JFMC47-1202-C3 (ACHIEVE Trial)

A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil / *l*-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer.

ACHIEVE Trial

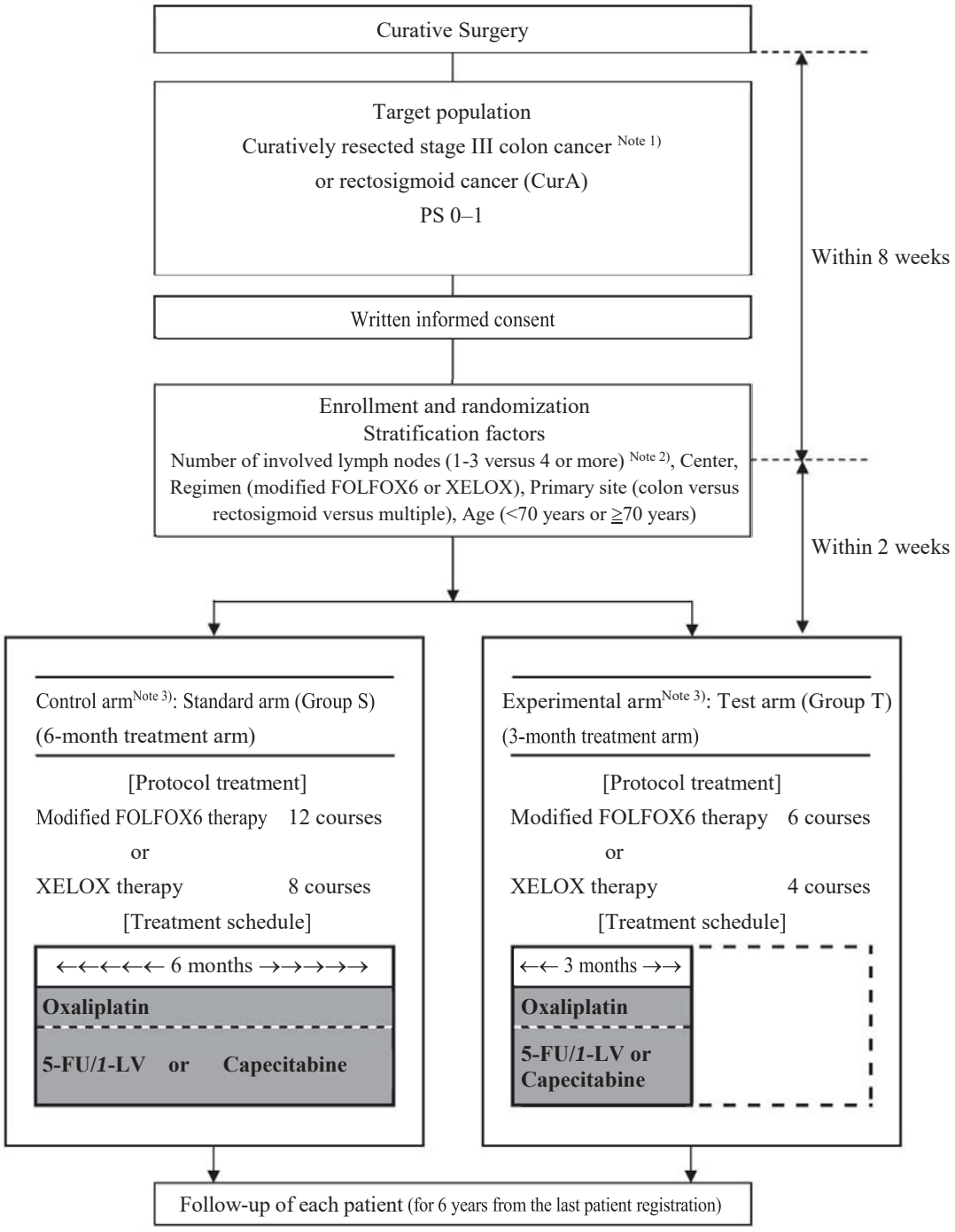
(Adjuvant Chemotherapy for colon cancer with HIgh EVidencE)

UMIN ID：000008543

6 Apr 2012, version 1.0
19 Apr 2012, version 1.1
25 Oct, 2013 version 1.2

0. Overview

0.1. Summary of the study



Note 1: Including cecal cancer

Note 2: N1c according to the International Union Against Cancer (UICC) tumor-node-metastasis (TMN) classification, 7th edn. is included.

Note 3: Switching from modified FOLFOX6 therapy to XELOX therapy or switching from XELOX therapy to modified FOLFOX6 therapy is not permitted.

0.2. Objectives

To investigate the non-inferiority of treatment for 3 months with modified FOLFOX6 or XELOX therapy as postoperative adjuvant chemotherapy versus 6 months of modified FOLFOX6 or XELOX therapy in terms of disease-free survival (IDEA[Note)]) in patients with curatively resected stage III colon cancer (including rectosigmoid cancer).
Note: IDEA (International Duration Evaluation of Adjuvant chemotherapy colon cancer prospective pooled analysis) is a study being conducted for the integrated analysis of data from six phase III randomized studies that are underway in Japan and five other nations. See *2.8. IDEA study* for details.

Primary endpoint:

Disease-free survival (DFS).[Note 1)]

Note 1: DFS is defined as survival until recurrence of colon cancer or death from any cause in the IDEA study, whereas it generally indicates relapse-free survival (RFS).

Secondary endpoint:

(1) Disease-free survival (DFS).[Note 2)]
Note 2: This is defined as survival until recurrence of colon cancer , onset of the other cancer (secondary cancer), or death from any cause.
(2) Time to treatment failure.
(3) Overall survival.
(4) Toxicity (according to the CTCAE v 4.0 - JCOG).
(5) Completion rate of the study treatment.
(6) Percent of dose received versus planned dose.
(7) Correlation of the clinical outcome with the number of involved lymph nodes and that of the dissected lymph nodes.
(8) Incidence and nature of peripheral sensory neuropathy (PSN).
(9) Identification of single nucleotide polymorphisms (SNPs) using the genome-wide association study (GWAS) associated with toxicityand clinical outcome (additional protocol: pharmacogenomics).

0.3. Patients eligibility criteria

0.3.1. Inclusion criteria

(1) Histologically confirmed adenocarcinoma of the colon.
(2) Predominantly located in the cecum, colon, or rectosigmoid region based on the findings from surgery and/or examination of the resected specimen.*
*: Multiple colorectal cancer with up to two infiltrating tumors† is eligible ("multiple" is applied as one of the stratification factors).
†: Infiltrating carcinoma is defined as cancer that has spread at least beyond the submucosal layer and does not mean intramucosal cancer.
(3) Colectomy with D2 or D3 lymph node dissection.
(4) Curability A surgery (no residual tumor visible macroscopically and/or microscopically).
(5) Stage III (T any N1 [Note 1)]/2/3 M0) (cf. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, The 7th Edition, revised version.).
Note 1: N1c (UICC TNM 7th edn.) is defined as tumor deposit(s), that is, satellite nodule(s) in the subserosa, or non-peritonealized pericolic or perirectal soft tissues without regional lymph node metastasis.
(6) Registration within 8 weeks after resection and commencing chemotherapy within 2 weeks after registration.
(7) Age ≥20 years.
(8) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
(9) Body surface area (DuBois) ≤2.2 m^2.

(10) No prior chemotherapy, immunotherapy, or radiation therapy.
(11) Adequate organ function (data obtained within 14 days before registration)[Note 2]:
  i) neutrophil count ≥1,500/mm^3
  ii) platelet count ≥100,000/mm^3
  iii) serum creatinine ≤1.5 times the upper limit of normal (ULN)
  iv) CCr (calculated value)*≧30 mL/min
  v) total bilirubin ≤2.0 mg/dL
  vi) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100 IU/L
  vii) carcinoembryonic antigen (CEA) ≤10 ng/mL
  * CCr is calculated using the Cockcroft–Gault equation (the measured value is not used)
  Male: CCr = [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)]
  Female: CCr = 0.85 × [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)]
(12) Written informed consent with the patient's signature and the date.

0.3.2. Exclusion criteria

(1) Cancer of the appendix.
(2) Past history of malignancy.[Note 1]
  Note 1: Patients with a recurrence-free period of 5 years or longer are eligible, and so are patients with endoscopic curative resection of intramucosal carcinoma (stomach, colon, or esophagus), curative resection of cervical cancer, and resected basal cell cancer and/or squamous cell cancer of the skin.
(3) Women who are pregnant or breast-feeding.
(4) Women who may become pregnant and fertile men.[Note 2]
  Note 2: Eligible if a patient agrees to use contraception during the study period and for 1 month after completion of treatment, and he/she understands the risks related to pregnancy.
(5) Participation in another clinical trial within 30 days before registration.
(6) Existing Grade 1 or worse peripheral sensory neuropathy.
(7) Uncontrolled diabetes mellitus (including insulin therapy as absolutely imperative).
(8) Uncontrolled congestive heart failure, angina pectoris, hypertension, and/or arrhythmia.
(9) Continuous systemic steroid therapy (either oral or intravenous administration).
(10) A history and/or current evidence of significant neurological and/or mental illness.
(11) Active infectious disease, including known HBV, HCV, HIV infection and so on.
(12) Known dihydropyrimidine dehydrogenase (DPD) deficiency.
(13) A history of allergy to 5-FU, *l*-LV, oxaliplatin, and/or capecitabine.
(14) Prior chemotherapy with a regimen containing oxaliplatin.
(15) Other reasons for being unfit for the study as determined by the attending physician.

0.4. Protocol treatment

Either modified FOLFOX6 therapy or XELOX therapy is selected before registration in the study, and the choice is made by the investigator. Switching treatment is not allowed after registration. If continuing modified FOLFOX6 or XELOX therapy is considered to be difficult due to oxaliplatin-related adverse events, the patient can be switched from modified FOLFOX6 to 5-FU/*l*-LV (sLV5FU2) or from XELOX to capecitabine alone. Subsequent escalation of the 5-FU or capecitabine dose is not allowed.

The recommended initial dose of each drug is calculated from the body surface area (DuBois) at the time of registration, and the actual dosage should be calculated at each study site.

0.4.1. Control arm: Group S (6-month treatment group)

<u>*Modified FOLFOX6 therapy*</u>

On Day 1, oxaliplatin (85 mg/m^2) is administered in combination with *l*-LV (200 mg/m^2), followed by 5-FU (bolus: 400 mg/m^2) . Infusion of 5-FU (2,400 mg/m^2) is performed from Day 1 to Day 3, followed by a rest period from

Day 4 to Day 14. This completes one course of treatment and a total of 12 courses are given.
After the completion of protocol treatment, follow-up is performed without any further chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed.

XELOX therapy
On Day 1, oxaliplatin (130 mg/m^2) is administered in combination with oral capecitabine* (1,000 mg/m^2 or 750 mg/m^2 administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the morning of Day 15: 28 doses in total),[Note)] followed by a 1-week rest period . This completes one course of treatment and a total of 8 courses are given.
After the completion of protocol treatment, follow-up is performed without any further chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed.
Note: Commencing the administration of capecitabine from the morning of Day 2 is acceptable. If treatment is commenced after dinner on Day 1, the last dose is given after breakfast on Day 15, while if treatment is started after breakfast on Day 2, the last dose is given after dinner on Day 15.
*The starting dose for capecitabine will be as follows in accordance with CCr value and age at the time of enrollment.
2,000 mg/m^2/day (1,000 mg/m^2/dose): CCr > 50 mL/min
1,500 mg/m^2/day (750 mg/m^2/dose): 30 mL/min ≦ CCr ≦ 50 mL/min or ≥70 years of age.

0.4.2. Experimental arm: Group T (3-month treatment group)

Modified FOLFOX6 therapy
On Day 1, oxaliplatin (85 mg/m^2) is administered in combination with *l*-LV (200 mg/m^2), followed by 5-FU (bolus: 400 mg/m^2). Infusion of 5-FU (2,400 mg/m^2) is performed from Day 1 to Day 3, followed by a rest period from Day 4 to Day 14. This completes one course of treatment and a total of 6 courses are given.
After the completion of protocol treatment, follow-up is performed without any further chemotherapy for the primary disease until a recurrence occurs or the follow-up period is completed.

XELOX therapy
On Day 1, oxaliplatin (130 mg/m^2) is administered in combination with oral capecitabine* (1,000 mg/m^2 or 750 mg/m^2 administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the morning of Day 15: 28 doses in total,[Note)] followed by a 1-week rest period . This completes one course treatment and a total of 4 courses are given.
After the completion of protocol treatment, follow-up is performed without any further chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed.
Note: Commencing the administration of capecitabine from the morning of Day 2 is acceptable. If treatment is commenced after dinner on Day 1, the last dose is given after breakfast on Day 15, while if treatment is started after breakfast on Day 2, the last dose is given after dinner on Day 15.
*The starting dose for capecitabine will be as follows in accordance with CCr value and age at the time of enrollment.
2,000 mg/m^2/day (1,000 mg/m^2/dose): CCr > 50 mL/min
1,500 mg/m^2/day (750 mg/m^2/dose): 30 mL/min ≦ CCr ≦ 50 mL/min or ≥70 years of age.

0.5. Planned sample size and study period

Target sample size:	600 subjects for each group × 2	(total: 1,200 subjects)
Registration period:	3 years	August 2012 – July 2015
Follow-up period:	6 years after registration of the last patient	
Total study period:	9 years	August 2012 – July 2021

0.6. Research organization

Principal investigators:

Co-principal investigator from oncosurgeon:

Masaki Mori	Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine

Co-principal investigator from medical oncologist:

Atsushi Ohtsu	Research Center for Innovative Oncology, National Cancer Center Hospital East

Co-principal investigator from IDEA adjustment representative:

Takayuki Yoshino	Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East

Protocol coordinator:

Takayuki Yoshino	Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East

Number of institutions:	about 300 sites (see Appendix 1)
Study office:	Japanese Foundation for Multidisciplinary Treatment of Cancer

1. Objectives

To investigate the non-inferiority of treatment for 3 months with modified FOLFOX6 or XELOX therapy as postoperative adjuvant chemotherapy versus 6 months of modified FOLFOX6 or XELOX therapy in terms of disease-free survival (IDEA[Note)]) in patients with curatively resected stage III colon cancer (including rectosigmoid cancer).
Note: IDEA (International Duration Evaluation of Adjuvant chemotherapy colon cancer prospective pooled analysis) is a study being conducted for the integrated analysis of data from six phase III randomized studies that are underway in Japan and five other nations. See *2.8. IDEA study* for details.

Primary endpoint:

Disease-free survival (DFS).[Note 1)]

Note 1: This is defined as survival until recurrence of colon cancer or death from any cause in the IDEA study, whereas it generally indicates relapse-free survival (RFS).

Secondary endpoint:

(1) Disease-free survival (DFS).[Note 2)]
Note 2: This is defined as survival until recurrence of colon cancer, onset of the other cancer (secondary cancer), or death from any cause.
(2) Time to treatment failure.
(3) Overall survival.
(4) Toxicity (according to the CTCAE v 4.0 - JCOG).
(5) Completion rate of the study treatment.
(6) Percent of dose received versus planned dose.
(7) Correlation of the clinical outcome with the number of involved lymph nodes and that of the dissected lymph nodes.
(8) Incidence and nature of peripheral sensory neuropathy (PSN).
(9) Identification of single nucleotide polymorphisms (SNPs) using the genome-wide association study (GWAS) associated with toxicity and clinical outcome (additional protocol: pharmacogenomics).

2. Background

2.1. Target disease

In Japan, the incidence rate of colorectal cancer (cancer of the colon and rectum) is increasing year by year and the annual number of colorectal cancer patients has expanded from 25,000 in 1980 to more than 100,000 in 2005.[1] Along with this increase of the incidence rate, the number of deaths from colorectal cancer has risen to reach about 43,000 in 2008.[2] According to Ohno *et al.*, the number of colorectal cancer patients is eventually estimated to exceed 150,000 annually, making it the number one cancer followed by stomach and lung cancer. Moreover, the number of female colorectal cancer patients is expected to increase until it becomes equal with breast cancer in 2020, whereas male patients have already shown a marked increase.[3]

2.2. Standard treatment for colon cancer

The therapeutic strategy for colon cancer is decided in accordance with the stage of the disease. Either surgery alone or the combination of surgical resection and postoperative chemotherapy has mainly been used to treat colon cancer. Surgical resection is the first option for the treatment of stage I to III colon cancer, with radical resection of the primary tumor and regional lymph nodes being performed as curative treatment. However, colon cancer can recur even after curative resection (CurA), because residual tumor cells and micrometastases cannot be removed completely. The recurrence rate is reported to be 3.7% for stage I disease, 13.3% for stage II disease, and 30.8% for stage III disease. For patients with stage III colon cancer (which has the higher recurrence rate), adjuvant chemotherapy is incorporated into the therapeutic strategy to reduce the risk of recurrence by destroying undetectable tumor cells.[4] For stage II colon cancer, the effectiveness of adjuvant chemotherapy still remains in question, although its usefulness has been suggested by the reports of Mamounas *et al.*,[5] the QUASAR Collaborative Group,[6] and McKenzie *et al.*[7] Adjuvant chemotherapy is also suggested to have a preventive effect on the recurrence of colon cancer associated with risk factors such as T4, undifferentiated carcinoma, perforated onset tumor, and examination of <12 lymph nodes.[8,9] Based on the above findings, the importance of adjuvant chemotherapy has been recognized for stage II colon cancer with a high risk of recurrence.

2.3. Adjuvant chemotherapy for colon cancer

2.3.1. Adjuvant chemotherapy for colon cancer patients

In the United States and Europe, the usefulness of adjuvant chemotherapy with 5-fluorouracil (5-FU) and other agents for colon cancer was demonstrated by large-scale clinical studies as long as the 1980s. Moertel *et al.* reported the well-known early INT-0035 study that compared surgery alone with surgery and 12 months of 5-FU plus levamisole (LEV) combination therapy after curative resection of Dukes B or C (stage II or III) colon cancer, revealing significant improvement of relapse-free survival (RFS) and overall survival (OS) in stage III patients receiving 5-FU plus LEV.[10,11] Based on this result, 12 months of 5-FU plus LEV was defined as the standard adjuvant chemotherapy for administration after curative resection of stage III colon cancer at the NIH consensus conference in 1990.[12]

Subsequently, 5-FU/Leucovorin (LV) therapy attracted attention because of its apparent effectiveness for advanced/recurrent colorectal cancer, and its usefulness as adjuvant therapy was assessed in further studies. Three studies (INT0089, NSABP C-04, and QUASAR) were conducted to compare the usefulness of 5-FU/LEV with that of 5-FU/LV, and the results showed significant improvement of DFS with 5-FU/LV therapy relative to 5-FU/LEV therapy, as well as only a limited benefit of adding LEV to 5-FU/LV.[13-16] Similar results were obtained the NCCTG89-46-51 study conducted by Dencausse *et al.*[17] Because of these findings, 5-FU/LV therapy became the standard adjuvant chemotherapy for patients with colon cancer. In later studies, infusional 5-FU/LV, oral treatment with the fluoropyrimidine capecitabine (Cape), and UFT/LV were proven to be as effective as bolus 5-FU/LV therapy.[18-20] However, further improvement in the outcome of treatment result is still required.

In 1998, oxaliplatin (L-OHP) plus infusional 5-FU/LV (LV5FU2) (FOLFOX) therapy was confirmed to be a useful first-line treatment for advanced/recurrent colorectal cancer,[21] and the MOSAIC study was subsequently carried out to assess its usefulness as adjuvant chemotherapy after curative resection of colon cancer.[22] Comparison of LV5FU2 therapy with FOLFOX4 therapy after curative resection of stage II or III colon cancer showed that FOLFOX4 was superior to LV5FU2 in terms of the primary endpoint, which was 3-year DFS (78.2% vs. 72.9%, hazard ratio [HR]=0.77, p=0.002). Based on these results, FOLFOX therapy was approved as adjuvant chemotherapy for Stage III colon cancer in the United States and Europe in 2004. In 2009, the follow-up study also showed significant improvement of 5-year DFS (73.3% vs. 67.4%, HR=0.80, p=0.003) and 6-year OS (78.5% vs. 76.0%, HR=0.84, p=0.046) with FOLFOX4 therapy.[23] Further, the NSABP C-07 study comparing bolus 5-FU/LV with L-OHP plus

bolus 5-FU/LV (FLOX) for patients with curative resection of stage II or III colon cancer also revealed significant improvement of 3-year DFS in the FLOX group (76.1% vs. 71.8%, HR=0.80, p=0.0034).[24]
Significant improvement of the primary endpoint (3-year DFS) and improvement of 5-year OS were also observed with XELOX therapy compared with bolus 5-FU/LV therapy (3-year DFS: 70.9% vs. 66.1%, HR=0.80, p=0.0045) (5 years OS: 77.6% vs. 74.2%, HR=0.72, p=0.1486) in the NO16968 study targeting patients with curative resection of stage III colon cancer.[25] These findings confirmed an additive effect of L-OHP when used with 5-FU/LV and capecitabine therapy as adjuvant chemotherapy for colon cancer. However, other chemotherapy agents or molecular-targeting drugs that are as effective for advanced/recurrent colorectal cancer as oxaliplatin, such as irinotecan (CPT-11),[26-28] bevacizumab (BV),[29,30] and cetuximab (Cmab)[31,32] failed to show an additive effect in any study and therefore the use of these drugs is not recommended.
Based on the above results, FOLFOX and XELOX are positioned as the standard adjuvant chemotherapy regimens for treatment of stage III colon cancer in 2012.

2.3.2. Adjuvant chemotherapy for colon cancer in Japan

Japan has led the US and Europe in the discussion of adjuvant chemotherapy for colon cancer since a large-scale comparative study was initiated in 1974 by the Colorectal Cancer Research Group supported by the Japanese Ministry of Health, Labor and Welfare, which revealed significant improvement of survival time with chemotherapy versus surgery alone. Six comparative studies were performed up until 1990, and only one study (JFMC15-8901) revealed significant improvement of DFS and overall survive (OS) with adjuvant chemotherapy versus surgery alone. However, meta-analysis of the Japanese studies on adjuvant chemotherapy was performed by Sakamoto *et al.*, revealing significant improvement of DFS and OS after adjuvant chemotherapy with oral fluoropyrimidines for colorectal cancer.[33] Usefulness of adjuvant chemotherapy for stage II colon cancer was also suggested by the data. Based on these results, oral fluoropyrimidines are widely used in Japan as adjuvant therapy for colorectal cancer. In Japan, study JCOG0205MF (assessing non-inferiority of 5-FU/*1*-LV versus UFT/LV) is currently underway in patients with curative resection of stage III colon cancer.
In Japan, approval was given for L-OHP (as part of FOLFOX) in August 2009 as adjuvant therapy for treatment of colon cancer based on the results of the MOSAIC study described above, and the JFMC41-1001-C2 study is currently underway to assess tolerability. In November 2011, based on the results of the NO16968 study, an application was also made for combined use of L-OHP with oral fluoropyrimidines and other antineoplastic drugs.

2.4. Efficacy and Safety of L-OHP as adjuvant chemotherapy for colon cancer

The usefulness of FOLFOX therapy and XELOX therapy as adjuvant chemotherapy for stage III colon cancer was confirmed by the MOSAIC study and NO16968 study performed and both are recommended as standard treatments in a guideline.[34] However, no domestic efficacy and safety data on these regimens have been obtained in Japan since both were approved on the basis of the results of studies. Accordingly, clinical studies and drug use surveys are being conducted in Japan to assess the safety of these regimens for patients with advanced/recurrent colorectal cancer.
Details of the efficacy of these regimens are explained in *2.4.1. FOLFOX therapy (MOSAIC study)* and *2.4.2. XELOX therapy (NO16968 study)*. Also, details of the safety of these regimens are explained in *2.4.3. Safety of FOLFOX therapy in Japan (advanced/recurrent colorectal cancer)* and *2.4.4. Safety of XELOX therapy in Japan (advanced/recurrent colorectal cancer)*.

2.4.1. FOLFOX therapy (MOSAIC study)

The usefulness of FOLFOX therapy as adjuvant chemotherapy for colon cancer was demonstrated by de Gramont *et al.* in a large-scale, randomized, comparative study (the MOSAIC study) targeting patients who had undergone curative resection of stage II or III colon cancer (including RS cancer).[22,23]
This study was performed to compare FOLFOX4 therapy with 5-FU/LV (LV5FU2) therapy, which is the standard adjuvant chemotherapy for the patients mentioned above. Both groups were given 12 courses of treatment for 2 weeks per course.
A total of 2,246 patients were enrolled in the study, and half each were randomly assigned to the LV5FU2 group (control group) or the FOLFOX4 group (study group). Significant improvement of the primary endpoint (3-year DFS) was observed in the FOLFOX4 group (p=0.002).
Furthermore, a significant difference of 3-year DFS was confirmed by a comparison between FOLFOX4 and LV5FU2 in patients stratified by stage, especially in stage III colon cancer patients with a poor prognosis. The overall

DFS results and those for stage III patients are shown in ***Table 2.4.1.1.*** and ***Table 2.4.1.2.***, respectively.

Table 2.4.1.1. DFS in the MOSAIC study

	FOLFOX4	LV5FU2
No. of patients (intention-to-treat)	1,123	1,123
Number of recurrences/deaths (%)	237 (21.1)	293 (26.1)
Disease-free survival [95% confidence interval] at 3 years	78.2% [75.6–80.7]	72.9% [70.2–75.7]
Hazard ratio [95% confidence interval]	0.77 [0.65–0.91]	
P value (log rank test)	p=0.002	

Table 2.4.1.2. DFS of stage III patients

	FOLFOX4	LV5FU2
No. of patients (intention-to-treat)	672	675
Number of recurrences/deaths (%)	181 (26.9)	226 (33.5)
Disease-free survival [95% confidence interval] at 3 years	72.2% [68.6–75.8]	65.3% [61.6–69.1]
Hazard ratio [95% confidence interval]	0.76 [0.62–0.92]	

As shown in ***Table 2.4.1.3.***, the incidence rate of major adverse events (grade 3 or 4) was higher in the FOLFOX4 group compared with the LV5FU2 group, being 41.1% and 4.7% for granulocytopenia, 1.8% and 0.2% for granulocytopenia with fever or infection, 12.4% and 0.2% for peripheral sensory neuropathy, 10.8% and 6.7% for diarrhea, 5.9% and 1.4% for vomiting, 5.1% and 1.8% for nausea, and 2.9% and 0.2% for allergic reactions. A total of six deaths due to adverse events occurred within 28 days after the last dose in each group, showing no difference in incidence (0.5%).

Table 2.4.1.3. Incidence rate of adverse events (grade 3 or 4)

Adverse events	FOLFOX4 (%)	LV5FU2 (%)
Granulocytopenia	41.1	4.7
(with fever or infection)	(1.8)	(0.2)
Nausea	5.1	1.8
Vomiting	5.9	1.4
Diarrhea	10.8	6.7
Stomatitis	2.7	2.2
Peripheral sensory neuropathy	12.4	0.2
Allergic reactions	2.9	0.2

2.4.2. XELOX therapy (study NO16968)

The usefulness of XELOX therapy as adjuvant chemotherapy for colon cancer was demonstrated by Haller *et al.* in a large-scale randomized comparative study (NO16968) targeting stage III colon cancer patients after curative resection.[25]

This study was performed to compare XELOX therapy (XELOX group) with 5-FU/LV therapy (either RPMI or Mayo regimen groups), which is the standard adjuvant chemotherapy for the patients mentioned above. The XELOX group received eight 3-week courses of treatment, the RPMI regimen group received four 8-week courses of treatment, and the Mayo regimen group received six 4-week courses of treatment.

A total of 1,886 patients were enrolled in the study, and were randomized to 5-FU/LV therapy (RPMI regimen group or Mayo regimen group; n=942) or XELOX therapy (XELOX group; n=944). A significant improvement of DFS (the primary endpoint) was observed in the XELOX group (p=0.0045). The DFS data are as shown in ***Table 2.4.2.1.***

Table 2.4.2.1. DFS in study NO16968

	XELOX	5-FU/LV
No. of patients (intention-to-treat)	944	942
Number of recurrences/deaths (%)	295 (31.3)	353 (37.5)
Disease-free survival [95% confidence interval] at 3 years	70.9% [67.9–73.9]	66.5% [63.4–69.6]
Hazard ratio [95% confidence interval]	0.80 [0.69–0.93]	
P value (log rank test)	p=0.0045	

As shown in ***Table 2.4.2.2.***, the incidence rate of major adverse events (grade 3 or 4) in the XELOX group and 5-FU/LV group was respectively 9% vs. 16% for neutropenia (higher in the 5-FU/LV group) and 11% vs. <1% for peripheral sensory neuropathy, and 5% vs. <1% for hand-foot syndrome (both higher in the XELOX group). There were six deaths (0.6%) within 28 days after the last dose in each group, all of which were due to adverse events, showing no difference between the two groups.[35]

Table 2.4.2.2. Incidence rate of adverse events (grade 3 or 4)

Adverse events	XELOX (%)	5-FU/LV (%)
Neutropenia	9	16
Thrombocytopenia	5	<1
Nausea	5	4
Vomiting	6	3
Diarrhea	19	20
Stomatitis	<1	9
Peripheral sensory neuropathy	11	<1
Hand-foot syndrome	5	<1

2.4.3. Safety of FOLFOX therapy in Japan (advanced/recurrent colorectal cancer)

In August 2009, approval was given for the use of FOLFOX as adjuvant chemotherapy for colon cancer in Japan. However, domestic efficacy and safety data were lacking, since approval was based on the results of overseas clinical studies. Accordingly, study JFMC41-1001-C2 is currently underway in Japan to assess the tolerability of modified FOLFOX6 therapy as adjuvant chemotherapy for colon cancer.

Currently, allergic reactions and peripheral sensory neuropathy are regarded as the major problems related to performing and continuing FOLFOX therapy. Type I allergy (immediate allergy) is the main kind of allergic reaction to FOLFOX therapy and the incidence of grade 3 or 4 adverse events associated with adjuvant chemotherapy is about 3%.[22,23] According to the drug use survey of Elplat® (L-OHP: oxaliplatin) conducted by Yakult Honsha Co., Ltd. in 4,998 patients with advanced/recurrent colorectal cancer who were enrolled for safety evaluation, the median onset of allergic symptoms (range) was after 7.0 courses (1 to 27 courses) of therapy. The median total dose of L-OHP was 479.3 (21.3 to 1,685.1) mg/m^2 and the median number of days from the beginning of treatment to the onset of allergy symptoms was 103.0 days (0 to 509) days (***Table 2.4.3.1.***).[36] Accordingly, FOLFOX treatment-related allergic reactions may occur after only 1 to 2 courses or after many courses, and therefore the condition of each patient should be monitored carefully during FOLFOX therapy. If an event occurs, treatment should be discontinued and appropriate countermeasures should be taken depending on the symptoms.

Table 2.4.3.1. Number of courses until allergic symptoms, total dose of oxaliplatin, and number of days until occurrence of symptoms

	Average	Median (range)	
No. of courses until onset	6.7	7.0	(1–27)
Total dose at the time of onset (mg/m^2)	487.4	479.3	(21.3–1685.1)
No. of days from the start of treatment to the onset	110.1	103.0	(0–509)

The grade of FOLFOX therapy-related peripheral nervous symptoms is known to become higher as the total dose of oxaliplatin increases. 10% of patients experienced grade 3 peripheral nervous symptoms at a total dose of 850 mg/m^2 and 20% did at 1,020 mg/m^2.[21] The relationship between the total dose of oxaliplatin and the cumulative incidence of peripheral nervous symptoms of each grade was assessed from the drug use survey data obtained in Japan. As was found overseas, where the cumulative incidence of peripheral nervous symptoms increased with the total dose of oxaliplatin, it was observed that when the total dose of oxaliplatin reached 850 mg/m^2, the cumulative incidence of peripheral sensory neuropathy was 60.1% for grade 1 or higher, 35.3% for grade 2 or higher, and 2.3% for grade 3 or higher (***Figure 2.4.3.1.*** and ***Table 2.4.3.2.***).[36] Thus, patients should be carefully monitored during FOLFOX therapy for the occurrence of peripheral sensory neuropathy. Suspension of treatment or dose reduction may be required to prevent progression to grade 3 dysfunction that affects daily life, depending on the patient's condition.

Table 2.4.3.2. Cumulative incidence of peripheral sensory neuropathy versus the total dose of oxaliplatin

		Cumulative incidence (%)			
		Grade 1 or higher	Grade 2 or higher	Grade 3 or higher	Grade 4*
No. of events		2,036	876	63	1
Total dose	85 mg/m^2	576 (11.769%)	61 (1.263%)	1 (0.021%)	0 (0.000%)
	170 mg/m^2	1,054 (22.686%)	127 (2.761%)	3 (0.066%)	0 (0.000%)
	255 mg/m^2	1,409 (31.766%)	236 (5.550%)	5 (0.116%)	0 (0.000%)
	340 mg/m^2	1,596 (37.426%)	312 (7.772%)	8 (0.205%)	0 (0.000%)
	425 mg/m^2	1,725 (42.119%)	415 (11.374%)	14 (0.413%)	1 (0.037%)
	510 mg/m^2	1,833 (46.965%)	503 (15.001%)	18 (0.574%)	1 (0.037%)
	595 mg/m^2	1,906 (50.940%)	580 (18.875%)	23 (0.825%)	1 (0.037%)
	680 mg/m^2	1,958 (54.701%)	661 (24.094%)	31 (1.356%)	1 (0.037%)
	765 mg/m^2	1,981 (56.951%)	722 (29.223%)	37 (1.891%)	1 (0.037%)
	850 mg/m^2	2,004 (60.086%)	777 (35.291%)	40 (2.276%)	1 (0.037%)
	935 mg/m^2	2,019 (63.133%)	818 (41.829%)	46 (3.326%)	1 (0.037%)
	1,020 mg/m^2	2,024 (64.596%)	839 (46.293%)	56 (5.611%)	1 (0.037%)

*: Oral hypoesthesia

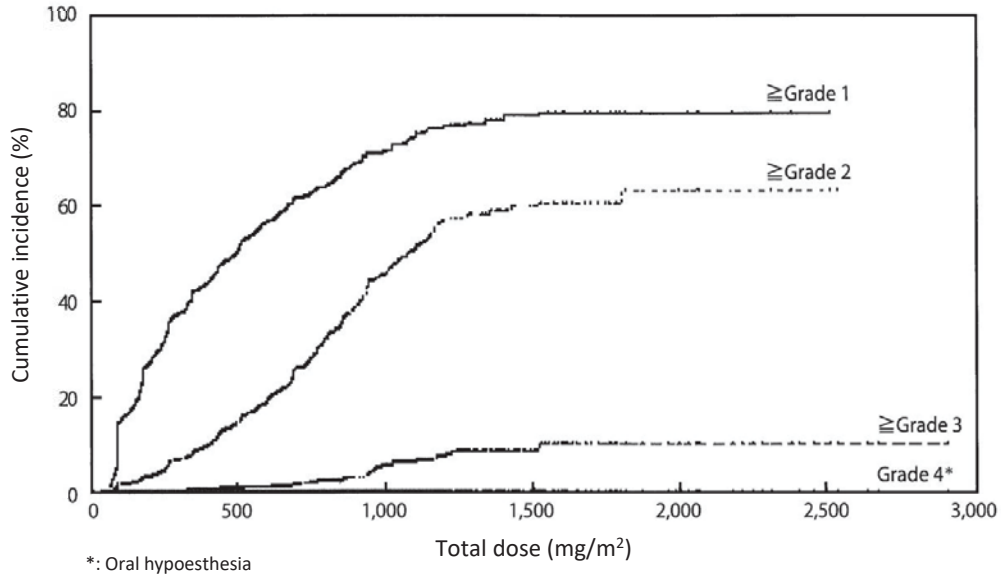


Figure 2.4.3.1. Cumulative incidence of peripheral sensory neuropathy in relation to the total dose of L-OHP

2.4.4. Safety of XELOX therapy in Japan (advanced/recurrent colorectal cancer)

In November 2011, approval was given for the use of XELOX as adjuvant chemotherapy for colon cancer in Japan. However, there are no domestic efficacy and safety data on this therapy for colorectal cancer, since approval was based on data from overseas clinical studies.

In September 2009, XELOX therapy was approved as a treatment for non-curatively resected advanced/recurrent colon and rectal cancer prior to being approved as adjuvant chemotherapy. The efficacy and safety of XELOX was assessed in a domestic phase I/II clinical study (study JO19380) of XELOX plus BV therapy prior to the filing of this application.[37]

With regard to safety, neutropenia and peripheral sensory neuropathy were the adverse events of grade 3 or 4 associated with XELOX plus BV therapy (***Table 2.4.4.1.***). Allergic reactions and peripheral peripheral sensory neuropathy are regarded as the major problems related to performing and continuing FOLFOX therapy, while hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome) is the major problem associated with capecitabine monotherapy. Patients take capecitabine every day during XELOX therapy, and therefore they should be carefully monitored for the occurrence of hand-foot syndrome and given instructions about its treatment. Suspension of therapy or dose reduction may be required, depending on the patient's condition.

Table 2.4.4.1. Incidence of adverse events in study JO19380 (XELOX + BV)

	All grades	Grades 3/4
Neutropenia	51.7	15.5
Thrombocytopenia	22.4	6.9
Nausea	74.1	0
Vomiting	44.8	1.7
Diarrhea	55.2	3.4
Stomatitis	56.9	1.7
Peripheral sensory neuropathy	93.1	17.2
Hand-foot syndrome	77.6	1.7

2.5. Duration of adjuvant chemotherapy for colon cancer

2.5.1. Duration of 5-FU therapy

The duration of adjuvant chemotherapy for colon cancer is set at 6 months based on the study results described below.

Study INT-0089 targeting patients with curative resection of Dukes B/C (stage II or III) colon cancer was performed to compare the usefulness of 5-FU/low-dose LV for 6 months, 5-FU/high-dose LV for 8 months, and 5-FU/low-dose LV plus LEV for 6 months with control treatment using 5-FU plus LEV for 12 months, which was the standard therapy at the time. From the results, 5-FU/LV therapy (for 6 months or 8 months) was calculated to be the most effective regimen because there were no differences of DFS and OS among the four groups and 5-FU/LV has a lower cost and toxicity.[13,14] Also, the effect of adding LEV to 5-FU/LV was found to be small.

Similarly, study NCCTG89-46-51 targeting patients with curative resection of Dukes B/C (stage II or III) colon cancer was performed to compare the usefulness of 5-FU plus LEV (for 6 months or 12 months) or 5-FU/LV plus LEV (for 6 months or 12 months) with the control regimen of 5-FU plus LEV for 12 months. As a result, 5-FU/LV plus LEV for 6 months achieved significant improvement of 5-year OS relative to 5-FU plus LEV for 6 months, but there was no difference between the 12-month treatment groups. Based on the above results, the treatment period for 5-FU/LV plus LEV was recommended to be 6 months.[17]

Also, the GERCOR C96.1 study targeting patients with curative resection of stage II or III colon cancer compared the usefulness of infusional 5-FU/LV (LV5FU2) (for 24 weeks or 36 weeks) and bolus 5-FU/LV (for 24 weeks or 36 weeks). There were no differences of OS among the four groups, so the usefulness of treatment for 36 weeks was not confirmed.[38]

From these representative study results, the standard treatment period for 5-FU/LV regimen was set at 6 months.

Meanwhile, the SAFFE study targeting patients with curative resection of stage II or III colorectal cancer compared infusional 5-FU for 3 months with 5-FU/LV for 6 months (Mayo regimen group). This study revealed higher 5-year RFS and 5-year OS, as well as a significantly lower incidence of adverse events, with infusional 5-FU for 3 months.[39,40] Also, the possibility of infusional 5-FU for 3 months being inferior to 5-FU/LV for 6 months (Mayo regimen group) was shown to be very unlikely. However, further discussion is still needed about the effect of shortening the treatment period for the 5-FU/LV regimen.

Regarding adjuvant chemotherapy for colon cancer such as capecitabine monotherapy[18,19] and UFT/LV therapy,[20] the ongoing JFMC33 and JFMC37 studies are being performed to assess the effectiveness of extended treatment period.

From the above results, shortening of the treatment period for 5-FU/LV from 6 months to 3 months is considered likely. However, shortening of the treatment period with L-OHP should also be discussed since FOLFOX and XELOX are the current standard regimens.

2.5.2. Duration of oxaliplatin therapy

The standard duration of treatment with FOLFOX and XELOX as adjuvant chemotherapy for colon cancer is set at 6 months, but the influence of shortening the treatment period with L-OHP or reducing the total dose has not been assessed. If efficacy can be maintained after shortening the oxaliplatin treatment period and reducing the total dose, the incidence of dose-dependent adverse events (peripheral sensory neuropathy and allergic reactions/ anaphylaxis) may be reduced.

In study EFC2962, which demonstrated the effectiveness of FOLFOX4 therapy for advanced/recurrent colorectal cancer, the median number of FOLFOX4 courses was 12, the response rate (antitumor effect) was 50.7%, and the incidence of serious peripheral sensory neuropathy (grade 3 or 4) was 16.3%. The median time from the beginning of treatment to the detection of an antitumor effects was 9 weeks, which corresponded to 4 to 5 courses of FOLFOX4 therapy.[21] An antitumor effect was observed in about 40% of patients after 6 courses (total oxaliplatin does of 510 mg/m^2) and was seen in about 50% of patients after 8 courses (680 mg/m^2). The occurrence of dose-dependent serious peripheral sensory neuropathy (grade 3 or 4) increased gradually from the 6th course onward (***Figure 2.5.2.1.***).[41]

Base on the above results, the possibility of shortening the treatment period is discussed by focusing on the effectiveness of oxaliplatin, the incidence of serious peripheral sensory neuropathy, and the median total dose derived from the results of the MOSAIC study,[22,23] NSABP C-07 study[24], and NO16968 study.[25] The data described above are shown in ***Table 2.5.2.1.***

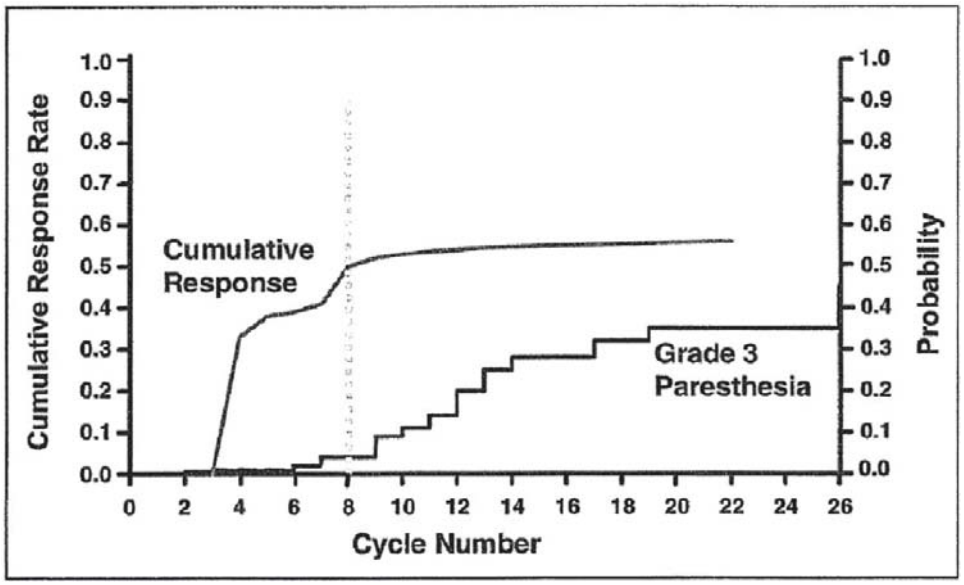


Figure 2.5.2.1. Antitumor effect and serious peripheral sensory neuropathy in study EFC2962

Table 2.5.2.1. Comparison of the efficacy of oxaliplatin, incidence of serious peripheral sensory neuropathy, and median total dose

Study	3-year DFS (%)	Incidence of peripheral sensory neuropathy (grade 3 or 4)	Planned dose of L-OHP	Median total dose of L-OHP
MOSAIC[22,23] (stage II or III)	78.2%	12.4%	1,020 mg/m^2	810 mg/m^2
NSABP C-07[24] (stage II or III)	76.1%	8.2%	765 mg/m^2	667 mg/m^2
NO16968[25] (stage III)	70.9%	11%	1,040 mg/m^2	905 mg/m^2

Compared with 5-FU/LV treatment (LV5FU2 and RPMI), the FOLFOX4 group in the MOSAIC study and the FLOX group in study NSABP C-07 showed significant improvement of 3-year DFS to 78.2% and 76.1%, respectively. The incidence of serious peripheral sensory neuropathy (grade 3 or 4) at the completion of treatment differed between the studies, being 12.4% in the MOSAIC study and 8.2% in study NSABP C-07. This was considered to be due to the difference of the median total dose (810 mg/m^2 for the MOSAIC study and 667 mg/m^2 for the NSABP C-07 study), which was equivalent to about 80% of the planned dose in both studies. These results suggest the possibility of reducing the incidence of serious peripheral sensory neuropathy while shortening the treatment period and reducing the total dose of oxaliplatin. Incidentally, the dose delivered in NSABP C-07 study (667 mg/m^2) corresponded to 8 courses of FOLFOX4 therapy or modified FOLFOX6 therapy.

As described above, cross-sectional comparison of clinical studies revealed the possibility of reducing the incidence of serious adverse events while maintaining efficacy by shortening the duration of adjuvant chemotherapy and reducing the dose of oxaliplatin. At present, the IDEA study is being conducted overseas to assess the non-inferiority of modified FOLFOX6 or XELOX therapy for 3 months versus 6 months as adjuvant chemotherapy.

2.6. Significance of this study

Currently 6 months of FOLFOX or XELOX therapy is recommended as adjuvant chemotherapy for colon cancer in various guidelines, but occurrence of serious adverse events remains a problem despite the high efficacy. Therefore, shortening the treatment period while maintaining the efficacy of adjuvant chemotherapy could be beneficial for patients, healthcare workers, and medical costs.

For these reasons, it is considered significant to determine the appropriate treatment period for modified FOLFOX6/XELOX therapy as a new approach to adjuvant chemotherapy after curative resection of colon cancer.

2.7. Proposal for this study

The treatment period of modified FOLFOX6 therapy and XELOX therapy, as adjuvant chemotherapy, is for 3 months by reference to the results of *2.5.1. Duration of 5-FU therapy* that suggested the possibility of shortening 5-FU/LV treatment to 3 months and *2.5.2. Duration of oxaliplatin therapy* that suggested the possibility of shortening oxaliplatin treatment. And in this study targeting Stage III curative resected colon cancer patients, the non-inferiority of DFS of 3-months modified FOLFOX6 or XELOX therapy (Test arm: Group T) is compared with that of 6 months of modified FOLFOX6 or XELOX therapy (Control arm: Group S). The non-inferiority study of DFS is planned as the integrated analysis of the global IDEA study.

2.8. IDEA study

Recently, integrated analysis of data from several groups participating in different studies with the same design has been conducted as a new approach to the large-scale clinical study.

The IDEA (International Duration Evaluation of Adjuvant chemotherapy colon cancer prospective pooled analysis) study is a large-scale prospective pooled analysis targeting patients with curatively resected stage III colon cancer for the purpose of assessing non-inferiority of modified FOLFOX6 or XELOX therapy for 3 months versus treatment for 6 months (non-inferiority margin: HR $\leq$1.1) as adjuvant chemotherapy.

At present, collection of data from five randomized phase III clinical trials (GERCOR, SCOT, CALGB/SWOG C80702, TOSCA, and HORG) is ongoing in the IDEA study. As of November 2011, the number of patients for whom data had been collected reached about 5,000, with the target sample size being 10,500.

At the request of the main members of the IDEA study, data from this study will also be integrated into the IDEA study. Data from this study will not be disclosed until publication of the results of the IDEA study, on the grounds that the results of this study may significantly affect the policy with regard to adjuvant chemotherapy for colon cancer.

3. Patients eligibility criteria

3.1. Inclusion criteria

(1) Histologically confirmed adenocarcinoma of the colon.
(2) Predominantly located in the cecum, colon, or rectosigmoid region based on the findings from surgery and/or examination of the resected specimen.*
*: Multiple colorectal cancer with up to two infiltrating tumors† is eligible ("multiple" is applied as one of the stratification factors).
†: Infiltrating carcinoma is defined as cancer that has spread beyond the submucosal layer and does not mean intramucosal cancer.
(3) Colectomy with D2 or D3 lymph node resection.
(4) Curability A surgery (no residual tumor visible macroscopically and/or microscopically).
(5) Stage III (T any N1 Note)/2/3 M0) (cf. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, The 7th Edition, revised version.).
Note: N1c (UICC TNM 7th edn.) is defined as tumor deposit(s), that is, satellite nodule(s) in the subserosa, or non-peritonealized pericolic or perirectal soft tissues without regional lymph node metastasis.
(6) Registration within 8 weeks after resection and commencing chemotherapy within 2 weeks after registration.
(7) Age ≥20 years.
(8) ECOG performance status of 0–1.
(9) Body surface area (DuBois) ≤2.2 m^2.
(10) No prior chemotherapy, immunotherapy, or radiation therapy.
(11) Adequate organ function (data obtained within 14 days before registration):
i) neutrophil count ≥1,500/mm^3
ii) platelet count ≥100,000/mm^3
iii) serum creatinine ≤1.5 times the upper limit of normal (ULN)
iv) CCr (calculated value)*≧30 mL/min
v) total bilirubin ≤2.0 mg/dL
vi) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100 IU/L
vii) carcinoembryonic antigen (CEA) ≤10 ng/mL
* CCr is calculated using the Cockcroft–Gault equation (the measured value is not used)
Male: CCr = [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)]
Female: CCr = 0.85 × [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)].
(12) Written informed consent with the patient's signature and the date.

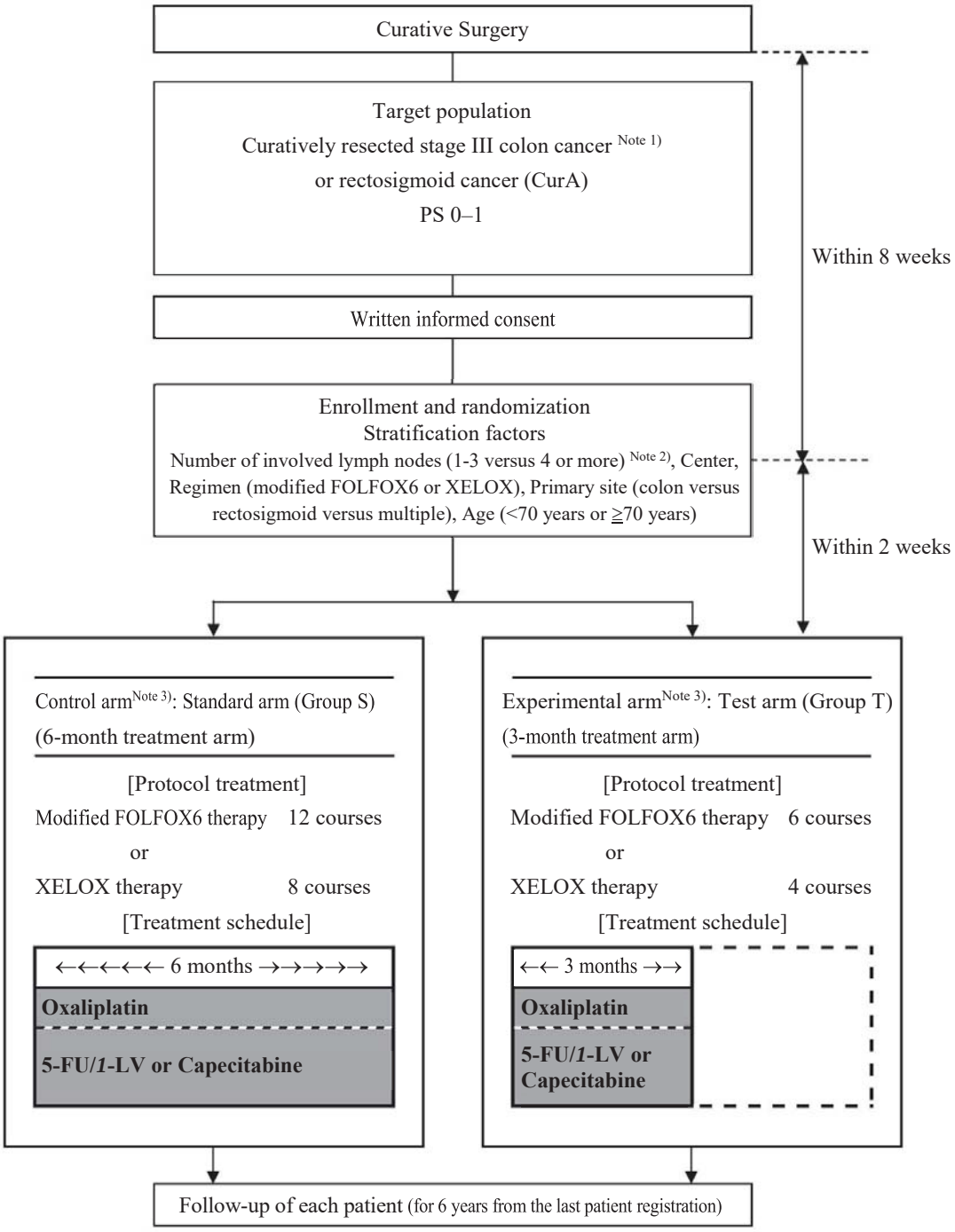
3.2. Exclusion criteria

(1) Cancer of the appendix.
(2) Past history of malignancy.Note 1)
Note 1: Patients with a recurrence-free period of 5 years or longer are eligible, and so are patients with endoscopic curative resection of intramucosal carcinoma (stomach, colon, or esophagus), curative resection of cervical cancer, and resected basal cell cancer and/or squamous cell cancer of the skin.
(3) Women who are pregnant or breast-feeding.
(4) Women who may become pregnant and fertile men.Note 2)
Note 2: Eligible if a patient agrees to use contraception during the study period and for 1 month after completion of treatment, and he/she understands the risks related to pregnancy.
(5) Participation in another clinical trial within 30 days before registration.
(6) Existing Grade 1 or worse peripheral sensory neuropathy.
(7) Uncontrolled diabetes mellitus (including insulin therapy as absolutely imperative).
(8) Uncontrolled congestive heart failure, angina pectoris, hypertension, and/or arrhythmia.
(9) Continuous systemic steroid therapy (either oral or intravenous administration).
(10) A history and/or current evidence of significant neurological and/or mental illness.
(11) Active infectious disease, including known HBV, HCV, HIV infection and so on.

(12) Known dihydropyrimidine dehydrogenase (DPD) deficiency.
(13) A history of allergy to 5-FU, *l*-LV, oxaliplatin, and/or capecitabine.
(14) Prior chemotherapy with a regimen containing oxaliplatin.
(15) Other reasons for being unfit for the study as determined by the attending physician.

4. Case Registration and Assignment

4.1. Summary of the study



Note 1: Including cecal cancer

Note 2: N1c according to the International Union Against Cancer (UICC) tumor-node-metastasis (TMN) classification, 7th edn. is included.

Note 3: Switching from modified FOLFOX6 therapy to XELOX therapy or switching from XELOX therapy to modified FOLFOX6 therapy is not permitted.

4.2. Registration procedures

Registration of subjects will be carried out by using a central registration system.

Subjects must be registered within 8 weeks [Note 1)] after surgery upon confirmation of meeting the inclusion criteria listed in *3. Patients' eligibility criteria*.

After obtaining informed consent from eligible patients, access the EDC [Note 2)] (web-based system) of this study, and enter the necessary information on the registration page. A registration number is issued when the patient is deemed to be eligible, and this indicates the completion of "registration." A registration number is not issued when there is missing information or the patient is ineligible, and this indicates the failure of "registration."

Cancellation of registration (deletion from the database) cannot be done once a patient has been registered. If double registration occurs accidentally, the initial registration data (registration number) will be employed. The data center should be contacted promptly if a mis-registration or double registration is found.

Check the starting dose that is calculated from the body surface area on the starting dose confirmation screen after registration (after the registration number has been issued) and initiate treatment within 2 weeks.

After registration, persons at each study site must manage and identify the patient registration number and each registered patient by creating management records.

Note 1: Eight weeks can be calculated from the day of surgery to the same day of the week.

Note 2: Electronic data capture for clinical study data. This system is used for case report as well as case registration. An application form for using the EDC system has to be submitted to the data center to obtain a personal account number and password prior to using this system.

Office of Japanese Foundation for Multidisciplinary Treatment of Cancer

FAX: 03-5627-7595 (+81-3-5627-7595); TEL: 0120-184100 (+81-120-184100) (toll free) / 03-5627-7594 (+81-3-5627-7594) (Data center)

E-mail: jfmc47@jfmc.or.jp (e-mail address for this study)

Contact hours: Mon–Fri 9:00–17:00 (excl. holidays and Dec 29 to Jan 4)

4.3. Assignment procedure

Patients will be randomly assigned to the control arm (Group S) and the test arm (Group T) by the data center. A minimization method with five stratification factors (listed below) will be applied to eliminate bias during randomization. The details of the allocation procedure are not disclosed to investigators at the study sites.

Stratification factors [Note)]: number of involved lymph nodes (1-3 versus 4 or more), participating centers, regimen (modified FOLFOX6 or XELOX), primary site (colon or rectosigmoid or multiple), and age (<70 years or ≥70 years).Note: Rationale for selecting the stratification factors:

- Number of involved lymph nodes (1-3 versus 4 or more)
  The N stage was included as a stratification factor because the prognosis of colon cancer is significantly influenced by the number of metastatic lymph nodes.
- Participating centers
  The participating centers was included as a stratification factor considering the difference in the outcome of colon cancer surgery among hospitals.
- Regimen
  The regimen was included as a stratification factor because no comparative studies of FOLFOX therapy and XELOX therapy have been conducted yet, although similar results are reported when these regimens are used as adjuvant chemotherapy for colon cancer.
- Primary site (colon/rectosigmoid/multiple)
  Colon or rectosigmoid or multiple were included as stratification factors because of a possible difference in the prognosis depending on the primary tumor sites (colon vs. rectosigmoid) and the eligibility of patients with up to two infiltrating tumors for this study.
- Age (<70 years or ≥70 years)
  Data from the MOSAIC (patients with stage II or III colon cancer receiving adjuvant chemotherapy) and NSABP C-07 study were comparatively analyzed after stratification by age. As a result, the effect of oxaliplatin on DFS and OS was found to be smaller in the age group of 70 years or older. The results of NO16968 study (patients with stage III colon cancer receiving adjuvant chemotherapy) indicated significant improvement of DFS and OS in the age group of 70 years or older, but age was still included as a stratification factor due to the small additional effect of oxaliplatin.

5. Treatment Method

5.1. Initiation of protocol treatment

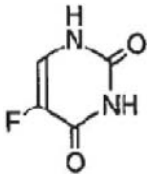
The protocol treatment assigned to each patient must be initiated within 2 weeks [Note)] after registration. The dosage is calculated based on the patient's height and body weight at the time of registration and there is no dose adjustment for changes of weight.

Note: Two weeks can be calculated from the day of registration to the same day of the week.

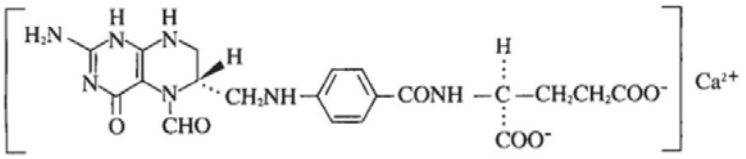
5.2. Medications

Package inserts should be consulted for the details of handling the medications. A summary of the medications used in this study is given below.

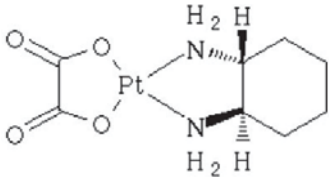
5.2.1. Fluorouracil (5-FU)

Generic name (abbreviation)	Fluorouracil (5-FU)
Structural formula	
Brand name (Marketing approval holder)	5-FU Injection 250 Kyowa (Kyowa Hakko Kirin Co., Ltd.) etc. 5-FU Injection 1000 (Kyowa Hakko Kirin Co., Ltd.)
Dosage form	Injection (tube)
Active ingredient	Fluorouracil (JAN)
Inactive ingredient	Tris aminomethane (trometamol)
Color	Fluorouracil is a colorless to transparent pale yellow solution for injection
pH	8.2–8.6
Storage and expiration date	Store at room temperature / for up to 3 years

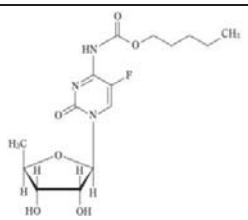
5.2.2. Levofolinate calcium (1-LV)

Generic name (abbreviation)	Levofolinate calcium (*1*-LV)	
Structural formula		
Brand name (Marketing approval holder)	Levofolinate For Intravenous Infusion 25 mg "Yakult" (Yakult Honsha Co., Ltd.) Levofolinate For Intravenous Infusion 100 mg "Yakult" (Yakult Honsha Co., Ltd.) etc.	
Dosage form	Injection (vial)	
Active ingredient	Levofolinate calcium 27.0 mg (25.0 mg as levofolinate)	Levofolinate calcium 108.0 mg (100.0 mg as levofolinate)
Inactive ingredient	D-mannitol 25.0 mg Appropriate amount of hydrochloric acid Appropriate amount of sodium hydrate	D-mannitol 100.0 mg Appropriate amount of hydrochloric acid Appropriate amount of sodium hydrate
Color	Levofolinate calcium is a white to yellowish white to slightly yellow white powder or mass	
pH	6.8–8.2 (Levofolinate 10 mg/mL solution for injection)	
Storage and expiration date	Store at room temperature / for up to 3 years	

5.2.3. Oxaliplatin (L-OHP)

Generic name (abbreviation)	Oxaliplatin (L-OHP)	
Structural formula		
Brand name (Marketing authorization holder)	Elplat® I.V. Infusion Solution 100 mg (Yakult Honsha Co., Ltd.) Elplat® I.V. Infusion Solution 50 mg (Yakult Honsha Co., Ltd.)	
Dosage form	Injection (vial)	
Active ingredient/content	Oxaliplatin 100 mg/20 mL	Oxaliplatin 50 mg/10 mL
Osmotic pressure ratio (to physiological saline)	About 0.04	
Color	Oxaliplatin is a colorless and transparent liquid	
pH	4.0–7.0	
Storage and expiration date	Store at room temperature / for up to 2 years	

5.2.4. Capecitabine (Cape)

Generic name (abbreviation)	Capecitabine (Cape)
Structural formula	
Brand name (Marketing authorization holder)	XELODA® Tablet 300 (Chugai Pharma Manufacturing Co., Ltd.)
Dosage form	White film-coated tablets
Active ingredient/content	Capecitabine 300 mg
Inactive ingredient	Anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate, talc, titanium dioxide
Storage and expiration date	Store at room temperature / for up to 4 years

5.3. Protocol treatment

Either modified FOLFOX6 therapy or XELOX therapy must be selected prior to patient registration, and selection of treatment is done by the doctor's decision. Switching of treatment after registration is not permitted. If continuing modified FOLFOX6 or XELOX therapy is considered to be difficult due to oxaliplatin-related adverse events, modified FOLFOX6 therapy is switched to 5-FU/*l*-LV therapy (sLV5FU2) or XELOX therapy is switched to capecitabine monotherapy. Subsequent dose escalation of the 5-FU or capecitabine is not allowed.
The recommended initial dose of each drug is calculated from the body surface area (DuBois) at the time of registration, and the actual dosage should be calculated at each study site.

5.3.1. Modified FOLFOX6 therapy

For modified FOLFOX6 therapy, oxaliplatin (85 mg/m^2) is administered concurrently with *l*-LV (200 mg/m^2) followed by 5-FU (bolus; 400 mg/m^2) on Day 1. From Day 1 to Day 3, 5-FU infusion (2,400 mg/m^2) is performed.
Treatment is continued for up to 12 courses in the control arm (Group S; 6 months of treatment) and up to 6 courses in the Experimental arm (Group T; 3 months of treatment), with the duration of each course being 2 weeks (14 days), unless any of the criteria listed in *5.6.1. Withdrawal of protocol treatment* are met (see ***Table 5.3.1.1.***).
After the completion of protocol treatment, follow-up is performed without any further adjuvant chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed.
The recommended initial dose of each drug (oxaliplatin in 10 mg increments, *l*-LV in 25 mg increments, and 5-FU in 50 mg increments) calculated based on the body surface area (DuBois formula) is reported by the study office to the study site at the time of case registration. Therefore, these dosages should be used to determine actual drug doses at each site when performing treatment. If another body surface area formula is used at the study site, however, the dosage thus calculated is permitted.

Modified FOLFOX6 (Day 1) ex) Method of administration

1. Dissolve oxaliplatin (85 mg/m^2) in 250 mL of 5% glucose solution.
2. Dissolve *l*-LV (200 mg/m^2) in 250 mL of 5% glucose solution.
3. The solutions obtained in 1 and 2 are given intravenously over 120 minutes at the same time in separate bags using a Y-line.
4. 5-FU (400 mg/m^2) is administered as an intravenous bolus within 15 minutes.
5. 5-FU (2,400 mg/m^2) is administered intravenously over 46 hours using a disposable infuser or an infusion pump.

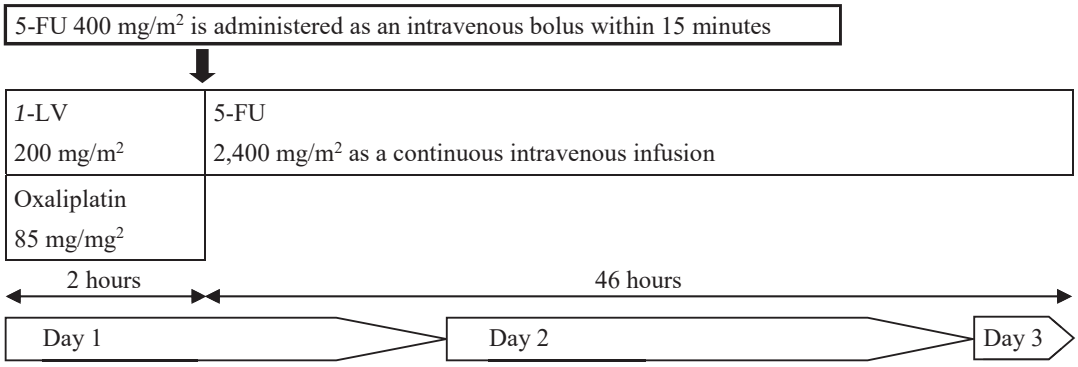


Table 5.3.1.1. Administration schedule for modified FOLFOX6 therapy

Course no.	1	2	3	4	5	6	7	8	9	10	11	12
Control arm: Group S (6 months)	●	●	●	●	●	●	●	●	●	●	●	●
Experimental arm: Group T (3 months)	●	●	●	●	●	●						

5.3.2. XELOX therapy

For XELOX therapy, oxaliplatin (130 mg/m^2) is administered on Day 1 and capecitabine (2,000 mg/m^2/day or 1,500 mg/m^2/day**) is administered from the evening of Day 1 to the morning of Day 15. Capecitabine* is administered at 1,000 mg/m^2 or 750 mg/m^{2**} twice a day, within 30 minutes after breakfast and dinner, for a total of 28 doses (treatment for 14 days) (see ***Tables 5.3.2.1-1.*** and ***-2.***). *: The administration period of capecitabine can also run from the morning of Day 2 to the evening of Day 15.

**: The starting dose for capecitabine will be as follows in accordance with CCr value and age at the time of enrollment.

2,000 mg/m^2/day (1,000 mg/m^2/dose) : CCr > 50 mL/min

1,500 mg/m^2/day (750 mg/m^2/dose) : 30 mL/min ≦ CCr ≦ 50 mL/min or ≥ 70 years of age

Treatment is continued for up to 8 courses in the control arm (Group S: 6 months of treatment) and up to 4 courses in the Experimental arm (Group T; 3 months of treatment), with the duration of each course being 3 weeks (21 days), unless any of the criteria listed in *5.6.1. Withdrawal of protocol treatment* are met (see ***Table 5.3.2.2.***).

After the completion of protocol treatment, follow-up is performed without any further adjuvant chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed.

The recommended initial dose of each drug (oxaliplatin in 10 mg increments, and see ***Table 5.3.2.3***-1 and -2**.** for capecitabine) calculated based on the body surface area (DuBois formula) is reported by the study office to the study site at the time of case registration. Therefore, these dosages should be used to determine actual dose drug doses at each site when performing treatment. If another body surface area formula is used at the study site, however, the dosage thus calculated is permitted.

XELOX (Days 1–21) ex)Method of administration

1. Dissolve oxaliplatin (130 mg/m^2) in 250 mL to 500 mL of 5% glucose solution and infuse it intravenously over 2 hours.
2. Capecitabine** (1,000 mg/m^2 or 750 mg/m^2) is administered orally within 30 minutes after a meal.

Table 5.3.2.1-1. Recommended administration schedule for XELOX therapy

Day	1	8	14	15	21
Oxaliplatin	●	130 mg/m^2 (2hrs, iv)			
Capecitabine 2,000 or 1,500 mg/m^2/day	Morning			Morning	
	Evening			Evening	

Table 5.3.2.1-2. Acceptable administration schedule for XELOX therapy

Day	1	8	14	15	21
Oxaliplatin	●	130 mg/m^2 (2hrs, iv)			
Capecitabine 2,000 or 1,500 mg/m^2/day	Morning			Morning	
	Evening			Evening	

**: The starting dose for capecitabine will be as follows in accordance with CCr value and age at the time of enrollment.

2,000 mg/m^2/day (1,000 mg/m^2/dose) : CCr > 50 mL/min

1,500 mg/m^2/day (750 mg/m^2/dose) : 30 mL/min ≦ CCr ≦ 50 mL/min or ≥ 70 years of age

Table 5.3.2.2. Administration schedule for XELOX therapy

Course no.	1	2	3	4	5	6	7	8
Control arm: Group S (6 months)	●	●	●	●	●	●	●	●
Experimental arm: Group T (3 months)	●	●	●	●				

Table 5.3.2.3.-1 Initial dose of capecitabine (1,000 mg/m^2/dose)		
Body surface area (BSA)	**Single dose (no. of tablets)**	**Daily dose (no. of tablets)**
<1.36 m^2	1,200 mg (4 tablets)	2,400 mg (8 tablets)
1.36 m^2 ≤ BSA < 1.66 m^2	1,500 mg (5 tablets)	3,000 mg (10 tablets)
1.66 m^2 ≤ BSA < 1.96 m^2	1,800 mg (6 tablets)	3,600 mg (12 tablets)
1.96 m^2 ≤ BSA ≤ 2.2m^2	2,100 mg (7 tablets)	4,200 mg (14 tablets)

Table 5.3.2.3.-2 Initial dose of capecitabine (750 mg/m^2/dose)		
Body surface area (BSA)	**Single dose (no. of tablets)**	**Daily dose (no. of tablets)**
<1.41 m^2	900 mg (3 tablets)	1,800 mg (6 tablets)
1.41 m^2 ≤ BSA < 1.81 m^2	1,200 mg (4 tablets)	2,400 mg (8 tablets)
1.81 m^2 ≤ BSA < 2.2 m^2	1,500 mg (5 tablets)	3,000 mg (10 tablets)

5.4. Criteria for dose hold and resumption for modified FOLFOX6 therapy

5.4.1. Initiation and dose hold/resumption criteria for modified FOLFOX6 therapy

Administration is started on Day 1 or the day before when all of the initiation criteria listed in ***Table 5.4.1.1.*** *"Initiation and dose hold/resumption criteria for each course of modified FOLFOX6 therapy"* are confirmed to have been met. If any of the criteria are not met, treatment is suspended until the laboratory test values and/or symptoms have recovered. Administration can be delayed by the investigator when any adverse event occurs, even if all the criteria in ***Table 5.4.1.1.*** *"Initiation and dose hold/resumption criteria for each course of modified FOLFOX6 therapy"* are confirmed to have been met.

The protocol treatment (chemotherapy) is discontinued if any of the initiation criteria are not met after 29 days have passed from the scheduled day of starting the next course (Day 15). The schedule for modified FOLFOX6 therapy can be changed due to holidays or patient factors, and can be started up to two days before or three days after the planned administration day (Day 0).

When initiation of treatment is suspended, the actual day of starting administration is set as Day 1 and the subsequent treatment schedule is shifted accordingly.

Table 5.4.1.1. Initiation and dose hold/resumption criteria for each course of modified FOLFOX6 therapy

Adverse event	Initiation and resumption criteria	Hold criteria
Neutropenia	≤ Grade 1 (neutrophil count ≥1,500 /mm^3)	Administration can be suspended for up to 29 days. Protocol treatment will be discontinued if the patient fails to recover after 29 days.
Thrombocytopenia	≤ Grade 1 (platelet count ≥75,000 /mm^3)	
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	≤ Grade 1	
Others	Administration can be suspended by the investigator when an adverse event occurs that does not fit any of the above.	

5.4.2. Dose modification criteria for modified FOLFOX6 therapy (excl. peripheral sensory neuropathy)

The dose of oxaliplatin and 5-FU is reduced based on the grade of adverse events during the previous course, in accordance with ***Table 5.4.2.1.*** *"Dose reduction levels for modified FOLFOX6 therapy"* and ***Table 5.4.2.2.*** *"Dose modification criteria for modified FOLFOX6 therapy."*

The dose of oxaliplatin and 5-FU can be reduced to the second dose reduction level (level-2) if similar toxicity is observed in the patient after the first dose reduction (level-1). If similar toxicity still occurs after the second reduction (level-2), further reduction of the dose is not done and modified FOLFOX6 therapy is discontinued.

Dose reduction of *1*-LV is not acceptable.

A subsequent increase of the dose is not allowed even if the patient recovers after dose reduction. For other adverse events, dose reduction can be performed according to each study site's criteria at the decision of the investigator, if necessary.

Dose reduction must not be double-counted. That is, even if two toxicities (such as grade 3 neutropenia and grade 3 diarrhea) are observed during the previous course, the dose is reduced by a single level for the next course.

Table 5.4.2.1. Dose reduction levels for modified FOLFOX6 therapy

Dose level	Oxaliplatin	5-FU (intravenous bolus)[Note)]	5-FU (continuous intravenous infusion)[Note)]	*1*-LV
Initial dose	85 mg/m^2	400 mg/m^2	2,400 mg/m^2	200 mg/m^2
Level-1	75 mg/m^2	0 mg/m^2	1,900 mg/m^2	200 mg/m^2
Level-2	55 mg/m^2	0 mg/m^2	1,400 mg/m^2	200 mg/m^2

Note: The above dose modification are recommended for dose reduction of 5-FU (intravenous bolus and continuous intravenous infusion), but the dose can be changed at the decision of the physician. For level-2, however, the dose must not be reduced below

the recommended dose listed above.

Table 5.4.2.2. Dose modification criteria for modified FOLFOX6 therapy

Adverse event (excl. peripheral sensory neuropathy [peripheral nervous symptoms])	Grade	Dose level		
		Oxaliplatin	5-FU intravenous bolus	5-FU continuous intravenous infusion
Neutropenia, thrombocytopenia	3/4	Level-1	Level-1	Level-1
Persistent grade 2 neutropenia or thrombocytopenia for 1 week or longer	2	Level-1 or no change (doctor's decision)	Level-1 or no change (doctor's decision)	Level-1 or no change (doctor's decision)
Persistent grade 2 neutropenia or thrombocytopenia for 2 weeks or longer	2	Level-1	Level-1	Level-1
Diarrhea, oral mucositis (stomatitis), palmar-plantar erythrodysesthesia syndrome* (hand-foot syndrome*)	3	No change	Level-1	Level-1
	4	Discontinuation of protocol treatment	Discontinuation of protocol treatment	Discontinuation of protocol treatment
Allergic reaction/anaphylaxis	3/4	Discontinuation of administration	No change	No change
Persistent grade 2 diarrhea, stomatitis, or palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) for 2 weeks or longer	2	No change	Level-1	Level-1
Other apparent drug-related adverse events (excluding hematologic toxicity)	3	Level-1	Level-1	Level-1
	4	Discontinuation of protocol treatment	Discontinuation of protocol treatment	Discontinuation of protocol treatment

: Grading criteria for palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome*) (Blum classification)[42]

Grade	Physiological symptoms	Functional severity
1	Numbness, hyperesthesia, tingling, painless swelling, painless erythema	Symptoms that do not affect daily life
2	Painful erythema with swelling	Symptoms that affect daily life
3	Wet desquamation, ulcers, blisters, severe pain	Symptoms that impede daily activities

If a symptom occurs that has a different grade from the functional severity, the grade judged to be more appropriate is selected.[42]

5.4.3. Dose modification criteria for modified FOLFOX6 therapy (peripheral sensory neuropathy)

The dose of oxaliplatin is reduced based on the grade of peripheral sensory neuropathy during the previous course in accordance with ***Table 5.4.2.1.*** *"Dose reduction levels for modified FOLFOX6 therapy"* and ***Table 5.4.3.1.*** *"Criteria for dose modification of oxaliplatin in relation to peripheral sensory neuropathy."*

The doses of oxaliplatin and 5-FU can be reduced to the second dose reduction level if similar toxicity is observed after the first dose reduction. If similar toxicity still occurs after the second dose reduction, further dose reduction is not done and oxaliplatin treatment is discontinued while 5-FU treatment is continued.

A subsequent increase of the dose is not allowed even if the patient recovers after dose reduction. If peripheral sensory neuropathy occurs, the dose of 5-FU is not reduced unless it contravenes ***Table 5.4.2.2.*** *"Dose modification criteria for modified FOLFOX6 therapy."*

Dose reduction must not be double-counted. That is, even if two toxicities (such as grade 3 neutropenia and grade 3 diarrhea) are observed during the previous course, the dose is reduced by a single level for the next course. The criteria listed in ***Table 5.4.2.2.*** *"Dose modification criteria for modified FOLFOX6 therapy"* and in ***Table 5.4.3.1.*** *"Criteria for dose modification of oxaliplatin in relation to peripheral sensory neuropathy"* must also not be double-counted.

Table 5.4.3.1. Criteria for dose modification of oxaliplatin in relation to peripheral sensory neuropathy

Adverse event	Handling of oxaliplatin		
	Duration		
	≤7 days	8–13 days	≥14 days
Dysesthesia with cold stimulus	No change	No change	No change
Dysesthesia without pain	No change	No change	Suspended until recovery → Level-1 after recovery
Dysesthesia with pain	No change	Level-1	Level-2
Dysesthesia with functional disorder	Level-1	Level-2 (discontinuation)[Note)]	Discontinuation of oxaliplatin

Note: Administration of oxaliplatin must be discontinued if "dysesthesia with pain" persisting for more than 14 days becomes "dysesthesia with functional disorder" persisting for 8 to 13 days.

5.4.4. Criteria for prolonging the infusion of oxaliplatin

Patients may suffer from laryngopharyngeal dysesthesia (dyspnea) within 2 hours after the administration of oxaliplatin. When this type of acute dyspnea without respiratory dysfunction occurs, oxaliplatin treatment is discontinued. From the next course, it is administered over 4 to 6 hours from 2 to 4 hours prior to the start of *1*-LV administration.

In addition, the administration time can be extended to 2 to 6 hours to avoid allergic reaction.

5.4.5. Prevention of allergic reactions to oxaliplatin

The following dosing methods that have been used previously are recommended for the prevention of oxaliplatin-related allergic reactions.

(1) Ordinary prophylaxis (no prior allergic reactions)
Infusion of dexamethasone (8 mg) from 30 minutes before starting the infusion of oxaliplatin

(2) If an allergic reaction has occurred during the previous course:
Intravenous infusion of dexamethasone (20 mg) and an H_2-receptor antagonist (famotidine at 20 mg, ranitidine at 50 mg, or cimetidine at 300 mg) plus oral administration of H_1-receptor antagonist (diphenhydramine at 50 mg) from 30 minutes before starting the infusion of oxaliplatin.

5.4.6. Managing allergic reactions to oxaliplatin

If an allergic reaction of grade 2 or lower occurs, protocol treatment is continued in accordance with the procedures listed under *5.4.5. Prevention of allergic reactions to oxaliplatin* from the next course, in principle. If administration of oxaliplatin is discontinued at the discretion of the investigator for unavoidable reasons, treatment with 5-FU or *1*-LV (sLV5FU2) will be continued.

If an allergic reaction of grade 3 or higher or anaphylaxis occurs, administration of oxaliplatin is discontinued and treatment with 5-FU or *1*-LV (sLV5FU2) is continued.

5.5. Criteria for dose hold and resumption for XELOX therapy

5.5.1. Initiation and dose hold/resumption criteria for XELOX therapy and capecitabine withholding criteria

Administration is started on Day 1 or the day before when all of the initiation criteria listed in ***Table 5.5.1.1.*** *"Initiation and dose hold/resumption criteria for each course of XELOX therapy"* are confirmed to have been met. If any of the criteria are not met, treatment is suspended until the laboratory test values and/or symptoms have recovered. Administration can be delayed by the investigator when any adverse event occurs, even if all the criteria in ***Table 5.5.1.1.*** *"Initiation and dose hold/resumption criteria for each course of XELOX therapy"* are confirmed to have been met.

After the start of each course, if in conflict with "***Table 5.5.1.2***: *Capecitabine withholding criteria after the start of each cours*e," administration of capecitabine for the course concerned is to be withheld. After withholding capecitabine, if recovery from the adverse event has been achieved by day 15, capecitabine therapy may be resumed. Upon resumption, the capecitabine dose shall be in accordance with "***Table 5.5.2.1***: *Criteria for dose changes in XELOX therapy.*" Furthermore, capecitabine is not to be administered after day 16.

The protocol treatment (chemotherapy) is discontinued if any of the initiation criteria are not met after 29 days have passed from the scheduled day of starting the next course (Day 22). The schedule for XELOX therapy period can be changed due to holidays or patient factors, and it can be initiated up to two days before or three days after the planned administration day (Day 0).

When initiation of treatment is suspended, the actual day of starting administration is set as Day 1 and the subsequent treatment schedule is shifted accordingly.

Table 5.5.1.1. Initiation and dose hold/resumption criteria for each course of XELOX therapy

Adverse event	Initiation and resumption criteria	Hold criteria
Neutropenia	≤ Grade 1 (neutrophil count ≥1,500 /mm^3)	Administration can be suspended for up to 29 days. Protocol treatment is discontinued if the patient fails to recover after 29 days.
Thrombocytopenia	≤ Grade 1 (platelet count ≥75,000 /mm^3)	
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), diarrhea, and oral mucositis	≤ Grade 1	
Others	Administration can be suspended by the investigator when an adverse event occurs that does not fit any of the above.	

Table 5.5.1.2. Capecitabine withholding criteria after the start of each course

Adverse event	Withholding criteria	Withholding details
Palmar–plantar erythrodysesthesia syndrome (hand–foot syndrome), diarrhea, and oral mucositis	≥ Grade 2	After the start of each course, if in conflict with "Table 5.5.1.2: Capecitabine withholding criteria after the start of each course," administration of capecitabine for the course concerned is to be withheld. After withholding capecitabine, if recovery from the adverse event has been achieved by day 15, capecitabine therapy may be resumed. Upon resumption, the capecitabine dose shall be in accordance with "Table 5.5.2.1: Criteria for dose changes in XELOX therapy." Furthermore, capecitabine is not to be administered after day 16.
Others	Drugs may be withheld upon the appearance of adverse events that do not correspond to the above at the discretion of the trial attending physician.	

5.5.2. Dose modification criteria for XELOX therapy (excl. peripheral sensory neuropathy)

The dose of oxaliplatin and capecitabine is reduced based on the grade of adverse events during the previous course, in accordance with ***Table 5.5.2.1.*** *"Dose modification criteria for XELOX therapy,"* ***Table 5.5.2.2.*** *"Dose reduction levels for XELOX therapy (oxaliplatin),"* and ***Table 5.5.2.3.-1*** *"Dose reduction level in XELOX therapy (capecitabine: starting dose of 1,000 mg/m^2/dose),"* and ***Table 5.5.2.3.-2*** "*Dose reduction level in XELOX therapy (capecitabine: starting dose of 750 mg/m^2/dose).*"

The dose of oxaliplatin and capecitabine can be reduced to the second dose reduction level (Level-2) if similar toxicity is observed in the patient after the first dose reduction (Level-1). If similar toxicity still occurs after the second dose reduction (Level-2), further reduction of the dose is not done and XELOX therapy is discontinued.

A subsequent increase of the dose is not allowed even if the patient recovered after dose reduction. If peripheral sensory neuropathy occurs, the dose of 5-FU is not reduced unless it contravenes ***Table 5.4.2.2.*** *"Dose modification criteria for modified FOLFOX6 therapy."*

Dose reduction must not be double-counted. That is, even if two toxicities (such as grade 3 neutropenia and grade 3 diarrhea) are observed during the previous course, the dose is reduced by a single level for the next course.

Table 5.5.2.1. Dose modification criteria for XELOX therapy

Adverse event (excl. peripheral sensory neuropathy [peripheral nervous symptoms])	Grade	Incidence	Dose level	
			Oxaliplatin	Capecitabine
Neutropenia, thrombocytopenia	3/4	1	Level-1	Level-1
Persistent grade 2 neutropenia or thrombocytopenia for 1 week or longer	2	1	Level-1 or no change (doctor's decision)	Level-1 or no change (doctor's decision)
Persistent grade 2 neutropenia or thrombocytopenia for 2 weeks or longer	2	1	Level-1	Level-1
Diarrhea, oral mucositis (stomatitis)	3	1	No change	Level-1
	4	1	Discontinuation of protocol treatment	Discontinuation of protocol treatment
Palmar-plantar erythrodysesthesia syndrome* (hand-foot syndrome*)	2	1 (< 1 week)	No change	No change
		2	No change	Level-1
		3	No change	Level-2
	3	1	No change	Level-1
Allergic reaction/anaphylaxis	3/4	1	Discontinuation of administration	No change
When hand–foot syndrome*, diarrhea, or oral mucositis of grade 2 persists for 1 week or more.	2	1	No change	Level-1
When two or more of the following are observed during the same course: hand–foot syndrome1, diarrhea, or oral mucositis of grade 2.	2	1	No change	Level-1
Persistent grade 2 diarrhea or stomatitis for 2 weeks or longer	2	1	No change	Level-1
Other apparent drug-related adverse events (excluding hematologic toxicity)	3	1	Level-1	Level-1
	4	1	Discontinuation of protocol treatment	Discontinuation of protocol treatment

: Grading criteria for palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome*) (Blum classification)[42]

Grade	Physiological symptoms	Functional severity
1	Numbness, hyperesthesia, tingling, painless swelling, painless erythema,	Symptoms that do not affect daily life
2	Painful erythema with swelling	Symptoms that affect daily life
3	Wet desquamation, ulcer, blister, severe pain	Symptoms that impede daily activities

If a symptom occurs that has a different grade from the functional severity, the grade judged to be more appropriate is selected.[42]

Table 5.5.2.2. Dose reduction levels for XELOX therapy (oxaliplatin)

Dose level	Oxaliplatin
Initial dose	130 mg/m^2
Level-1	100 mg/m^2
Level-2	85 mg/m^2

Table 5.5.2.3-1. Dose reduction levels for XELOX therapy (capecitabine; starting dose of 1,000mg/m^2/dose**)**

Body surface area	Single dose		
	Initial dose	Level-1	Level-2
<1.36 m^2	1,200 mg (4 tablets)	900 mg (3 tablets)	600 mg (2 tablets)
1.36 m^2 ≤ BSA < 1.41 m^2	1,500 mg (5 tablets)		
1.41 m^2 ≤ BSA < 1.51 m^2		1,200 mg (4 tablets)	
1.51 m^2 ≤ BSA < 1.66 m^2			900 mg(3 tablets)
1.66 m^2 ≤ BSA < 1.81 m^2	1,800 mg (6 tablets)		
1.81 m^2 ≤ BSA < 1.96 m^2		1,500 mg (5 tablets)	
1.96 m^2 ≤ BSA < 2.11 m^2	2,100 mg (7 tablets)		
2.11 m^2 ≤ BSA ≤ 2.2 m^2			1,200 mg (4 tablets)

Table 5.5.2.3.-2 Dose reduction level for XELOX therapy (capecitabine: starting dose of 750 mg/m2/dose)

Body surface area	Single dose		
	Initial dose	Level-1	Level-2
<1.36 m^2	900 mg (3 tablets)	600 mg (2 tablets)	300 mg (1 tablet)
1.36 m^2 ≤ BSA < 1.41 m^2			
1.41 m^2 ≤ BSA < 1.51 m^2	1,200 mg (4 tablets)		
1.51 m^2 ≤ BSA < 1.66 m^2		900 mg (3 tablets)	600 mg (2 tablets)
1.66 m^2 ≤ BSA < 1.81 m^2			
1.81 m^2 ≤ BSA < 1.96 m^2	1,500 mg (5 tablets)		
1.96 m^2 ≤ BSA < 2.11 m^2			
2.11 m^2 ≤ BSA ≤ 2.2 m^2		1,200 mg (4 tablets)	900 mg(3 tablets)

5.5.3. Dose modification criteria for XELOX therapy (peripheral sensory neuropathy)

The dose of oxaliplatin is reduced based on the grade of peripheral sensory neuropathy during the previous course, in accordance with ***Table 5.5.2.2.*** *"Dose reduction levels for XELOX therapy (oxaliplatin)"* and ***Table 5.5.3.1.*** *"Criteria for modification the oxaliplatin dose in relation toperipheral sensory neuropathy."*

The dose of oxaliplatin can be reduced to the second level if similar toxicity is observed after the first dose reduction. If similar toxicity still occurs at the second level, further dose reduction is done made and oxaliplatin is discontinued while capecitabine is continued.

A subsequent dose increase is not allowed even if the patient recovers after a dose reduction. If peripheral sensory neuropathy occurs, the dose of capecitabine is not reduced unless it contravenes ***Table 5.5.2.1.*** *"Dose modification criteria for XELOX therapy."*

Dose reduction must not be double-counted. That is, even if two toxicities (such as peripheral sensory neuropathy

persisting for more than 21 days and peripheral sensory neuropathy with pain persisting for more than 8 days) are observed during the previous course, the dose is reduced by a single level for the next course. The criteria of ***Table 5.5.2.1.*** *"Dose modification criteria for XELOX therapy"* and ***Table 5.5.3.1.*** *"Criteria for dose modificationof oxaliplatin in relation to peripheral sensory neuropathy"* must also not be double-counted.

Table 5.5.3.1. Criteria for dose modification of oxaliplatin in relation to peripheral sensory neuropathy

Adverse event	Handling of oxaliplatin		
	Duration		
	≤7 days	8–20 days	≥21 days
Dysesthesia with cold stimulus	No change	No change	No change
Dysesthesia without pain	No change	No change	Suspended until recovery → Level-1 after recovery
Dysesthesia with pain	No change	Level-1	Level-2
Dysesthesia with functional disorder	Level-1	Level-2 (discontinuation)[Note)]	Discontinuation of oxaliplatin treatment

Note: Administration of oxaliplatin must be discontinued if "dysesthesia with pain" persisting for more than 21 days becomes "dysesthesia with functional disorder" persisting for 8 to 20 days.

5.5.4. Criteria for prolongation of oxaliplatin administration

Patients may suffer from laryngopharyngeal dysesthesia (dyspnea) within 2 hours after the administration of oxaliplatin. When this type of acute dyspnea without respiratory dysfunction occurs, oxaliplatin treatment is discontinued. From the next course, oxaliplatin is administered over 4 to 6 hours.
In addition, the administration time can be extended to 2 to 6 hours to avoid allergic reaction.

5.5.5. Prevention of allergic reactions to oxaliplatin

The following dosing methods that have been used previously are recommended for the prevention of oxaliplatin-related allergic reactions.

(1) Ordinary prophylaxis (no prior allergic reactions)
Infusion of dexamethasone (8 mg) from 30 minutes before starting the infusion of oxaliplatin

(2) If an allergic reaction has occurred during the previous course:
Infusion of dexamethasone (20 mg) and an H_2-receptor antagonist (famotidine at 20 mg, ranitidine at 50 mg or cimetidine at 300 mg) and oral administration of an H_1-receptor antagonist (diphenhydramine at 50 mg) from 30 minutes before starting the infusion of oxaliplatin.

5.5.6. Managing allergic reactions to oxaliplatin

If an allergic reaction of grade 2 or lower occurs, protocol treatment is continued in accordance with *5.5.5. Prevention of allergic reactions to oxaliplatin* from the next course, in principle. If administration of oxaliplatin is discontinued at the discretion of the investigator for unavoidable reasons, treatment with capecitabine is continued.
If an allergic reaction of grade 3 or higher or anaphylaxis occurs, administration of oxaliplatin is discontinued and treatment with capecitabine is continued.

5.6. Discontinuation of protocol treatment

5.6.1. Criteria for discontinuation

In the following cases, protocol treatment is discontinued at the investigator's discretion and appropriate measures are taken. At the time of discontinuation, the observations and evaluations specified in ***Table 6.1.*** *"Test items and evaluation schedule (Group S; 6-month treatment group)"* and ***Table 6.4.*** *"Test items and evaluation schedule (Group T; 3-month treatment group)"* must be done, and the findings and reasons for discontinuation must be reported via the EDC*[2] (web-based system). Investigators must promptly report the discontinuation of treatment via the EDC*[2] (web-based system).

(1) Recurrence of the primary disease.

(2) Occurrence of the other cancer.

(3) Discontinuation of protocol treatment due to adverse events

  (a) If grade 4 adverse events, such as diarrhea, mucositis (stomatitis), skin rash, vomiting, or other apparent drug-related adverse events, occur despite the maximum supportive care (excl. hematological toxicity).

  (b) If adverse events of grade 2 or higher, such as transient ischemic attacks or cerebral infarction, or cardiac adverse events of grade 3 or higher, are observed.

  (c) If evidence of interstitial pneumonia is detected.

  (d) If any criteria listed in ***Table 5.4.1.*** *"Initiation and dose hold/resumption criteria for each course of modified FOLFOX6 therapy"* and ***Table 5.5.1.*** *"Initiation and dose hold/resumption criteria for each course of XELOX therapy"* is not satisfied and the next course cannot be initiated by 29 days after the planned start day.

  (e) If a patient has reached the second dose reduction level (Level-2) and suffers an adverse event that need the further dose modification (excluding the case where only oxaliplatin violates the criteria).

  (f) If the investigator decides that discontinuation of treatment is required due to adverse events that do not fit the dose modification criteria.

(4) If withdrawal of protocol treatment is requested by a patient for reasons related to adverse events (in cases where a relationship with adverse events cannot be ruled out).

(5) If withdrawal of protocol treatment is requested by a patient for reasons unrelated to adverse events (in cases where a relationship with adverse events can be ruled out, such as the patient moving house).

(6) If death occurs during protocol treatment (death prior to discontinuation of treatment for other reasons).

(7) If a patient is found to be ineligible after registration.

(8) Is there is deviation from the protocol treatment.

  (a) If treatment is not initiated within 2 weeks after registration.

  (b) If the dose is increased again after dose reduction.

  (c) If the dose is reduced by more than the amount specified.

  (d) Other reasons.

(9) Other circumstances (failure of treatment for the primary disease after registration, etc.).

5.6.2. Discontinuation of protocol treatment

After discontinuation of protocol treatment, patients were followed up to investigate the presence/absence of recurrence or development of other cancers and the outcome. However, follow-up is not performed in the cases set out below:

(1) Withdrawal of consent to follow-up after discontinuation of treatment.

(2) Death of the patient.

(3) Difficulty in performing follow-up for other reasons.

5.7. Concomitant medication

5.7.1. Prohibited concomitant medications

Any chemotherapy (except modified FOLFOX6 therapy or XELOX therapy), endocrine therapy, molecular targeting therapy, radiation therapy, or other therapies that are considered likely to affect evaluation of this trial by an investigator cannot be used. Other investigational drugs (including non-anticancer drugs) are also not used concomitantly.

5.7.2. Precautions for concomitant use

(1) Oral coumarin anticoagulants
In patients receiving oral coumarin anticoagulants concomitantly with capecitabine and 5-FU, frequent monitoring of the prothrombin time is required to adjust the anticoagulant dose.

(2) Phenytoin
An increase of the plasma phenytoin concentration is detected following the concomitant use of this anti-epileptic drug with capecitabine or 5-FU. Therefore, when using capecitabine or 5-FU in combination with phenytoin, the plasma concentration of phenytoin must be checked regularly, and changes of symptoms/signs or laboratory data must be carefully watched.

5.7.3. Concomitant drugs

Concomitant therapy for alleviation of allergic reactions and oxaliplatin-induced peripheral sensory neuropathy is optional. Use of drugs or therapies that do not affect the evaluation of this study is also acceptable. If granulocyte colony-stimulating factor (G-CSF) is used to treat neutropenia, the name of the G-CSF drug must be reported via the EDC (web-based system).

(1) Administration of anti-histamines, steroids, and oxaliplatin can be extended up to 6 hours for the alleviation of allergic reactions.

(2) Ca/Mg, goshajinkigan, and carbamazepine can be used concomitantly to prevent or alleviate oxaliplatin-induced peripheral sensory neuropathy.

(3) 5-HT3 receptor antagonists (Sinseron, Kytril, Serotone, Zofran, Aloxi, etc.), NK_1 receptor antagonists (Emend) and other antiemetic agents (including steroids) can be used to prevent or alleviate nausea and vomiting.

(4) The criteria for using G-CSF (Neu-up, Gran, or Neutrogin) are as follows. However, these criteria do not apply if an investigator decides that G-CSF is necessary to ensure the safety of a patient.
   1) Occurrence of grade 4 neutropenia ($<500/mm^3$).
   2) Occurrence of grade 3 neutropenia ($<1,000/mm^3$) with fever ($\geq 38.0°C$).
   3) Occurrence of grade 3 neutropenia ($<1,000/mm^3$) in a patient who previously received G-CSF according to the criteria 1) or 2) above.

(5) Topical steroids, moisturizing creams, and vitamin B6 can be used concomitantly for the alleviation of capecitabine-induced palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome).
   [Reference: Approved dosage of vitamin B6]
   Pyridoxal phosphate hydrate (Pydoxal tablet): 60 mg/twice/day
   Pyridoxal phosphate hydrate (Aderoxal powder 7.8%): 60 mg/three times/day
   Pyridoxal hydrochloride (Aderoxin tablet): 100 mg/day

(6) Other treatments for complications and adverse events are optional.

5.8. Precautions for safety

Modified FOLFOX6 therapy and XELOX therapy are expected to be administered to outpatients. Accordingly, there is a possibility that if a patient suffers from an adverse event such as diarrhea, symptoms may rapidly worsen. Patients must be advised to contact the hospital promptly if adverse events occur and follow their doctor's advice until the planned hospital visiting day. Most adverse events induced by capecitabine and oxaliplatin are reversible, hence discontinuation of treatment may not be required. However, suspension of treatment or dose reduction may be required in some cases.

(1) Diarrhea

Severe diarrhea may occur following treatment with capecitabine and 5-FU. If severe diarrhea occurs, careful monitoring of the patient's condition and symptomatic treatment such as correction of electrolyte imbalance by intravenous infusion will be necessary. Administration of loperamide and other general antidiarrheal drugs can be effective for diarrhea.

(2) Renal dysfunction

The incidence of grade 3 or 4 adverse events is higher in patients with moderate renal impairment than in those with normal renal function after capecitabine treatment. Patients with moderate or severe renal dysfunction (serum creatinine >1.5 times the upper limit of normal (ULN)) prior to the start administration are ineligible for this study. Dose adjustment may not be required for patients with mild renal dysfunction.

(3) Cardiac toxicity

Occurrence of myocardial infarction, myocardial ischemia, angina pectoris, arrhythmia, cardiac arrest, heart failure, sudden death, ECG abnormalities, and cardiomyopathy have been reported in patients who received a capecitabine monotherapy. Such cardiac events have been experienced by patients receiving fluoropyrimidine drugs overseas. Patients with a history of cardiovascular disease must be carefully monitored after administration of capecitabine. In addition, since cardiac toxicity related to oxaliplatin also have been reported, careful monitoring after administration of oxaliplatin is needed.

(4) Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)

The severity of palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) is classified into grades 1 to 3. If grade 2 or 3 palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) occurs according to the "grading criteria for palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)," the dose is adjusted as set out in ***Table 5.4.2.2.*** *"Dose modification criteria for modified FOLFOX6 therapy"* or ***Table 5.5.2.1.*** *"Dose modification criteria for XELOX therapy."*

(5) Laryngopharyngeal dysesthesia

Patients may suffer from laryngopharyngeal dysesthesia (dyspnea) within 2 hours after the administration of oxaliplatin. If this type of acute dyspnea without respiratory dysfunction occurs, oxaliplatin treatment is discontinued. From the next course, oxaliplatin is administered over 4 to 6 hours.
In addition, the administration time can be extended to 2 to 6 hours to avoid this allergic reaction.

(6) Peripheral sensory neuropathy

The severity of peripheral sensory neuropathy is classified into grades 1 to 4. If grade 2 or 3 peripheral sensory neuropathy occurs, the dose is adjusted according to ***Table 5.4.3.1.*** and ***Table 5.5.3.1.***

5.9. Subsequent therapy (off-protocol treatment)

After the completion of protocol treatment, follow-up is performed without any further adjuvant chemotherapy for the primary disease until recurrence occurs or the follow-up period is completed. Following the discontinuation of protocol treatment, any type of therapy can be permitted. However, the use and the details of subsequent chemotherapy must be reported via the EDC (web-based system).

6. Study Schedules

In this study, Group S (6-month treatment group) is tested in accordance with ***Table 6.1.*** *"Study Schedules (Group S; 6-month treatment arm),"* ***Table 6.2.*** *"Study Schedules during adjuvant chemotherapy (Group S: modified FOLFOX6 therapy),"* and ***Table 6.3.*** *"Study Schedules during adjuvant chemotherapy (Group S: XELOX therapy),"* while Group T (3-month treatment arm) is tested in accordance with ***Table 6.4.*** *"Study Schedules (Group T; 3-month treatment group),"* ***Table 6.6.*** *"Study Schedules during adjuvant chemotherapy (Group T: XELOX therapy),"* and ***Table 6.6.*** *"Study Schedules during adjuvant chemotherapy (Group T: XELOX therapy)."* Regarding the results of blood biochemistry tests and adverse events during each course, the worst grade is reported via EDC (web-based system). The acceptable range of the CT test schedule is from 2 weeks before to 4 weeks after the planned examination date.

Table 6.1. Study Schedules (Group S: 6-month treatment arm)

	Before registration	Period after registration															
		1 year				2 years				3 years				4-6 years			
		3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12
Informed consent	●																
Patient characteristic	●																
Evaluation of the tumor	●																
Concomitant diseases, treatments	●																
Hematology	●	See Table 6.2 and Table 6.3.															
Serum Chemistry	●																
Adverse events, symptoms, and signs Note 1)	●																
Dose																	
Peripheral sensory neuropathy				●	●	●	●	●	●	●	●	●	●		●		●
Allergic reaction																	
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)				●	●	●	●	●	●	●	●	●	●		●		●
CEA, CA19-9	●			●	●	●	●	●	●	●	●	●	●		●		●
History and examination		●	●	●	●	●	●	●	●	●	●	●	●		●		●
Outcome					●				●				●				●
Chest CT Note 2)	●		●		●		●		●		●		●		●		●
Abdominal CT Note 3)	●		●		●		●		●		●		●		●		●
Pelvic CT			●		●		●		●		●		●		●		●
Colonoscopy Note 4)					●								●				

Note 1: Symptoms and signs are assessed before registration.

Note 2: Chest CT is preferable, but it may be substituted by a chest X-ray film.

Note 3: Abdominal CT is preferable, but it may be substituted by abdominal ultrasound.

Note 4: If total colonoscopy cannot be done, it must be performed within 1 year after registration. It must be repeated every 3 to 5 years if neoplastic lesions are not detected. If it was done before surgery or registration, it must be repeated every 3 to 5 years.

Table 6.2. Study Schedules during adjuvant chemotherapy (Group S: modified FOLFOX6 therapy)

Period after registration (months)	1		2		3		4		5		6		7
Course no.	1	2	3	4	5	6	7	8	9	10	11	12	4 weeks after the completion of 12 courses
Hematology	●	●	●	●	●	●	●	●	●	●	●	●	●*
Serum Chemistry	●	●	●	●	●	●	●	●	●	●	●	●	●*
Adverse events, symptoms, and signs	●	●	●	●	●	●	●	●	●	●	●	●	●
Dose	●	●	●	●	●	●	●	●	●	●	●	●	
Peripheral sensory neuropathy	●	●	●	●	●	●	●	●	●	●	●	●	●
Allergic reactions	●	●	●	●	●	●	●	●	●	●	●	●	
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	●	●	●	●	●	●	●	●	●	●	●	●	●
CEA, CA19-9	●						●						

*: The allowance of range for testing is up to 2 weeks before the planned date.

Table 6.3. Study Schedules during adjuvant chemotherapy (Group S: XELOX therapy)

Period after registration (months)	1		2		3		4		5		6		7
Course no.	1	2	3	4	5	6	7	8					4 weeks after the completion of 8 courses
Hematology	●	●	●	●	●	●	●	●					●*
Serum Chemistry	●	●	●	●	●	●	●	●					●*
Adverse events, symptoms, and signs	●	●	●	●	●	●	●	●					●
Dose	●	●	●	●	●	●	●	●					
Peripheral sensory neuropathy	●	●	●	●	●	●	●	●					●
Allergic reactions	●	●	●	●	●	●	●	●					
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	●	●	●	●	●	●	●	●					●
CEA, CA19-9	●				●								

*: The allowance of range for testing is up to 2 weeks before the planned date.

Table 6.4. Study Schedules (Group T; 3-month treatment group)

	Before registration	Period after registration															
		1 year				2 years				3 years				4-6 years			
		3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12
Informed consent	●																
Patient characteristics	●																
Evaluation of the tumor	●																
Concomitant diseases, treatments	●																
Hematology	●	◎															
Serum Chemistry	●	◎															
Adverse events, symptoms, and signs [Note 1)]	●	◎															
Dose		◎															
Peripheral sensory neuropathy		◎	●	●	●	●	●	●	●	●	●	●	●		●		●
Allergic reactions		◎															
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)		◎	●	●	●	●	●	●	●	●	●	●	●		●		●
CEA, CA19-9	●	◎	●	●	●	●	●	●	●	●	●	●	●		●		●
History and examination		●	●	●	●	●	●	●	●	●	●	●	●		●		●
Outcome					●				●				●				●
Chest CT [Note 2)]	●		●		●		●		●		●		●		●		●
Abdominal CT [Note 3)]	●		●		●		●		●		●		●		●		●
Pelvic CT			●		●		●		●		●		●		●		●
Colonoscopy [Note 4)]					●								●				

◎: See Table 6.5. and Table 6.6.

Note 1: Symptoms and signs are assessed before registration.

Note 2: Chest CT is preferable, but it may be substituted by a chest X-ray film.

Note 3: Abdominal CT is preferable, but it may be substituted by abdominal ultrasound.

Note 4: If total colonoscopy cannot be done, it must be performed within 1 year after registration. It must be repeated every 3 to 5 years if neoplastic lesions are not detected. If it was done before surgery or registration, it must be repeated every 3 to 5 years.

Table 6.5. Study Schedules during adjuvant chemotherapy (Group T: modified FOLFOX6 therapy)

Period after registration (months)	1		2		3		4
Course no.	1	2	3	4	5	6	4 weeks after the completion of 6 courses
Hematology	●	●	●	●	●	●	●*
Serum Chemistry	●	●	●	●	●	●	●*
Adverse events, symptoms, and signs	●	●	●	●	●	●	●
Dose	●	●	●	●	●	●	
Peripheral sensory neuropathy	●	●	●	●	●	●	●
Allergic reaction	●	●	●	●	●	●	
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	●	●	●	●	●	●	●
CEA, CA19-9	●						

*: The allowance of range for testing is up to 2 weekss before the planned date.

Table 6.6. Study Schedules during adjuvant chemotherapy (Group T: XELOX therapy)

Period after registration (months)	1		2		3	4
Course no.	1	2	3	4		4 weeks after the completion of 4 courses
Hematology	●	●	●	●		●*
Serum Chemistry	●	●	●	●		●*
Adverse events, symptoms, and signs	●	●	●	●		●
Dose	●	●	●	●		
Peripheral sensory neuropathy	●	●	●	●		●
Allergic reactions	●	●	●	●		
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	●	●	●	●		●
CEA, CA19-9	●					

*: The allowance of range for testing is up to 2 weeks before the planned date.

6.1. Items examined before case registration and initiation of protocol treatment

(1) Patient characteristics
Sex, age at registration, and date of written informed consent.

(2) Evaluation of the tumor
Histopathological findings of the primary tumor (site, histologic type, macroscopic appearance, depth of invasion, number of lymph nodes examined, lymph node metastasis (number and N level: N0, N1, N2, N3 [cf. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, The 7th Edition, revised version., General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 6th edn.], Degree of lymph node dissection, number of dissected lymph nodes, tumor size, liver metastasis, peritoneal metastasis, other distant metastasis, stage classification, residual cancer after surgery, curability, the presence/absence of lymphatic invasion, presence/absence of venous invasion, date of operation, presence/absence of postoperative complications, surgical procedures, approach (open surgey or laparoscopic surgery), combined resection of adjacent organs, etc.

(3) Pregnancy test (if necessary).

(4) Complications (major diseases that require attendance or admission to hospital, excluding postoperative complications).

(5) Past medical history (major diseases that required hospital attendance or admission).

(6) Multiple cancer, drug allergies.

(7) Electrocardiogram (ECG). (A preoperative ECG is optional.)

(8) Chest X-ray film or chest CT, abdominal ultrasound or abdominal CT. (Preoperative testing is optional.)

(9) Vital signs and PS (ECOG), body weight (within 14 days before registration), height. (Preoperative measurement is optional for height.)

(10) Hematology tests (within 14 days before registration)
Hemoglobin, white blood cell count, neutrophils, platelet count

(11) Biochemistry tests (within 14 days before registration)
Serum total bilirubin, AST, ALT, ALP, albumin, serum creatinine

(12) Tumor markers (within 14 days before registration)
CEA, CA19-9

(13) Symptoms and signs (within 14 days before registration)

6.2. Items examined during protocol treatment and follow-up

(1) PS (ECOG)

(2) Hematology tests
Hemoglobin, white blood cell count, neutrophils, platelet count

(3) Biochemistry test
Serum total bilirubin, AST, ALT, ALP, albumin, serum creatinine

(4) Tumor markers
CEA, CA19-9

(5) Chest X-ray film or chest CT

(6) Abdominal ultrasound or abdominal CT

(7) Colonoscopy
If total colonoscopy cannot be done, it must be performed within 1 year after registration. It must be repeated every 3 to 5 years if neoplastic lesions are not detected. If it was done before surgery or registration, it must be repeated every 3 to 5 years.

(8) Adverse events, symptoms, and signs
Investigation of adverse events, as well as any symptoms and signs, must be done at least once on the day before or the day of starting protocol treatment and at least once at four weeks after the completion of protocol treatment in accordance with ***Table 6.2.*** *"Study Schedules during adjuvant chemotherapy (Group S: modified FOLFOX6 therapy),"* ***Table 6.3.*** *"Study Schedules during adjuvant chemotherapy (Group S: XELOX therapy),"* ***Table 6.5.*** *"Study Schedules during adjuvant chemotherapy (Group T: modified FOLFOX therapy),"* and ***Table 6.6.*** *"Study Schedules*

during adjuvant chemotherapy (Group T: XELOX therapy)." For adverse events and their assessment, which must be done carefully, refer to *7.5.4. Adverse reactions*. For patients with peripheral sensory neuropathy and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), an outcome study will be done every 6 months and will continue from even 4 weeks after the completion of protocol treatment, in accordance with ***Table 6.1.*** *"Study Schedules (Group S: 6-month treatment arm)"* and ***Table 6.4.*** *"Study Schedules (Group T: 3-month treatment arm)."* (Please see *6.4. Outcome on the recovery of peripheral sensory neuropathyand palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome).*)

Other tests are carried out if required clinically.

6.3. Recurrence and new cancerous lesions (secondary cancer)

In principle, a history is obtained and tumor markers are measured to check for recurrence every 3 months until 3 years after registration and then every 6 months from 3 to 6 years after the registration. CT scanning (contrast chest, abdominal and pelvic CT, in principle) is done every 6 months for 6 years from registration. Chest CT may be substituted by a chest X-ray film. The allowance of range for performing CT is from 2 weeks before to 4 weeks after the planned date.

The following imaging methods are used for the detection of recurrence.

1. Liver metastasis: ultrasound, CT, or MRI.
2. Lung metastasis: chest X-ray film or CT.
3. Abdominal lymph node metastasis: ultrasound or CT.
4. Local recurrence: CT, MRI, barium enema, or colonoscopy.

When a new cancerous lesion occurs, its site and date of confirmation must be reported via the EDC (web-based system). Note)

Note: Occurrence of intramucosal carcinoma is not classified as recurrence.

Definition of recurrence

Evidence of recurrence that meets under any of the following criteria is defined as "recurrence." The earlier date from the dates of imaging diagnosis and pathological diagnosis is defined as the date of recurrence. Diagnosis by biopsy is preferable in cases where the diagnosis of recurrence is difficult. An increase of tumor markers alone is not sufficient to diagnose recurrence.

1. Imaging diagnosis
   The day when a definitive diagnosis of recurrence is made by imaging is defined as the date of recurrence.
2. Pathological diagnosis
   If a diagnosis of recurrence is not made from the history but by biopsy, the day when the diagnosis of recurrence is made from biopsy findings is defined as the date of recurrence.
3. Clinical diagnosis
   If only clinical findings are obtained because imaging diagnosis or pathological diagnosis cannot be done due to an acute change of symptoms or transfer to another hospital, the day when exacerbation of symptoms is detected clinically is defined as the date of recurrence. The clinical findings which suggested recurrence, as well as the date of confirming the exacerbation of symptoms, are reported via the EDC (web-based system).

The date and the method of confirming recurrence are reported via the EDC (web-based system) as well.

6.4. Outcome on the recovery of peripheral neuropathy and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)

The presence or absence of peripheral sensory neuropathy and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), as well as the grade and the causative relationship of these symptoms, are investigated in all registered patients every 6 months. The day of the interview (consultation) is defined as the date of assessing the outcome.

6.5. Outcome

Survival and the presence and absence/recurrence are investigated in the registered patients every year. Long-term

results may be analyzed after the completion of this study.
The day of the interview (consultation) is defined as the date of assessing the outcome.

7. Study populations and endpoints

7.1. Analysis sets

(1) All registered patients: all patients who are registered, excluding multiple registrations or mis-registrations.
(2) All eligible patients: patients who are confirmed to fit the patients eligibility criteria and not to violate any of the exclusion criteria after the registration and who receive the protocol treatment.
(3) All treated patients: all registered patients who receive the protocol treatment.

7.2. Primary endpoint:

Disease-free survival (DFS) [Note 1)]

Note 1: In the IDEA study, DFS was defined as survival until recurrence of colon cancer or death from any cause, which is generally considered to be relapse-free survival (RFS).

7.3. Analysis of primary endpoints

In this study, the non-inferiority of disease-free survival (DFS) in the experimental arm (Group T: modified FOLFOX6 therapy for 6 courses or XELOX therapy for 4 courses) is assessed relative to the survival of the control group (Group S: modified FOLFOX6 therapy for 12 courses or XELOX therapy for 8 courses) by integrated analysis with data from the IDEA study.

7.3.1. Disease-free survival (DFS) [Note 1)]

The definition of DFS [Note 1)] is as follows. Follow-up of surviving patients is defined as being discontinued on the last day when the absence of recurrence or secondary colorectal cancer is confirmed after the registration (confirmation by phone is optional, but it must be stated in the medical record).

Note 1: In the IDEA study, DFS was defined as survival until recurrence or death, which is generally considered to be relapse-free survival (RFS).

(1) Definition of DFS
Following the definition of disease-free survival (DFS [Note 1)]) in the IDEA study, DFS is defined as the period from the day of registration to the earliest event such as recurrence or occurrence of a newly detected colon cancer (second cancer) detected for the first time after registration (intramucosal carcinoma or dysplasia is not counted as an event) or until death from any cause.

(2) Definition of events
Occurrence of any of the following is defined as an event.

1. Recurrence
An event that fits any of the following criteria is defined as "recurrence." The earlier date between the date of imaging diagnosis and that of pathological diagnosis is defined as the date of recurrence. Diagnosis by biopsy is preferable in cases where making a diagnosis of recurrence is difficult. An increase of tumor markers alone is not sufficient to diagnose recurrence.
    1) Imaging diagnosis
    The day when a definitive diagnosis of recurrence is made by imaging is defined as the date of recurrence.
    2) Pathological diagnosis
    If a diagnosis of recurrence is not made from the history but by biopsy, the day when the diagnosis of recurrence is made from biopsy findings is defined as the date of recurrence.
    3) Clinical diagnosis
    If only clinical findings are obtained because imaging diagnosis or pathological diagnosis cannot be done due to an acute change of symptoms or transfer to another hospital, the day when exacerbation of symptoms is detected clinically is defined as the date of recurrence. The clinical findings which suggested recurrence, as well as the date of confirming the exacerbation of symptoms, are reported via the EDC (web-based system).
2. Secondary colorectal cancer newly detected after registration
The day of detection is defined as the day when a secondary colorectal cancer (not recurrence) is found after registration. Intramucosal cancer or dysplasia is not counted as an event.

3. Death from any cause

7.4. Secondary endpoint:

(1) Disease-free survival (DFS) Note 2)
Note 2: This is defined as survival until recurrence of colon cancer, onset of the other cancer (secondary cancer),, or death from any cause.

(2) Time to treatment failure.

(3) Overall survival.

(4) Toxicity (according to the CTCAE v 4.0 - JCOG).

(5) Completion rate of the study treatment.

(6) Percent of dose received versus planned dose.

(7) Correlation of the clinical outcome with the number of involved lymph nodes and that of the dissected lymph nodes.

(8) Incidence and nature of peripheral sensory neuropathy (PSN).

(9) Identification of single nucleotide polymorphisms (SNPs) using the genome-wide association study (GWAS) associated with toxicityand clinical outcome (additional protocol: pharmacogenomics).

7.5. Analysis of secondary endpoint

*7.5.1. Disease-free survival (DFS)*Note 2)

The definition of DFS Note 2) is as follows. Follow-up of surviving patients is defined as being discontinued on the last day when the absence of recurrence is confirmed (confirmation by phone is optional, but it must be stated in the medical record).

Note 2: DFS is defined as survival until recurrence of colon cancer, onset of the other cancer (secondary cancer), or death from any cause.

(1) Definition of DFSNote 2)
DFS Note 2) is defined as the period from the day of registration to the earliest day of any of the following events: occurrence, detection of any type of the other cancer (second cancer), or death from any cause.

(2) Definition of events
Occurrence of any of the following is defined as an event.

1. Recurrence
Recurrence is defined according to the definition of recurrence under *7.3.1. Disease-free survival (DFS)* Note1).
2. Detection of any type of the other cancer (secondary cancer)
This is defined as detection of some other cancerous lesion (second cancer), which is not recurrence. Gastric cancer, colon cancer, or esophageal cancer localized to mucosa and curatively resected cervical cancer, basal cell carcinoma, or squamous cell carcinoma are not counted as events.
3. Death from any cause.

7.5.2. Time to treatment failure (TTF)

The definition of is as follows. For patients who are receiving protocol treatment and have no evidence of recurrence, follow-up is discontinued on the last day when their survival is confirmed (confirmation by phone is optional, but it must be stated in the medical record). For patients who have completed protocol treatment and have no evidence of recurrence, follow-up is discontinued on the last day when the absence of recurrence is confirmed. Occurrence of secondary cancer is not counted as an event or censoring but as TTF until other events are detected.

(1) Definition of TTF
TTF is the period from the day of registration to the earliest day of an event such as recurrence, death from any cause, or withdrawal from protocol treatment for any reasons.

(2) Definition of events

Occurrence of any of the following is defined as an event.

1. Recurrence
   Defined according to DFS[Note 2)].
2. Death from any cause.
3. Withdrawal from protocol treatment for any reasons.

7.5.3. Overall survival (OS)

The definition of OS is as follows.

(1) Definition of OS

OS is the period from the day of registration to the day of death from any cause.

If the patient remains alive, follow-up is defined as being discontinued on the last day when survival is confirmed (confirmation by phone is optional, but it must be stated in the medical record). If a patient is lost to follow-up, their follow-up is defined as being discontinued on the last day when survival was confirmed before contact was lost.

7.5.4. Adverse reactions

Evaluation of the incidence and incidence rate of adverse events will be done in all treated patients. An adverse event is defined as any undesirable or unintended sign (including abnormal laboratory test values), symptom, or disease in a patient who is being administered a test drug and it does not necessarily have a causal relationship with the drug. Adverse events that do not fit the criteria below are listed and are graded as follows: 1, mild; 2, moderate; 3, severe; and 4, serious. Evaluation of adverse events is performed in accordance with the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0-JCOG).

1. Laboratory tests: decreased white blood cell count, neutropenia, decreased platelet count, weight loss, increased bilirubin, increased AST (GOT), increased ALT (GPT), increased serum creatinine
2. General disorders and administration local conditions: fever
3. Skin and subcutaneous tissue disorders: palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), alopecia
4. Gastrointestinal disorders: constipation, diarrhea, nausea, mucositis oral, vomiting
5. Metabolic and nutritional disorders: anorexia, dehydration, hypoalbuminemia
6. Infections and infestations: pharyngitis
7. Blood and lymphatic system disorders: anemia, febrile neutropenia
8. Nervous system disorders: peripheral sensory neuropathy
9. Respiratory, thoracic and mediastinal disorders: dyspnea, hypoxia, pneumonitis

An outcome study on the recovery of peripheral sensory neuropathy and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) is performed every 6 months to assess the incidence and incidence rate (see *6.4. Outcome on the recovery of peripheral sensory neuropathy and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)*).

Other adverse events (toxicities) are only reported via the EDC (web-based system) if an event of grade 3 or 4 occurs (except for hematologic toxicity: blood/bone marrow). Therefore, the incidence rate is not calculated, except in the case where specific adverse events are observed frequently.

7.5.5. Completion rate of the study treatment

The following formulae are used to calculate the completion rate for eligible patients in each arm.

Control arm (Group S: 6-month treatment arm):

Modified FOLFOX6 therapy group: completion rate (%) = number of the last course/12 × 100

XELOX therapy group: completion rate (%) = number of the last courses/8 × 100

Experimental arm (Group T: 3-month treatment arm):

Modified FOLFOX6 therapy group: completion rate (%) = number of the last course/6 × 100

XELOX therapy group: completion rate (%) = number of the last courses/4 × 100

7.5.6. Percent of dose received versus planned dose

The following formulae are used to calculate the Relative dose intensity (RDI) for each eligible patient, each course, and each drug (oxaliplatin, capecitabine, or 5-FU).

Modified FOLFOX6 therapy:

Relative dose intensity (RDI) (%) = (actual dose/prespecified dose) × (14/number of days in the treatment courses) × 100

XELOX therapy:

Relative dose intensity (RDI) (%) = (actual dose/ prespecified dose) × (21/number of days in the treatment courses) × 100

7.5.7. Correlation of the clinical outcome with the number of involved lymph nodes and that of the dissected lymph nodes.

The relationship of the prognosis (DFS, RFS, and OS) to the age at the time of registration, sex, tumor size, depth of tumor invasion, tumor histology, macroscopic appearance, N stage (cf. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, The 7th Edition, revised version, General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus , 6th edn.), ly factor, v factor, grade of lymph node dissection, number of dissected lymph nodes, number of lymph nodes examined, number of lymph node metastases, and lymph node ratio (LNR: number of lymph node metastases/number of dissected lymph nodes) is explored in the eligible patients.

7.5.8. Incidence and nature of peripheral sensory neuropathy (PSN)

The followings are investigated in all treated patients.

(1) Incidence

(2) Incidence rate

(3) Number of courses until the occurrence of each grade of peripheral sensory neuropathy

(4) Total dose of oxaliplatin (mg/m^2) administered until the occurrence of each grade of peripheral sensory neuropathy

7.5.9. Identification of single nucleotide polymorphisms (SNPs) using the genome-wide association study (GWAS) associated with toxicity and clinical outcome (additional protocol: pharmacogenomics).

In order to investigate prognostic indicators and predictors of adverse events in an exploratory manner, a pharmacogenomics analysis of polymorphism will be carried out.

See “additional study protocol” for the details.

8. Statistical Analysis

8.1. Primary objective and assessment criteria for results

(1) The primary objective of this study is to obtain data for Japan by participating in the prospective international IDEA study. In the IDEA study, data from patients receiving 3 months of adjuvant chemotherapy (Group T: modified FOLFOX6 therapy for 6 courses or XELOX therapy for 4 courses) or 6 months of adjuvant chemotherapy (Group S: modified FOLFOX6 therapy for 12 courses or XELOX therapy for 8 courses) in various countries will be integrated to compare the therapeutic effect (non-inferiority) of treatment for 3 months to that of treatment for 6 months. If the treatment period can be reduced from 6 months to 3 months while maintaining efficacy, this would have benefits for all patients in terms of fewer adverse reactions, a shorter treatment period, and lower cost. It would also achieve a significant decrease of medical costs. Since the non-inferiority margin of the hazard ratio for disease-free survival (*7.3.1. Disease-free survival (DFS)* [Note 1]) in the 3-month treatment group versus the 6-month treatment group is assumed to be 1.10, data from at least 10,000 cases is planned to be collected in this study so that the upper limit of two-sided 95% confidence interval for a hazard ratio below 1.10 reaches 90% or more.

(2) At present, five ongoing studies (GERCOR, SCOT, CALGB/SWOG C80702, TOSCA, and HORG) are participating in the IDEA study around the world. After the completion of registration and follow-up in these studies, analysis of the data will be performed in accordance with the integrated statistical analysis plan prepared by the IEDA study office. The present study is the sixth study to join IDEA, following the five studies mentioned above. In principle, a specific analysis of the Japanese data will not be undertaken before the integrated analysis. Instead, this study will provide the necessary data for integrated analysis of the primary endpoints to the IDEA study office.

(3) The evaluation criteria based on the IDEA study data are as follows:

- The therapy for Group T will be defined as the new standard treatment if non-inferiority of Group T is proved by the IDEA study.
- The therapy for Group S will remain the standard treatment if non-inferiority of Group T is not proved by the IDEA study.

8.2. Analyses done in this study

After the IDEA study data are presented, subgroup analyses will be performed. The details will be specified in the integrated analysis plan that will be prepared before the start of integrated analysis. An outline of the analyses is set out below.

8.2.1. Primary endpoint

For DFS,[Note 1)] DFS curves are derived by Kaplan-Meier estimation, and the annual DFS rate and confidence intervals are also determined. The hazard ratio and 95% confidence intervals are calculated from the Cox proportional hazard model as summary measures of the difference in therapeutic effect between Group T and Group S, and the results are compared with overall hazard ratios for the IDEA study. If an interaction between study and treatment is observed, more specific analysis will be planned and conducted separately.

8.2.2. Secondary endpoints

(1) DFS,[Note 2)] overall survival (OS), and time to treatment failure (TTF) are analyzed in the same way as the primary endpoint, and are compared with the results of the IDEA study.

(2) Regarding adverse events, the incidence of the worst grade in all courses is calculated in accordance with the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0-JCOG) for each treatment group. The incidence of any adverse event showing a difference among the treatment groups is calculated by Fisher's exact test for reference.

(3) Completion rate and relative dose intensity are calculated as defined in *Section 7.5.5. and 7.5.6.* An appropriate test is performed for reference if any differences are found among the treatment groups.

(4) When examining prognostic factors, analysis using the Cox proportional hazard model is performed to investigate the relationship among age at the time of registration, sex, stage, tumor size, depth of tumor invasion, tumor histology, macroscopic features, N stage (cf. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, The 7th Edition,

revised version , General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus 6th edn.), ly factor, v factor, number of lymph node examined, grade of lymph node dissection, number of dissected lymph nodes, number of lymph node metastases, lymph node ratio (LNR: number of lymph node metastases/number of dissected lymph nodes), and DFS/OS.

8.3. Target sample size

Target sample size: 1,200 patients (600 patients in each group).

Five ongoing studies (GERCOR, SCOT, CALGB/SWOG C80702, TOSCA, and HORG) are participating in the IDEA study around the world. Japan has also been requested to provide data for more than 1,000 patients to the IDEA study to allow analysis of rapid and regional differences. In the previous JFMC41-1001-C2 study (JOIN Trial: targeting patients with stage II or III curatively resected colon cancer), about 600 patients were collected during the 1-year. The rate of enrollment is assumed to be lower for the single-arm JOIN Trial, so more than 400 patients are estimated to be registered annually with an estimated informed consent rate of 70%. Therefore, the patient population is expected to reach 1,200 cases during the 3-year registration period. Because the registration period is as long as 3 years, it will be possible to provide data to the IDEA study in line with the completion of other ongoing studies even after completing a 6-year follow-up period. Accordingly, following conditions have been set: 3 years for the registration period, 6 years (from registration of the last case) for the follow-up period, and 1,200 patients (600 patients per group) for the target number of subjects.

8.4. Interim analysis

An interim analysis of efficacy will not be performed due to the characteristics of this study (during the early part of the study, monitoring of adverse events will not be done since adjuvant chemotherapy is being provided and the primary objective of this study is to obtain data for IDEA). The status of safety monitoring, treatment compliance, and study implementation will be regularly provide to the Data and Safety Monitoring Committee for review. Other analyses, apart from those mentioned above, may be carried out during the registration or follow-up period, but only if the Data and Safety Monitoring Committee accepts their necessity.

9. Emergency Safety Information

9.1. Reporting

The following procedures will be followed if any of the adverse events listed below occurs.
A report to the director of the study site, a voluntary report from the medical facility to the Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labor, and Welfare under the "Pharmaceutical Safety Information Reporting System," and a voluntary report from the medical facility to the company ("Company Reporting System") under The Pharmaceutical Affairs Law must be provided in an appropriate manner while complying with the rules of each medical facility. These reports are the responsibility of the attending physician (investigator).

9.2. Emergency reports

If any of the following adverse events occur during protocol treatment or within 30 days after the last dose, reporting is required.

(1) Death of a patient.
(2) A life-threatening adverse event, such as grade 4 non-hematological toxicity or grade 4 hematological toxicity with fever and hemorrhage.
(3) Any adverse event that requires hospitalization for treatment or prolongs hospitalization.
(4) An irreversible adverse event.
(5) An unexpected adverse event that is not listed in the drug package insert and may have an impact on continuation of the study.

9.2.1. Procedures for making emergency reports

Initial report

When a serious adverse event listed under *9.2. Emergency reports* occurs and information is obtained from the attending doctor, the responsible physician (investigator) completes the necessary items in the "serious adverse event report (initial report)" (Attached Table 1-2) and submits the report to the study office by fax. If the responsible physician (investigator) cannot be contacted, the attending physician is required to perform these duties on behalf of the responsible physician.

Follow-up report

The responsible physician (investigator) fills in the blank parts of the "serious adverse event report (initial report)" and prepares a case report (A4, free format) that contains more detailed information, such as a summary, severity level, onset time, handling, outcome, and causal relationship with the study drugs. This must be sent by mail or fax to the study office within 15 days after detection of the adverse event.

9.3. Ordinary reports

Adverse events that fit any of the following criteria and for which a causal relationship with protocol treatment cannot be ruled out by an attending physician are reported in an ordinary report.

(1) Death of a patient from Day 31 onward after the finish of protocol treatment.
(2) Expected grade 4 non-hematologic toxicity that is listed in the latest drug package insert.
(3) Unexpected grade 3 non-hematologic toxicity that is not listed in the latest drug package insert.
(4) Any other important medical event.

This includes adverse events that do not fall under any of (1) to (3) above, but whose information should be shared by study sites and research organizations participating in this study.

9.3.1. Procedures for making ordinary reports

If a serious adverse event listed under *9.3. Ordinary reports* occurs and relevant information is obtained from the attending doctor, the responsible physician (investigator) promptly fills out the necessary items in a "serious adverse event report (initial report)" (Attached Table 1-2) and also prepares a case report (A4, free format) containing more detailed information such as a summary, severity level, onset time, handling, outcome, and causal relationship with the study drugs. The reports must be sent by mail or fax to the study office within 15 days after detection of the adverse event. If the responsible physician (investigator) cannot be contacted, the attending doctor is required to perform these duties on behalf of the investigator.

9.4. Actions taken by the study office

9.4.1. Deciding on suspension of registration and reporting to the participating facilities

The study office will submit reports about adverse events to the research representative and the director of the Office of Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC). After obtaining advice from the research representative (or the acting representative) about the urgency, importance, and impact of the adverse events reported, the office will discuss suspension of the registration process and the details of a report to the participating facilities so that the necessary measures can be taken.

9.4.2. Responsibilities of the research representatives and discussion with the director of the Data and Safety Monitoring Committee

After receiving a report about a serious adverse event that falls under *9.2. Emergency reports* or *9.3. Ordinary reports* from the study office, the research representatives will discuss the contents with the director of JFMC. Following such discussion, they will inform the study office about the necessary actions to be taken, including sending a report to the Data and Safety Monitoring Committee and making a request for judgment. Taking the necessary actions themselves, the representatives will seek an objective opinion from JFMC about the appropriateness of their actions and the appropriateness of continuing the study, and will request a judgment from the Data and Safety Monitoring Committee.

Adverse events that are already described in the package insert are treated as known events.

The Data and Safety Monitoring Committee will discuss the report from the research representatives and give advice to the representatives about the handling of cases and actions to be taken in the future.

The research representatives will report the results of these deliberations to the study sites.

10. Discontinuation of the Study

If the incidence of serious adverse events and treatment-related mortality is anticipated to be clinically problematic or the efficacy of study drug becomes questionable based on new data, the Data and Safety Monitoring Committee will advise each research representative to discontinue the study.

The research representatives will discuss the advice and decide on discontinuation of the study with approval of the Institutional Review Board (IRB). The research representatives will promptly send out a document that specifies the content and detailed reasons for discontinuation.

11. Data Collection and Storage

11.1. Submission of case report forms

The following forms are collected via the EDC (web-based system), fax, or mail.

(1) Case registration form

(2) Case report form

1. Prior to the initiation of treatment
2. Treatment period (administration/primary endpoint/laboratory values/adverse events/outcome)
3. Follow-up period

(3) Emergency adverse event report

(4) Notification of a change in participating doctors

11.2. Storage of reports

Case reports are stored at the Office of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) for 10 years after completion of the study.

12. Protocol Compliance, Deviations, Changes, and Revision

12.1. Compliance with the protocol

Researchers participating in this study must comply with the protocol unless it violates the safety and rights of a patient.

12.2. Changes to the protocol

The research representatives can revise the protocol with approval of the Institutional Review Board (IRB) when a change to the protocol or a new explanation form for patients is required during the study. The revised protocol or explanation form for patients must be approved by the Institutional Review Board (IRB) at each study site.

This does not apply to changes of the protocol that do not increase the risks for patients participating in the study and are not related to the primary endpoint.

When a change of protocol is required, registration of patients is suspended, and it is resumed after the change. However, this does not apply if a change does not affect the registration process.

13. Ethics

13.1. Observation of ethical principles

The ethical principles of the Helsinki Declaration and "the Ethical Guideline for Clinical Research (Public Notice No. 415 issued by the Ministry of Health, Labor and Welfare [MHLW], revised on July 31st 2008, and implemented on April 1st 2009)" shall be observed when carrying out this study to protect the rights, welfare, and safety of the subjects to the maximum extent.

Prior to commencing this study, the Institutional Review Board (IRB) or a corresponding organization at each study site will investigate the appropriateness of participation in the study from ethical and scientific perspectives.

13.2. Informed consent

13.2.1. Informed consent of patients

Prior to case registration at the study office, the contents of *13.2.2. Contents of explanatory document* must be explained in detail by an attending physician to the patient using the explanatory document approved by the Institutional Review Board (IRB) or a corresponding organization at each study site. After receiving the explanation, the patient signs the informed consent of his/her own free will. A copy of the informed consent form is given to the patient, and the other copy is stored at the study site according to the site's regulations. The signatures of the doctor and patient and the date of obtaining consent shall be displayed in the informed consent form. If revision of the explanatory document is required due to a protocol change during the study, the details of the change shall be explained to each patient and consent will be obtained again.

13.2.2. Contents of the explanatory documents

The following items are explained using the explanatory documents prior to obtaining informed consent.

(1) Introduction
(2) Clinical study
(3) Participation in the clinical study
(4) Stage III colorectal cancer
(5) Adjuvant chemotherapy for colorectal cancer
(6) Purpose and methods of this clinical study
(7) Planned study period and number of subjects
(8) Treatment used in this clinical study
(9) Tests
(10) Discontinuation of treatment
(11) Expected effects, adverse reactions, and other undesirable effect
(12) Advantages and disadvantages of participating in this clinical study
(13) Other adjuvant chemotherapy regimens for colorectal cancer
(14) Cost of treatment
(15) Conflict of interest
(16) Participation in this clinical study
(17) Voluntary withdrawal from this clinical study
(18) Treatment for health problems
(19) Ethical review of this clinical study
(20) Protection of privacy
(21) Rules
(22) Completion and publication of the clinical study results
(23) Supervisor of this clinical study
(24) Inquiries
(25) Contact information for your doctor

13.3. Protecting personal information and the identity of patients

Case registration forms, reports, and study site – When making contact with a patient, the study office shall only use the case number issued at the time of registration for identification of the patient, instead of information that could identify the patient to a third party. Also, the names of patients shall not be given to the study office.

13.4. Approval by the IRB

Prior to participating in this study, the study protocol, explanatory document for patients, and informed consent form must be approved by the review committee (IRB) of the study site.

14. Expenses and Compensation

14.1. Relationship with the funding source

This study will be performed under contract from Yakult Honsha Co., Ltd. on behalf of the Japanese Foundation for Multidisciplinary Treatment of Cancer. Research fees will be paid to the participating study sites by the foundation based on the number of registered patients. This study will be carried out using anticancer drugs manufactured by Yakult Honsha Co., Ltd., but the company will not influence the study result.

14.2. Cost of the study

This study will be carried out within the scope of normal treatment covered by health insurance, hence the monitoring/testing, drugs, and other procedures during the study will be covered by the national health insurance scheme.

14.3. Conflict of interest

Any financial benefit or other related interest of companies or organizations that may potentially benefit from this study shall be subjected to an appropriate COI test. Conflicts of interest shall be discussed and documented at each study site by the IRB and the Conflict of Interest Board.

14.4. Compensation for health problems

If any health problems are caused by this study, the attending doctors and study sites shall provide appropriate treatment and take any other necessary measures for the patients. Such treatment will be covered by the health insurance system and no monetary compensation will be provided.

15. Monitoring

Annual monitoring will be carried out for the purpose of confirming whether the study is progressing safely according to the protocol and whether data are being gathered correctly. If there are any significant deviations from protocol treatment or shortening of the administration period that may affect the primary endpoint of the study, monitoring may be carried out urgently.

This in-house monitoring will be performed using data accumulated at the data center via the EDC system. On-site monitoring (including source document verification at the study sites) is not planned.

The items subjected to monitoring will be as follows:

- Case series status.
- Eligibility.
- Protocol treatment/completion.
- Serious adverse events.
- Adverse reactions/adverse events.
- Deviations from the protocol.
- Survival (OS, DFS, etc.)
- Any problems associated with the progress and safety of the study.

Regular monitoring reports from the data center will be submitted to the research representatives, the chief investigator, the protocol designer, and the Data and Safety Monitoring Committee.

If there is a failure to complete the study due to delayed case registration and frequent deviations from the protocol, or if unexpected serious adverse events, or any deaths that obviously related to treatment occur, the research representatives and the Data and Safety Monitoring Committee from the data center will discuss whether the study should be continued. The research representatives will report the decision to all study sites.

16. Ownership of Study Results

Ownership of the data obtained by integrated analysis in the IDEA study shall be discussed and determined by the IDEA study group and JFMC.

The data from this study and the study-related documents, records, and information shall belong to Yakult Honsha Co., Ltd. If new intellectual property rights (patents) are granted, the ownership shall be discussed and determined by JFMC and Yakult Honsha Co., Ltd.

17. Publication of the Study Results

Data on the primary endpoint will not be analyzed or publicized in Japan since the results of integrated analysis will be published after the IDEA study is completed and this will be done according to the regulations of the IDEA study group. After publication of the primary endpoint data from the IDEA study, JFMC, the research representatives, the co-principal investigators, and the protocol coordinator will discuss publication of the results of this study (conference presentation and manuscript submission). Based on these discussions, JFMC and Yakult Honsha Co., Ltd. will make a final decision about publication of the study results.

Yakult Honsha Co., Ltd. can use the data obtained from this study for the purpose of promoting rational use of its drugs.

18. Study Period

Registration period:	3 years	August 2012－July 2015
Follow-up period:	6 years after the registration of the last patient	
Total study period:	9 years	August 2012－July 2021

19. Research Organization

19.1. Principal Investigators:

Co-principal investigator from oncosurgeon:
Masaki Mori, Department of Gastroenterological Surgery,
Osaka University Graduate School of Medicine
Co-principal investigator from medical oncologist:
Atsushi Ohtsu, Research Center for Innovative Oncology, National Cancer Center Hospital East
Co-principal investigator from IDEA adjustment representative:
Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East

19.2. Protocol coordinator :

Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology National Cancer Center Hospital East

19.3. Reseach management Investigators

Surgical group: Tsunekazu Mizushima, Department of Surgery,
Osaka University Graduate School of Medicine
Medical group:Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East

19.4.Independent Data and Safety Monitoring Committee

Junichi Sakamoto, Nagoya University Graduate School of Medicine, Department of Social Life Science
Yasuo Ohashi, Department of Biostatistics, School of Public Health, Graduate School of Medicine, Tokyo University
Satoshi Morita, Department of Biostatistics and Epidemiology, Graduate School of Medicine, Yokohama City University
Kuniaki Shirao, Department of Medical Oncology, Oita University, Faculty of Medicine

19.5. Person in charge of statistical analysis

Takeharu Yamanaka, Research Center for Innovative Oncology, National Cancer Center Hospital East

19.6. Number of institutions:

About 300 sites (see Exhibit 1).

19.7. Study office:

Japanese Foundation for Multidisciplinary Treatment of Cancer
1-28-6 Kameido, Koto-ku, Tokyo 136-0071, Japan
TEL: 03-5627-7594 (data center)
03-5627-7593 (main office)
0120-184100 (toll free)
FAX: 03-5627-7595
E-mail: jfmc47@jfmc.or.jp (e-mail address for this study)
jfmc@jfmc.or.jp (main office)

19.8. Contact information

Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East
E-mail: j47-yoshino@jfmc.or.jp (e-mail address for this study)

20. References

1) Grant for cancer research from the Ministry of Health, Labor and Welfare. The Research Group for Population-based Cancer Registration in Japan (1975–1999); Health & Labor Sciences Research Grant, the 3rd Comprehensive 10-Year Strategy for Cancer Control. The Cancer Incidence and Mortality Trend Research Group (2000–).
2) Statistics and Information Dept., Minister's Secretariat, Ministry of Health, Labor, and Welfare. Vital Statistics of Japan.
Available from: http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suii04/index.html
3) Ohno Y, Nakamura T, Murata K, *et al.*: Prediction of cancer incidence in Japan: Cancer Statistics-2004. Shinohara Shuppan, Tokyo, 2004;202–17.
4) Japanese Society for Cancer of the Colon and Rectum: JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer. Kanehara & Co., Ltd., Tokyo, 2010.
5) Momounas E, Wieand S, Wolmark N, *et al.*: Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: Results from four national surgical adjuvant breast and bowel project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol. 1999;17:1349–55.
6) QUASAR Collaborative Group: Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370:2020–9.
7) McKenzie S, Nelson R, Mailey B, *et al.*: Adjuvant chemotherapy improves survival in patients with American Joint Committee on Cancer stage II colon cancer. Cancer. 2011;117(24):5493–9.
8) Benson III AB, Schrag D, Somerfield MR, *et al.*: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for Stage II colon cancer. J Clin Oncol. 22:3408–19.
9) Morris EJA, Maughan NJ, Forman D, *et al.*: Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology. Gut. 2007;56:1419–25.
10) Moertel CG, Fleming TR, Macdonald JS, *et al.*: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990;322:352–8.
11) Moertel CG, Fleming TR, Macdonald JS, *et al.*: Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med. 1995;122:321–6.
12) National Institute of Health Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264:1444–50.
13) Haller DC, Catalano PJ, Macdonald JS, *et al.*: Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: Five-year final report of INT-0089. Proc Am Soc Clin Oncol. 1998;17:256a (abstract 982).
14) O'Connell MJ, Laurie JA, Kahn M, *et al.* Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol. 1998;16:295–300.
15) QUASAR collaborative group: Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. Lancet. 2000;355:1588–96.
16) Wolmark N, Rockette H, Mamounas E, *et al.*: Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from national surgical adjuvant breast and bowel project C-04. J Clin Oncol. 1999;17:3553–9.
17) O'Connell MJ, Laurie JA, Kahn M, *et al.*: Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol. 1998;16:295–300.
18) Twelves C, Wong A, Nowacki MP, *et al.*: Capecitabine as adjuvant treatment for Stage III colon cancer. N Engl J Med. 2005;352:2696–704.
19) Twelves C, Scheithauer W, McKendrick J, *et al.*: Capecitabine versus 5-fluorouracil/folinic acid

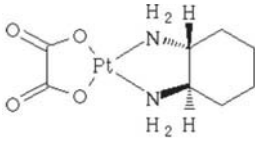
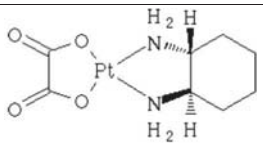
as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol. 2012;23:1190–7.
20) Lembersky BC, Wieand HS, Petrelli NJ, *et al.*: Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol. 2006;1;24(13):2059–64.
21) de Gramont A, Figer A, Seymour M, *et al.*: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938–47.
22) Andre T, Boni C, Mounedji-Boudiaf L, *et al.*: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350:2343–51.
23) Andre T, Boni C, Navarro M, *et al.*: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–16.
24) 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. 2007;1;25(16):2198–204.
25) 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. 2011;Apr10;29(11):1465–71.
26) Saltz LB, Niedzwiecki D, Hollis D, *et al.*: Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol. 2007;25:3456–61.
27) Van Cutsem E, Labianca R, Bodoky G, *et al.*: Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol. 2009,27:3117–25.
28) Ychou M, Raoul JL, Douillard JY, *et al.*: A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCCAccord02/FFCD9802). Ann Oncol. 2009,20:674–80.
29) De Gramont A, Van Cutsem E, Tabernero J, *et al.* AVANT: Results from a randomized, three-arm multinational phase III study to investigate bevacizumab with either XELOX or FOLFOX4 versus FOLFOX4 alone as adjuvant treatment for colon cancer. J Clin Oncol. 29: 2011 (suppl 4; abstr 362).
30) Allegra CJ, Yothers G, O'Connell MJ, *et al.*: Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2011;Jan1;29(1):11–6.
31) Goldberg RM, Sargent DJ, Thibodeau SN, *et al.*: Adjuvant mFOLFOX6 plus or minus cetuximab (Cmab) in patients (pts) with KRAS mutant (m) resected stage III colon cancer (CC): NCCTG Intergroup Phase III Trial N0147. J Clin Oncol. 2010;28:15s (suppl; abstr 3508).
32) Alberts SR, Sargent DJ, Smyrk TC, *et al.*: Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (pts) with resected stage III colon cancer (CC): Results from NCCTG Intergroup Phase III Trial N0147. J Clin Oncol. 2010;28:18s (suppl; abstr CRA3507).
33) Sakamoto J, Ohashi Y, Hamada C, *et al.*, Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum; Meta-Analysis Group in Cancer: Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. J Clin Oncol. 2004;22:484–92.
34) National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology, Colon Cancer – Version 2.2012
Available from: http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf

35) 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. 2007;Jan1;25(1):102–9.
36) Yakult Honsha Co., Ltd.: Final Report on the Drug Use Survey of Elplat® I.V. Infusion Solution 100 mg.
37) Doi T, Boku N, Kato K, *et al.*: Phase I/II study of capecitabine plus oxaliplatin (XELOX) plus bevacizumab as first-line therapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol. 2010;Oct;40(10):913–20.
38) André T, Quinaux E, Louvet C, *et al.*: Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol. 2007;Aug20;25:3732–8.
39) Saini A, Norman AR, Cunningham D, *et al.*: Twelve weeks of protracted venous infusion of fluorouracil (5FU) is as effective as 6 months of bolus 5FU and folinic acid as adjuvant treatment in colorectal cancer. Br J Cancer. 2003;Jun16;88(12):1859–65.
40) Chau I, Norman AR, Cunningham D, *et al.*: A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol. 2005;Apr;16(4):549–57.
41) Haller DG: Safety of oxaliplatin in the treatment of colorectal cancer. Oncology (Williston Park). 2000;Dec;14(12 Suppl 11):15–20.
42) Blum JL. Jones SE, Aman U, *et al.*: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol. 1999;17:485–493.

A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil / l-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer.

History of Protocol Update (v1.0 → v1.1)

Updates are written in red words.

<table>
<tr><th>ge</th><th>Item</th><th colspan="2">Protocol Ver.1.0 (6 Apr 2012)</th><th>Protocol Ver.1.1 (19 Apr 2012)</th></tr>
<tr><td>26</td><td>5.Treatment Method
5.2. Medications
5.2.3. Oxaliplatin (L-OHP)</td><td colspan="2"></td><td>(Typographical error)</td></tr>
<tr><td></td><td></td><td>Generic name (abbreviation)</td><td>Oxaliplatin (L-OHP)</td><td>Generic name (abbreviation)</td><td>Oxaliplatin (L-OHP)</td></tr>
<tr><td></td><td></td><td>Structural formula</td><td>  </td><td>Structural formula</td><td>  </td></tr>
<tr><td></td><td></td><td>Brand name (Marketing authorization holder)</td><td>Elplat® I.V. Infusion Solution 100 mg (Yakult Honsha Co., Ltd.)
Elplat® I.V. Infusion Solution 50 mg (Yakult Honsha Co., Ltd.)</td><td>Brand name (Marketing authorization holder)</td><td>Elplat® I.V. Infusion Solution 100 mg (Yakult Honsha Co., Ltd.)
Elplat® I.V. Infusion Solution 50 mg (Yakult Honsha Co., Ltd.)</td></tr>
<tr><td></td><td></td><td>Dosage form</td><td colspan="2">Injection (vial)</td><td>Dosage form</td><td colspan="2">Injection (vial)</td></tr>
<tr><td></td><td></td><td>Active ingredient/content</td><td>Oxaliplatin 100 mg</td><td>Oxaliplatin 50 mg</td><td>Active ingredient/content</td><td>Oxaliplatin 100 mg/20 mL</td><td>Oxaliplatin 50 mg/10 mL</td></tr>
<tr><td></td><td></td><td>Inactive ingredient/ content</td><td>Lactose •900mg</td><td>Lactose •450mg</td><td colspan="3"></td></tr>
<tr><td></td><td></td><td>Color</td><td colspan="2">A white lump or powder, frozen powder formulation to be used upon dissolution at the time of use</td><td>Osmotic pressure ratio (to physiological saline)</td><td colspan="2">About 0.04</td></tr>
<tr><td></td><td></td><td>pH</td><td colspan="2">4.0–7.0</td><td>Color</td><td colspan="2">Oxaliplatin is a colorless and transparent liquid</td></tr>
<tr><td></td><td></td><td>Storage and expiration date</td><td colspan="2">Store at room temperature / for up to 2 years</td><td>pH</td><td colspan="2">4.0–7.0</td></tr>
<tr><td></td><td></td><td>Brand name (Marketing authorization holder)</td><td colspan="2">Elplat® I.V. Infusion Solution 100 mg (Yakult Honsha Co., Ltd.)
Elplat® I.V. Infusion Solution 50 mg (Yakult Honsha Co., Ltd.)</td><td>Storage and expiration date</td><td colspan="2">Store at room temperature / for up to 2 years</td></tr>
<tr><td></td><td></td><td>Dosage form</td><td colspan="2">Injection (vial)</td><td colspan="3"></td></tr>
<tr><td></td><td></td><td>Active ingredient/content</td><td>Oxaliplatin 100 mg/20 mL</td><td>Oxaliplatin 50 mg/10 mL</td><td colspan="3"></td></tr>
<tr><td></td><td></td><td>Osmotic pressure</td><td colspan="2">About 0.04</td><td colspan="3"></td></tr>
</table>

			ratio □fo p□ysio□ogi□a□ sa□ine□	
			□o□or	□xa□ip□atin is a □o□or□ess and transparent □i□uid
			p□	□0–7.0
			Storage and expiration date	Store at room temperature / for up to 2 years

A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil / l-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer.

History of Protocol Update (v1.1 → □□□)□□

Updates are written in red words.

Page	Item	Protocol Ver.1.1 (19 Apr 2012)	Protocol Ver.1.2 (October 25, 2013)
6 20	0.3.Patients eligibility criteria 0.3.1. Patients eligibility criteria (11) 3. Patients eligibility criteria 3.1.Inclusion criteria (11)	(11) Adequate organ function (data obtained within 14 days before registration)Note 2): neutrophil count ≧1,500 /mm^3 platelet count ≧100,000 /mm^3 serum creatinine ≦1.5 times the upper limit of normal (ULN) total bilirubin ≦2.0 mg/dL aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≦100 IU/L carcinoembryonic antigen (CEA) ≦10 ng/mL	(11)Adequate organ function (data obtained within 14 days before registration)Note 2): neutrophil count ≧1,500 /mm^3 platelet count ≧100,000 /mm^3 serum creatinine ≦1.5 times the upper limit of normal (ULN) ***CCr (calculated value)* ≧30 mL/min*** total bilirubin ≦2.0 mg/dL aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≦100 IU/L carcinoembryonic antigen (CEA) ≦10 ng/mL ****CCr is calculated using the Cockcroft–Gault equation (the measured value is not used)*** ***Male: CCr = [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)]*** ***Female: CCr = 0.85 × [(140 − age) × body weight (kg)]/[72 × serum creatinine value (mg/dL)]***
7	0.4.Protocol treatment 0.4.1. Control arm: Group S *XELOX therapy*	*XELOX therapy* On Day 1, oxaliplatin (130 mg/m2) is administered in combination with oral capecitabine (1,000 mg/m2 administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the	XELOX therapy On Day 1, oxaliplatin (130 mg/m2) is administered in combination with oral capecitabine* (1,000 mg/m2 ***or 750 mg/m2*** administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the morning of

Page	Item	Protocol Ver.1.1 (19 Apr 2012)	Protocol Ver.1.2 (October 25, 2013)
	0.4.2. Experimental arm: Group T *XELOX therapy*	morning of Day 15: 28 doses in total),Note) followed by a 1-week rest period . This completes one course of treatment and a total of 8 courses are given XELOX therapy On Day 1, oxaliplatin (130 mg/m2) is administered in combination with oral capecitabine (1,000 mg/m2 administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the morning of Day 15: 28 doses in total,Note) followed by a 1-week rest period . This completes one course treatment and a total of 4 courses are given.	Day 15: 28 doses in total),Note) followed by a 1-week rest period . This completes one course of treatment and a total of 8 courses are given. ***The starting dose of capecitabine will be as follows in accordance with baseline CCr value and age at enrollment.*** ***2,000 mg/m2/day (1,000 mg/m2/dose): CCr > 50 mL/min*** ***1,500 mg/m2/day (750 mg/m2/dose): 30 mL/min ≦ CCr ≦ 50 mL/min or ≥70 years of age.*** XELOX therapy On Day 1, oxaliplatin (130 mg/m2) is administered in combination with oral capecitabine* (1,000 mg/m2 ***or 750 mg/m2*** administered twice daily within 30 minutes after breakfast and dinner from the evening of Day 1 to the morning of Day 15: 28 doses in total,Note) followed by a 1-week rest period . This completes one course treatment and a total of 4 courses are given. **** The starting dose of capecitabine will be as follows in accordance with baseline CCr value and age at enrollment.*** ***2,000 mg/m2/day (1,000 mg/m2/dose): CCr > 50 mL/min*** ***1,500 mg/m2/day (750 mg/m2/dose): 30 mL/min ≦ CCr ≦ 50 mL/min or ≥70 years of age.***
26	5.2. Medications 5.2.4. Capecitabine (Cape)	pH 8.2～8.6	(deleted)
28	5.3. Protocol treatment 5.3.2. XELOX therapy	For XELOX therapy, oxaliplatin (130 mg/m2) is administered on Day 1 and capecitabine (2,000 mg/m2/day) is administered from the evening of Day 1 to the morning of Day 15. Capecitabine* is administered at 1,000 mg/m2 twice a day, within 30 minutes after breakfast and dinner, for a total of 28 doses (treatment for 14 days) (see Tables 5.3.2.1-1. and -2.). *: The administration period of	For XELOX therapy, oxaliplatin (130 mg/m2) is administered on Day 1 and capecitabine (2,000 mg/m2/day ***or 1,500 mg/m2/day*****) is administered from the evening of Day 1 to the morning of Day 15. Capecitabine* is administered at 1,000 mg/m2 ***or 750 mg/m2***** twice a day, within 30 minutes after breakfast and dinner, for a total of 28 doses (treatment for 14 days) (see Tables 5.3.2.1-1. and -2.). *: The administration period of capecitabine can also run from the

<table>
<tr><th>Page</th><th>Item</th><th>Protocol Ver.1.1 (19 Apr 2012)</th><th>Protocol Ver.1.2 (October 25, 2013)</th></tr>
<tr><td></td><td></td><td>capecitabine can also run from the morning of Day 2 to the evening of Day 15.</td><td>morning of Day 2 to the evening of Day 15.
**: The starting dose of capecitabine will be as follows in accordance with baseline CCr value and age at enrollment.
2,000 mg/m2/day (1,000 mg/m2/dose) : CCr > 50 mL/min
1,500 mg/m2/day (750 mg/m2/dose) : 30 mL/min ≦ CCr ≦ 50 mL/min or ≥ 70 years of age</td></tr>
<tr><td>28</td><td>5.3. Protocol treatment
5.3.2. XELOX therapy</td><td>The recommended initial dose of each drug (oxaliplatin in 10 mg increments, and see Table 5.3.2.3. for capecitabine) calculated based on the body surface area (DuBois formula) is reported by the study office to the study site at the time of case registration.</td><td>The recommended initial dose of each drug (oxaliplatin in 10 mg increments, and see Table 5.3.2.3-1 and -2. for capecitabine) calculated based on the body surface area (DuBois formula) is reported by the study office to the study site at the time of case registration.</td></tr>
<tr><td>28</td><td>5.3. Protocol treatment
5.3.2. XELOX therapy</td><td>2.Capecitabine (1,000 mg/m2) is administered orally within 30 minutes after a meal.</td><td>2.Capecitabine ** (1,000 mg/m2 or 750 mg/m2) is administered orally within 30 minutes after a meal.
**: The starting dose of capecitabine will be as follows in accordance with baseline CCr value and age at enrollment.
2,000 mg/m2/day (1,000 mg/m2/dose) : CCr > 50 mL/min
1,500 mg/m2/day (750 mg/m2/dose) : 30 mL/min ≦ CCr ≦ 50 mL/min or ≥ 70 years of age</td></tr>
<tr><td>26</td><td>5.3. Protocol treatment
5.3.2. XELOX therapy
Table 5.3.2.1-1.
Table 5.3.2.1-2.</td><td>Capecitabine 2,000 mg/m2/day</td><td>Capecitabine 2,000 or 1,500 mg/m2/day</td></tr>
<tr><td>29</td><td>5.3. Protocol treatment
5.3.2. XELOX therapy</td><td>Table 5.3.2.3. Initial dose of capecitabine</td><td>Table 5.3.2.3.-1 Initial dose of capecitabine (1,000 mg/m2/dose)

Table 5.3.2.3.-2 Initial dose of capecitabine (750 mg/m²/dose)
<table><tr><th>Body surface area (BSA)</th><th>Single dose (no. of tablets)</th><th>Daily dose (no. of tablets)</th></tr><tr><td><1.41 m²</td><td>900 mg (3 tablets)</td><td>1,800 mg (6 tablets)</td></tr><tr><td>1.41 m² ≤ BSA < 1.81 m²</td><td>1,200 mg (4 tablets)</td><td>2,400 mg (8 tablets)</td></tr><tr><td>1.81 m² ≤ BSA < 2.2 m²</td><td>1,500 mg (5 tablets)</td><td>3,000 mg (10 tablets)</td></tr></table></td></tr>
<tr><td>33</td><td>5.5. Criteria for dose hold and resumption for XELOX therapy
5.5.1. Initiation and dose</td><td>5.5.1. Initiation and dose hold/resumption criteria for XELOX therapy</td><td>5.5.1. Initiation and dose hold/resumption criteria for XELOX therapy and capecitabine withholding criteria
After the start of each course, if in conflict with “Table 5.5.1.2: Capecitabine</td></tr>
</table>

<table>
<tr><th>Page</th><th>Item</th><th>Protocol Ver.1.1 (19 Apr 2012)</th><th>Protocol Ver.1.2 (October 25, 2013)</th></tr>
<tr><td></td><td>hold/resumption criteria for XELOX therapy and capecitabine withholding criteria</td><td></td><td>withholding criteria after the start of each course," administration of capecitabine for the course concerned is to be withheld. After withholding capecitabine, if recovery from the adverse event has been achieved by day 15, capecitabine therapy may be resumed. Upon resumption, the capecitabine dose shall be in accordance with "Table 5.5.2.1: Criteria for dose changes in XELOX therapy." Furthermore, capecitabine is not to be administered after day 16.</td></tr>
<tr><td>33</td><td>5.5. Criteria for dose hold and resumption for XELOX therapy
5.5.1. Initiation and dose hold/resumption criteria for XELOX therapy and capecitabine withholding criteria</td><td>Table 5.5.1.1. Initiation and dose hold/resumption criteria for each course of XELOX therapy
Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)</td><td>Table 5.5.1.1. Initiation and dose hold/resumption criteria for each course of XELOX therapy
Palmar–plantar erythrodysesthesia syndrome (hand–foot syndrome), diarrhea, oral mucositis</td></tr>
<tr><td>33</td><td>5.5. Criteria for dose hold and resumption for XELOX therapy
5.5.1. Initiation and dose hold/resumption criteria for XELOX therapy and capecitabine withholding criteria</td><td>-</td><td>Table 5.5.1.2. Capecitabine withholding criteria after the start of each course
<table>
<tr><th>Adverse event</th><th>Withholding criteria</th><th>Withholding details</th></tr>
<tr><td>Palmar–plantar erythrodysesthesia syndrome (hand–foot syndrome), diarrhea, and oral mucositis</td><td>≥ Grade 2</td><td rowspan="2">After the start of each course, if in conflict with "Table 5.5.1.2: Capecitabine withholding criteria after the start of each course," administration of capecitabine for the course concerned is to be withheld. After withholding capecitabine, if recovery from the adverse event has been achieved by day 15, capecitabine therapy may be resumed. Upon resumption, the capecitabine dose shall be in accordance with "Table 5.5.2.1: Criteria for dose changes in XELOX therapy." Furthermore, capecitabine is not to be administered after day 16.</td></tr>
<tr><td>Others</td><td>Drugs may be withheld upon the appearance of adverse events that do not correspond to the above at the discretion of the trial attending physician.</td></tr>
</table></td></tr>
</table>

Page	Item	Protocol Ver.1.1 (19 Apr 2012)	Protocol Ver.1.2 (October 25, 2013)
32	5.5. Criteria for dose hold and resumption for XELOX therapy 5.5.2. Dose modification criteria for XELOX therapy	The dose of oxaliplatin and capecitabine is reduced based on the grade of adverse events during the previous course, in accordance with Table 5.5.2.1. "Dose modification criteria for XELOX therapy," Table 5.5.2.2. "Dose reduction levels for XELOX therapy (oxaliplatin)," and Table 5.5.2.3. "Dose reduction levels for XELOX therapy (capecitabine).	The dose of oxaliplatin and capecitabine is reduced based on the grade of adverse events during the previous course, in accordance with Table 5.5.2.1. "Dose modification criteria for XELOX therapy," Table 5.5.2.2. "Dose reduction levels for XELOX therapy (oxaliplatin)," and ***Table 5.5.2.3.-1 "Dose reduction level in XELOX therapy (capecitabine: starting dose of 1,000 mg/m^2/dose)," and Table 5.5.2.3.-2*** "Dose reduction level in XELOX therapy (capecitabine: ***starting dose of 750 mg/m^2/dose***)."

<table>
<tr><th>Page</th><th>Item</th><th>Protocol Ver.1.1 (19 Apr 2012)</th><th>Protocol Ver.1.2 (October 25, 2013)</th></tr>
<tr><td>34</td><td>5.5. Criteria for dose hold and resumption for XELOX therapy
5.5.2. Dose modification criteria for XELOX therapy</td><td>Table 5.5.2.1. Dose modification criteria for XELOX therapy
<table>
<tr><th rowspan="2">Adverse event (excl. peripheral sensory neuropathy [peripheral nervous symptoms])</th><th rowspan="2">Grade</th><th rowspan="2">Incidence</th><th colspan="2">Dose level</th></tr>
<tr><th>Oxaliplatin</th><th>Capecitabine</th></tr>
<tr><td>Neutropenia, thrombocytopenia</td><td>3/4</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td>Persistent grade 2 neutropenia or thrombocytopenia for 1 week or longer</td><td>2</td><td>1</td><td>Level-1 or no change (doctor’s decision)</td><td>Level-1 or no change (doctor’s decision)</td></tr>
<tr><td>Persistent grade 2 neutropenia or thrombocytopenia for 2 weeks or longer</td><td>2</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td rowspan="2">Diarrhea, oral mucositis (stomatitis)</td><td>3</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>4</td><td>1</td><td>Discontinuation of protocol treatment</td><td>Discontinuation of protocol treatment</td></tr>
<tr><td rowspan="4">Palmar-plantar erythrodysesthesia syndrome* (hand-foot syndrome*)</td><td rowspan="3">2</td><td>1</td><td>No change</td><td>No change</td></tr>
<tr><td>2</td><td>No change</td><td>Level-1</td></tr>
<tr><td>3</td><td>No change</td><td>Level-2</td></tr>
<tr><td>3</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>Allergic reaction/anaphylaxis</td><td>3/4</td><td>1</td><td>Discontinuation of administration</td><td>No change</td></tr>
<tr><td>Persistent grade 2 diarrhea or stomatitis for 2 weeks or longer</td><td>2</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td rowspan="2">Other apparent drug-related adverse events (excluding hematologic toxicity)</td><td>3</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td>4</td><td>1</td><td>Discontinuation of protocol treatment</td><td>Discontinuation of protocol treatment</td></tr>
</table></td><td>Table 5.5.2.1. Dose modification criteria for XELOX therapy
<table>
<tr><th rowspan="2">Adverse event (excl. peripheral sensory neuropathy [peripheral nervous symptoms])</th><th rowspan="2">Grade</th><th rowspan="2">Incidence</th><th colspan="2">Dose level</th></tr>
<tr><th>Oxaliplatin</th><th>Capecitabine</th></tr>
<tr><td>Neutropenia, thrombocytopenia</td><td>3/4</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td>Persistent grade 2 neutropenia or thrombocytopenia for 1 week or longer</td><td>2</td><td>1</td><td>Level-1 or no change (doctor’s decision)</td><td>Level-1 or no change (doctor’s decision)</td></tr>
<tr><td>Persistent grade 2 neutropenia or thrombocytopenia for 2 weeks or longer</td><td>2</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td rowspan="2">Diarrhea, oral mucositis (stomatitis)</td><td>3</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>4</td><td>1</td><td>Discontinuation of protocol treatment</td><td>Discontinuation of protocol treatment</td></tr>
<tr><td rowspan="4">Palmar-plantar erythrodysesthesia syndrome* (hand-foot syndrome*)</td><td rowspan="3">2</td><td>1 (< 1 week)</td><td>No change</td><td>No change</td></tr>
<tr><td>2</td><td>No change</td><td>Level-1</td></tr>
<tr><td>3</td><td>No change</td><td>Level-2</td></tr>
<tr><td>3</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>Allergic reaction/anaphylaxis</td><td>3/4</td><td>1</td><td>Discontinuation of administration</td><td>No change</td></tr>
<tr><td>When hand–foot syndrome*, diarrhea, or oral mucositis of grade 2 persists for 1 week or more.</td><td>2</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>When two or more of the following are observed during the same course: hand–foot syndrome1, diarrhea, or oral mucositis of grade 2.</td><td>2</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td>Persistent grade 2 diarrhea or stomatitis for 2 weeks or longer</td><td>2</td><td>1</td><td>No change</td><td>Level-1</td></tr>
<tr><td rowspan="2">Other apparent drug-related adverse events (excluding hematologic toxicity)</td><td>3</td><td>1</td><td>Level-1</td><td>Level-1</td></tr>
<tr><td>4</td><td>1</td><td>Discontinuation of protocol treatment</td><td>Discontinuation of protocol treatment</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Page</th><th>Item</th><th>Protocol Ver.1.1 (19 Apr 2012)</th><th>Protocol Ver.1.2 (October 25, 2013)</th></tr>
<tr><td>35</td><td>5.5. Criteria for dose hold and resumption for XELOX therapy
5.5.2. Dose modification criteria for XELOX therapy</td><td>Table 5.5.2.3. Dose reduction levels for XELOX therapy (capecitabine)
<table>
<tr><th rowspan="2">Body surface area</th><th colspan="3">Single dose</th></tr>
<tr><th>Initial dose</th><th>Level-1</th><th>Level-2</th></tr>
<tr><td><1.36 m²</td><td>1,200 mg (4 tablets)</td><td rowspan="2">900 mg (3 tablets)</td><td rowspan="3">600 mg (2 tablets)</td></tr>
<tr><td>1.36 m² ≤ BSA < 1.41 m²</td><td rowspan="3">1,500 mg (5 tablets)</td></tr>
<tr><td>1.41 m² ≤ BSA < 1.51 m²</td><td rowspan="4">1,200 mg (4 tablets)</td></tr>
<tr><td>1.51 m² ≤ BSA < 1.66 m²</td><td rowspan="4">900 mg(3 tablets)</td></tr>
<tr><td>1.66 m² ≤ BSA < 1.81 m²</td><td rowspan="2">1,800 mg (6 tablets)</td></tr>
<tr><td>1.81 m² ≤ BSA < 1.96 m²</td><td rowspan="3">1,500 mg (5 tablets)</td></tr>
<tr><td>1.96 m² ≤ BSA < 2.11 m²</td><td rowspan="2">2,100 mg (7 tablets)</td></tr>
<tr><td>2.11 m² ≤ BSA ≤ 2.2 m²</td><td>1,200 mg (4 tablets)</td></tr>
</table></td><td>Table 5.5.2.3-1. Dose reduction levels for XELOX therapy (capecitabine; starting dose of 1,000mg/m2/dose)
<table>
<tr><th rowspan="2">Body surface area</th><th colspan="3">Single dose</th></tr>
<tr><th>Initial dose</th><th>Level-1</th><th>Level-2</th></tr>
<tr><td><1.36 m²</td><td>1,200 mg (4 tablets)</td><td rowspan="2">900 mg (3 tablets)</td><td rowspan="3">600 mg (2 tablets)</td></tr>
<tr><td>1.36 m² ≤ BSA < 1.41 m²</td><td rowspan="3">1,500 mg (5 tablets)</td></tr>
<tr><td>1.41 m² ≤ BSA < 1.51 m²</td><td rowspan="4">1,200 mg (4 tablets)</td></tr>
<tr><td>1.51 m² ≤ BSA < 1.66 m²</td><td rowspan="4">900 mg(3 tablets)</td></tr>
<tr><td>1.66 m² ≤ BSA < 1.81 m²</td><td rowspan="2">1,800 mg (6 tablets)</td></tr>
<tr><td>1.81 m² ≤ BSA < 1.96 m²</td><td rowspan="3">1,500 mg (5 tablets)</td></tr>
<tr><td>1.96 m² ≤ BSA < 2.11 m²</td><td rowspan="2">2,100 mg (7 tablets)</td></tr>
<tr><td>2.11 m² ≤ BSA ≤ 2.2 m²</td><td>1,200 mg (4 tablets)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Page</th><th>Item</th><th>Protocol Ver.1.1 (19 Apr 2012)</th><th>Protocol Ver.1.2 (October 25, 2013)</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td rowspan="2">Body surface area</td><td colspan="3">Single dose</td></tr>
<tr><td>Initial dose</td><td>Level-1</td><td>Level-2</td></tr>
<tr><td><1.36 m²</td><td rowspan="2">900 mg (3 tablets)</td><td rowspan="3">600 mg (2 tablets)</td><td rowspan="3">300 mg (1 tablet)</td></tr>
<tr><td>1.36 m² ≤ BSA < 1.41 m²</td></tr>
<tr><td>1.41 m² ≤ BSA < 1.51 m²</td><td rowspan="3">1,200 mg (4 tablets)</td></tr>
<tr><td>1.51 m² ≤ BSA < 1.66 m²</td><td rowspan="3">900 mg (3 tablets)</td><td rowspan="3">600 mg (2 tablets)</td></tr>
<tr><td>1.66 m² ≤ BSA < 1.81 m²</td></tr>
<tr><td>1.81 m² ≤ BSA < 1.96 m²</td><td rowspan="3">1,500 mg (5 tablets)</td></tr>
<tr><td>1.96 m² ≤ BSA < 2.11 m²</td><td rowspan="2">1,200 mg (4 tablets)</td><td rowspan="2">900 mg(3 tablets)</td></tr>
<tr><td>2.11 m² ≤ BSA ≤ 2.2 m²</td></tr>
</table>
Table 5.5.2.3.-2 Dose reduction level for XELOX therapy (capecitabine: starting dose of 750 mg/m2/dose)
</td></tr>
<tr><td>50</td><td>7.5. Analysis of secondary endpoint
7.5.6. Percent of dose received versus planned dose</td><td>Modified FOLFOX6 therapy:
Relative dose intensity (RDI) (%) = (actual dose/initial dose) × (14/number of days in the treatment courses) × 100mFOLFOX6
XELOX therapy:</td><td>Modified FOLFOX6 therapy:
Relative dose intensity (RDI) (%) = (actual dose/prespecified dose) × (14/number of days in the treatment courses) × 100
XELOX therapy:</td></tr>
</table>

Page	Item	Protocol Ver.1.1 (19 Apr 2012)	Protocol Ver.1.2 (October 25, 2013)
		Relative dose intensity (RDI) (%) = (actual dose/ initial dose) × (21/number of days in the treatment courses) × 100	Relative dose intensity (RDI) (%) = (actual dose/ ***prespecified*** dose) × (21/number of days in the treatment courses) × 100

JFMC47-1202-C3 (ACHIEVE Trial)

A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil / l-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer

ACHIEVE Trial

Efficacy Analysis Plan

1st version

Statistician: Takeharu Yamanaka

Date of preparation: 15 April, 2017

Approved by: Japanese Foundation for Multidisciplinary Treatment of Cancer

Date of approval: 15 April, 2017

Table of Contents

1. OBJECTIVE

1.1 Objective of the Study

Pooled analysis of the IDEA* studies will be performed to evaluate the non-inferiority of disease-free survival after 3 months of mFOLFOX6 or XELOX therapy (study group: T group) versus 6 months of mFOLFOX6 or XELOX therapy (control group: S group) as postoperative adjuvant chemotherapy following curative resection of stage III colon cancer (including rectosigmoid cancer).

* IDEA (International Duration Evaluation of Adjuvant chemotherapy colon cancer prospective pooled analysis) is a project that involves the integrated analysis of data from 6 ongoing randomized Phase III clinical trials that are being run by clinical study groups around the world, including Japan.

1.2. Objective of This Analysis Plan

The primary objective of the ACHIEVE Trial is to provide data for the IDEA pooled analysis. In addition, specific analysis of efficacy in the ACHIEVE trial itself will be performed according to this plan.

2. STUDY DESIGN

2.1 Target Patients

Patients who have undergone curative resection (CurA) of stage III colon cancer, including rectosigmoid cancer, with a PS of 0–1 and an age of 20 years or older.

2.2 Subject Allocation

Subjects were randomly assigned to either the control group (S group) or the study group (T group) by the minimization method with adjustment for the following five factors.

Factors for assignment

N-factor (except N1 / N1)

Study site

Regimen (mFOLFOX6 / XELOX)

Tumor location (colon / rectosigmoid / multiple)

Age (< 70 years / ≥ 70 years)

2.3 Protocol Treatment

Physicians must select mFOLFOX6 or XELOX therapy prior to registration of the subject in the trial and the attending physician judges which treatment is better for the patient. Changing the treatment is not permitted after registration unless adverse events associated with oxaliplatin are severe enough to preclude continuation of the study, in which case mFOLFOX6 therapy is changed to 5-FU/1LV (sLV5FU2) and XELOX therapy is changed to capecitabine monotherapy. After changing treatment, the dose of 5-FU cannot be increased again.

2.3.1 Control group: S group (6-month group)

mFOLFOX6 therapy

Each cycle consists of oxaliplatin at a dose of 85 mg/m^2 on Day 1, bolus administration of 5-FU at a dose of 400 mg/m^2 and l-LV at a dose of 200 mg/m^2 on Day 1, and infusion of 5-FU at a dose of 2,400 mg/m^2 from Day 1 to Day 3, followed by a 14-day washout period. This regimen is repeated for 12 cycles.

XELOX therapy

Each cycle consists of oxaliplatin at a dose of 130 mg/m^2 on Day 1, and twice daily oral administration of capecitabine within 30 minutes after the morning and evening meals from the evening of Day 1 to the morning of Day 15* at a dose of 1000 mg/m^2/per day or 750 mg/m^2 per day (based on body surface area)** for a total of 28 doses, followed by a 7-day washout period. This regimen is repeated for 8 cycles.

2.3.2 Study group: T group (3-month group)

mFOLFOX6 therapy

Each cycle consists of oxaliplatin at a dose of 85 mg/m^2 on Day 1, bolus administration of 5-FU at a dose of 400 mg/m^2 and l-LV at a dose of 200 mg/m^2 on Day 1, and infusion of 5-FU at a dose of 2,400 mg/m^2 from Day 1 to Day 3, followed by a 14-day washout period. This regimen is repeated for 6 cycles.

XELOX therapy

Each cycle consists of oxaliplatin at a dose of 130 mg/m^2 on Day 1, and twice daily oral administration of capecitabine within 30 minutes after the morning and evening meals from the evening of Day 1 to the morning of Day 15* at a dose of 1000 mg/m^2/per day or 750 mg/m^2 per day (based on body surface area) for a total of 28 doses, followed by a 7-day washout period. This regimen is repeated for 4 cycles.

In all the treatment regimens, subjects should be monitored without treatment, providing no postoperative adjuvant chemotherapy except for the protocol treatment until recurrence or by the end of follow up in the protocol.

3. ANALYSIS POPULATION

3.1 Definition of the Analysis Population

Statistical analysis will be performed on the modified ITT population.

The modified ITT population is defined as the subjects who received protocol treatment at least once among all subjects who were assigned to treatment.

3.2 Statistical Analysis Software

Statistical analysis software: SAS version 9.2.

3.3 Handling of Missing Data

All missing data will be handled as missing and imputation will not be done.

3.4 Non-Inferiority Margin

Because this study is part of IDEA, a study-specific non-inferiority margin has not been set. Therefore, the p value for a specific non-inferiority margin will not be calculated for efficacy analysis in this study.

3.5 Safety Analysis

Since the safety analysis has already been performed separately, analysis of the disposition of the subjects, demographic and other baseline characteristics, treatment compliance, and safety (adverse events) has been completed. Therefore, this analysis will only cover efficacy and not safety.

4. STATISTICAL ANALYSIS

4.1 Calculation of the Median Observation Period

The median observation period will be calculated by the reverse Kaplan-Meier method.

1.1 Analysis of the Primary Endpoint (Disease-free Survival [DFS])

- In the modified ITT population, DFS curves will be calculated by the Kaplan-Meier method for each treatment group. Then the 1-year DFS, 2-year DFS, and 3-year DFS will be estimated with their two-sided 95% confidence intervals.
- The hazard ratio and its two-sided 95% confidence interval will be calculated using a Cox proportional-hazards model. The same analysis will also be performed for reference using the Cox proportional-hazards model stratified by allocation factors (except the study site), i.e., N-factor (N1 / N2), regimen (mFOLFOX6 / XELOX), tumor location (colon / rectosigmoid / multiple), and age (< 70 years / ≥ 70 years).
- For the following subgroups, the hazard ratio and its two-sided 95% confidence interval will be calculated using the unstratified Cox proportional-hazards model to generate a forest plot summarizing the results of each subgroup.
    - T-factor (T4/T1-3)
    - N-factor (N1/N2)
    - Risk (low [T1-3/N1], high [T4 or N2])
    - Regimen (mFOLFOX6/XELOX)
    - Risk × Regimen (low/mFOLFOX6, low/XELOX, high/mFOLFOX6, high/XELOX
    - Sex (Male/Female)
    - Age 1(≥ 65 years, < 65 years)
    - Age 2 (≥ 70 years,< 70 years)
    - ECOG: PS (0 vs. 1)
    - Tumor location (colon/rectosigmoid/multiple)
    - Number of lymph nodes examined [1] (< 12 nodes vs. ≥ 12 nodes)
    - Number of lymph nodes examined [2] (3/N1, less than 20 lymph nodes vs. 20 lymph nodes or more)
    - Number of positive lymph nodes [1] (1 node vs. ≥ 2 nodes)
    - Number of positive lymph nodes [2] (1–4 nodes vs. ≥ 5 nodes)

1.2 Analysis of the Secondary Endpoint (Overall Survival [OS])

- Regarding overall survival, the same analysis will be performed as for DFS in the modified ITT population.

JFMC47-1202-C3 (ACHIEVE Trial)

A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil / l-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer

ACHIEVE Trial

Safety Analysis Plan

1st version

Statistician: Takeharu Yamanaka

Date of preparation: 1 September, 2015

Approved by:

Date of approval: 1 September, 2015

Japanese Foundation for Multidisciplinary Treatment of Cancer

Table of contents

1. OBJECTIVE

1.1 Objective of the Study

Pooled analysis of the IDEA* studies will be performed to evaluate the non-inferiority of disease-free survival after 3 months of mFOLFOX6 or XELOX therapy (study group: T group) versus 6 months of mFOLFOX6 or XELOX therapy (control group: S group) as postoperative adjuvant chemotherapy following curative resection of stage III colon cancer (including rectosigmoid cancer).

* IDEA (International Duration Evaluation of Adjuvant chemotherapy colon cancer prospective pooled analysis) is a project that involves the integrated analysis of data from 6 ongoing randomized Phase III clinical trials that are being run by clinical study groups around the world, including Japan.

1.2 Objective of this Analysis Plan

This analysis will focus on safety data, particularly related to peripheral sensory neuropathy (peripheral neurological symptoms), because efficacy analysis of the ACHIEVE Trial will be performed and published separately under IDEA.

2. STUDY DESIGN

2.1 Target Patients

Patients who have undergone curative resection (CurA) of stage III colon cancer, including rectosigmoid cancer, with a PS of 0-1 and an age of 20 years or older.

2.2 Subject Allocation

Subjects were randomly assigned to either the control group (S group) or the study group (T group) by the minimization method with adjustment for the following five factors.

Factors for assignment

N-factor (except N1 / N1)

Study site

Regimen (mFOLFOX6 / XELOX)

Tumor location (colon / rectosigmoid / multiple)

Age (< 70 years / ≥ 70 years)

2.3 Protocol Treatment

Physicians must select mFOLFOX6 or XELOX therapy prior to registration of the subject in the trial and the attending physician judges which treatment is better for the patient. Changing the treatment is not permitted after registration unless adverse events associated with oxaliplatin are severe enough to preclude continuation of the study, in which case mFOLFOX6 therapy is changed to 5-FU/1LV (sLV5FU2) and XELOX therapy is changed to capecitabine monotherapy. After changing treatment, the dose of 5-FU cannot be increased again.

2.3.1 Control group: S group (6-month group)

mFOLFOX6 therapy

Each cycle consists of oxaliplatin at a dose of 85 mg/m^2 on Day 1, bolus administration of 5-FU at a dose of 400 mg/m^2 and l-LV at a dose of 200 mg/m^2 on Day 1, and infusion of 5-FU at a dose of 2,400 mg/m^2 from Day 1 to Day 3, followed by a 14-day washout period. This regimen is repeated for 12 cycles.

XELOX therapy

Each cycle consists of oxaliplatin at a dose of 130 mg/m^2 on Day 1, and twice daily oral administration of capecitabine within 30 minutes after the morning and evening meals from the evening of Day 1 to the morning of Day 15* at a dose of 1000 mg/m^2/per day or 750 mg/m^2 per day (based on body surface area)** for a total of 28 doses, followed by a 7-day washout period. This regimen is repeated for 8 cycles.

2.3.2 Study group: T group (3-month group)

mFOLFOX6 therapy

Each cycle consists of oxaliplatin at a dose of 85 mg/m^2 on Day 1, bolus administration of 5-FU at a dose of 400 mg/m^2 and l-LV at a dose of 200 mg/m^2 on Day 1, and infusion of 5-FU at a dose of 2,400 mg/m^2 from Day 1 to Day 3, followed by a 14-day washout period. This regimen is repeated for 6 cycles.

XELOX therapy

Each cycle consists of oxaliplatin at a dose of 130 mg/m^2 on Day 1, and twice daily oral administration of capecitabine within 30 minutes after the morning and evening meals from the evening of Day 1 to the morning of Day 15* at a dose of 1000 mg/m^2/per day or 750 mg/m^2 per day (based on body surface area) for a total of 28 doses, followed by a 7-day washout period. This regimen is repeated for 4 cycles.

In all the treatment regimens, subjects should be monitored without treatment, providing no postoperative adjuvant chemotherapy except for the protocol treatment until recurrence or by the end of follow up in the protocol.

2.4 Target Sample Size

600 subjects in each group × 2

2.5 Endpoints

(1) Adverse events
(2) Treatment completion rate
(3) Relative dose intensity
(4) Peripheral sensory neuropathy (peripheral neurological symptoms)

3. ANALYSIS POPULTION

3.1 Definition of the Analysis Population

Statistical analysis will be performed on the safety analysis population.

The safety analysis population is defined as the subjects who received protocol treatment at least once among all subjects who were assigned to treatment.

3.2 Statistical Analysis Software

Statistical analysis software: SAS version 9.2.

3.3 Handling of Missing Data

All missing data will be handled as missing and imputation will not be done.

3.4 Level of Significance and Confidence Coefficient of the Confidence Interval

The level of significance is set at α = 5% (two-sided) (2.5% one sided). The confidence coefficient (1-α) of the confidence interval is set at 95%.

The criterion for selection of variables during multivariate analysis is α=0.100.

4. STATISTICAL ANALYSIS

4.1 Disposition of Subjects and Subject Characteristics

4.1.1 Disposition of subjects

Among the randomized subjects, the following will be calculated with stratification by the assigned treatment group (T group [3-month group] or S group [6-month group]) and by the total number of subjects and treatment method (mFOLFOX6 or XELOX therapy): the number of randomized subjects, number of subjects withdrawn before treatment, number of ineligible subjects, number of subjects starting treatment, number of subjects discontinuing treatment, and number of subjects completing treatment. In addition, the reason for ineligibility will be stratified by the assigned treatment group and **the presence/absence of study drug administration**.

4.1.2 Demographic and other baseline characteristics

The following subject characteristics will be calculated in the safety analysis population.

Summary statistics of demographic and other baseline characteristics will be calculated by the assigned treatment group to test differences in distribution between the T group and the S group. In addition, subject characteristics will be calculated by treatment (mFOLFOX6 versus XELOX therapy) in each assigned treatment group.

4.2 Treatment Status

Unless otherwise specified, the following calculations will be performed in the safety analysis population.

4.2.1 Treatment completion status of each cycle

The number of subjects completing each cycle of mFOLFOX6 therapy or XELOX therapy will be calculated for each treatment group. The percentage of subjects completing each cycle will be calculated by using the safety analysis population as the denominator.

4.2.2 Treatment completion and discontinuation

The number and percentage of subjects who completed or discontinued study treatment will be calculated for each treatment method, along with the disposition of completed subjects (postponement and dose reduction) and the disposition of discontinued subjects (postponement and dose reduction) in each treatment group.

4.2.3 Reasons for discontinuation of protocol treatment

The number and percentage of subjects with each reason for discontinuation of treatment will be calculated by the treatment method and by the total number in each treatment group.

4.2.4 Withdrawal by cycle

The number of subjects discontinuing treatment and the reasons for discontinuation will be determined in the T group and S group for each cycle of the mFOLFOX6 therapy and XELOX therapy groups.

4.2.5 Dose reduction

The number and percentage of patients with dose reduction will be calculated by the treatment method and by the total number in each treatment group. In addition, the number of patients with dose reduction and the reasons for dose reduction will be determined in the T group and S group for each cycle of mFOLFOX6 therapy and XELOX therapy.

4.2.6 Postponement

The number and percentage of patients with postponement of treatment will be calculated by the treatment method and by the total number in each treatment group. In addition, the number of patients with postponement and the reasons for postponement will be determined in the T group and S group for each cycle of mFOLFOX6 therapy and XELOX therapy.

4.2.7 Relative dose intensity (RDI)

Summary statistics on the RDI for each drug will be calculated by the treatment method and by the total number of patients in each treatment group. In addition, summary statistics on the RDI for each drug will be calculated with stratification by the assigned treatment group, the cycle, and the total number of cycles.

The RDI for each treatment group will be calculated by the following formulae.

mFOLFOX6 therapy:
RDI (%) = (actual dose/ prescribed dose) × (14/actual cycle days) × 100
XELOX therapy:
RDI (%) = (actual dose/ prescribed dose) × (21/actual cycle days) × 100

4.2.8 Treatment completion rate

Summary statistics on the treatment completion rate (%) will be calculated by the treatment method and by the total number of patients in each treatment group. In addition, the number and percentage of treatment completion rate (%) compartments will be calculated with stratification by the assigned treatment group, the cycle, and the total number of cycles.

The RDI for each group will be calculated by the following formulae.

Control group (S group: 6-month group):
mFOLFOX6 therapy: Treatment completion rate (%) = Final number of cycles/12 × 100
XELOX therapy: Treatment completion rate (%) = Final number of cycles /8 × 100
Study group (T group: 3-month group):
mFOLFOX6 therapy: Treatment completion rate (%) = Final number of cycles /6 × 100
XELOX therapy: Treatment completion rate (%) = Final number of cycles /4 × 100

4.3 Safety Analysis

4.3.1 Adverse events

The number and percentage of adverse events of each Grade (1, 2, 3, and 4) and the number and percentage of Grade 3–4 adverse events stratified by the treatment method and the total number of subjects will be calculated in each treatment group with stratification by adverse event type. For all treatments, the between-group difference of the incidence rate will be tested by Fisher's exact test. In addition, the same calculations will be performed for each grade of events.

4.4 Detailed Analysis of Peripheral Sensory Neuropathy, Allergic Reactions, and Other Events

4.1.1 Incidence of peripheral sensory neuropathy during each cycle stratified by severity

In the safety analysis population, the number and the percentage of at-risk subjects with neurological symptoms will be calculated with stratification by cycle and grade. The same calculations will also be performed in the mFOLFOX6 group, XELOX group, T group (3-month group), and S group (6-month group).

4.4.2 Peripheral sensory neuropathy and cumulative dose of oxaliplatin (L-OHP)

Regarding peripheral sensory neuropathy, the cumulative dose of L-OHP at the time of the onset of ≥ Grade 1, ≥ Grade 2, and ≥ Grade 3 adverse events will be calculated and the number of patients with each cumulative dose of L-OHP will be determined. The cumulative incidence of ≥ Grade 1, ≥ Grade 2, and ≥ Grade 3 peripheral nervous system disorders versus the cumulative dose of L-OHP, number of cycles, and number of days after the start of treatment will be graphed by using the Kaplan-Meier method. These calculations will be performed separately in the safety analysis population, mFOLFOX6 group, XELOX group, T group (3-month group), and S group (6-month group).

4.4.3 Incidence of allergic reactions during each cycle stratified by severity

In the safety analysis population, the number of allergic reactions and the percentage of allergic reactions in the at-risk subjects will be calculated with stratification by cycle and grade. The same calculations will also be performed in the mFOLFOX6 group, XELOX group, T group (3-month group), and S group (6-month group).

4.4.4 Univariate and multivariate analysis of ≥ Grade 1 and ≥ Grade 2 peripheral neuropathy

Univariate analysis will be performed with the Cox proportional-hazards model, using the number of days before the occurrence of ≥ Grade 1 and ≥ Grade peripheral nervous system symptoms as the time-to-event variable. Because the cumulative dose of L-OHP is a confounder of time, it will be excluded from multivariate analysis.

4.4.5 Univariate and multivariate analysis of ≥ Grade 1 and ≥ Grade 3 allergic reactions

Univariate analysis will be performed with the Cox proportional-hazards model, using the number of days before the occurrence of ≥ Grade 1 and ≥ Grade 2 allergic reactions as the time-to-event variable. Because the cumulative dose of L-OHP is a confounder of time, it will be excluded from multivariate analysis.

4.6.6 Incidence of adverse reactions stratified by background factors

In the safety analysis population, the following will be calculated with stratification by background factors: the number of subjects evaluated, the number of subjects without adverse events, and the percentage of ≥ Grade 1 and ≥ Grade 3 adverse events in the subjects with events and in the evaluated subjects.