dose of oxaliplatin is reduced to 75 mg/m², bolus 5-FU is reduced to 300 mg/m², and infusional 5-FU is reduced to 2,000 mg/m². If a similar AE occurs subsequently, the doses are reduced further to 50, 200 and 1,500 mg/m², respectively. If grade ≥3 skin toxicity or stomatitis occurs, the doses of bolus 5-FU and infusional 5-FU are reduced to 300 and 2,000 mg/m², respectively. If a similar AE occurs subsequently, the doses are reduced further to 200 and 1,500 mg/m², respectively. If peripheral neuropathy occurs, dose reduction or withdrawal of treatment is performed (Table 1).

XELOX: The dose of capecitabine is reduced for grade ≥3 neutropenia, thrombocytopenia, diarrhea, hand-foot syndrome, stomatitis, skin toxicity, or other non-hematologic toxicity, or for a second or subsequent occurrence of hand-foot syndrome (Table 2). If peripheral neuropathy occurs, dose reduction or withdrawal of treatment is performed (Table 1).

<p>| Table 1. Dose reduction for oxaliplatin in mFOLFOX6 therapy if peripheral neuropathy occurs |</p>
<table>
<thead>
<tr>
<th>CTCAE grade</th>
<th>&lt;14 days</th>
<th>≥14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>75 mg/m²</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Withdrawal of L-OHP</td>
<td></td>
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<tr>
<td></td>
<td>Continuation of 5-FU/L-V</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Withdrawal of L-OHP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuation of 5-FU/L-V</td>
<td></td>
</tr>
</tbody>
</table>

Acute pharyngolaryngeal paresthesia:

Increase infusion time to 4-6 hours without dose reduction

CTCAE, Common Terminology Criteria for Adverse Events; L-OHP, oxaliplatin
neuropathy occurs, dose reduction or withdrawal of treatment is performed (Table 3).

Criteria for Starting the Next Cycle
The following criteria must be met on the day before or on the planned first day (Day 1) of each cycle of treatment. If all of the criteria are not fulfilled, treatment is postponed until they are met.
1) White blood cell count >3,000/mm$^3$ and <12,000 mm$^3$
2) Neutrophil count >1,500/mm$^3$
3) Platelet count >75,000 mm$^3$
4) Hemoglobin >9.0 g/dL
5) Total bilirubin <2.0 mg/dL
6) AST (GOT) <100 IU/L
7) ALT (GPT) <100 IU/L
8) Serum creatinine below the institutional upper limit of normal
9) Peripheral neuropathy: grade ≤2

Discontinuation Criteria
If any of the following criteria are met, protocol treatment is discontinued.
1. Recurrence of the primary tumor or a new cancer occurs after initiation of treatment.
   1) Recurrence of the primary tumor.
   2) Development of a new cancer.
2. Protocol treatment cannot be continued because of an AE.
   1) Occurrence of grade ≥2 hypersensitivity.
   2) The criteria for starting the next cycle are not met within 3 weeks (21 days) after the planned day of initiating treatment because of an AE.
   3) Occurrence of further toxicity meeting the dose reduction criteria after two dose reductions.
   4) Discontinuation is considered necessary by the investigator because of an AE, even if the criteria are not met.
3. The patient makes a request to discontinue treatment.
5. A protocol violation is found or the pathological diagnosis is changed after enrollment and the patient becomes ineligible.

Follow-up
After completion of scheduled treatment, patients are followed up for at least 5 years or until recurrence, development of another malignancy, or death. All patients are required to undergo physical examination, routine laboratory tests, and measurement of tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) at 3-month intervals for the first 3 years of follow-up, while these examinations are performed every 6 months for the subsequent 2 years. In addition, chest, abdominal, and pelvic computed tomography will be performed at 6-month intervals throughout the follow-up period.

Table 2. Dose levels of capecitabine

<table>
<thead>
<tr>
<th>Body surface area</th>
<th>Dose level 0</th>
<th>Dose level -1</th>
<th>Dose level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting dose</td>
<td>After dose reduction</td>
<td>After further reduction</td>
</tr>
<tr>
<td>&lt;1.36 m$^2$</td>
<td>1,200 mg</td>
<td>900 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>≥1.36 m$^2$ and &lt;1.41 m$^2$</td>
<td>1,500 mg</td>
<td>1,200 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>≥1.41 m$^2$ and &lt;1.51 m$^2$</td>
<td>1,800 mg</td>
<td>1,500 mg</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>≥1.51 m$^2$ and &lt;1.66 m$^2$</td>
<td>2,100 mg</td>
<td>1,800 mg</td>
<td>1,500 mg</td>
</tr>
<tr>
<td>≥1.66 m$^2$ and &lt;1.81 m$^2$</td>
<td>2,400 mg</td>
<td>2,100 mg</td>
<td>1,800 mg</td>
</tr>
<tr>
<td>≥1.81 m$^2$ and &lt;2.11 m$^2$</td>
<td>2,700 mg</td>
<td>2,400 mg</td>
<td>2,100 mg</td>
</tr>
<tr>
<td>≥2.11 m$^2$</td>
<td></td>
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<td></td>
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</tbody>
</table>

Table 3. Dose reduction for oxaliplatin in XELOX therapy if peripheral neuropathy occurs

<table>
<thead>
<tr>
<th>CTCAE grade</th>
<th>≤14 days</th>
<th>≥14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>100 mg/m$^2$</td>
<td>85 mg/m$^2$</td>
</tr>
<tr>
<td>3</td>
<td>Withdrawal of L-OHP</td>
<td>Withdrawal of L-OHP</td>
</tr>
<tr>
<td></td>
<td>Continuation of capecitabine</td>
<td>Continuation of capecitabine</td>
</tr>
<tr>
<td>4</td>
<td>Withdrawal of L-OHP</td>
<td>Withdrawal of L-OHP</td>
</tr>
<tr>
<td></td>
<td>Continuation of capecitabine</td>
<td>Continuation of capecitabine</td>
</tr>
</tbody>
</table>

Acute pharyngolaryngeal paresthesia
Increase infusion time to 4-6 hours without dose reduction

CTCAE, Common Terminology Criteria for Adverse Events; L-OHP, oxaliplatin


**Study Assessments**

DFS is defined as the time from the date of surgery until relapse, development of another malignancy, or death, whichever comes first, while OS is defined as the time until death. The types and severities of AEs are evaluated according to NCI-CTCAE version 4.0<sup>30</sup>, while neurotoxicity is evaluated by DEB-NTC<sup>20-22</sup>. The most severe grade of each AE during the entire treatment period is reported.

**Statistical Analyses**

According to previous reports on treatment with 5-FU-based regimens (LV5FU2, Mayo, and capecitabine), 3-year DFS was 64.2% (capecitabine) and 60.6% (Mayo regimen) in the X-ACE study<sup>10</sup>, 65.3% (LV5FU2 regimen) in the MOSAIC study<sup>11</sup>, and 60.0% (LV5FU2 regimen) in the ACCORD02 study<sup>3</sup>. The mean 3-year DFS across these studies was 62.5%. In an ancillary study, 3-year DFS was 72.2% with FOLFOX4 and 72.4% with mFOLFOX6 in the MOSAIC and NSABP C08 studies, respectively<sup>60</sup>, with mean 3-year DFS being 72.3% for these two studies. Based on such data, 3-year DFS is expected to be 10% higher with FOLFOX than with 5-FU-based therapy. Since the 2009 Japanese guidelines for treatment of colorectal cancer<sup>17</sup> stated that patients with Stage III colorectal cancer had a 3-year relapse-free survival rate of 73.2% after surgery, the threshold for 3-year DFS has been set at 73.2% in the present study. The expected 3-year DFS is 8.5% higher and thus is set at 81.7%. Using SWOG Statistical Tools and assuming that the threshold 3-year DFS is 73.2% and the expected 3-year DFS is 81.7% (α=0.05 [one-sided], β=0.2), the required sample size was calculated to be 124 patients. Approximately 5% of the patients are expected to drop out because of infertility, and the planned sample size for this study is 130.

Because analysis of secondary endpoints to provide supplementary data will be done on an exploratory basis after primary analysis, adjustment for multiplicity will not be considered. The time-to-event dates will be analyzed by using the Kaplan-Meier method. Statistical analyses will be performed with SPSS for Windows, version 21 (SAS Institute, Cary, NC, USA).

**Ancillary Study**

In an ancillary study, we will assess the prognostic factors related to survival and recurrence or AEs associated with mFOLFOX6 therapy and XELOX therapy in patients who have undergone curative resection of stage III colon cancer.

**Participating Institutions**

Patients were accrued from 16 institutions and hospitals. Data processing is currently ongoing.

**References**


covorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109-16.
14) Sargent D, Shi Q, Yothers G, van Cutsem E, Cassidy J, Saltz L, Wolmark N, Bot B, Grothey A, Buyse M, de Gramont A (2011) Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan. Data from 12,676 patients from MOSAIC, N-ACT, PETACC-3, C-06, C-07 and C09803. Eur J Cancer 47:990-6.