A Phase II Clinical Study of mFOLFOX6 Plus Bevacizumab as First-line Therapy for Japanese Advanced/Recurrent Colorectal Cancer Patients

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Objective: In Japan, there had been no prospective clinical studies conducted in terms of modified FOLFOX6 + bevacizumab therapy. We performed a post-marketing Phase II multicenter clinical study to examine the efficacy and safety of this regimen as first-line therapy for Japanese patients with advanced/recurrent colorectal cancer.

Methods: Bevacizumab (5 mg/kg) was administered intravenously, and then oxaliplatin (85 mg/m^2) and levofolinate calcium (200 mg/m^2) were infused intravenously over 2 h. Subsequently, a bolus dose of 5-fluorouracil (400 mg/m^2) was injected, followed by infusion of 5-fluorouracil (2400 mg/m^2) for 46 h. This regimen was repeated every 2 weeks until 24 cycles unless there was disease progression, unacceptable toxicity or patient refusal. The primary end point was the response rate.

Results: Among the 70 patients enrolled, two patients withdrew the study before treatment, and 68 patients were eligible for analysis of efficacy and safety. The response rate was 51.5% (95% confidence interval: 39.0−63.8%). The median progression-free survival and median overall survival time were 12.6 months (95% confidence interval: 10.4−14.5 months) and 28.5 months [95% confidence interval: 23.1 months−(not applicable)], respectively. There were no treatment-related deaths observed. The most common Grade 3 and 4 adverse events included neutropenia in 35.3% of the patients, peripheral neuropathy in 16.2% and hypertension in 16.2%. All adverse events were manageable and tolerable. The exploratory analysis of polymorphisms of three genes, *ERCC1*, *XPD* and *GSTP1*, did not show any trends in terms of correlation with the efficacy or safety of modified FOLFOX6 + bevacizumab therapy.

Conclusions: Modified FOLFOX6 + bevacizumab therapy was manageable and tolerable in Japanese patients, achieving a high response rate.

Key words: FOLFOX − bevacizumab − colorectal cancer

INTRODUCTION

Colorectal cancer is the third most common type of cancer reported in men and is the second reported in women, with 1.2 million of new cases being diagnosed and 608 700 people dying of it in 2008 worldwide (1). In Japan, 353 499 patients died of cancer in 2010, with colorectal cancer accounting for 44 620 deaths (2). Colorectal cancer is the third highest cause of cancer death (11.4%), following lung and gastric cancers, for men in Japan, and is the highest cause for women (14.4%).

While patients with an early stage of colorectal cancer can be cured by endoscopic resection or other surgical procedures, these treatment modalities cannot be applied to advanced and/or recurrent cancer with distant metastasis, and chemotherapy and/or radiation therapy is the primary option for these patients (3,4). The combination regimen of 5-fluorouracil (5-FU), levofolinate calcium (*l*-LV) and oxaliplatin (FOLFOX) is widely employed, with its efficacy having been demonstrated by many randomized controlled trials conducted in patients with advanced and/or recurrent colorectal cancer (5). FOLFOX4 was the first regimen established, with at least three cycles being tolerated by Japanese patients with advanced colorectal cancer (6). Modified FOLFOX6 (mFOLFOX6) was established as a simplified regimen of FOLFOX4 with antitumor activity equivalent to that of FOLFOX4 (7). mFOLFOX6 has been widely employed because it avoids bolus intravenous infusion of 5-FU on Day 2 and is more appropriate for the therapy on an outpatient basis.

Recently, with the approval of molecular-targeting agents, including bevacizumab, cetuximab and panitumumab, new regimens combining these agents with FOLFOX or with 5-FU, *l*-LV and irinotecan (FOLFIRI) have become common (3,4). Bevacizumab in combination with mFOLFOX6 has become one of the standard regimens after the approval of this humanized monoclonal antibody. However, no Phase II/III clinical studies of this combination therapy as a first-line setting had been conducted in Japan when this study was planned. The use of FOLFOX has been increasing in Japan based on the results of clinical studies performed in Europe and the United States, but only Suenaga et al. have reported the results of a prospective clinical study of FOLFOX therapy in Japanese patients with advanced and/or recurrent colorectal cancer. They concluded that FOLFOX4 could be administered safely for three cycles, but safety from the fourth cycle onward was not confirmed in prospective clinical studies. Therefore, we considered it to be necessary to investigate the efficacy and safety of FOLFOX plus bevacizumab in a prospective clinical study.

In recent years, attention has been drawn to the relationship between the efficacy/safety of oxaliplatin therapy and genetic polymorphisms, which include those of the excision repair cross complementing group 1 (*ERCC1*), xeroderma pigmentosum group D (*XPD*) and glutathione *S*-transferase pi 1 (*GSTP1*) genes (8–10). The *T/T* genotype of *ERCC1-118* was associated with higher efficacy of oxaliplatin when compared with the *C/C* or *C/T* genotypes; the *C/C* genotype of *ERCC1-504* reported longer survival than the *A/A* or *C/A*

genotypes (8,9). The *C/C* genotype of *XPD-751* was associated with higher efficacy of oxaliplatin than the *A/A* or *C/A* genotypes, while the *G/G* genotype of *XPD-312* was associated with longer progression-free survival (PFS) than either *A/A* or *A/G* (8). Furthermore, a higher incidence of peripheral neuropathy was reported to be associated with the *G/G* or *A/G* genotype of *GSTP1-105* rather than the *A/A* genotype (8).

We herein report the results of a post-marketing Phase II multicenter clinical study of first-line mFOLFOX6 + bevacizumab therapy in Japanese patients with advanced and/or recurrent colorectal cancer. In this study, the influence of genetic polymorphisms on the efficacy and safety of oxaliplatin was also examined on an exploratory basis to investigate their significance as predictive biomarkers.

PATIENTS AND METHODS

STUDY POPULATION

The eligibility criteria for inclusion into the study were: age ≥20 years at the time of enrollment; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; histopathologically confirmed diagnosis of colorectal cancer; chemotherapy-naïve advanced and/or recurrent disease that was not curatively resectable; at least 6-months interval between the completion of adjuvant chemotherapy containing 5-FU and the day of diagnosing recurrence; measurable lesions; life expectancy ≥3 months; no serious impairment of major organs and written informed consent.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the institutional review board of each participating hospital. The study was registered with the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm; no. UMIN000001490).

TREATMENT SCHEDULE

Bevacizumab (5 mg/kg) was administered intravenously over 30–90 min, and then oxaliplatin (85 mg/m^2) and *l*-LV (200 mg/m^2) were infused for 2 h. Subsequently, a bolus dose of 5-FU (400 mg/m^2) was injected intravenously, followed by infusion of 5-FU (2400 mg/m^2) for 46 h. This regimen was repeated every 2 weeks. If the discontinuation of oxaliplatin or bevacizumab treatment was necessary, simplified leucovorin and 5-FU (sLV5FU2) with or without bevacizumab treatment were accepted as a study treatment. Treatment could be continued for up to a maximum of 24 cycles unless there was disease progression, adverse event(s) occurred that prevented further study treatment, the decision of the study physician, the patient refused further treatment or the curative resection of tumor was expected. Study treatment was delayed if any of the following criteria was met on the scheduled day of administration or its previous day: neutrophil count <1500/mm^3; platelet count <75 000/mm^3; aspartate aminotransferase

>100 IU/l; alanine aminotransferase >100 IU/l; total bilirubin >1.5 mg/dl; serum creatinine >1.50 mg/dl; Grade 3 or 4 peripheral neuropathy; Grade 2 or worse proteinuria, hemorrhage, stomatitis or fatigue and/or diarrhea. The oxaliplatin dose was decreased to 65 mg/m^2 in the next cycle if Grade 4 neutropenia or Grade 3 and 4 thrombocytopenia had occurred, or Grade 2 peripheral neuropathy was noted on the first day of next cycle. The oxaliplatin administration was discontinued if Grade 3 or 4 peripheral neuropathy occurred. The doses of 5-FU for infusion and bolus injection were reduced to 2000 mg/m^2 or 1600 mg/m^2 and 300 mg/m^2 or 200 mg/m^2, respectively, if any of the following events occurred: Grade 4 neutropenia, Grade 3 or 4 thrombocytopenia, diarrhea or stomatitis or Grade 3 hand-foot skin reactions. Dose modification was not allowed for bevacizumab or *l*-LV. During the study period, reintroduction of oxaliplatin or bevacizumab was not permitted even after adverse events recovered. Any post-study treatments were permitted if considered appropriate and feasible by study physicians.

EVALUATION OF EFFICACY AND SAFETY

The primary end point of this study was the response rate (RR), and the secondary end points included the time to treatment failure (TTF), time to failure of strategy (TFS), PFS, overall survival (OS) and incidence of adverse events. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines (RECIST version 1.0) by independent external review board (10), and the RR was calculated. Tumor diameters were measured by using the image by computed tomography or magnetic resonance imaging within 1 month prior to registration (baseline), and the measurement was repeated every 8 weeks. The disease control rate (DCR) was defined as the sum of complete response, partial response and stable disease ratios. PFS was defined as the duration from the first day of study treatment to the date of first following event; tumor progression or patient death. Patients undergoing curative resection of metastases were censored at the time of surgery. TTF was defined as the interval from the first day of study treatment to the date of the first of any of the following events: tumor progression, death or treatment failure. Data on patients who had completed 24 cycles of treatment or who discontinued treatment for curative resection were censored at the date of final observation. TFS was defined as the duration from the first day of study treatment to the date of first following event: tumor progression, patient death or initiation of a new treatment, e.g. irinotecan, cetuximab, panitumumab or oral 5-FUs, following the definition described in (11). Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC version 3.0) (12).

STATISTICAL ANALYSIS

Considering that RRs of first-line FOLFOX and FOLFOX + bevacizumab were reported to be 35−50% (13,14) and 47−53% (15−17), respectively, the expected RR and the threshold RR were assumed to be 53 and 35%, respectively. On this assumption, 60 patients were required with a one-sided α-level of 2.5% and a power of 80%. The Kaplan−Meier method was used to estimate the probabilities of time-to-event parameters.

The chi-square test for independence (Fisher's exact test when the expected value was <5) was performed to compare the RR in patients with each polymorphism. To compare PFS for each gene polymorphism, point estimates of the hazard ratio were made by Cox regression analysis (proportional hazards model) and the log-rank test was performed. The chi-square test for independence (Fisher's exact test when the expected value was <5) was employed to compare the incidence of adverse events for each polymorphism.

GENOTYPING

Genomic DNA was extracted from peripheral blood leukocytes, and polymorphisms of three genes [*ERCC1 Asn118Asn*([*19007T > C*), *ERCC1 Gln504Lys* (*8092C > A*), *XPD Asp312Asn* (*23591G > A*), *XPD Lys751Gln* (*35931A > C*) and *GSTP1 Ile105Val* (*562A > G*)] were identified by the real-time polymerase chain reaction (7900HT; Applied Biosystems, Foster City, CA, USA) using the TaqMan method. The primers included in the TaqMan SNP Genotyping Assay (Applied Biosystems) were used for the assay.

RESULTS

PATIENT CHARACTERISTICS

A total of 70 patients were enrolled from 15 institutions between 9 December 2008 and 28 February 2010. Sixty-eight patients were included in the analysis of efficacy and safety, while two were excluded due to their refusal before receiving the study treatment. The characteristics of the 68 patients are shown in Table 1. Their median age was 63 years (range 28−81 years). The ECOG PS was 0 in 54 patients and 1 in 14 patients. Four patients had received adjuvant chemotherapy, while the remaining 64 had not.

TREATMENT

The median cycle of study treatment was 13.5 (range 1−24). The median total dose of oxaliplatin was 755 mg/m^2. The median relative dose intensity of oxaliplatin in all cycles treated with mFOLFOX6 and sLV5FU2 was 69.2% (Table 2), and that in cycles treated with mFOLFOX6 was 78.0%.

Reasons for treatment discontinuation included disease progression (*n* = 20, 29.4%), the decision of the study physician and/or patient refusal (*n* = 14, 20.6%) and adverse events (*n* = 8, 11.8%). In addition, eight patients (11.8%) were withdrawn from the study because of expectation for curative resection, and five patients (7.4%) actually underwent R0 resection, i.e. negative margins. Since post-study treatments

were specified in this study, these were allowed following the decision of the study physician. Actually thirty-eight patients (54%) continued to receive mFOLFOX6 ± bevacizumab or sLV5FU2 ± bevacizumab after the completion of study

Table 1. Patient characteristics (*n* = 68)

Sex	
Male	38
Female	30
Median age (years)	63
Range	28–81
ECOG PS	
0	54
1	14
Primary site	
Colon	44
Rectum	24
Histological type	
Well-differentiated	16
Moderately differentiated	43
Poorly differentiated	6
Mucinous	2
Mixture of well-differentiated and moderately differentiated	1
Number of metastatic organs	
1	30
≥2	38
Adjuvant chemotherapy	
Yes	4
No	68

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Total dose, dose intensity and relative dose intensity of each study drug

	Median total dose (mg/m^2)	Median dose intensity[a] (mg/m^2/2 weeks)	Median relative dose intensity (%)
Oxaliplatin	755	58.8	69.2
Bevacizumab	55[b]	4.244[c]	84.9
5-FU (bolus injection)	3600	302.5	75.6
5-FU (intravenous infusion)	30 000	1926	80.2
Levofolinate calcium	2700	172.1	86.0

5-FU, 5-fluorouracil
[a]Including the cycles treated with simplified LV5FU2 ± BV.
[b]mg/kg.
[c]mg/kg/2 weeks.

treatment for 24 cycles or the discontinuation of study treatment due to adverse events, if their adverse events resolved. Furthermore, 56 patients (82.4%) received irinotecan, 48 patients (70.6%) received bevacizumab, 18 patients (26.5%) received cetuximab and 18 patients (26.5%) received panitumumab as post-study treatments.

EFFICACY

The RR was 51.5% [95% confidence interval (CI): 39.0–63.8%], with a complete response being achieved in 1.5% (1 of 68) and a partial response in 50.0% (34/68) of patients (Table 3). Stable disease was observed in 47.1% (32/68), while progression was seen in 1.5% (1/68). The DCR was 98.5% (95% CI: 92.1–100%).

The median TTF, TFS, PFS and OS were 8.0 months (95% CI: 7.1–10.6 months), 10.5 months (95% CI: 8.0–13.1 months), 12.6 months (95% CI: 10.4–14.5 months) and 28.5 months [95% CI: 23.1–(not applicable)], respectively (Figs 1 and 2). The median duration of follow-up was 29.0 months (range 7.9–42.4 months).

TOXICITY

The incidence of adverse events is summarized in Table 4. The most common Grade 3 or 4 adverse event was neutropenia (35.5%). Most patients (95.6%) developed peripheral neuropathy, with Grades 3 and 4 in 16.2% of patients. Grade 1 or more and 3 or more allergic reactions were observed in 20.6 and 4.4% of the patients, respectively, and none of the patients suffered from anaphylaxis. The median number of cycles at which allergic reactions first occurred was nine (range five to nine cycles). All of these reactions recovered after discontinuing oxaliplatin and/or initiating antihistamine therapy. There were no treatment-related deaths observed, and none of the patients died within 30 days after the last study treatment.

CLINICAL OUTCOME AND THE GENOTYPE

With regard to *ERCC1-118* polymorphism, 42.6, 55.9 and 1.5% of the patients had the *C/C*, *C/T* and *T/T* genotype,

Table 3. Response

		n = 68
RR (95% CI)	51.5% (39.0–63.8%)	35
DCR (95% CI)	98.5% (92.1–100.0%)	67
CR	1.5%	1
PR	50.0%	34
SD	47.1%	32
PD	1.5%	1

RR, response rate; CI, confidence interval; CR, complete response; PR; partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate.
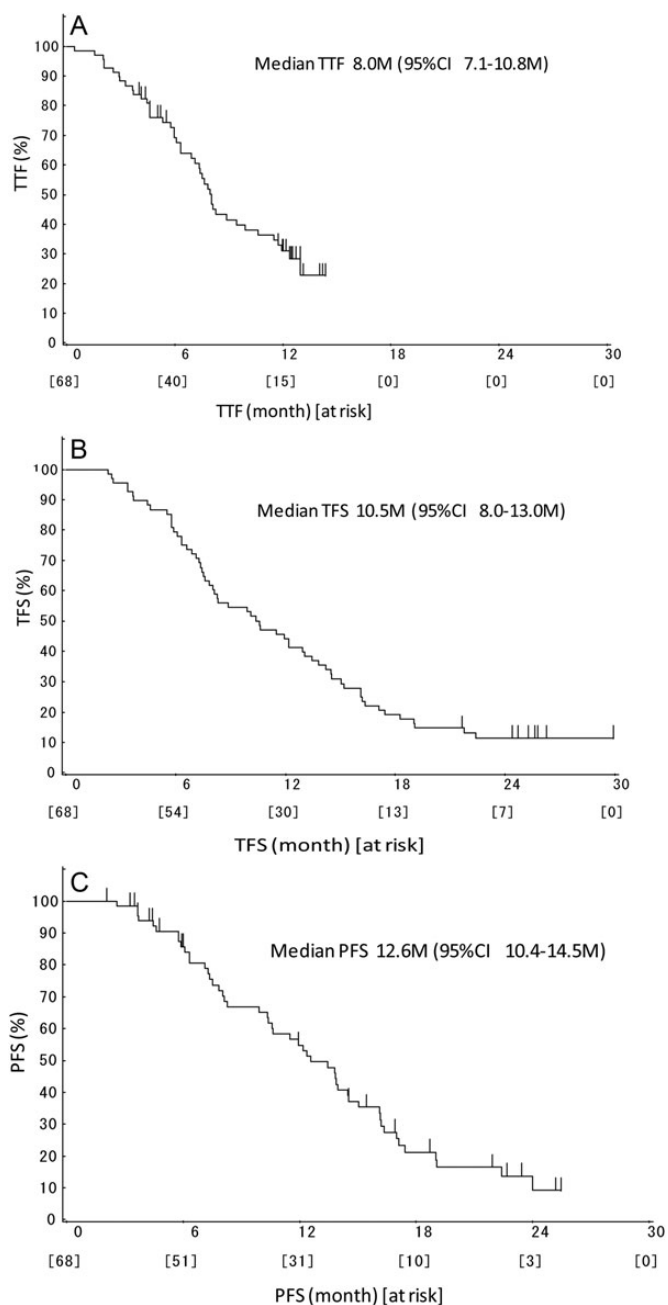
Figure 1. Kaplan−Meier curves for the study end points. (A) Time to treatment failure (TTF). (B) Time to failure of strategy (TFS). (C) Progression-free survival (PFS).

Figure 2. Kaplan−Meier curve for overall survival (OS). NA, not applicable.

Table 4. Adverse events ($n = 68$)

Event	Grade 1 or more		Grade 3 or more	
	n	%	*n*	%
Hematological toxicity				
Neutropenia	58	85.3	24	35.3
Leukopenia	50	73.5	4	5.9
Anemia	19	27.9	1	1.5
Thrombocytopenia	7	10.3	0	0
Non-hematological toxicity				
Peripheral neuropathy	65	95.6	11	16.2
Nausea	55	80.9	4	5.9
Fatigue	49	72.1	1	1.5
Anorexia	47	69.1	4	4.4
Epistaxis	39	57.4	0	0
Stomatitis	32	47.1	1	1.5
Proteinuria	31	45.6	0	0
Diarrhea	28	41.2	1	1.5
Vomiting	27	39.7	2	2.9
Hypertension	26	38.2	11	16.2
Dyschromia	24	35.3	0	0
Hand-foot skin reactions	19	27.9	0	0
Allergic reactions	14	20.6	3	4.4
Bleeding	8	11.8	0	0
Febrile neutropenia	2	2.9	2	2.9
Thrombosis/thrombus/embolism	5	7.4	2	2.9
Gastrointestinal perforation	1	1.5	1	1.5

respectively. In the case of *ERCC1-504* polymorphism, 60.5, 33.8 and 5.9% of the patients had *C/C*, *C/A* and *A/A*, respectively. The analysis of *GSTP1-105* polymorphism showed that 72.1, 25.0 and 2.9% had *A/A, A/G* and *G/G*, respectively. There were no significant correlations observed between the RR or PFS and genetic polymorphism of *ERCC1-118*, *ERCC1-504* and *GSTP1-105* (Table 5). The incidence of Grade 3 or 4 peripheral neuropathy was 20.4% in patients with the *A/A* genotype for *GSTP1-105* polymorphism, whereas it was 5.3% in patients with *A/G* or *G/G*, but the difference in incidence wa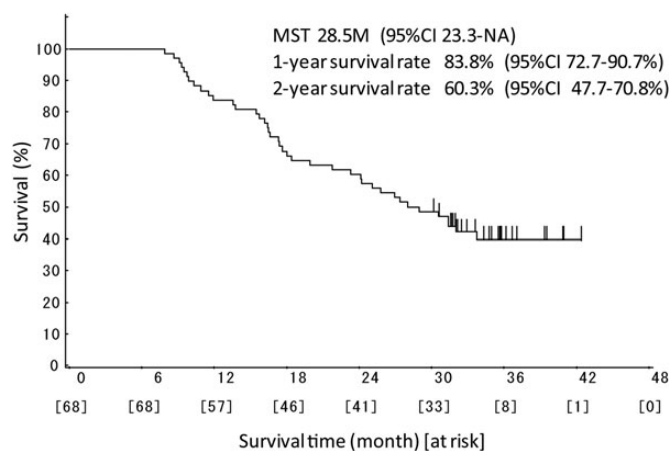s not significant ($P = 0.1625$). In addition, the incidence of Grade 1 or more peripheral neuropathy and that of Grade 1 or more or 3 or more allergic reactions did not show any significant correlation with polymorphism of these genes. *XPD-312* and *XPD-751* could not be evaluated for

Table 5. Polymorphism of *ERCC1* or *GSTP1* and clinical outcomes

	Polymorphism	Frequency *n* (%)	RR *n* (%)	*P* value[a]	PFS (M)	Hazard ratio	*P* value[b]
ERCC1-118	C/C	29 (42.6)	17 (58.6)	0.3090	13.5	1.077	0.7976
	C/T + T/T	39 (57.4)	18 (46.2)		12.6		
ERCC1-504	C/C	41 (60.3)	19 (46.3)	0.2970	13.8	1.117	0.7088
	C/A + A/A	27 (39.7)	16 (59.3)		12.6		
GSTP1-105	A/A	49 (72.1)	27 (55.1)	0.3359	13.5	0.806	0.5222
	A/G + G/G	19 (27.9)	8 (42.1)		10.4		

[a]Pearson's χ^2 test.
[b]Log-rank test.

efficacy because these were *G/G* and *A/A* genotype in all patients, respectively.

DISCUSSION

The present study was conducted to examine the efficacy and safety of first-line treatment with mFOLFOX6 + bevacizumab for Japanese patients with advanced/recurrent colorectal cancer prospectively. The RR achieved with this therapy was 51.5%, which was very close to the expected RR of 53%, and the lower limit of the CI (39%) was above the threshold RR (35%) estimated before the study. This efficacy of mFOLFOX6 + bevacizumab treatment in Japanese patients was similar to the results of first-line treatments reported by Hochster et al. (15,16) and Saltz et al. (17).

The median TTF (8.0 months) and PFS (12.6 months) in Fig. 1 show a 4.6-month difference, which is similar to those reported by Green et al. (18). This difference may have been due to the introduction of irinotecan-based chemotherapy after the discontinuation of mFOLFOX6 therapy due to adverse events, e.g. peripheral neuropathy, before disease progression, and actually this introduction occurred in 23.5% (16 of 68) of patients. Since 18 patients completed the treatment of 24 cycles and these patients were included in the events of TTF following our definition, but not Green et al., to diminish this influence on TTF values and, furthermore, to reflect the influence of introduction of new treatment, including irinotecan, TFS was also calculated in our study. TFS has recently been proposed to evaluate an adequate treatment strategy under the situation where new drugs have been introduced in the treatment of advanced/recurrent colorectal cancer (11). The median TFS was 10.5 months, which is longer than the median TTF. The median survival time of 28.5 months in this study was compared favorably with 26.1 months reported in the treatment with mFOLFOX6 + bevacizumab (16). This favorable OS may have been due to the post-treatment with irinotecan-based chemotherapy, which was given to 82.4% (56 of 68) of patients, suggesting that the importance of appropriate combination of all the three drugs: oxaliplatin, 5-FU and irinotecan.

In this study, R0 resection was expected in eight patients (11.8%) after study treatment, and five patients (7.4%) actually underwent R0 resection, liver metastasis alone in four patients and liver and lung metastases in one patient, without postoperative complications. The rate of R0 resection in this study is similar to that of FOLFOX4 regimen in N9741 (4.1%) and that of FOLFOX4/XELOX + bevacizumab in NO16966 (6.3%) (19,20). Therefore, these oxaliplatin-based regimens may give favorable conversion rates from unresectable to resectable disease.

The safety profile of mFOLFOX6 + bevacizumab in Table 4 was similar to those previously reported in both hematological and non-hematological toxicities (16,17,21). Gastrointestinal perforation, a serious adverse event reported in bevacizumab therapy, occurred in only one patient (1.5%), and its incidence was similar to that reported in the NO16966 study and other bevacizumab studies (15–17,22,23). Peripheral neuropathy is a characteristic adverse event of oxaliplatin therapy and it occurred in 16.2% of our patients at the Grade 3 and 4 level, which indicates that the incidence was similar to that reported with regimens like FOLFOX or capecitabine + oxaliplatin with or without bevacizumab, i.e. 17–18% in (16, 21, 24). On the other hand, the lower incidence was reported in Asian colorectal and gastric cancer patients (25,26). Since this study was a post-marketing clinical study which investigated the daily safety of study treatment, peripheral neuropathy might have been monitored more carefully, and as a result, the incidence of Grade 3 peripheral neuropathy might become higher than that reported by the previous literature.

We also analyzed genetic polymorphisms to assess their possible influence on the efficacy and safety. Unfortunately, the relation between genetic polymorphisms and these outcomes was insufficient because variations in *ERCC-118*, *ERCC1-504* and *GSTP1-105* showed a lower frequency compared with previous reports (8,9), and all of the patients had the wild-type genotype for both *XPD-312* and *XPD-751*. Further studies will be needed to clarify the correlation between genetic polymorphisms and the clinical outcome.

In conclusion, mFOLFOX6 + bevacizumab therapy was manageable and tolerable in Japanese patients and gave a high RR. These results are comparable with those reported in

western countries, which indicates that mFOLFOX6 + beva-cizumab could be applied in Japanese patients with advanced/recurrent colorectal cancer as one of the outpatient treatments.

Conflict of interest statement

None declared.

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Appendix

Apart from the 12 listed authors, the doctors below also participated (as authors) in the study through subject enrollment: Dr Teranishi from Southern Tohoku General Hospital; Dr D. Minabe and Dr Y. Mochizuki from Yokohama Municipal Citizen's Hospital; Dr S. Samejima, Dr S. Koketsu and Dr H. Ojima from Gunma Prefectural Cancer Center; Dr H. Mishima and Dr K. Fujitani from National Hospital Organization Osaka National Hospital; Dr J. Ikeda from Kitami Red Cross Hospital and Dr K. Ikejiri from National Hospital Organization Kyushu Medical Center.