

## Phase I/II Study of Capecitabine Plus Oxaliplatin (XELOX) Plus Bevacizumab As First-line Therapy in Japanese Patients with Metastatic Colorectal Cancer

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Received January 8, 2010; accepted April 6, 2010

**Objective:** The addition of bevacizumab to fluoropyrimidine-based combination chemotherapy as first-line therapy for metastatic colorectal cancer results in clinically significant improvements in patient outcome. However, clinical trials have been conducted primarily in Caucasian patients with only a small proportion of Asian patients. This Phase I/II study was designed to evaluate the efficacy and safety of XELOX (capecitabine plus oxaliplatin) plus bevacizumab in Japanese patients with metastatic colorectal cancer.

**Methods:** Patients with previously untreated, measurable metastatic colorectal cancer received bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m<sup>2</sup> on day 1, plus capecitabine 1000 mg/m<sup>2</sup> twice daily on days 1–14, every 3 weeks. A three-step design evaluated in: step 1, initial safety of XELOX in six patients; step 2, initial safety of XELOX plus bevacizumab in six patients; and step 3, efficacy and safety in a further 48 patients. The primary study endpoints were safety and response rate.

**Results:** No dose-limiting toxicity occurred during Steps 1 and 2. Fifty-eight patients were enrolled in Steps 2 and 3 and received XELOX plus bevacizumab. In the 57 patients assessed for response, the overall response rate was 72% (95% confidence interval, 58.5–83.0). Median progression-free survival was 11.0 months (95% confidence interval, 9.6–12.5) and median overall survival was 27.4 months (95% confidence interval, 22.0–not calculated). Eight patients (14%) underwent surgery with curative intent. The most common grade 3/4 adverse events were neurosensory toxicity (17%) and neutropenia (16%).

**Conclusions:** XELOX plus bevacizumab is effective and has a manageable tolerability profile when given to Japanese patients with metastatic colorectal cancer.

*Key words:* xelox – bevacizumab – colorectal cancer – Japanese

### INTRODUCTION

Colorectal cancer is the third leading cause of cancer deaths worldwide. The number of patients affected by this disease continues to increase steadily (1–3) and ~42 000 deaths occur annually in Japan (3).

FOLFOX4, a bi-weekly schedule of intravenous bolus and infusional 5-fluorouracil/folinic acid plus oxaliplatin (Elplat<sup>®</sup>) is a widely used regimen for the first-line treatment of metastatic colorectal cancer (MCR) (4,5). However, oral fluoropyrimidines can replace the intravenous

fluoropyrimidine component of combination regimens. Capecitabine (Xeloda<sup>®</sup>) is an oral fluoropyrimidine with similar efficacy to bolus 5-fluorouracil/folinic acid when given as first-line treatment for MCRC (6–8) or as adjuvant therapy for stage III colon cancer (9). It has also been successfully combined with oxaliplatin as the capecitabine plus oxaliplatin (XELOX) regimen, which consists of a 21-day intermittent schedule of capecitabine combined with a 3-weekly dose of oxaliplatin (10,11). A pivotal phase III study (NO16966) recently demonstrated that XELOX was non-inferior in terms of efficacy to FOLFOX4 as the first-line treatment for patients with MCRC (12). The same study further showed that adding bevacizumab (Avastin<sup>®</sup>) to oxaliplatin-based chemotherapy significantly improved progression-free survival (PFS) by 20% in the first-line treatment of MCRC (13). However, most of the clinical development of these regimens has been performed in Europe and the USA, although the NO16966 study included a small number of centers in Central and Eastern Asia (12,13). It has not been clarified if XELOX with the dose and schedule applied mainly to Caucasian patients shows a similar efficacy and toxicity profile in Japanese patients. To address this issue, we conducted a Phase I/II study to evaluate the safety and efficacy of XELOX plus bevacizumab in Japanese patients with MCRC.

## PATIENTS AND METHODS

### STUDY DESIGN

A prospective, multicenter, open-label study with a three-step design was conducted to evaluate the efficacy and safety of the commonly used dose of XELOX plus bevacizumab in Japanese patients with MCRC. The purpose of step 1 was to evaluate the initial safety of XELOX in six patients; step 2 was to evaluate the initial safety of XELOX plus bevacizumab in six patients; and step 3 was to evaluate the efficacy and safety of XELOX plus bevacizumab in 48 patients plus the six patients from step 2. The criterion for proceeding to the next phase was the occurrence of dose-limiting toxicity (DLT) in less than or equal to two of six patients. An independent review committee (IRC) was scheduled to evaluate safety immediately after the first cycle in steps 1 and 2. The previous phase I trial determined the recommended dose of the XELOX regimen (14) and DLT was defined as grade 4 neutropenia for 5 days or more, or febrile neutropenia, or grade  $\geq 3$  neutropenia associated with grade 3/4 complications (e.g. stomatitis, diarrhea); or grade  $\geq 3$  gastrointestinal toxicities, grade 3 hand-foot syndrome (HFS), grade  $\geq 3$  peripheral neuropathy, or any grade 4 hematological toxicity or any other clinically significant grade  $\geq 3$  non-hematological toxicity which did not recover within 2 days with appropriate therapy.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients participating

in this study. The protocol was approved by the independent ethics committee or institutional review board at each site.

### PATIENTS

At study enrollment, patients were required to fulfill all of the following criteria: age  $\geq 20$  and  $\leq 74$  years, Eastern Cooperative Oncology Group (EGOG) performance status of 0 or 1, life expectancy  $\geq 3$  months, histologically proven adenocarcinoma of the colon or rectum that was considered to be unrespectable with at least one measurable metastasis (RECIST guidelines) (15), no prior systemic chemotherapy for MCRC, no progression within 6 months of adjuvant therapy completion (if received), neutrophil count  $\geq 1500/\text{mm}^3$ , platelet count  $\geq 100\,000/\text{mm}^3$ , hemoglobin level  $\geq 9.0$  g/dl, total bilirubin  $\leq 1.5$  times the institutional upper limit of normal (ULN), aspartate aminotransferase (AST), alanine aminotransferase and alkaline phosphatase  $\leq 2.5$  times ULN, creatinine  $\leq 1.5$  times ULN and creatinine clearance  $\geq 50$  ml/min. Some of the exclusion criteria were as follows: brain tumors or brain metastases, clinically detectable ascites; major surgery, open biopsy or significant traumatic injury within 4 weeks before enrollment, fine needle aspiration biopsy or central venous line placement within 1 week before enrollment, bleeding diathesis or coagulopathy, international normalized ratio  $\geq 1.5$  within 1 week before enrollment, non-healing bone fracture, urinary protein  $\geq 1+$  within 1 week before enrollment, uncontrolled hypertension or peptic ulcer, clinically significant cardiovascular disease, chronic, daily treatment with high-dose aspirin ( $\geq 325$  mg/day) or non-steroidal anti-inflammatory medications, or peripheral neuropathy of at least grade 1. The inclusion and exclusion criteria were almost identical to those used in the NO16966 study (12,13).

### TREATMENT

Oxaliplatin was supplied by Yakult Honsha Co., Ltd (Tokyo, Japan) and capecitabine and bevacizumab were supplied by Chugai Pharmaceutical Co., Ltd (Tokyo, Japan). XELOX consisted of a 2-h intravenous infusion of oxaliplatin  $130\text{ mg}/\text{m}^2$  on day 1 plus oral capecitabine  $1000\text{ mg}/\text{m}^2$  twice daily for 2 weeks of a 3-week cycle. The first dose of capecitabine was given in the evening of day 1 and the last dose in the morning of day 15. Bevacizumab at a dose of  $7.5\text{ mg}/\text{kg}$  was administered as a 30- to 90-min intravenous infusion before oxaliplatin on day 1 of the 3-week cycle. Treatment was continued until disease progression, intolerable adverse events or withdrawal of consent.

Treatment was to be interrupted if grade 2–4 toxicities occurred. No dose modification of bevacizumab was performed. The dose of capecitabine was to be adjusted for grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia or non-hematological toxicities of grade 2 or higher, according to a standard scheme described in detail by Blum et al. (16). The dose of oxaliplatin was to be

reduced to 100 or 85 mg/m<sup>2</sup> if patients experienced grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia, or grade 3 non-hematological toxicity, and for grade 3 neurosensory toxicity lasting more than 7 days, or grade 2 neurosensory toxicity persisting between cycles. For grade 3 neurosensory toxicity persisting between cycles, oxaliplatin was to be discontinued. This treatment plan was almost identical to that of the NO16966 study (12,13).

If oxaliplatin and/or bevacizumab were discontinued, treatment with the remaining components could be continued, such as capecitabine with or without bevacizumab after discontinuation of oxaliplatin, and XELOX or capecitabine after discontinuation of bevacizumab. Continuation of oxaliplatin or bevacizumab without capecitabine was not permitted.

#### EFFICACY AND SAFETY EVALUATION

Tumor assessments with computed tomography scan were performed within 2 weeks before registration to this study and repeated every 6 weeks. Response rate was evaluated by the investigators according to RECIST version 1.0 (15). Tumor responses were confirmed by the IRC.

PFS was defined as the duration from the date of the first dose of the study drug to the date of first confirmation of disease progression as determined by the IRC, or death from any cause, and censored at the last tumor assessment if a patient withdrew before progression. Overall survival (OS) was defined as the duration from the first dose of study drug to death. Time to response was defined as the time interval from the first dose of study drug to the first detection of  $\geq 30\%$  decrease of tumor size assessed by the IRC for patients with a confirmed overall response of PR or CR. Response duration was defined as the time interval from the first detection of  $\geq 30\%$  decrease of tumor size to disease progression assessed by the IRC and censored at the last tumor assessment if a patient withdrew before progression.

Safety was assessed weekly for the first eight cycles of the treatment. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (17). All adverse events were evaluated until 28 days after the last dose of study drug.

#### STATISTICAL ANALYSIS

The primary study endpoints were safety and overall response rate (ORR) as assessed by the IRC. Secondary endpoints were PFS, OS, time to response and response duration.

Forty-eight patients were required to test the null hypothesis ( $P = p_0$  or lower) versus the alternative hypothesis ( $P = p_A$  or higher) with a one-sided  $\alpha$ -level of 2.5% and a power of 80% when the critical ORR ( $p_0$ ) was 35% and the expected ORR ( $p_A$ ) was 55%. The total number of patients recruited to receive XELOX plus bevacizumab was estimated to be 54 (6 for Step 2 and 48 for Step 3) to allow for patients who might be ineligible for efficacy evaluation.

ORRs were presented with 95% confidence interval (CI). The probabilities of time-to-event parameters were estimated using the Kaplan–Meier method with 95% CI.

## RESULTS

#### PATIENT CHARACTERISTICS

A total of 64 patients were enrolled between February 2006 and November 2006 from 11 centers in Japan. Six patients were enrolled in step 1 and received XELOX and 58 patients were enrolled in steps 2 and 3 and received XELOX plus bevacizumab. All patients ( $n = 64$ ) were included in the safety analysis. One patient was excluded from the efficacy analysis because he received bevacizumab as part of a different clinical trial. Therefore, six patients were included in the efficacy evaluation of XELOX and 57 patients were included in the efficacy evaluation of XELOX plus bevacizumab.

The baseline demographic characteristics of the enrolled study patient population are shown in Table 1. The median age of the patients treated with XELOX was 58.5 years (range, 40–68 years) and with XELOX plus bevacizumab was 57.0 years (range, 33–74 years). ECOG performance status with XELOX was 0 in all 6 patients, and with XELOX plus bevacizumab was 0 in 50 patients and 1 in 8 patients.

#### TREATMENT DURATION

In the six patients participating in step 1, the median duration of treatment was 6.5 months (range, 0.5–14 months) with a median of 8.5 treatment cycles (range, 1–17 cycles). XELOX combination therapy was administered for a median of 7.0 cycles (range, 1–17 cycles). One patient subsequently went on to receive a further 6 cycles of capecitabine monotherapy for a total of 13 cycles.

In steps 2 and 3, the median duration of treatment was 7.6 months (range, 0.1–34.8 months) with a median of 10.5 treatment cycles (range, 1–47 cycles). XELOX plus bevacizumab combination therapy was administered for a median of 9.0 cycles (range, 1–27 cycles). After discontinuation of oxaliplatin, 17 patients (29%) continued with capecitabine and bevacizumab combination therapy and received a median of 5.0 cycles (range, 1–34 cycles). Four patients (7%) received XELOX therapy for a median of 2.0 cycles (range, 1–5 cycles) during permanent or temporary discontinuation of bevacizumab.

The median relative dose intensity (ratio of dose received to dose planned) was 0.74 (range: 0.41–1.00) for capecitabine, 0.86 (range: 0.55–1.00) for oxaliplatin and 0.91 (range: 0.58–1.01) for bevacizumab.

#### EFFICACY

At the final data cut-off date (30 June 2009), the median duration of follow-up was 32.0 months. Thirty-three patients

**Table 1.** Baseline demographic characteristics

Characteristic	XELOX (n = 6)		XELOX plus bevacizumab (n = 58)	
	No. of patients	%	No. of patients	%
Sex				
Male	5	83	40	69
Female	1	17	18	31
Age				
Median	58.5		57.0	
Range	40–68		33–74	
ECOG performance status				
0	6	100	50	86
1	0	0	8	14
Primary tumor site				
Colon	4	67	31	53
Rectum	2	33	27	47
Metastatic site				
Liver	5	83	45	78
Lung	2	33	28	48
Lymph node	0	0	27	47
Other	3	50	5	9
No. of organs involved				
1	2	33	25	43
2	4	67	21	36
3	0	0	10	17
>3	0	0	2	3
Adjuvant therapy				
Yes	1	17	8	14
No	5	83	50	86

ECOG, Eastern Cooperative Oncology Group.

had died of disease progression and two patients were still receiving study medication. Tumor responses (ORR, time to response, response duration and PFS) are based on the median duration of follow-up of 15.2 months.

The analysis of efficacy is shown in Table 2. The ORR (complete plus partial response) with XELOX was 67% (4/6) (95% CI: 22.3–95.7%), and with XELOX plus bevacizumab was 72% (41/57) (95% CI: 58.5–83.0%). The median PFS with XELOX plus bevacizumab was 11.0 months (95% CI: 9.6–12.5 months) (Fig. 1) and the median OS was 27.4 months (95% CI: 22.0 months–not calculated) (Fig. 2).

Eight patients (14%) treated with XELOX plus bevacizumab underwent surgery with curative intent: none experienced a serious adverse event as a result of surgery and four patients (7%) had no residual disease. The sites of resection being curative by surgery were liver (n = 7), lymph node (n = 1), cholesty (n = 2) and colon primary tumor (n = 2).

**Table 2.** Analysis of efficacy

Endpoint	XELOX (n = 6)	XELOX plus bevacizumab (n = 57)
Median progression-free survival, months	8.3	11.0
95% confidence interval	5.8–13.8	9.6–12.5
Median overall survival, months	–	27.4
95% confidence interval	–	22.0–NC
Response rate, %	67	72
95% confidence interval	22.3–95.7	58.5–83.0
Complete response	0	2
Partial response	4	39
Stable disease	1	9
Progressive disease	0	1
Not evaluable	1	6
Median time to response, months	2.6	2.7
95% confidence interval	1.2–NC	1.5–2.8
Median response duration, months	6.4	9.7
95% confidence interval	2.8–11.3	6.7–9.9

NC, not calculated.

**SAFETY**

No DLT occurred during either step 1 or step 2. All six patients treated with XELOX and 31 (53%) patients treated with XELOX plus bevacizumab discontinued study treatment because of disease progression. Ten (17%) patients withdrew from XELOX plus bevacizumab because of adverse events, which comprised dehydration and anorexia; gastric varices haemorrhage; enteritis infectious; anorexia, herpes zoster and nausea; neutropenia; AST increased and alanine aminotransferase increased; infected epidermal cyst; peripheral sensory neuropathy; epididymitis; HFS (one patient, respectively). No patient died within 28 days after study medication.

All patients (n = 64) experienced at least one adverse event during the study, most of which were mild to moderate in severity (Table 3). The most common adverse events with XELOX plus bevacizumab were neurosensory toxicity (93%), anorexia (90%), fatigue (83%) and HFS (78%). The most common grade 3/4 adverse events were neurosensory toxicity (17%) and neutropenia (16%).

For patients receiving XELOX plus bevacizumab, dose reductions were required for capecitabine in 32 patients (55.2%); the major reasons were HFS (n = 7), neutropenia (n = 6) and diarrhea (n = 6). Capecitabine doses were reduced to 75% of starting dose in 18 patients and to 50% in 14 patients. Dose reductions were required for oxaliplatin in 30 patients (51.7%) due to neurosensory toxicity (n = 15), neutropenia (n = 7) and other toxicities, and in most of

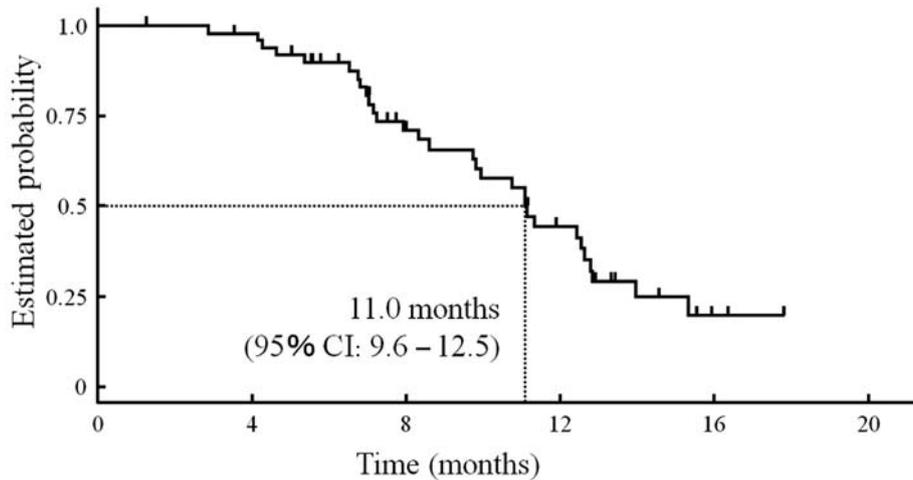


Figure 1. Progression-free survival (XELOX plus bevacizumab).

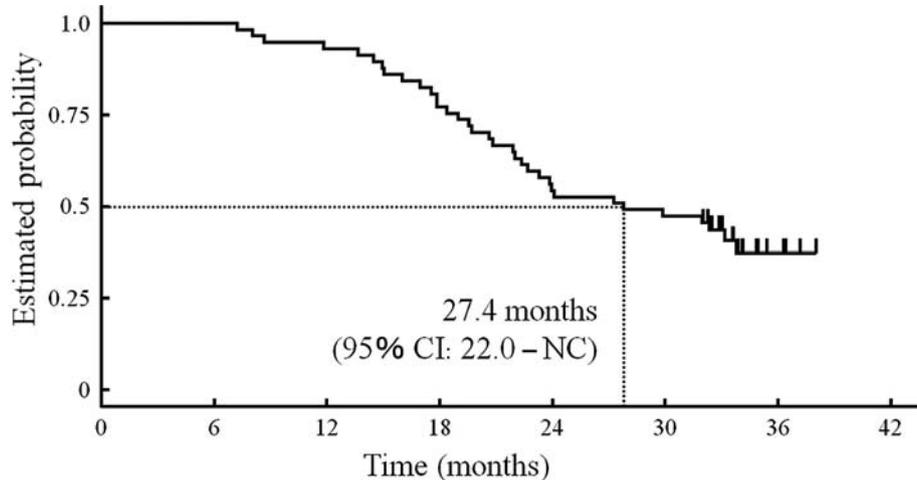


Figure 2. Overall survival (XELOX plus bevacizumab). NC, not calculated.

these patients ( $n = 27$ ) the oxaliplatin dose was reduced to  $100 \text{ mg/m}^2$ .

## DISCUSSION

In this prospective trial for Japanese patients with MCRC, XELOX plus bevacizumab achieved a high response rate of 72%, and eight patients (14%) proceeded to surgery with curative intent. The median PFS and the median OS for XELOX plus bevacizumab were 11.0 and 27.4 months, respectively.

Previous randomized or observational trials which included the XELOX plus bevacizumab regimen as first-line therapy have been conducted mainly in North America and Europe (13,18–22). The NO16966 study showed a longer PFS and OS in the XELOX plus bevacizumab arm compared with the XELOX plus placebo arm in a subgroup analysis, which reported a median PFS of 9.3 versus 7.4 months, HR = 0.77 (95% CI: 0.63–0.94,  $P = 0.0026$ ) and a median

OS of 21.6 versus 19.0 months (HR was not shown) (23,24). Furthermore, another phase III trial (CAIRO2) reported a response rate of 50.0%, a median PFS of 10.7 months and a median OS of 20.3 months in the XELOX plus bevacizumab arm (18). The patient baseline demographic characteristics of the enrolled study patient population were similar to those of previous clinical trials in Western patients, except that the proportion of rectal cancer whose prognosis is worse than that of colon cancer was higher in this study (47% versus 23–35%) (4,6–8,11,12). Thus, the efficacy data from our study compares favorably with that reported in other recently conducted studies in predominantly Western patients, although in comparing the efficacy data from 57 patients of this single arm study to those of randomized phase III trials caution should be exercised.

The administration schedule and doses selected for our study were identical to those used in the NO16966 study (12,13). The median relative dose intensity was similar with that in the XELOX plus bevacizumab arm of the NO16966

**Table 3.** Incidence of common adverse events

Adverse event	XELOX (n = 6)				XELOX plus bevacizumab (n = 58)			
	Grade 1–4		Grade 3–4		Grade 1–4		Grade 3–4	
	No.	%	No.	%	No.	%	No.	%
Neurosensory toxicity	6	100	1	17	54	93	10	17
Anorexia	5	83	0	0	52	90	2	3
Fatigue	4	67	0	0	48	83	3	5
Hand-foot syndrome	4	67	1	17	45	78	1	2
Nausea	6	100	0	0	43	74	0	0
Pigmentary disturbance	2	33	0	0	36	62	0	0
Stomatitis	2	33	0	0	33	57	1	2
Diarrhea	4	67	0	0	32	55	2	3
Neutropenia	3	50	0	0	30	52	9	16
Vomiting	1	17	0	0	27	47	1	2
Nose bleed	1	17	0	0	23	40	0	0
Proteinuria	0	0	0	0	19	33	3	5
Hypertension	0	0	0	0	19	33	3	5
Thrombocytopenia	2	33	1	17	13	22	4	7
Pulmonary thrombosis	0	0	0	0	1	2	1	2
Jugular vein thrombosis	0	0	0	0	1	2	0	0

study (0.74 versus 0.73 for capecitabine, 0.86 versus 0.81 for oxaliplatin and both 0.91 for bevacizumab). The relative dose intensity was reported in another phase II trial (TREE-2) as well, a median of 0.76 for capecitabine, 0.91 for oxaliplatin and 0.96 for bevacizumab in the XELOX plus bevacizumab arm, whereas the starting dose of capecitabine was reduced to 850 mg/m<sup>2</sup> twice daily and the median duration of the therapy was 19 weeks in that study (14). The safety profile observed in our study was similar to that observed in previous clinical trials with Western patients, including the NO16966 study (12,13,18–22). It is notable that the incidence of grade 3/4 diarrhea was only 3%, which is considerably lower than that reported with XELOX plus bevacizumab in the previous phase II and III studies (19–21%) (12,18,19,22). A lower incidence of diarrhea has been reported in other studies of Japanese or Asian patients treated with fluoropyrimidine-based chemotherapy (25–27). In addition, clinical trials including other oral fluoropyrimidines, such as UFT, have reported lower incidence of grade 3/4 diarrhea in Japanese patients than in Western patients (9.1 versus 22.2%) (28). A reason for this regional variation remains unclear, but it is speculated that differences in dietary folate intake may be a potential explanation (29). Regarding to HFS, although the overall incidence of HFS in our study (78%) was higher than that in the XELOX plus bevacizumab arm of the NO16966 study (39%), the incidence of grade 3 HFS appeared significantly lower (2

versus 12%). The incidence of dose modification (including treatment interruption and delay) due to HFS was similar among the studies (data not shown), as well as the dose intensity of capecitabine as described above. Therefore, the difference in incidences of grade 3 HFS, unfortunately, is not well explained at this time. However, a number of factors may explain this difference. The dose modification of capecitabine due to adverse events other than HFS (e.g. neutropenia, increase of AST, fatigue, anorexia), which occurred at higher incidences in our study compared with the NO16966 study, might be one such factor (data not shown). Difference in frequency of visits could also be factor. Patients received medical examination once every week during first eight cycles in this study, resulting in the treatment interruption in the middle of first 2 weeks of a cycle in four patients among eleven patients who developed grade 2 or grade 3 HFS. Another potential reason might be differences in prophylactic administration (e.g. a moisturizer, steroid ointment, urea ointment etc.). In terms of hematologic toxicities, grade 3/4 neutropenia occurred at 16% in patients receiving XELOX plus bevacizumab in our study which was higher than in the XELOX/XELOX + placebo arm of the NO16966 study (6%) (12), whereas no febrile neutropenia was observed in any patient in our study. The difference in the incidence of grade 3/4 neutropenia may in part be derived from an increased frequency of hematological examination, which was performed once every week in this study in contrast to once every 3 weeks at day 1 in the pivotal phase III study. Known bevacizumab-specific events (i.e. coagulopathy, hypertension, bleeding) were generally mild to moderate in severity in our study, and grade 3/4 events occurred at similar or lower incidence to that reported in Western patients (13). It is concluded that XELOX plus bevacizumab is well tolerated in Japanese patients with MCRC.

Only one patient (2%) treated with XELOX plus bevacizumab experienced grade 3 HFS, compared with an incidence of 13% in a previous phase II study of capecitabine monotherapy (1250 mg/m<sup>2</sup> twice daily) in Japanese patients with MCRC (25). In addition, dose reduction of capecitabine due to HFS was required for less patients in our study (12.1 versus 31.7%). This may be attributable to the 20% reduced dose of capecitabine used in the XELOX regimen compared with capecitabine monotherapy.

In the present trial, six patients received only XELOX. The ORR was 67%, grade 3 adverse events developed in three patients (one event each, respectively) and no significant safety finding was observed. XELOX without bevacizumab is a widely used regimen in a first-line setting for MCRC patients (NCCN guideline) (30). The NO16966 study demonstrated an encouraging efficacy as described above, and another phase III trial showed an ORR of 42%; PFS of 9.3 months; and median OS of 19.9 months in the XELOX arm, with a good safety profile (31). Thus, XELOX seems to be acceptable as an option for a standard regimen for MCRC in Japan, although the data provided in our study is limited to a small population.

In conclusion, in this study, XELOX plus bevacizumab was effective with manageable tolerability profile for Japanese patients with MCRC. The efficacy and safety profile of XELOX plus bevacizumab in this study was consistent with that observed in Western patients, whereas showing a notably lower incidence of diarrhea. Moreover, the XELOX regimen requires only one visit per 3-week cycle for a 2- or 3-h infusion, which may provide a marked advantage over the FOLFOX regimen in terms of the convenience for both patients and clinical staff. Therefore, XELOX plus bevacizumab may be considered as a possible standard treatment for Japanese patients with MCRC.

**Acknowledgements**

We are indebted to Dr Yuh Sakata, Dr Ichinosuke Hyodo and Dr Kunihisa Miyakawa for their help in the assessment of efficacy and evaluation of safety. We are also grateful to Dr Tetsuo Taguchi, Dr Nagahiro Saijo and Dr Atsushi Ohtsu for supporting the study.

**Funding**

This work was supported by Chugai Pharmaceutical Co. Ltd and Yakult Honsha Co. Ltd.

**Conflict of interest statement**

None declared.

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## Appendix

The following investigators cared for the patients in this study: Kuniaki Shirao (Oita University, Faculty of Medicine, Yufu, Oita) and Takashi Sekikawa (Toyosu Hospital, Showa University School of Medicine, Tokyo).