Bevacizumab (Avastin; Genentec, Inc., South San Fran cisco, CA), a recombinant, humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF) is one of the biological agents and was proved to improve overall survival (OS) and progression-free survival (PFS) in bevacizumab-naïve patients with metastatic CRC when administered to first- and second-line chemotherapy.

For patients with previously treated metastatic CRC, treatment results of FOLFIRI or FOLFOX as a second-line therapy were reported from the phase III study. PFS was 2.5 and 4.2 months, respectively (5). Treatment results of FOLFIRI plus bevacizumab at 5 mg/kg and FOLFOX plus bevacizumab at 5 mg/kg as a second-line treatment were reported from the phase II study. PFS was 7.8 and 5.3 months, respectively (6). In addition, the treatment result of FOLFOX4 plus bevacizumab at 10 mg/kg as a second-line therapy was reported from a randomized phase III study. OS as the primary objective was 12.9 months compared with 10.8 months of FOLFOX4 alone (HR, 0.66; $P < 0.0011$). PFS was 7.3 months, which is also significantly improved compared with 4.7 months of FOLFOX4 alone (HR, 0.61; $P < 0.0001$) (7). However, all of these treatments were examined for previously bevacizumab-naïve patients.

A key element of continuous administration of bevacizumab beyond progression is as shown below. In basic research, regrowth of tumor vessels are often observed soon after cessation of bevacizumab administration (8–10) and VEGF expression is identified across the board from the initial period of the tumor lifecycle (11). Several experimental studies have examined that the muMAb 4.6.1 antibody, mouse monoclonal precursor of VEGF inhibitors in CRC xenograft models prevents growth of tumor cells at metastatic sites dose dependently (12). In addition, the BRiTE study (13), one of the observational cohort studies in the USA provides supportive clinical data about the foregoing. Median OS were 12.6, 19.9 and 31.8 months in the no post-progressive disease (PD) treatment, chemotherapy without bevacizumab and chemotherapy with bevacizumab groups, respectively.

After adjustment for other prognostic factors, bevacizumab treatment beyond progression maintained a statistically significant effect on survival after PD, compared with no post-PD bevacizumab (HR, 0.49; 95% CI, 0.41–0.58; $P < 0.001$). In this study, the proportion of bevacizumab doses administered as the second-line therapy were 90.7% (5 mg/kg), 3.6% (7.5 mg/kg) and 2.3% (10 mg/kg). These results from the BRiTE study suggest that continuous VEGF inhibition with bevacizumab beyond initial PD could play an important role for prolonging survival of patients with metastatic CRC.

There are three major clinical questions to be solved about second-line biological agents in metastatic colorectal cancer. The first clinical question about the continuation of bevacizumab after exposure to bevacizumab treatment will be revealed from the results of the on-going trial 'AIO 0504'. The second clinical question about the drug selection between bevacizumab and anti-epidermal growth factor receptor antibodies with KRAS wild type after a first-line bevacizumab-containing regimen will also be answered by the on-going trial 'SPIRITT'.

On the other hand, the third clinical question about the optimal doses of bevacizumab as second-line treatment followed by a bevacizumab-containing regimen is still remains unsolved. The verified data indicates the efficacy of bevacizumab at 5 mg/kg/weekly (=10 mg/kg/biweekly) in the second-line setting followed by bevacizumab-naïve treatment (7). The recommended dose of bevacizumab is 5 mg/kg/weekly (=10 mg/kg/biweekly) in non-small cell lung cancer, breast cancer, renal cell cancer and second-line colorectal cancer (14–19), but 2.5 mg/kg/weekly (=5 mg/kg/biweekly) in the first-line CRC treatment. The dose of bevacizumab 2.5 mg/kg/weekly (=5 mg/kg/biweekly) could be lower than the recommended dose in the second-line CRC treatment.

Thus, it is necessary for us to investigate the effectiveness of high-dose bevacizumab for metastatic CRC.

Accordingly, we have conducted a randomized phase III study of FOLFIRI plus bevacizumab 5 mg/kg versus 10 mg/kg as second-line therapy in patients with metastatic CRC who have failed first-line bevacizumab plus oxaliplatin-based therapy (EAGLE study).

The study protocol was approved by the institutional review boards of each participating institution. The study met the ethical guidelines for clinical studies of the Health, Labor and Welfare Ministry in Japan, and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

PROTOCOL DESIGN FOR EAGLE STUDY

Objective

A multicenter randomized phase III study of adding bevacizumab 5 or 10 mg/kg to FOLFIRI in advanced/metastatic CRC who have failed prior bevacizumab plus oxaliplatin-based first-line therapy.

Endpoint

The primary endpoint is PFS. The secondary endpoints are the toxicity, response rate, time to treatment failure, OS, OS from the start of the first-line treatment and second PFS (time duration from the initiation of the first-line treatment until progression after the protocol treatment). The progression will be evaluated on the basis of response evaluation criteria in solid tumors (RECIST) ver. 1.1.

Eligibility Criteria

Inclusion Criteria

(i) PD after chemotherapy with bevacizumab plus oxaliplatin-based therapy as the first-line treatment

(with measurable lesions in the RECIST criteria) or difficult to continue the first-line therapy due to the other reasons.
(ii) Oxaliplatin and bevacizumab were administered for more than four times in the first-line treatment.
(iii) Cytologically and/or histologically proven CRC.
(iv) Written informed consent.
(v) Aged 20 years old and above.
(vi) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
(vii) Life expectancy estimated $\geq$3 months.
(viii) Sufficient organ functions.

Exclusion Criteria

(i) Previous irinotecan treatment.
(ii) Administration of transfusion/hematopoietic factor or antithrombotic drug within 14 days.
(iii) Serious renal dysfunction.
(iv) Serious drug hypersensitivity or a history of drug allergy.
(v) Active concomitant malignancy.
(vi) Active infections.
(vii) Symptomatic or asymptomatic heart disease that is being treated at the time of registration to the trial.
(viii) History of thrombosis, interstitial pneumonia, pulmonary fibrosis or high-grade pulmonary emphysema.
(ix) Fresh hemorrhage from the digestive tube, intestinal tube paralysis, intestinal obstruction and peptic ulcer.
(x) Pleural effusion, peritoneal fluid and pericardial fluid.
(xi) Symptomatic brain metastasis.
(xii) History of mental disturbances or cerebrovascular accident.
(xiii) High blood pressure and diabetes that cannot be controlled.
(xiv) Uncontrolled diarrhea.
(xv) Serious non-healing wound and/or major surgical procedure within 4 weeks prior to enrolling in this trial.
(xvi) Traumatic fracture that has not been headed at the time of enrollment.
(xvii) Bleeding tendency and anti-platelet therapy (including aspirin and non-steroidal anti-inflammatory drugs).
(xviii) Pregnant women, possibly pregnant women, wishing to become pregnant and nursing mothers.
(xix) Needing treatment with atazanavir sulfate.
(xx) Paralyzed bowel.

Registration

Any medical institution that would like to participate could contact a secretariat at Epidemiological and Clinical Research Information Network (ECRIN) or publicly contact: Hideyuki Mishima at the Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan.

Registration forms are sent from the ECRIN to the medical institution for registration.

Registered patients are allocated randomly into the FOLFIRI + 5 mg of bevacizumab arm (arm A) or the FOLFIRI + 10 mg of bevacizumab arm (arm B) at the data-center. For randomization, a minimization method or dynamic randomization is used with five balancing factors: baseline ECOG PS, number of metastasis ($2>$, $2\leq$), reason for a change in therapy to second-line treatment (PD in first-line treatment/non-PD), early recurrence within 6 months (during/after adjuvant treatment) and institutions.

Treatment Methods

FOLFIRI plus bevacizumab consists of bevacizumab at 5 mg/kg (or 10 mg/kg) as a 30-min infusion and *l*-leucovorin 200 mg/m^2 as a 2-h infusion, and concurrently irinotecan 150 mg/m^2 as an over 90-min infusion, followed by bolus fluorouracil (5-FU) 400 mg/m^2 within 15 min and 46-h infusion of 5-FU 2400 mg/m^2. Patients randomly assigned to arm A receive FOLFIRI plus bevacizumab 5 mg/kg. FOLFIRI plus bevacizumab 10 mg/kg is administered to patients randomly assigned to arm B. These treatments are repeated every 2 weeks until disease progression, unacceptable toxicity or patient choice.

Follow-Up

Disease progression and occurrence of new diseases are monitored by using abdominal radiography, abdominal computed tomography (CT) or magnetic resonance imaging, and thoracic CT, and by measuring levels of the tumor markers CEA and CA19–9 at the baseline and every 8 weeks during the treatment period (tumor marker levels are measured every 4 weeks). Blood tests and symptom checks (collecting adverse events) will be carried out throughout the treatment period. In case of dyspnea, arterial blood gases will be tested and chest X-ray test will be carried out. In case of arrhythmia, a 12 lead electrocardiogram will be carried out. The follow-up period is 1 year after the registration of the last patient.

Study Design and Statistical Analysis

The primary objective of this trial is to evaluate whether arm B (FOLFIRI plus 10 mg/kg of bevacizumab therapy) significantly improves PFS compared with arm A (FOLFIRI plus 5 mg/kg of bevacizumab therapy). The null hypothesis, if the PFS of both arms is equal, is tested by the stratified log-rank test with the balancing variables (except for the institutions) as the stratification factor. If arm B showed a statistically significant prolonging effect on PFS compared with the other arm, it is concluded that arm B is more

beneficial therapy. The overall significance level of the trial is set as 5% for the two-sided test.

PFS curves are depicted by the Kaplan–Meier method. Median PFS and the annual PFS rates are also estimated using the Kaplan–Meier method with the two-sided 95% confidence interval using the Greenwood formula (20). The stratified Cox proportional hazards model is used to assess the hazard ratio with Wald-type 95% confidence intervals for the treatment effect between both arms.

Median PFS of arm A in this trial is assumed to be 5.0 months based on previous studies (6,7) and it is considered as a clinically relevant prolongation if the median PFS of arm B is 7.0 months (risk reduction 30%). At the start of this trial, the planned sample size was 280 patients to detect 30% risk reduction with 80% power for a log-rank test comparing two survival curves with a two-sided significance level of 0.05, assuming an accrual time of 2 years and a follow-up time of 1 year (21). This calculation was carried out by employing nQuery Advisor 7.0 software (Statistical Solutions, Saugus, MA, USA). On 8 April 2011, an independent data monitoring committee of the EAGLE trial recommended that the statistical power be amended from 80 to 90% with the consideration of the promising enrollment of patients. As a result, 358 patients (330 events) will be needed to detect 90% power under the same assumption. Taking some dropouts into account, the sample size to be accrued was set at 370 patients in total.

THE EAGLE TRIAL GROUP

Principal investigator: H. Mishima (Osaka National Hospital, Osaka, Japan).
Promotion committee chairman: Y. Maehara (Graduate School of Medical Science, Kyushu University, Fukuoka, Japan).
Data and safety monitoring board: I. Hyodo (University of Tsukuba Graduate School of Comprehensive Human Sciences, Ibaraki, Japan), K. Muro (Aichi Cancer Center Hospital, Aichi, Japan) and T. Yoshino (National Cancer Center Hospital East, Chiba, Japan).
Data center: J. Sakamoto (Nagoya University Graduate School of Medicine, Aichi, Japan) and C. Abe (ECRIN, Kyoto, Japan).
Statistical advisor: K. Oba (Hokkaido University, Hokkaido, Japan).
Participating institutions: Approximately 150 Japanese institutions and hospitals are participating in this trial.

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Conflict of interest statement

None declared.

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Cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer: results from the randomised phase II part of a phase I/II study

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Background: Colorectal cancer (CRC) is the second most common malignancy in Japan. Treatment with inhibitors of the vascular endothelial growth factor (VEGF) signalling pathway has proven benefit in metastatic CRC. Cediranib is an oral highly potent VEGF signalling inhibitor that inhibits all three VEGF receptors.

Patients and methods: In this phase II, double-blind, placebo-controlled study, 172 patients with metastatic CRC were randomised to receive once-daily cediranib (20 or 30 mg) or placebo, each combined with modified FOLFOX6 (mFOLFOX6). The primary objective was comparison of progression-free survival (PFS).

Results: The comparison of cediranib 20 mg versus placebo met the primary objective of PFS prolongation [hazard ratio = 0.70 (95% confidence interval 0.44–1.11), $P = 0.167$], which met the protocol-defined criterion of $P < 0.2$. Median PFS was 10.2 versus 8.3 months, respectively. The PFS comparison for cediranib 30 mg versus placebo did not meet the criterion. The most common adverse events (AEs) in the cediranib-containing groups were diarrhoea and hypertension.

Conclusions: Cediranib 20 mg plus mFOLFOX6 met the predefined criteria in terms of improved PFS compared with placebo plus mFOLFOX6. Cediranib 20 mg was generally well tolerated and the AE profile was consistent with previous studies.

Key words: cediranib, colorectal cancer, mFOLFOX6, placebo, progression-free survival

introduction

In Japan, the incidence of colorectal cancer (CRC) has increased nearly fivefold in the last 25 years, owing primarily to changing Japanese dietary habits, which are becoming increasingly similar to those of Western countries. In 2008, there were 101 656 new cases of CRC in Japan and 43 349 deaths attributed to this disease [1]. CRC is now the second most common malignancy in Japan and is predicted to become the most common by 2015. Fluorouracil (5-FU) was one of the first chemotherapies used for the treatment of CRC, and the combination of 5-FU with leucovorin and oxaliplatin (FOLFOX) has improved outcomes. Treatment with these components (plus irinotecan in some regimens) can provide a median overall survival (OS) of up to 20 months, compared with ~6 months with best supportive care [2]. Japanese clinical guidelines recommend FOLFOX as standard treatment of metastatic colorectal cancer (mCRC) [3]. To reduce toxicity associated with the FOLFOX regimen, a number of modifications have been tried [4, 5]; the current standard is modified FOLFOX6 (mFOLFOX6).

Inhibition of the vascular endothelial growth factor (VEGF) signalling pathway with bevacizumab has demonstrated additional clinical benefit in CRC when used with 5-FU-based regimens in the first-line setting in mCRC [6, 7]. Cediranib is an oral highly potent VEGF tyrosine kinase inhibitor (TKI) that inhibits all three VEGF receptors [8, 9]. Cediranib is suitable for once-daily dosing and has demonstrated antitumour activity during early phase clinical evaluation in patients with advanced cancer [10]. Further studies demonstrated that cediranib was generally well tolerated as monotherapy [11–15] and in combination with various anticancer agents at doses ≤30 mg/day [16–21].

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The efficacy of cediranib in combination with chemotherapy has been investigated in two phase III studies—HORIZON II [22] and HORIZON III [23]—in Western patients with previously untreated mCRC. Two cediranib doses were initially selected for investigation in the HORIZON programme: 20 (lowest biologically active dose) and 30 mg/day (maximum dose suitable for chronic dosing in combination with chemotherapy). The decision to investigate cediranib 20 and 30 mg/day doses in this study was taken before an end-of-phase II decision from the HORIZON programme to proceed with only the 20 mg/day dose. As such, this two-part phase I/II study, which mirrored HORIZON II, investigated cediranib, at the same doses used initially in the Western studies, plus mFOLFOX6 in Japanese patients with previously untreated mCRC (ClinicalTrials.gov identifier NCT00494221; AstraZeneca study code D8480C00039). The phase I part of this study demonstrated that both doses of cediranib were generally well tolerated in combination with mFOLFOX6 [24]. Here, we report the results of the randomised, double-blind, phase II part of this study, which assessed the efficacy of cediranib (20 or 30 mg/day) plus mFOLFOX6 compared with mFOLFOX6 alone.

patients and methods

eligibility

Eligible patients were aged ≥18 years with histological or cytological confirmation of carcinoma of the colon or rectum. Patients required chemotherapy for stage IV (metastatic) disease, had a World Health Organisation (WHO) performance status (PS) of zero or one, and one or more measurable lesions according to the RECIST (version 1.0). Any adjuvant oxaliplatin or 5-FU therapy must have been completed >12 and >6 months, respectively, before study entry. Patients with brain or meningeal metastases were considered eligible if they were clinically stable and had not required corticosteroid treatment of 10 days. Exclusion criteria included prior systemic therapy for metastatic disease and prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including bevacizumab and cediranib.

study design

This phase II, randomised, double-blind, placebo-controlled study assessed the efficacy of first-line treatment with cediranib plus mFOLFOX6 compared with mFOLFOX6 alone. Patients were randomised 1 : 1 : 1 to receive once-daily cediranib (20 or 30 mg) or placebo, each in combination with 14-day treatment cycles of mFOLFOX6 (oxaliplatin 85 mg/m^2 IV, day 1; leucovorin 200 mg/m^2 IV, day 1; 5-FU 400 mg/m^2 IV bolus, day 1 and then 2400 mg/m^2 continuous IV infusion over 46 h). Patients were stratified at randomisation according to a two-level liver function covariate [based on baseline albumin and alkaline phosphatase (ALP) levels] and WHO PS (0 versus 1). Randomised treatment was continued until objective disease progression (as defined by RECIST) or until the occurrence of toxicity, death, withdrawal of patient consent or other discontinuation criteria. RECIST measurements were made using computed tomography or magnetic resonance imaging scans; clinical assessment of these scans was conducted by the study investigators.

The primary objective was to determine the efficacy of cediranib plus mFOLFOX6 compared with mFOLFOX6 alone by assessment of progression-free survival (PFS). Secondary objectives included comparison of OS, objective response rate (ORR: complete response + partial response), duration of response, change in tumour size and assessment of the safety and tolerability of cediranib plus mFOLFOX6. An exploratory end point was to investigate the effect of treatment on soluble markers of angiogenesis (VEGF and sVEGFR-2). VEGF and sVEGFR-2 were measured by enzyme-linked immunosorbent assay of plasma samples from patients who provided separate informed consent.

PFS and ORR were determined from objective tumour assessments (RECIST) carried out at weeks 6, 12, 18, 24 and then every 12 weeks until disease progression or death. Adverse events (AEs) were recorded and graded according to Common Terminology Criteria for Adverse Events version 3.0. The study was approved by each centre's institutional review board and was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

statistical analysis

Assuming a median PFS of 9 months in the placebo group, an 18-month accrual period and a minimum 12-month follow-up, a total of 55 patients per group was required to have 80% power to detect a true PFS hazard ratio (HR) of 0.6 at two-sided significance level of $P < 0.2$ (one-sided $P < 0.1$), which was considered appropriate evidence of activity for a randomised phase II study [25]. The primary PFS analysis was conducted using a log-rank test stratified by WHO PS (0 or 1) and a two-level baseline liver function covariate (covariate 1 for baseline albumin < 3.5 g/l or ALP > 320 U/l; covariate 0 for all other values). PFS and OS were summarised by treatment group using the Kaplan–Meier method. The formal analysis was conducted when ~105 progression events had occurred across the three groups. No formal statistical analysis was carried out on safety data.

The results in the present study were relatively immature (65% of PFS events versus 81% in HORIZON II) and the HR was favourable compared with HORIZON II (HR = 0.84). Furthermore, there was a higher proportion of patients with a PS of zero. Therefore, further analysis of efficacy and safety outcomes was carried out when 81% of progression events had occurred.

results

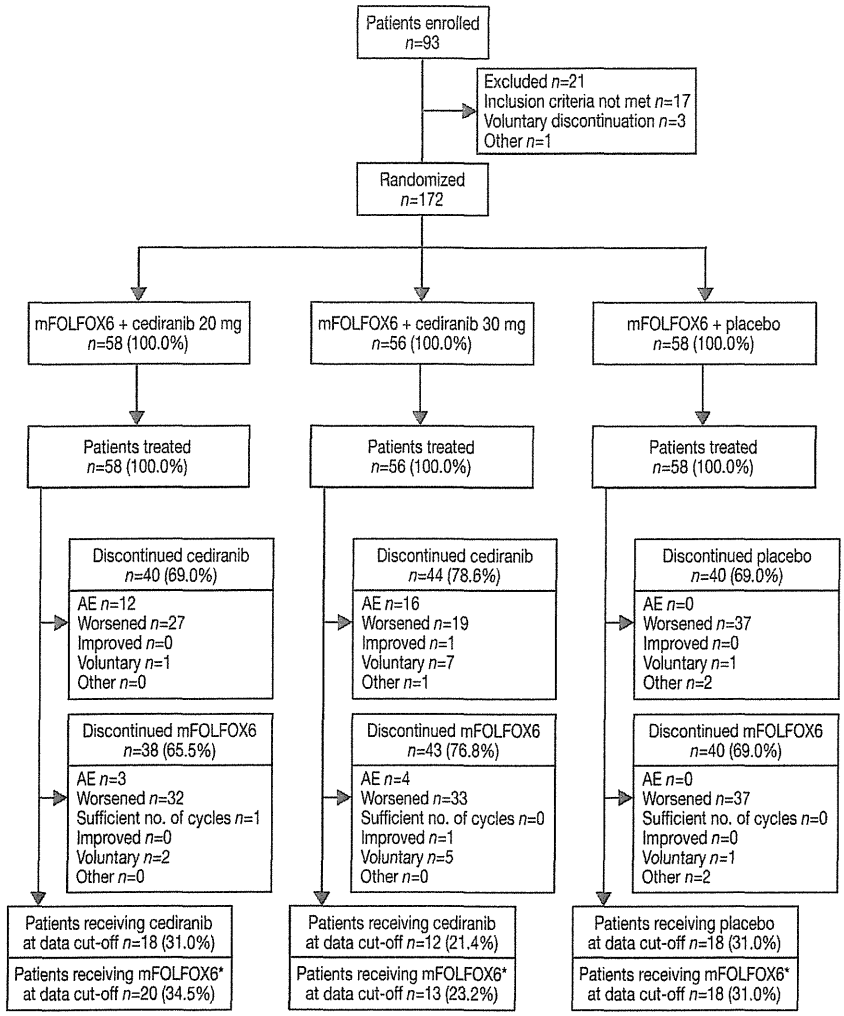
patients

Between January 2008 and January 2009, 172 Japanese patients were randomised to treatment with cediranib 20 mg plus mFOLFOX6 ($n = 58$), cediranib 30 mg plus mFOLFOX6 ($n = 56$) or placebo plus mFOLFOX6 ($n = 58$) (Figure 1). Patient characteristics were representative of the patient population (Table 1). All patients were Japanese and 20% were receiving antihypertensive treatment at baseline. Baseline characteristics were generally well balanced across the groups, although there were more female patients in the cediranib 30 mg group. Imbalances were noted in metastases at baseline, time from initial diagnosis to randomisation, tumour grading, baseline ALP and baseline liver function (Table 1).

At the protocolled data cut-off (13 October 2009), 65% (112) of patients had progressed and 22% (38) had died. The most common reason for discontinuation of placebo/cediranib was worsened condition. At the second data cut-off (11 June 2010), 81% of patients had progressed and median OS follow-up was 19.0 months with 74 OS events.

efficacy

For the PFS comparison of cediranib 20 mg versus placebo, the HR was 0.70 [95% confidence interval (CI) 0.44–1.11],



*Patients may be receiving either 5-FU/leucovorin or 5-FU/leucovorin/oxaliplatin.

Figure 1. CONSORT diagram.

two-sided $P = 0.167$ (Figure 2A), which met the protocol-defined criterion for evidence of activity ($P < 0.2$). Median PFS was 10.2 and 8.3 months, respectively. For the PFS comparison of cediranib 30 mg versus placebo, the HR was 0.82 (95% CI 0.54–1.31), two-sided $P = 0.261$ (Figure 2B), which did not meet the predefined criterion. Median PFS was 8.9 months in the cediranib 30 mg arm. Predefined subgroup analysis of PFS for both dose groups did not identify a particular patient population that derived a differential PFS benefit from cediranib versus placebo (supplemental Figure S1, available at *Annals of Oncology* online).

The ORR was 53.4%, 69.6% and 53.4% in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively; RECIST best response is summarised in Table 2. The median best percentage changes in tumour size were −37.3% (cediranib 20 mg), −43.4% (cediranib 30 mg) and −40.0% (placebo). The median duration of response was 9.2 (cediranib 20 mg), 6.7 (cediranib 30 mg) and 7.1 months (placebo) (Figure 3). At the primary analysis, there were insufficient deaths (total = 38; 15, 9 and 14 in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively) to draw conclusions on OS.

safety and tolerability

Overall, the most common AEs were diarrhoea and hypertension (Table 3); neither caused discontinuation of cediranib at the 20 mg dose. The incidence of AEs leading to discontinuation of cediranib/placebo was higher in the cediranib 30 mg group (27%) compared with the cediranib 20 mg (19%) or placebo (0%) groups; of these, only decreased appetite, diarrhoea and pneumonia (all $n = 2$) were reported in multiple patients.

The incidence of grade 3/4 AEs was 66%, 75% and 36% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The most common grade 3/4 AEs are summarised in Table 4. The incidence of serious adverse events (SAEs) was 39.7%, 39.3% and 19.0% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. No AEs had an outcome of death.

Clinical laboratory evaluation showed that treatment with cediranib plus mFOLFOX6 caused decreases in leucocyte, neutrophil and platelet counts and an increase in thyroid-stimulating hormone, but no new clinically important trends were observed in either cediranib group.

Table 1. Patient demographics and baseline characteristics

Characteristic	Cediranib 20 mg + mFOLFOX6 ($n = 58$)	Cediranib 30 mg + mFOLFOX6 ($n = 56$)	Placebo + mFOLFOX6 ($n = 58$)
Median age (range), years	63.5 (33–79)	64.5 (40–82)	64.0 (36–80)
Sex, *n* (%)			
Male	38 (65.5)	30 (53.6)	39 (67.2)
Female	20 (34.5)	26 (46.4)	19 (32.8)
World Health Organisation performance status, *n* (%)			
0	44 (75.9)	43 (76.8)	47 (81.0)
1	14 (24.1)	13 (23.2)	11 (19.0)
Type of cancer, *n* (%)			
Colon	39 (67.2)	34 (60.7)	36 (62.1)
Rectal	19 (32.8)	22 (39.3)	22 (37.9)
Tumour grading, *n* (%)			
Well differentiated (G1)	11 (19.0)	14 (25.0)	16 (27.6)
Moderately differentiated (G2)	44 (75.9)	38 (67.9)	36 (62.1)
Poorly differentiated (G3)	2 (3.4)	3 (5.4)	4 (6.9)
Undifferentiated (G4)	1 (1.7)	1 (1.8)	1 (1.7)
Unassessable (GX)	0	0	1 (1.7)
Metastatic sites, *n* (%)			
1	32 (55.2)	29 (51.8)	28 (48.3)
>1	26 (44.8)	27 (48.2)	30 (51.7)
Metastases at baseline, *n* (%)			
Patients with liver only metastases at baseline	14 (24.1)	10 (17.9)	14 (24.1)
Patients with liver and other metastases at baseline	25 (43.1)	22 (39.3)	32 (55.2)
Patients with no liver involvement at baseline	19 (32.8)	24 (42.9)	12 (20.7)
Prior adjuvant therapy, *n* (%)			
Yes	13 (22.4)	9 (16.1)	8 (13.8)
No	45 (77.6)	47 (83.9)	50 (86.2)
Time from initial diagnosis to randomisation, *n* (%)			
<6 months	36 (62.1)	38 (67.9)	45 (77.6)
6 to <12 months	2 (3.4)	0	1 (1.7)
12 to <24 months	6 (10.3)	10 (17.9)	4 (6.9)
24 to <36 months	6 (10.3)	2 (3.6)	3 (5.2)
≥36 months	8 (13.8)	6 (10.7)	5 (8.6)
Baseline ALP, *n* (%)			
≤320 U/l	31 (53.4)	35 (62.5)	29 (50.0)
>320 U/l	27 (46.6)	21 (37.5)	29 (50.0)
Baseline liver function			
ALP > 320U/l or albumin < 35 g/l	29 (50.0)	22 (39.3)	30 (51.7)
Other	29 (50.0)	34 (60.7)	28 (48.3)
Baseline vascular endothelial growth factor			
n	36	37	38
Mean (standard deviation), pg/ml	146.5 (416.3)	74.3 (56.6)	96.9 (100.7)
Median (min, max), pg/ml	46.6 (31.2, 2520.5)	55.5 (31.2, 243.3)	54.6 (31.2, 508.1)

mFOLFOX6, modified FOLFOX6; ALP, alkaline phosphatase.

The median duration of exposure was 241.5, 213.0 and 223.5 days in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The proportion of patients experiencing a dose reduction/pause was highest in the cediranib 30 mg group (83.9%) versus the cediranib 20 mg (79.3%) and placebo (56.9%) groups (supplemental Figure S2, available at *Annals of Oncology* online). The dose intensity of cediranib/placebo was lower in the 30 mg group compared with the 20 mg and placebo groups; the mean daily dose of cediranib was 16.6 and 22.8 mg in the cediranib 20 and 30 mg groups, respectively. Exposure to mFOLFOX6 was similar in all arms; the median numbers of cycles of 5-FU, leucovorin and oxaliplatin were 17.0, 17.0 and 12.5, respectively, in the cediranib 20 mg group, 14.0, 14.0 and 11.0, respectively, in the cediranib 30 mg group and 15.0, 15.0 and 11.5, respectively, in the placebo group. However, more patients in the cediranib 30 mg group (33%) stopped oxaliplatin >12 weeks before progression compared with those in the cediranib 20 mg (14%) or placebo (8%) groups.

soluble biomarkers

Median VEGF levels ranged from 47 to 55 pg/ml at baseline; during treatment, levels remained similar to baseline in the placebo group but increased in cediranib-treated patients. In the cediranib 20 mg group, levels increased to 89 pg/ml by day 28

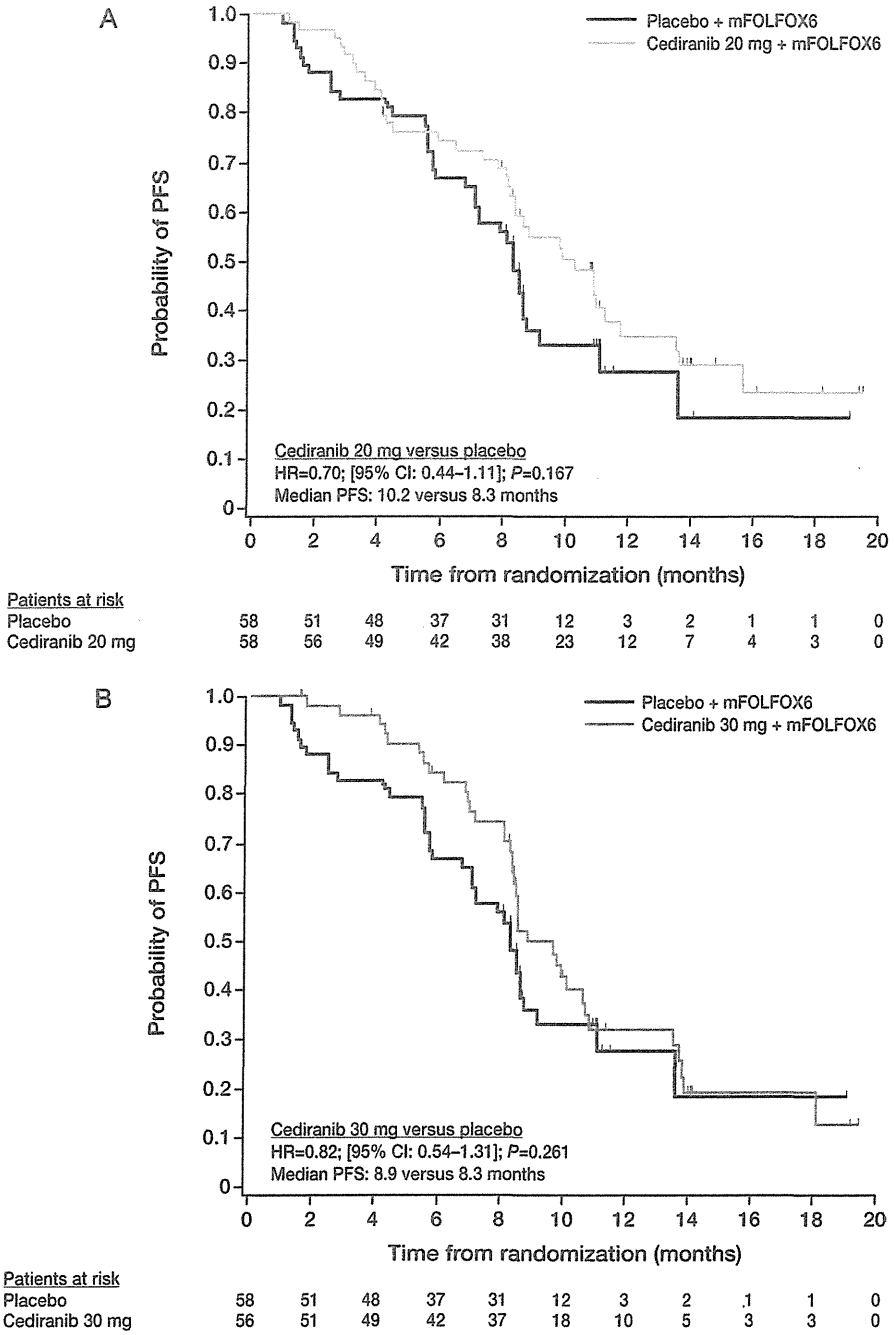


Figure 2. (A) Progression-free survival (PFS) for patients who received cediranib 20 mg + modified FOLFOX6 (mFOLFOX6) versus placebo + mFOLFOX6. (B) PFS for patients who received cediranib 30 mg + mFOLFOX6 versus placebo + mFOLFOX6.

Table 2. Best RECIST response

Best response, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
CR	0	0	2 (3.4)
PR	31 (53.4)	39 (69.6)	29 (50.0)
Stable disease ≥6 weeks	24 (41.4)	14 (25.0)	20 (34.5)
Progressive disease	3 (5.2)	1 (1.8)	7 (12.1)
Non-evaluable	0	2 (3.6)	0

mFOLFOX6, modified FOLFOX6; CR, complete response; PR, partial response.

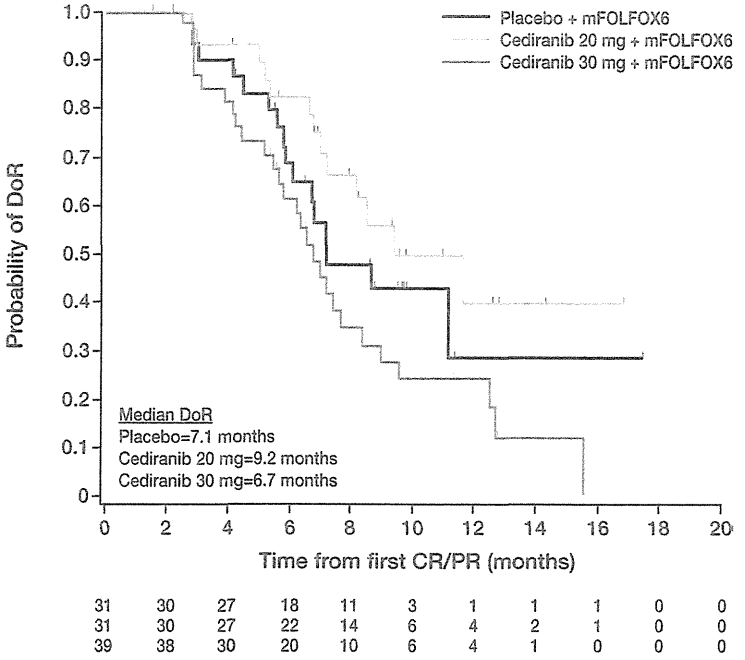


Figure 3. Duration of response for patients who received cediranib 20 mg, cediranib 30 mg or placebo, each in combination with modified FOLFOX6.

Table 3. AEs (frequency ≥30% in any group)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
Diarrhoea	53 (91.4)	49 (87.5)	22 (37.9)
Hypertension	47 (81.0)	48 (85.7)	18 (31.0)
Decreased appetite	43 (74.1)	43 (76.8)	39 (67.2)
Fatigue	39 (67.2)	40 (71.4)	36 (62.1)
Peripheral neuropathy	42 (72.4)	35 (62.5)	38 (65.5)
Nausea	39 (67.2)	37 (66.1)	37 (63.8)
PPES	31 (53.4)	34 (60.7)	8 (13.8)
Stomatitis	33 (56.9)	30 (53.6)	25 (43.1)
Vomiting	24 (41.4)	27 (48.2)	14 (24.1)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)
Dysgeusia	18 (31.0)	17 (30.4)	18 (31.0)
Constipation	21 (36.2)	14 (25.0)	16 (27.6)
Alopecia	12 (20.7)	17 (30.4)	15 (25.9)
Epistaxis	15 (25.9)	19 (33.9)	9 (15.5)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)

AE, adverse event; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

and to ~130 pg/ml thereafter. In the cediranib 30 mg group, levels increased to 160–170 pg/ml from days 28 to 84 before decreasing to 151 pg/ml by day 112.

Median sVEGFR-2 levels ranged from 9095 to 10 126 pg/ml at baseline. In the placebo group, median levels decreased to 7204 pg/ml on day 112. In the cediranib 20 mg group, median levels decreased to 7091 pg/ml on day 28 and 6403 pg/ml on day 112. The corresponding median levels in the cediranib 30 mg group were 5836 and 5789 pg/ml.

extended follow-up

At second data cut-off, PFS events had been observed in 47 (81%), 46 (82%) and 46 (79%) patients in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The PFS HR for the cediranib 20 mg group versus placebo was 0.76 (95% CI 0.51–1.15), two-sided $P = 0.0879$. Median PFS was 10.9 and 8.3 months, respectively. In the cediranib 20 mg group, 40.5% of patients were event free at 12 months compared with 28.9% in the placebo group. The PFS comparison for cediranib 30 mg versus placebo was 0.96 (95% CI 0.64–1.46), two-sided $P = 0.429$. Median PFS was 9.8 and 8.3 months, respectively, and 36.1% of patients were event free at 12 months in the cediranib 30 mg group versus 28.9% in the placebo group.

At final data cut-off, 24 (41.4%), 27 (48.2%) and 23 (39.7%) patients had died in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. For the comparison of cediranib

Table 4. CTC grade 3/4 AEs (>5% frequency in any arm)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
Decreased appetite	11 (19.0)	10 (17.9)	1 (1.7)
PPES	8 (13.8)	12 (21.4)	0
Diarrhoea	6 (10.3)	12 (21.4)	1 (1.7)
Hypertension	4 (6.9)	6 (10.7)	1 (1.7)
Peripheral neuropathy	5 (8.6)	3 (5.4)	2 (3.4)
Peripheral sensory neuropathy	2 (3.4)	5 (8.9)	2 (3.4)
Neutropenia	3 (5.2)	0	0
Ileus	0	0	3 (5.2)

AE, adverse event; CTC, Common Terminology Criteria; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

20 mg versus placebo, the HR was 1.09 (95% CI 0.61–1.95), two-sided $P = 0.543$; median OS was not reached in the cediranib 20 mg group. For the comparison of cediranib 30 mg versus placebo, the HR was 1.28 (95% CI 0.73–2.24), two-sided $P = 0.706$. Median OS was 22.4 and 23.3 months in the cediranib 30 mg and placebo groups, respectively.

discussion

Patients enrolled in this study were representative of the target population of Japanese patients with previously untreated mCRC and consistent with previous studies [26, 27]. Although baseline characteristics were generally well balanced across the three groups, imbalances were noted. The imbalances in ALP and albumin levels probably occurred because the data were analysed at a central laboratory, whereas stratification according to baseline liver function was carried out in individual centres.

The median PFS of patients who received mFOLFOX6 alone in this study (8.3 months) was consistent with the SWIFT-2 (8.2 months) [27] and TREE-1 (8.7 months) [28] studies, in which patients received mFOLFOX6 as first-line treatment of mCRC. Furthermore, the median PFS of patients in this study who received cediranib 20 mg plus mFOLFOX6 (10.2 months) compares well with the time to progression (9.9 months) for patients who received bevacizumab plus mFOLFOX6 in the TREE-2 study [28]. It is worth noting that TREE-2 was conducted in non-Japanese patients and there is a lack of phase III data for bevacizumab plus FOLFOX in the first-line setting in Japanese mCRC patients. A recent phase I/II study of first-line therapy comprising capecitabine plus oxaliplatin (XELOX) and bevacizumab in 64 Japanese patients with mCRC revealed a median PFS of 11 months, although the primary end points of this study were safety and ORR [29].

Here, the higher response rate observed in patients treated with cediranib 30 mg compared with the other arms did not translate into prolonged PFS, possibly due to differences in tolerability profiles of the cediranib arms. More patients in the cediranib 30 mg group experienced AEs (in particular, grade 3/4 diarrhoea) that led to discontinuation, dose reduction or dose interruption, than in the cediranib 20 mg or placebo groups. This appeared to impact on chemotherapy delivery—patients in the 30 mg arm received a lower dose intensity of oxaliplatin, which may reflect the differences in PFS outcomes. Due to these differences in tolerability, results from this study suggest that cediranib 20 mg is more suitable than 30 mg for long-term dosing in combination with mFOLFOX6 in Japanese patients with previously untreated mCRC. Cediranib 20 mg plus mFOLFOX6 was generally well tolerated, although the incidence of SAEs was higher compared with the placebo group. The most frequently reported AEs for the combination of cediranib 20 mg and mFOLFOX6 were diarrhoea and hypertension. The >50% incidence of palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome) in patients who received cediranib is consistent with a previous phase I study of cediranib monotherapy in Japanese patients and with studies of other targeted agents in Japanese patients with advanced cancer [30, 31]. Overall, no new safety issues were identified; no fatal AEs occurred and the AE profile was consistent with previous cediranib studies [10, 15]. With the exception of hypertension, diarrhoea, proteinuria, hypothyroidism, reversible posterior leukoencephalopathy syndrome, fatigue, hepatotoxicity, haematological toxicity and thrombocytopenia (for which specific management protocols were employed), cediranib-associated AEs were managed by dose interruption of up to 14 days or, if longer, treatment discontinuation. The incidences of grade ≥3 AEs and SAEs observed in this trial following addition of a TKI to FOLFOX therapy are consistent with those reported in trials involving vatalanib and bevacizumab in combination with a FOLFOX regimen [23, 32]. Cediranib treatment has shown a less favourable AE profile compared with bevacizumab in Western patients in the HORIZON III study [23]. In a phase I/II study in Japanese mCRC patients treated with XELOX plus bevacizumab, the most common grade 3/4 AEs were neurosensory toxicity (17%) and neutropenia (16%), both of which were managed by dose reduction of XELOX components; the incidence of grade 3/4 diarrhoea was only 3% [29]. It is not clear why the toxicity profiles of cediranib and bevacizumab differ, but it is probably related to differences in mechanism of action; cediranib is a potent inhibitor of the three VEGF receptor tyrosine kinases, whereas the activity of bevacizumab is dependent on preventing VEGF from binding to VEGF receptors, rather than blocking the receptors directly. In addition, the potential contribution of cediranib activity

versus non-VEGFR kinases, e.g. c-Kit inhibition [33], cannot be excluded. Furthermore, cediranib undergoes extensive metabolism, so it is possible that one or more metabolites may add to the toxicity profile.

An assessment of the levels of the soluble biomarkers VEGF and sVEGFR-2 was conducted as an exploratory objective. Owing to the limited data, caution should be taken when drawing conclusions from these findings; however, the observed increase in VEGF levels and decrease in sVEGFR-2 levels in cediranib-treated patients are consistent with previous cediranib trials [10, 21]. The increased VEGF levels may represent an acute stress response to inhibition of VEGF signalling by cediranib, whereas changes in sVEGFR-2 levels could be a surrogate marker for biological activity.

Analysis with an additional 8 months of follow-up data revealed similar findings to the pre-specified protocol analysis in both efficacy and safety outcomes. This additional analysis confirmed that PFS in this study (HR = 0.76) is consistent with the HORIZON II study (HR = 0.84), in which significantly improved PFS was observed with the addition of cediranib 20 mg to standard chemotherapy (FOLFOX/XELOX) [22].

This study met its primary end point for improved PFS with cediranib 20 mg plus mFOLFOX6 compared with placebo plus mFOLFOX6. The outcomes from this study, and from HORIZON II [22] and HORIZON III [23], provide some understanding of the potential role of VEGFR TKIs in the management of previously untreated mCRC. In unselected patient populations, cediranib provided marginal clinical benefit when added to standard oxaliplatin-based chemotherapy. These data did not support further development of cediranib in CRC; however, further investigation may reveal a particular benefit in a more selective patient population.

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disclosure

KY has received speaker fees (Merk Serono and Chugai Pharmaceutical). XS and KF are employees of AstraZeneca and own stock. All other authors have no conflicts of interest to declare.

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Multi-center Phase II Study of FLOX for Advanced Colorectal Cancer Patients in Japan: SWIFT 3 Study

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Abstract. *Aim: This is a multicenter phase II study to assess the efficacy and toxicity of the 5-FU, leucovorin, and oxaliplatin (FLOX) (SWIFT 3) regimen in Japanese patients with advanced colorectal cancer (CRC). Patients and Methods: Fifty-two patients were enrolled and evaluated from 12 institutions. The median age was 66 years, with 40.4% of patients with colon cancer and 59.6% with rectal cancer. Results: Forty-one patients underwent chemotherapy for first-line therapy and 11 patients for second-line. The response rate for first-line was 46.3% and that for second-line was 9.1%. The response rates categorized by metastatic sites were 59.4% for liver, 33.3% for lung, and 22.2% for lymph nodes. Grade 3/4 neutropenia occurred in 21.2% and Grade 3/4 non-hematologic toxicity in 46.1%. There were no deaths within 60 days following the administration. Conclusion: Standard FLOX regimen can be administered for Japanese patients. It is suggested that FLOX is an appropriate option for adjuvant therapy in CRC.*

In the past decade, significant progress has been made in the treatment of colorectal cancer (CRC), and it is one of the few malignant cancer types in which the 5-year survival rate for patients has improved. For many years, the treatment of metastatic CRC was restricted to 5-fluorouracil (5-FU) and the biomodulation of this agent (1, 2).

Oxaliplatin and irinotecan combined with continuous infusion of 5-FU significantly improved response rates, progression-free survival (PFS), and overall survival for CRC treatment (3, 4).

Oxaliplatin and irinotecan given with 5-FU and leucovorin (LV) are now standard chemotherapeutic agents for the treatment of advanced CRC (4-6). The National Surgical Adjuvant Breast and Bowel Project (NSABP) launched Protocol C-07 in 2000. This trial was designed to compare oxaliplatin and bolus 5-FU/LV to bolus 5-FU/LV alone (FLOX versus FULV, Roswell Park regimen (7) for resected stage II and III CRC). The results from this study confirmed the superiority of an oxaliplatin-based regimen in the adjuvant treatment of CRC. However, little is known about the feasibility of FLOX (SWIFT 3) regimens for advanced CRC in the Japanese population. Phase II studies of FOLFOX4 (SWIFT 1) and studies with modified FOLFOX6 regimens (SWIFT 2) for advanced CRC were conducted. The overall response rate was 50.9% (55.6% in SWIFT 1 and 46.6% in SWIFT 2) and toxicity was tolerable (8). To evaluate the value of FLOX (SWIFT 3) regimens in the treatment of advanced CRC, a retrospective analysis study was designed to assess the feasibility and efficacy of combining oxaliplatin with the LV5FU2 schedule (3) in a Japanese population. We therefore conducted a feasibility study of FLOX (SWIFT 3) in Japan.

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Key Words: Chemotherapy, FLOX regimen, metastatic colorectal cancer, phase II study, 5-FU, leucovorin, oxaliplatin.

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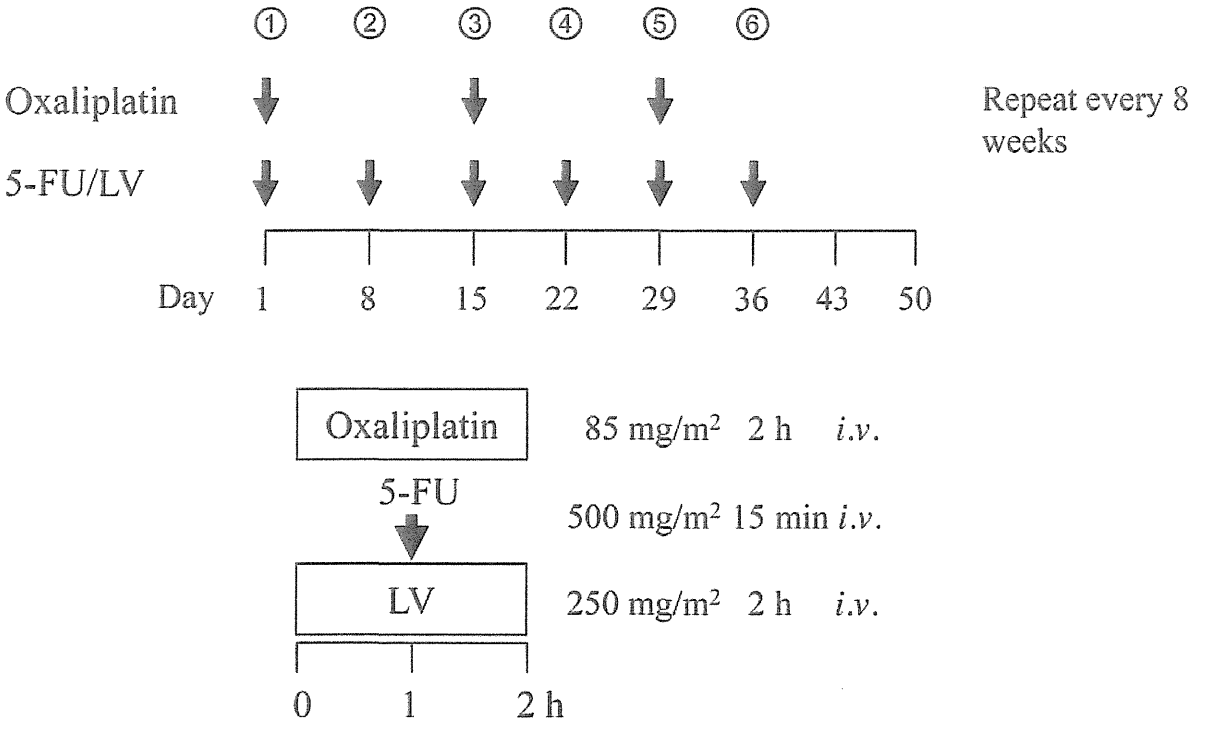

Figure 1. *Chemotherapy regimen of FLOX (SWIFT 3).*

Patients and Methods

Eligibility. Patients in this study had histologically proven metastatic CRC with measurable lesions; additionally, patient inclusion criteria were as follows: i) age of 20 to 80 years; ii) maximum of one prior chemotherapy regimen for metastatic disease and/or one adjuvant chemotherapy regimen completed 4 weeks before the current study; iii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; iv) life expectancy of more than 2 months; v) adequate bone marrow function (leukocyte count >3,000/mm^3, platelet count >100,000/mm^3, and hemoglobin >8.0 g/dl); adequate renal function (creatinine clearance >50 ml/min), adequate hepatic function (total bilirubin <1.5 mg/dl and Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) < triple the normal upper limit); vi) no other severe medical condition; vii) no active cancer in other organs. All patients gave written informed consent, conforming to institutional guidelines, indicating that they were aware of the investigational nature of the study. This study was approved by the Ethics Committees of the participating institutions.

Treatment. To prevent adverse effects of the chemotherapy, pre-medication was administered, consisting of dexamethasone (16 mg, *i.v.*) for hypersensitivity and cimetidine (50 mg, *i.v.*) for peptic ulcer given 30 min before each administration. One shot of LV was given as a 2-hour drip infusion with a dose of 250 mg/m^2 weekly, with 5-FU administered as an *i.v.* bolus 1-hour after the LV infusion was begun at a dose of 500 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of the treatment cycle, followed by a 2-week rest period. Oxaliplatin

Table I. *Patient characteristics.*

Parameter	No. of patients	%
	52	
Gender		
Male	28	53.8
Female	24	46.2
Age, years		
Median	66	
Range	47-78	
Performance status (ECOG)		
0	42	80.8
1	10	19.2
Primary cancer site		
Colon	21	40.4
Rectum	31	59.6
Site of metastases		
Liver	32	61.5
Lung	15	28.8
Lymph node	9	17.3
Prior treatment (colorectomy)		
Yes	41	78.8
Previous adjuvant chemotherapy		
Yes	11	21.2
Median number of courses		
Range	1-8	
Average	2.64	

Table II. *Toxicity due to FLOX therapy.*

Toxicity*	No. of patients (n=52) (%)					
	G0	G1	G2	G3	G4	G3 and 4
Leucocytopenia	21	12	17 (32.7%)	2 (3.8%)	0	2 (3.8%)
Neutropenia	29	2	10 (19.2%)	9 (17.3%)	2 (3.8%)	11 (21.2%)
Anemia	7	31	14 (26.9%)	0	0	0
Thrombocytopenia	18	21	10 (19.2%)	3 (5.8%)	0	3 (5.8%)
AST elevation	22	25	2 (3.8%)	3 (5.8%)	0	3 (5.8%)
ALT elevation	28	21	3 (5.8%)	0	0	0
Anorexia	18	22	6 (11.5%)	6 (11.5%)	0	6 (11.5%)
Nausea	25	18	7 (13.5%)	2 (3.8%)	0	2 (3.8%)
Vomiting	41	7	2 (3.8%)	2 (3.8%)	0	2 (3.8%)
Diarrhea	29	7	5 (9.6%)	11(21.2%)	0	11(21.2%)
Stomatitis	44	8	0	0	0	0
Hand-foot syndrome	41	11	0	0	0	0

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; *according to NCI-CTCAE v3.0.

was administered in the experimental regimen as a 2-hour infusion with a dose of 85 mg/m^2 prior to LV and 5-FU on days 1, 15, and 29 of the treatment cycle (Figure 1). Administration of granulocyte-colony stimulating factor (G-CSF) was permitted when leukopenia or neutropenia of grade 4 occurred. This administration was continued until the leukocyte or neutrophil counts recovered to 10,000/μl or more or 5,000/μl or more, respectively.

Patient evaluation and follow-up. Pretreatment evaluation included a baseline medical history and physical examination, in addition to laboratory studies, chest X-ray, and electrocardiogram. Computed tomography (CT) and magnetic resonance imaging were performed to clarify and document the location, size, and extent of disease, when measurable. A complete blood cell count, urinalysis, electrolytes, and renal and liver function tests were evaluated at least once weekly and before subsequent cycles, and at the end of patient participation in the study.

Response to treatment and adverse events. Treatment response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) (9). A complete response (CR) was defined as the disappearance of all clinical evidence of tumor for a period of at least 4 weeks. A partial response (PR) was defined as a 30% decrease in bi-dimensional tumor measurements for at least 4 weeks, without the appearance of any new lesions or progression of any existing lesions. Progressive disease (PD) was defined as the development of any lesion or a 20% increase in the sum of the products of all measurable lesions. Stable disease (SD) was defined as a tumor response that did not meet the criteria for CR, PR or PD. Toxicities were evaluated based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3, and peripheral sensory neuropathy was graded by following the Neurotoxicity Criteria of Debiopharm (DEB-NTC). During treatment, patients had weekly hematological blood cell counts, evaluation of hepatic and renal function, and assessment of non-hematological toxicities. Dose modification and treatment delay were performed as necessary according to the degree of hematological and organ toxicity.

Table III. *Neurologic toxicity due to FLOX therapy.*

Neurologic toxicity	No. of patients (n=52) (%)				
	G0	G1	G2	G3	≥G3
NCI-CTCAE	17 (32.7)	26 (50.0)	9 (17.3)	0 (0)	0 (0)
DEB-NTC	18 (34.6)	20 (38.5)	13 (25.0)	1 (1.9)	1 (1.9)

NCI-CTCAE: v3.0; DEB-NTC: oxaliplatin-specific scale. There were no G4 neurologic toxicities.

Statistical analysis. The primary endpoint of this study was the response rate to the FLOX regimen for advanced or metastatic CRC. Overall survival (OS) and progression-free survival (PFS) were secondary endpoints. OS was calculated from the start of the study registration until death. PFS was calculated from the start of registration until the date of progression. OS and PFS curves were obtained using the Kaplan-Meier method.

Results

Patient characteristics. A phase II study on FLOX (SWIFT 3) was initiated in patients with unresectable, advanced, and recurrent colorectal cancer in October 2006 as a multicenter cooperative clinical trial (by the SWIFT study group). Enrollment was completed in April 2008 with 52 patients with evaluable lesions from 12 medical institutions. The characteristics of all 52 patients are summarized in Table I. Twenty-eight patients were males and 24 females. The median age was 66 (range 47-78) years. Forty-two patients had ECOG PS 0, and 10 patients had PS 1. Eleven patients (21.2%) had received adjuvant chemotherapy. Major metastatic sites were liver (32 patients), lung (15 patients) and lymph nodes (9 patients).

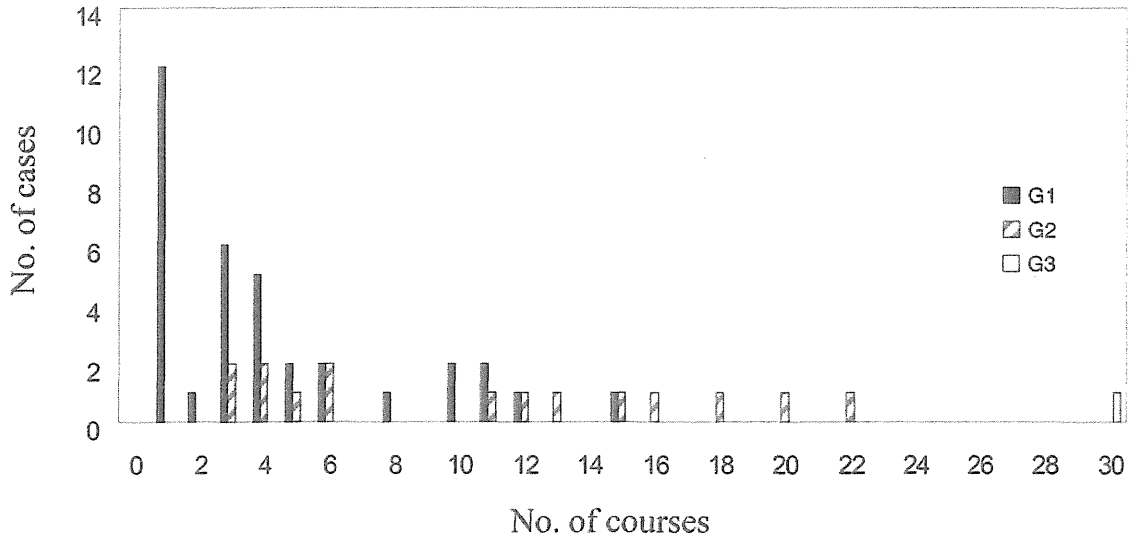

Figure 2. *Incidence of neuropathy during FLOX therapy.*

Toxicity. All 52 patients were fully evaluated for adverse reactions. Toxicities associated with treatment are listed in Table II and the incidence of neurotoxicity is listed in Table III. In this regimen, Grade 3 or more severe hematological toxicity included leukopenia, neutropenia and thrombocytopenia in 3.8%, 21.2% and 5.8% of patients, respectively. Grade 3 or greater non-hematologic toxicity included diarrhea and appetite loss in 21.2% and 11.5% of patients, respectively. Grade 2 or greater neurotoxicity, a characteristic adverse reaction of oxaliplatin, was 17.3% (9/52) by NCI-CTCAE and 26.9% (14/52) by DEB-NTC. Both hematological and non-hematological toxicities were tolerated. The incidence of neurotoxicity along with the number of treatment cycles is listed in Figure 2. Grade 1 neurotoxicity developed from the first treatment cycle. Grade 1 neurotoxicity was observed in 12 patients (23.1%) from the first cycle in SWIFT 3. In the third or later cycles, grade 2 neurotoxicity was frequently observed. The median relative dose intensities (RDI) in this trial were 91% for oxaliplatin, 87% for LV, and 86% for bolus 5-FU in SWIFT 3 (Table IV). Six patients (11.5%) were withdrawn from the study because of adverse events in SWIFT 3.

Efficacy. Overall, of 52 evaluable patients, the median number of treatment cycles was 2.64 (range 1-8 cycles). Objective responses are listed in Table V. Twenty patients had PR (38.5%) and 18 patients had SD (36.5%); 10 patients had PD (19.2%) as the best response and 4 patients could not be evaluated (7.7%). The objective response rate was 38.5% (95% confidence interval, CI=19.9% to 45.4%) to FLOX (SWIFT 3). The response by metastatic sites with a response rate (CR+PR) were 59.4% (19/32) in liver, 33.3% (5/15) in lung and 22.2% (2/9) in lymph nodes. The median PFS was 6.8 months (Figure 3) and the median OS was 25.5 months (Figure 4).

Table IV. *Relative dose intensity (RDI) (SWIFT 3).*

RDI (%)	Oxaliplatin	Leucovorin	5-Fluorouracil
Median	91	87	86
Min	53	47	43
Max	133	114	114

Discussion

The base of standard therapies to treat advanced CRC is oxaliplatin plus 5-FU/LV therapy (FOLFOX regimen) or irinotecan plus 5-FU/LV therapy (FOLFIRI regimen) (3, 5, 10). Phase III randomized controlled clinical trials have shown that combination therapies including irinotecan or oxaliplatin had a much better response rate and PFS period than 5-FU/LV (5, 11-13). Thus, these combinations replaced 5-FU/LV as the standard systemic treatments for metastatic advanced CRC. Additional molecular-targeting therapies and mean survival time (MST) after these therapies currently exceeds 20 months (14, 15). Additionally in Japan, infusion 5-FU/LV therapy was approved in February 2005, and the FOLFOX therapy became available. Phase II trials had been conducted in Japanese patients with advanced CRC to examine the combination therapies using FOLFOX4 or

Table V. *Response.*

	No. of patients (%)					
	CR	PR	SD	PD	NE	Response rate
All	0 (0)	20 (38.5)	18 (36.5)	10 (19.2)	4 (7.7)	20/52 (38.5)
First-line	0 (0)	19 (46.3)	13 (31.7)	7 (17.1)	2 (4.9)	19/41 (46.3)
Second-line	0 (0)	1 (9.1)	5 (45.5)	3 (27.3)	2 (18.2)	1/11 (9.1)

Table VI. *Comparison with other studies.*

	FLOX in first-line	FOLFOX4 in first-line				mFOLFOX6 in first-line		
	SWIFT3 Present study	SWIFT1 Nagata (8)	C95-1 de Gramont (3)	N9741 Goldberg (5)	OPTIMOX1 Tournigand (19)	SWIFT2 Nagata (8)	OxMdG Cheeseman (20)	FOCUS Seymour (21)
No. of patients	52	54	210	267	311	58	25	299
Age, years								
Median	65.87	62	63	61	65	63	62	64
Range	47-78	25-74	20-76	27-88	29-80	25-75	14-77	56-69
PS, %								
0	42	77.8	43.3	93	52	77.6	40	41
1	10	20.4	46.2	93	48	22.4	44	50
2	0			5	48		16	8
Metastatic site, %								
Liver	32	81.5	86.7	Unknown	71	70.7	Unknown	Unknown
Lung	15	22.2	23.4	Unknown	26	19.0	Unknown	Unknown
Others	15	27.8	12.4	Unknown	10	29.3	Unknown	Unknown
Adjuvant chemotherapy, %		24.1	20	16	22	20.7	24	Unknown
RR, %	38.5	55.6	50.7	45	58.5	46.6	72	56.2
PFS, months	6.8	9.4	9	8.7	9	8.5	10.6	9.1
OS, months	25.5	20.2	16.2	19.5	19.3	21.6	16.7	15.2

mFOLFOX6 (SWIFT 1&2) (8, 16). Adjuvant chemotherapy of oxaliplatin and bolus 5-FU/LV therapy (FLOX) has been performed. This regimen poses few difficulties when compared with continuous infusion chemotherapy (17). FLOX therapy does not require a central venous catheter and can be administered through a peripheral vein. It can be concluded that FLOX is an appropriate adjuvant therapy regimen for colon cancer (18). However, little is known about the feasibility of oxaliplatin and bolus 5-FU/LV regimen (FLOX) with advanced CRC in Japanese patients. Thus, this multicenter phase II clinical trial of FLOX was conducted to examine the feasibility in actual clinical practice.

This trial enrolled a total of 52 patients with evaluable lesions who were treated with FLOX (SWIFT 3). The overall response rate was 38.5% and the overall MST was 25.5 months, and the overall PFS was 6.8 months in SWIFT 3. These results are comparable to those reported in other regimens (3, 5, 19-21) and the study by Shimizu *et al.* (18). There was no significant difference in SWIFT 1 and 2 (8) (Table VI). It appears that FOLFOX and FLOX are similar in terms of efficacy. In this trial, many patients had liver metastases, and the response rate in the patients with liver metastasis was 59.4%, which was the highest value among patient groups by site of metastasis. This strongly suggests that FLOX therapy is effective and useful as an initial therapy in patients with liver metastases.

As for adverse reactions, the incidence of grade 3 or greater adverse events were 3.8% for leukopenia, 21.2% for neutropenia, and 0% for anemia. In this study, the FLOX regimen appeared to have reduced toxicity compared with previous reports of other regimens (3, 5, 19-21). The mean number of cycles administered to the patients was 2.6 (range 1-8) in the FLOX regimen. The incidence of grade 2

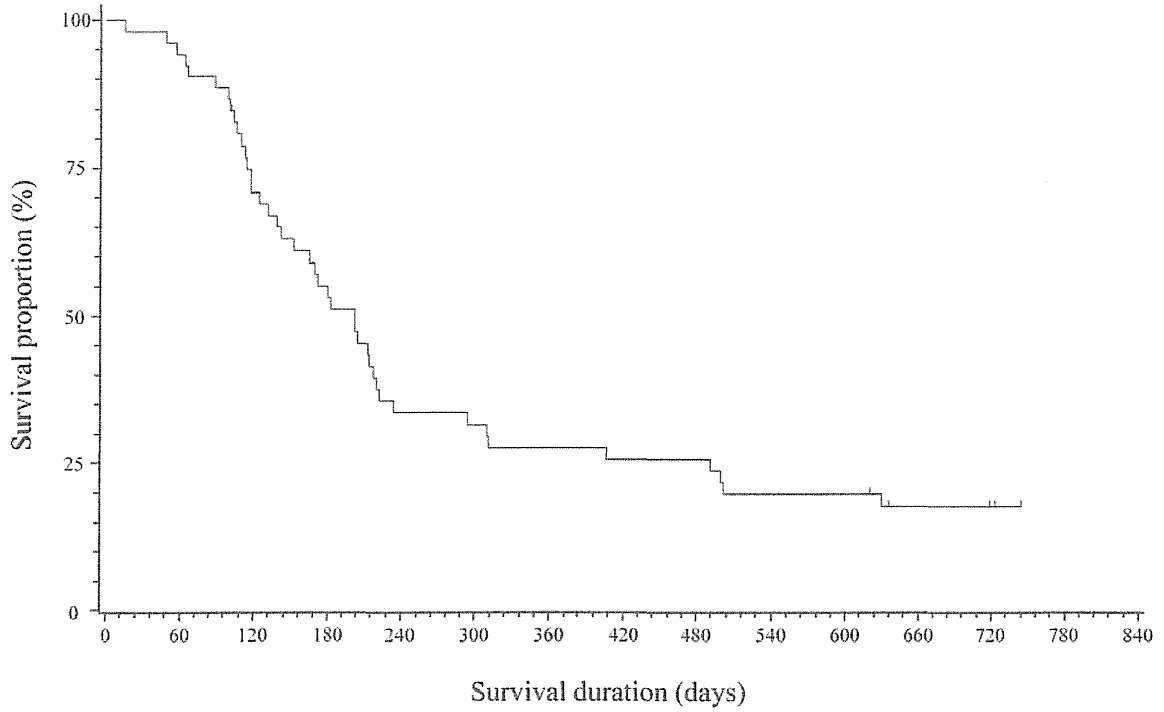

Figure 3. *Progression-free survival rate of all enrolled patients. The median progression-free survival time was 6.8 months in SWIFT 3.*

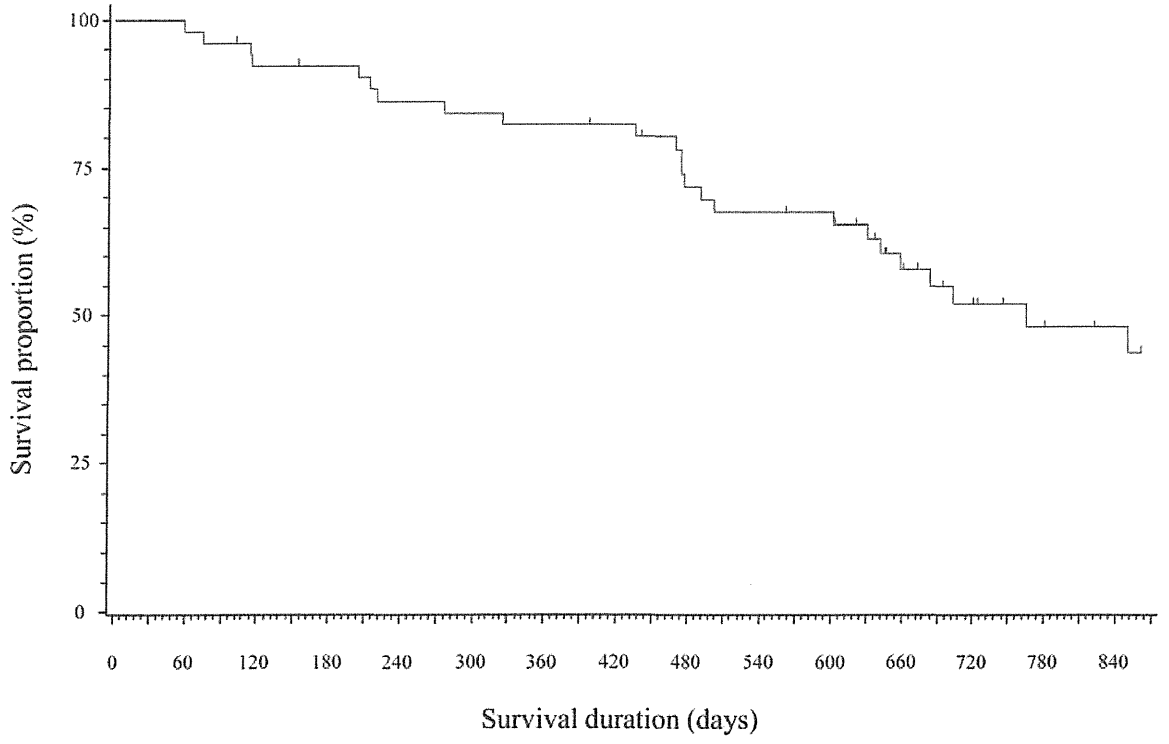

Figure 4. *Overall survival rate of all enrolled patients. The median survival time was 25.5 months in SWIFT 3.*

and grade 3 peripheral neuropathy, a characteristic adverse reaction to oxaliplatin, was 17.3%/0% by NCI-CTCAE and 25%/1.9% by DEB-NTC. In Western countries, the incidence of grade 2 and 3 peripheral neuropathy was reported as 29.2%/18.2% after the FOLFOX 4 therapy as the initial therapy (10, 19-21). Although a direct comparison is not appropriate, a higher incidence of grade 3/4 peripheral neuropathy occurred in FOLFOX-treated patients (18.2%) than FLOX-treated patients (1.9%). The significantly lower incidence of peripheral neuropathy seen in SWIFT 3 was likely a result of the lower cumulative dose of oxaliplatin given. Grade 1 peripheral neuropathy developed from the first cycle, and there was no difference in its frequency between FLOX and FOLFOX. In the third or later cycles, however, grade 2 and 3 peripheral neuropathy frequently developed. The grade of the disorder was higher in later courses as reported by de Gramont *et al*. (3). However, the toxicity profiles are different. These differences reflect both the different methods of administration of 5-FU and LV, as well as the addition of oxaliplatin. The rate of grade 3 or 4 diarrhea was 1.7% with SWIFT 1 and 2 versus 22.1% with SWIFT 3. Even though treatment-related mortality was not increased, clinicians using the FLOX regimen should be aware of the potential for severe diarrhea, select patients accordingly, carefully monitor patients (particularly during the first cycle of therapy), and provide vigorous supportive therapy if diarrhea occurs.

The relative dose intensities (RDI) in this trial were 91% for oxaliplatin, 86% for bolus 5-FU, and 87% for LV in FLOX. Factors for RDI decrease included hematotoxicity (leukopenia, neutropenia, and thrombocytopenia) and peripheral nerve disorder in this study. Response rates, PFS, MST and safety of FLOX combination therapies were equivalent in our multicenter phase II clinical trial, and were rather better than those reported from foreign trials and the SWIFT 1 and 2 studies. Although a direct comparison is not appropriate, these results are considered as almost comparable to those from FOLFOX (SWIFT 1 and 2).

The clinical trial demonstrated that FLOX therapy is as effective and safe in Japanese patients with unresectable advanced CRC as those in SWIFT 1 and 2 studies, and may provide significant clinical benefit when used in Japanese practice. However, since peripheral neuropathy increases with an increased number of doses, future treatment strategies need preventive measures in order to maintain the quality of life of patients.

Acknowledgements

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