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Safety Analysis of FOLFOX4 Treatment in Colorectal Cancer Patients: A Comparison Between Two Asian Studies and Four Western Studies

Kenichi Sugihara¹, Atsushi Ohtsu², Yasuhiro Shimada³, Nobuyuki Mizunuma⁴, Po-Huang Lee⁵, Aimery de Gramont⁶, Richard M. Goldberg⁷, Mace L. Rothenberg⁸, Thierry André⁹, Silvano Brienza¹⁰, and Katsushige Gomi¹¹

¹Department of Surgical Oncology, Tokyo Medical and Dental University, Tokyo, Japan

²Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan ³Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan ⁴Medical

Oncology, Cancer Institute Hospital, Tokyo, Japan ⁵Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan ⁶Department of Medical Oncology, Hôpital Saint-Antoine,

Paris, France ⁷Comprehensive Cancer Center, Ohio State University, Columbus, OH ⁸Vanderbilt-

Ingram Cancer Center, Nashville, TN ⁹Department of Hepato-Gastroenterology, Hôpital La Pitié

Salpêtrière, Paris, France ¹⁰Debiopharm S.A., Lausanne, Switzerland ¹¹Yakult Honsha Co, Ltd, Tokyo, Japan

Abstract

FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin) is a standard regimen for the treatment of advanced colorectal cancer. Its dose intensity and safety profile were compared between 2 Asian and 4 Western studies by analyzing 3359 patients. There was no evidence that Asian patients experienced worse toxicity than Western patients, and trends toward reduced neurotoxicity and diarrhea among Asian patients were observed.

Purpose—Oxaliplatin-based therapy, notably FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin), is a standard regimen approved globally for the treatment of metastatic colorectal cancer, and as adjuvant treatment of colon cancer. As part of the Japanese submission for the adjuvant indication, the safety profile of FOLFOX4 regimen was compared in Asian and Western patients.

Patients and Methods—A total of 3359 patients with colorectal cancer treated with the FOLFOX4 regimen were included in the analyses: 1515 from 2 Asian studies (Japanese Post Marketing Surveillance and Multicenter Asia Study in Adjuvant Treatment of Colon Cancer with Oxaliplatin/5-FU/LV), and 1844 from 4 Western studies (EFC2962, N9741, EFC4584, and Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant

Treatment of Colon Cancer). Doses administered and safety parameters were analyzed by using common definitions and programs.

Results—Demographic and baseline characteristics were comparable between Asian and Western patients. Patients received FOLFOX4 for a median of 6-12 cycles, which ranged from 16 to 28 weeks. Median dose intensities of oxaliplatin and of 5-fluorouracil, bolus and infusion, were within the ranges of 33 to 36 mg/m²/week, 297 to 338 mg/m²/week, and 467 to 510 mg/m²/week, respectively. Most frequently reported adverse events (AE) included hematologic, gastrointestinal, and neurosensory adverse events (NSAE). The incidence of grade 3 neutropenia ranged from 37% (422 of 1134) to 52% (83 of 159) in Asian and 41% (455 of 1108) to 56% (144 of 259) in Western studies; of diarrhea, ranged from 1.4% (3 of 222) to 6.3% (10 of 159) and 11% (30 of 268 or 120 of 1108) to 14% (36 of 259); of NSAEs, from 1.9% (21 of 1134) to 4.4% (7 of 159) and 9.3% (25 of 268) to 19% (39 of 209); and of allergic reactions, from 0.6% (7 of 1134) to 3.1% (5 of 159) and 1.1% (3 of 268) to 3.0% (33 of 1108), respectively. The probability of grade 3 NSAEs and diarrhea was statistically significantly lower in Asian than in Western studies by using a log-rank test.

Conclusion—There was no evidence that Asian patients experienced worse toxicity than did Western patients when treated with FOLFOX4, and trends toward reduced neurotoxicity and diarrhea among Asian patients were observed.

Keywords

Colorectal cancer; Ethnic difference; FOLFOX4; Oxaliplatin; Safety

Introduction

Oxaliplatin is a third-generation platinum antitumor drug having a unique *trans*-1,2-diaminocyclohexane moiety as the carrier ligand that forms DNA adducts that differ from those observed with cisplatin.^{1,2} Because oxaliplatin showed synergistic antitumor activity in vitro with 5-fluorouracil (5-FU),³ the combination regimen of 5-FU, leucovorin (LV), and oxaliplatin (FOLFOX4) was evaluated in patients and established as a fundamental standard treatment for metastatic colorectal cancer in the first- and second-line settings in Western countries.⁴⁻⁷ Similar efficacy was reported in Asian and Japanese patients, although the studies included fewer patients.⁸⁻¹² To evaluate the safety data of FOLFOX regimen in Japanese patients and to comply with a conditional approval commitment, a study termed “Post Marketing Surveillance” (J-PMS) was conducted in patients with metastatic colorectal cancer.

FOLFOX4 also became a standard-adjuvant treatment of colon cancer in Western countries based on the results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study.^{13,14} To evaluate the safety and tolerability of adjuvant FOLFOX4 in Asian patients, the Multicenter Asia Study in Adjuvant Treatment of Colon Cancer with Oxaliplatin/5-FU/LV (MASCOT) study was conducted in 5 Asian countries.¹⁵ Since then, the FOLFOX4 regimen has been used for the pivotal regulatory foundation or drugs for metastatic colorectal cancer and for adjuvant treatment of colon cancer as a control arm.¹⁶⁻¹⁹ The results of the FOLFOX4 regimen also

contributed to the establishment and application of other FOLFOX regimens, including modified FOLFOX6 (mFOLFOX6).²⁰

Recently, attention has been drawn to racial- or ethnicity-related differences in the prevalence of colorectal cancer as well as the therapeutic response to chemotherapy.^{21,22} Although these reports have generally focused on the comparisons between white and African American patients, there has been little information comparing the toxicity of FOLFOX4 treatment between Western and Asian patients. Here, we compare the safety profile of FOLFOX4 treatment between Asian and Western patients by using the data from 2 Asian and 4 Western studies, conducted for the first-line, second-line, or later treatment, and as adjuvant therapy.

Patients and Methods

Studies Analyzed

Safety data were extracted from 2 Asian and 4 Western studies in which patients received the FOLFOX4 treatment. The profile of 6 studies is summarized in Table 1. The FOLFOX4 regimen is oxaliplatin 85 mg/m² on day 1, LV 200 mg/m²/day or *l*-LV 100 mg/m²/day on days 1 and 2, and 5-FU bolus 400 mg/m²/day followed by continuous infusion 600 mg/m²/day on days 1 and 2, repeated every 2 weeks.

J-PMS was a prospective survey conducted in Japanese patients who were receiving FOLFOX, including FOLFOX4 for metastatic colorectal cancer. It was conducted to comply with a conditional approval commitment given by Japanese regulatory authority. Among 5119 patients enrolled, 1356 were to be treated with the standard FOLFOX4 regimen at least in the first cycle of therapy. Their experiences were extracted for this safety analysis. For patients to be eligible for this analysis they must have received oxaliplatin 80-90 mg/m², *l*-LV 75-125 mg/m²/day, and 5-FU bolus 350-450 mg/m²/day followed by continuous infusion 550-650 mg/m²/day on the same schedule described above.

To compare the safety profile, 4 pivotal Western studies (EFC2962, N9741, EFC4584, and MOSAIC) were selected because these studies had been conducted to obtain the regulatory approval of FOLFOX4 indication for metastatic cancer and adjuvant treatment, respectively. Furthermore, as an Asian equivalent of the MOSAIC study, the MASCOT study was selected. The MASCOT was a multicenter, open-label, single-arm study of adjuvant treatment with the FOLFOX4 for stage II and III colon cancer.¹⁵ Objectives were to assess the safety and tolerability of FOLFOX4, and the study design was almost identical to that of the FOLFOX4 arm in the MOSAIC study. A total of 162 patients were enrolled in 5 Asian countries, China, Hong Kong, Korea, Taiwan, and Thailand, and the safety analysis was performed on 159 patients. EFC2962 was a multicenter, open-label, randomized phase III study in previously untreated patients with metastatic colorectal cancer.⁴ Among 420 patients enrolled in European countries and Israel, 210 were assigned to the FOLFOX4 arm, and the safety analysis was performed on 209 patients. N9741 was a multicenter, open-label, randomized, 3-arm phase III study in previously untreated metastatic colorectal cancer.⁵ Among 795 patients enrolled in the United States and Canada, 267 were assigned to the FOLFOX4 arm, and the safety analysis was performed on 259 patients. EFC4584 was a

multicenter, open-label, randomized, 3-arm phase III study in patients with metastatic colorectal cancer that had progressed during or within 6 months of completion of first-line treatment with the irinotecan/5-FU/LV regimen.^{6,7} Among 821 patients enrolled in North America, 271 were assigned to the FOLFOX4 arm, and the safety analysis was performed on 268 patients. MOSAIC was a multicenter, international, open-label, randomized study of adjuvant treatment for patients with stage II and III colon cancer.^{13,14} Among 2246 patients enrolled in European countries, Australia, Israel, and Singapore, 1123 were assigned to FOLFOX4 arm, and the safety analysis was performed on 1108 patients.

Safety Analysis

All data collected prospectively from the 6 studies were provided in SAS version 8.1 format (SAS Institute, Cary, NC) and analyzed by the same programs. Descriptive analyses were done to evaluate demographic and baseline characteristics, dose duration, cumulative dose, and dose intensity. Percentages, medians, and ranges were provided to evaluate the comparability of patient populations of the 6 studies. All adverse events (AE) were graded by the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 1 (EFC2962, MOSAIC) or 2 (J-PMS, MASCOT, N9741, EFC4584), except for neurosensory AEs (NSAE) in J-PMS (the Neurotoxicity Criteria of Debiopharm, Lausanne, Switzerland [DEB-NTC]¹¹), and they were re-coded with the medical dictionary for regulatory activities (MedDRA) version 9.0. Eleven types of AEs were selected as medically relevant for FOLFOX4 treatment, grouped under the common MedDRA Preferred Terms, and subjected to further analyses. The examined toxicities included NSAE, neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, stomatitis, skin rash, allergic reaction, and interstitial pneumonia.

Statistical Analysis

The probability of NSAEs and diarrhea with grade 1, 2, and 3 was analyzed against oxaliplatin-cumulative dose by the Kaplan-Meier method. The statistical difference between each study was analyzed by a log-rank test.

Results

Demographic and Baseline Characteristics

The profile of 6 studies was summarized in Table 1, and the demographic and baseline characteristics of safety populations were compared in Table 2. In J-PMS, the patients were stratified into 2 groups: patients previously untreated with chemotherapy (PUT), and those previously treated with chemotherapy (PT). The ratio of patients with age <65 years to ≥65 years was approximately 6:4 in the 5 studies; there were more patients <65 years enrolled in MASCOT. The male-female ratio was approximately 6:4 and was well balanced in all studies. Although a small number of oriental or Asian patients were included in the Western studies (0.5%-2%), their influence on the objective of this analysis (comparison of ethnic differences) was deemed negligible. Body surface area was greater in Western than in Asian studies. Performance status (PS) of most of the patients was 1 in all studies, although a small number of PS-3/4 patients were included in J-PMS. In J-PMS, the patients with the worse PS and lower neutrophil, platelet, and hemoglobin counts were enrolled than in

EFC2962, N9741, or EFC4584 studies. In MOSAIC, baseline hematology data were not recorded in the database. The patients with rectosigmoid cancer as the primary site were included in both MOSAIC and MASCOT.

Dose Intensity of Oxaliplatin and 5-FU

Because the information on total doses and dose intensities of oxaliplatin and 5-FU was considered important for the comparison of safety profiles, these parameters were analyzed (Table 3). The administration duration of FOLFOX4 and the cumulative dose of oxaliplatin and 5-FU were lower in J-PMS than in Western studies. For PUT patients in J-PMS, the median dose duration was 21 weeks versus 28 and 24 weeks in EFC2962 and N9741, respectively, and the oxaliplatin-cumulative dose was 657 mg/m² versus 839 mg/m² and 765 mg/m² in EFC2962 and N9741, respectively. Similarly, the oxaliplatin-cumulative dose in PT patients in J-PMS was a little lower than that in EFC4584 (500 mg/m² versus 589 mg/m²). However, the dose intensities in J-PMS were similar to those in Western studies: 33 for PUT patients versus 33 mg/m²/week and 36 mg/m²/week in EFC2962 and N9741, respectively, and 33 for PT patients versus 36 mg/m² in EFC4584. All dosing parameters in MASCOT were comparable with MOSAIC, which indicated that oxaliplatin and 5-FU could have been administered to Asian and Western patients similarly in the adjuvant setting.

Incidence of 11 Common AEs

The incidences of 11 medically relevant AEs for FOLFOX4 treatment were compared (Table 4). The most frequently reported AEs were NSAEs, hematologic, and gastrointestinal. The incidences of grade 1 AEs were not markedly different in Asian and in Western studies: NSAEs 51% (574 of 1134)-84% (133 of 159) and 75% (201 of 268)-92% (1020 of 1108), neutropenia 55% (627 of 1134)-88% (140 of 159) and 58% (155 of 268)-83% (216 of 259), anemia 36% (80 of 222 or 407 of 1134)-69% (110 of 159) and 20% (53 of 268)-76% (159 of 209 or 838 of 1108), thrombocytopenia 42% (477 of 1134)-74% (117 of 159) and 16% (44 of 268)-77% (858 of 1108), nausea 47% (105 of 222 or 534 of 1134)-84% (134 of 159) and 68% (181 of 268)-74% (817 of 1108), vomiting 23% (50 of 222)-59% (94 of 159) and 41% (106 of 259)-54% (113 of 209), diarrhea 17% (189 of 1134)-59% (94 of 159) and 56% (624 of 1108)-66% (172 of 259), and stomatitis 13% (28 of 222 or 153 of 1134)-52% (83 of 159) and 23% (61 of 268)-44% (92 of 209), respectively. The incidences of grade 1 skin rash, allergic reaction, and interstitial pneumonia were lower than those of other AEs in both Asian and Western studies.

The incidences of grade 3 AEs were compared between the paired Asian and Western studies with similar patient characteristics. The ratio of incidences of grade 3 NSAEs of PUT in J-PMS to EFC2962 was 2.7:19 (0.14), that of PUT in J-PMS to N9741 was 2.7:18 (0.15), that of PT in J-PMS to EFC4584 was 1.9:9.3 (0.20), and that of MASCOT to MOSAIC was 4.4:12 (0.37), which indicated that the incidences were markedly less in Asian studies than in Western studies. Similarly, the ratio of incidences of grade 3 diarrhea of PUT in J-PMS to EFC2962 was 1.4:12 (0.12), that of PUT in J-PMS to N9741 was 1.4:14 (0.10), that of PT in J-PMS to EFC4584 was 1.7:11 (0.15), and that of MASCOT to MOSAIC was 6.3:11 (0.57), which indicated that the incidences were also markedly less in

Asian studies than in Western studies. The incidences of other grade 3 AEs, including neutropenia and allergic reaction, did not show any marked trends of ethnic difference.

Histogram of Incidences of 4 AEs

To know the incidences of NSAEs, neutropenia, diarrhea, and allergic reaction by cycle, histograms were constructed in all studies (Figure 1). Patient numbers on the first day of each cycle decreased differently in each study with increase in FOLFOX4 treatment cycles (Figure 1A, C, *x*-axis). The incidences of NSAEs (Figure 1A) and allergic reaction (Figure 1D) increased with increase of FOLFOX4 cycles in all studies. However, the incidences of neutropenia and diarrhea remained relatively constant throughout FOLFOX4 cycles in all studies (Figure 1B and C, respectively). There was no marked difference observed in overall incidences of 4 AEs between the 2 Asian and the 4 Western studies. However, grade 3 NSAEs and diarrhea showed trends to a lower incidence in J-PMS and MASCOT than in the 4 Western studies.

Kaplan-Meier Curves

Based on the results of a lower incidence of grade 3 NSAEs and diarrhea in J-PMS and MASCOT, the relationship between the oxaliplatin-cumulative dose and the probability of grade 1, 2, or 3 NSAEs and diarrhea was further analyzed by the Kaplan-Meier method (Figure 2). Interestingly, the probability of grade 3 NSAEs and diarrhea in J-PMS showed a pattern similar to that in MASCOT and was lower than that observed in the 4 Western studies. Statistical analysis was performed between the 2 paired studies, with similar patient characteristics by a log-rank test. The probability of grade 3 NSAEs in J-PMS, in which 84% (1134 of 1356) of patients were PUT, was statistically significantly lower than that in EFC4584 ($P < .001$). Similarly, that of grade 3 NSAEs in MASCOT was statistically significantly lower than that in MOSAIC ($P < .001$). The probability of grade 3 diarrhea was also statistically significantly lower in J-PMS than in EFC4584 ($P < .001$) and in MASCOT than in MOSAIC ($P < .05$). When the patterns of Kaplan-Meier curves in Figure 2 and the results of statistical analysis are considered collectively, we concluded that the incidences of grade 3 NSAEs and diarrhea were significantly lower in Asian than in Western studies. The similar trends of low incidence of NSAEs and diarrhea in Asian studies were also observed in grade 1 and 2. However, the results were not as dramatic compared with those for grade 3.

Discussion

In this study, the ethnic differences in safety profile after the FOLFOX4 treatment were compared between the 2 Asian studies and the 4 Western studies. J-PMS was a Post Market Surveillance to comply with a conditional approval commitment, and its design was thus different from the 5 other studies. Treatment regimens used were not limited to FOLFOX4 but only to those patients who were to receive a standard FOLFOX4 regimen were extracted in our analysis. As a result, the dose intensity in the population used in this analysis was similar to that in the 5 other studies (Table 3). Dose duration (weeks) and oxaliplatin-cumulative dose were lower in PUT patients in J-PMS than in EFC2962 and N9741, and in PT patients in J-PMS than in EFC4584, which may be associated with the enrollment of

patients with more advanced diseases in J-PMS than in the 5 other studies, as evidenced by baseline characteristics and, furthermore, the inclusion of patients for third-line or later treatment in PT of J-PMS (Tables 1, 2). However, dose duration and oxaliplatin-cumulative dose in MASCOT were almost equivalent to those in MOSAIC (Table 3). When taking into account these results, the comparison of safety data between the 2 Asian and the 4 Western studies was considered feasible and informative. Our results with the FOLFOX4 regimen will also be extrapolated to other oxaliplatin-containing regimens, including mFOLFOX6.

The results in Table 4 demonstrated that the incidences of the 9 most common AEs, excluding NSAEs and diarrhea, in patients enrolled in Asian studies were not markedly different from those in Western studies. The comparisons of neutropenia or allergic reaction shown in Figure 1 support the above conclusion, which indicate that FOLFOX4 can be given to Asian patients without worsening safety compared with Western patients. Interestingly, the incidences of grade 3 NSAEs and diarrhea were lower in the Asian than in the Western studies (Table 4; Figure 1). Further analysis of the relationship between the oxaliplatin-cumulative dose and the probability of NSAEs and diarrhea revealed that the probability of these AEs in J-PMS and MASCOT was statistically significantly lower than that in the corresponding Western studies with similar patient characteristics (Figure 2).

Grade 3 NSAEs were defined as “the functional impairment/interfering with ADL (activities of daily living).” They accrued only late in the course of oxaliplatin therapy and are thought to be different from acute NSAEs. Lecomte et al²³ reported that polymorphisms of the *GSTP1* gene correlated with the risk of delayed NSA by oxaliplatin. Recent retrospective pharmacogenetic analysis of the N9741 study demonstrated that a homozygous variant genotype for *GSTP1* was more commonly associated with the discontinuation of FOLFOX treatment due to neurotoxicity.²⁴ Because the frequencies of polymorphisms are known to differ among ethnic groups, the ethnic difference observed in our analysis may be explained by such mechanisms characteristic to delayed-type NSAEs. Gamelin, who first initiated Ca-Mg therapy, reported that Ca oxalate was the cause of NSAEs and the polymorphisms of the *AGT* gene, which was involved in the metabolism of oxalate, affected the incidence of NSAEs.²⁵ Such gene polymorphisms may also have been involved in the ethnic difference in the incidence of NSAEs in our analysis. Other possible explanations are that environmental and cultural factors such as patient's lifestyle, tolerance to or care for neurologic abnormality, and so forth, may have been relevant. The care for NSAEs may have been more in patients of J-PMS and MASCOT. Further investigations are expected in these regards.

Another grade 3 AE, the incidence of which was lower in Asian studies, was diarrhea (Table 4; Figure 2). It was reported by a multivariate analysis of an adjuvant colon cancer study that the relative risk of grade 3/4 treatment-related gastrointestinal AEs induced by fluoropyrimidines in US patients was more than 3 times higher than that in Eastern Asian patients.²⁶ The low incidence of grade 3 diarrhea observed in Asian studies compared with Western studies in our analysis may have been associated with 5-FU included in the FOLFOX4 regimen.

The main feature of our analysis is that all AEs recorded in the database of each study were recoded by using MedDRA, and the data of the 6 studies were reanalyzed by using the same SAS program. As a result, the data obtained were appropriately normalized to permit an accurate interstudy comparison of the results. Because of this, minor inconsistencies may be detected between the data reported in this article and those in the original articles.^{4-7,13-15} These inconsistencies can be explained by the following:

- Definitions and handling of dose-related data in our analysis might be slightly different from those in the original articles in terms of significant figures, rounding of data, and missing data.
- For the 11 common AEs, the grouping of synonym terms in MedDRA Preferred Terms was performed.

Even if these inconsistencies might exist, they would not result in any problematic effect on the comparison of ethnic differences.

Our results have some limitations. The safety analysis was retrospective, and the enrollment periods of the 6 studies were different. The design of J-PMS was different from the other 5 studies, although only the patients who received a standard FOLFOX4 regimen were selected. Nonetheless, the demographic and baseline characteristics in Table 2 and the treatment duration, cumulative dose, and dose intensity of oxaliplatin and 5-FU in Table 3 support our interpretations. This pooled analysis can have great impact on the ability for a patient to receive adjuvant FOLFOX versus standard 5-FU-based therapy.

Conclusion

The comparison of safety profiles of the FOLFOX4 treatment between 1515 Asian patients and 1844 Western patients demonstrated that there was no evidence that Asian patients experienced worse toxicity than Western patients, which indicates that regular FOLFOX4 treatment is also feasible for Asian patients. The trends toward reduced grade 3 neurotoxicity and diarrhea were observed in Asian patients, which suggest the existence of ethnic differences in these AEs.

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Clinical Practice Points

- FOLFOX4 became a standard regimen in Western countries for the treatment of metastatic colorectal cancer and as adjuvant treatment of colon cancer.
- Its efficacy and safety were also reported in Asian and Japanese studies; however, these studies included fewer patients.
- The safety profile of FOLFOX4 regimen was compared between 1515 Asian patients and 1844 Western patients.
- Demographic and baseline characteristics, doses administered and safety parameters were analyzed by using common definitions and programs. The results indicated that the comparison was feasible and informative.
- There was no evidence that Asian patients experienced worse toxicity than did Western patients, which indicated that FOLFOX4 treatment is also feasible for Asian patients.
- Unexpectedly, the probability of grade 3 neurosensory adverse effects in J-PMS was statistically significantly lower than that in EFC4584 and in MASCOT than in MOSAIC. The probability of grade 3 diarrhea was also statistically significantly lower in J-PMS than in EFC4584 and in MASCOT than in MOSAIC.
- These results suggest the existence of ethnic differences in these adverse effects.
- The FOLFOX4 regimen can be safely applied for Asian patients with more confidence, as well as for Western patients. These results will be extrapolated to other FOLFOX regimens, including mFOLFOX6.
- New drugs, including molecular-targeting agents, can be applied more easily for Asian patients when combined with FOLFOX regimens.
- The results of grade 3 neurotoxicity and diarrhea suggest the ethnic difference in pharmacogenomics between Asian and Western patients.

Figure 1.

Histogram of Incidences of Four Adverse Events (AE) by Cycle. Any Grade and Grade 3 Neurosensory AEs (A), Neutropenia (B), Diarrhea (C), and Allergic Reaction (D) in Japanese Post Marketing Surveillance (1), MASCOT (2), EFC2962 (3), N9741 (4), EFC4584 (5), and MOSAIC (6) Studies. The Patient Number at the First Day of Each Cycle was Shown Below the *x*-Axis in Each Study of (A-1) to (A-6) and (C-1) to (C-6)

Figure 2. Kaplan-Meier Curves. Neurosensory Adverse Events (AE) of Grade 1 (A), 2 (B), and 3 (C), and Diarrhea of Grade 1 (D), 2 (E), and 3 (F). The Patient Number of Each AE at 200, 600, 1000, 2000, and 3000 mg/m² of Oxaliplatin-cumulative Dose Was Shown Below the x-Axis in Each Study

Table 1

Profile of 6 FOLFOX4 Studies

Items	Asian Studies				Western Studies			
	J-PMS		MASCOT	EFC2962	N9741	EFC4584	MOSAIC	
	PUT	PT						
Phase of Study	PMS		IV	III	III	III	III	
Patients	Metastatic		Stage II/III	Metastatic	Metastatic	Metastatic	Stage II/III	
Treatment Line	First	Second	Adjuvant	First	First	Second	Adjuvant	
Arms	NA		1	2	3	3	2	
Primary Endpoint	Safety		Safety	PFS	TTP	OS	DFS	
Patient Number of FOLFOX4 Arm								
ITT Population	NA	NA	162	210	267	271	1123	
Safety population	222	1134	159	209	259	268	1108	
Enrollment Period (Range)	April 2005; March 2006		August 2004; December 2006	August 1995; July 1997	May 1999; April 2001	November 2000; February 2002	October 1998; January 2001	
Study Countries	Japan		Asia, 5 countries	Europe, Israel	United States, Canada	North America	Europe, Australia, Israel, Singapore	

Abbreviations: DFS = disease-free survival; FOLFOX4 = 5-fluorouracil/leucovorin/oxaliplatin; ITT = intent to treat; J-PMS = Post Marketing Surveillance study; NA = not applicable; OS = overall survival; PFS = progression-free survival; PT = previously treated with chemotherapy; PUT = previously untreated with chemotherapy; TTP = time to tumor progression.

Table 2

Demographic and Baseline Characteristics

Parameters	Asian Studies				Western Studies			
	J-PMS		Total Any Lines	MASCOT Adjuvant	N9741		EFC4584 Second Line	MOSAIC Adjuvant
Treatment	PUT First Line	PT Second Line			First Line	First Line		
Total No. Patients	222	1134	1356	159	209	259	268	1108
Median Age (range) (y)	62 (21-79)	62 (19-84)	62 (19-84)	55 (20-74)	63 (20-76)	61 (27-88)	59 (22-88)	61 (19-75)
Age, No. (%)								
<65y	132 (59)	675 (60)	807 (60)	119 (75)	124 (59)	160 (62)	172 (64)	715 (65)
65y	90 (41)	459 (40)	549 (40)	40 (25)	85 (41)	99 (38)	96 (36)	393 (35)
Sex, No. (%)								
Men	129 (58)	756 (67)	885 (65)	88 (55)	126 (60)	153 (59)	151 (56)	624 (56)
Women	93 (42)	378 (33)	471 (35)	71 (45)	83 (40)	106 (41)	117 (44)	484 (44)
Race, No. (%)								
White	0 (0)	0 (0)	0 (0)	0 (0)	207 (99)	231 (89)	234 (87)	1070 (97)
Oriental/Asian	222 (100)	1134 (100)	1356 (100)	158 (99)	1 (0.5)	4 (2)	6 (2)	23 (2)
Other	0 (0)	0 (0)	0 (0)	1 (1)	1 (0.5)	24 (9)	28 (10)	15 (1)
BSA, No. (%)								
<1.5 m ²	67 (30)	291 (26)	358 (26)	36 (23)	17 (8)	7 (3)	9 (3)	80 (7)
1.5 m ²	155 (70)	843 (74)	998 (74)	123 (77)	192 (92)	252 (97)	259 (97)	1028 (93)
PS, No. (%)								
0-1	214 (96)	1066 (94)	1280 (94)	158 (99)	187 (89)	244 (94)	261 (97)	1101 (99)
2	7 (3)	56 (5)	63 (5)	1 (0.6)	22 (11)	15 (6)	7 (3)	7 (0.6)
3	1 (0.5)	12 (1)	13 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Previous Chemotherapy, No. (%) ^a								
No	222 (100)	0 (0)	222 (16)	159 (100)	209 (100)	259 (100)	4 (1)	1108 (100)
Yes	0 (0)	1134 (100)	1134 (84)	0 (0)	0 (0)	0 (0)	264 (99)	0 (0)
Neutrophil Count, No. (%) ^b								
<2000/mm ³	11 (6)	62 (6)	73 (6)	12 (8)	1 (0.5)	0 (0) ^c	8 (3)	ND

Parameters	Asian Studies				Western Studies			
	J-PMS		MASCOT		EFC2962		EFC4584	
Treatment	PUT First Line	PT Second Line	Total Any Lines	Adjuvant	First Line	First Line	Second Line	Adjuvant
2000/mm ³	176 (94)	910 (94)	1086 (94)	146 (92)	208 (100)	222 (100) ^c	260 (97)	ND
Platelet Count, No. (%) ^b								
<10 ⁵ /mm ³	2 (1)	15 (1)	17 (1)	0 (0)	0 (0)	0 (0)	0 (0)	ND
10 ⁵ /mm ³	220 (99)	1116 (99)	1336 (99)	159 (100)	209 (100)	222 (100)	268 (100)	ND
Hemoglobin, No. (%) ^b								
<12 g/dL	118 (53)	579 (51)	697 (52)	83 (52)	87 (42)	91 (41)	113 (42)	ND
12 g/dL	103 (47)	552 (49)	655 (48)	76 (48)	121 (58)	131 (59)	155 (58)	ND

Abbreviations: BSA = body surface area; J-PMS = Post Marketing Surveillance study; ND = no data; PS = performance status; PT = previously treated with chemotherapy; PUT = previously untreated with chemotherapy.

^aThe adjuvant chemotherapy was not considered as the previous chemotherapy.

^bPatients with missing data were excluded from analysis.

^cGranulocyte count was analyzed instead of neutrophil count.

Table 3
Dose Duration, Cumulative Dose and Dose Intensity (in median [range]) of Oxaliplatin and 5-Fluorouracil

Parameters	Asian Studies				Western Studies			
	J-PMS		Total	MASCOT	EFC2962	N9741	EFC4584	MOSAIC
	PUT	PT						
FOLFOX4								
Treatment, wk	21 (2-89)	16 (2-104)	17 (2-104)	26 (2-43)	28 (2-93)	24 (2-98)	18 (2-71)	26 (2-42)
Treatment cycles	8 (1-31)	6 (1-34)	7 (1-34)	12 (1-12)	12 (1-35)	10 (1-47)	7 (1-28)	12 (1-12)
Oxaliplatin								
Cumulative dose (mg/m ²)	657 (80-2635)	500 (21-2912)	510 (21-2912)	967 (85-1036)	839 (83-2356)	765 (84-2959)	589 (83-2253)	888 (7-1064)
Dose intensity (mg/m ² /week)	33 (12-45)	33 (11-47)	33 (11-47)	35 (17-43)	33 (9-52)	36 (9-50)	36 (18-50)	34 (3-44)
Bolus 5-Fluorouracil								
Cumulative dose (mg/m ²)	5600 (774-24,812)	4505 (0-27,411)	4668 (0-27,411)	8598 (800-9720)	8624 (400-27,821)	6299 (0-37,612)	5471 (0-22,357)	8483 (0-10,107)
Dose intensity (mg/m ² /week)	297 (71-413)	299 (0-444)	298 (0-444)	319 (196-402)	320 (196-405)	309 (0-546)	338 (0-410)	332 (0-421)
Infusion 5-Fluorouracil								
Cumulative dose (mg/m ²)	9307 (1158-46,375)	7133 (0-42,772)	7200 (0-46,375)	13,400 (1200-14,815)	13,188 (600-41,732)	9581 (0-55,227)	8347 (0-33,537)	13,200 (0-15,918)
Dose intensity (mg/m ² /week)	471 (180-843)	468 (0-1125)	470 (0-1125)	496 (301-603)	486 (300-604)	467 (0-638)	510 (0-830)	509 (0-663)

Abbreviations: FOLFOX4 = 5-fluorouracil/leucovorin/oxaliplatin; J-PMS = Post Marketing Surveillance study; PT = previously treated with chemotherapy; PUT = previously untreated with chemotherapy.

Table 4

Incidence of 11 Common Adverse Events

Parameters	Asian Studies				Western Studies			
	J-PMS			MASCOT (n = 159)	EFC2962 (n = 209)	N9741 (n = 259)	EFC4584 (n = 268)	MOSAIC (n = 1108)
	PUT (n = 222)	PT (n = 1134)	Total (n = 1356)					
Neurosensory, No. (%)								
Any grade	130 (59)	574 (51)	704 (52)	133 (84)	173 (83)	207 (80)	201 (75)	1020 (92)
Grade 3	6 (2.7)	21 (1.9)	27 (2.0)	7 (4.4)	39 (19)	47 (18)	25 (9.3)	137 (12)
Neutropenia, No. (%)								
Any grade	141 (64)	627 (55)	768 (57)	140 (88)	155 (74)	216 (83)	155 (58)	874 (79)
Grade 3	95 (43)	422 (37)	517 (38)	83 (52)	93 (44)	144 (56)	124 (46)	455 (41)
Anemia, No. (%)								
Any grade	80 (36)	407 (36)	487 (36)	110 (69)	159 (76)	70 (27)	53 (20)	838 (76)
Grade 3	9 (4.1)	94 (8.3)	103 (7.6)	1 (0.6)	7 (3.3)	7 (2.7)	13 (4.9)	9 (0.8)
Thrombocytopenia, No. (%)								
Any grade	101 (45)	477 (42)	578 (43)	117 (74)	142 (68)	185 (71)	44 (16)	858 (77)
Grade 3	21 (9.5)	75 (6.6)	96 (7.1)	1 (0.6)	5 (2.4)	12 (4.6)	13 (4.9)	19 (1.7)
Nausea, No. (%)								
Any grade	105 (47)	534 (47)	639 (47)	134 (84)	151 (72)	184 (71)	181 (68)	817 (74)
Grade 3	17 (7.7)	63 (5.6)	80 (5.9)	5 (3.1)	12 (5.7)	16 (6.2)	26 (9.7)	56 (5.1)
Vomiting, No. (%)								
Any grade	50 (23)	300 (26)	350 (26)	94 (59)	113 (54)	106 (41)	118 (44)	523 (47)
Grade 3	5 (2.3)	40 (3.5)	45 (3.3)	6 (3.8)	12 (5.7)	9 (3.5)	23 (8.6)	65 (5.9)
Diarrhea, No. (%)								
Any grade	42 (19)	189 (17)	231 (17)	94 (59)	123 (59)	172 (66)	174 (65)	624 (56)
Grade 3	3 (1.4)	19 (1.7)	22 (1.6)	10 (6.3)	25 (12)	36 (14)	30 (11)	120 (11)
Stomatitis, No. (%)								
Any grade	28 (13)	153 (13)	181 (13)	83 (52)	92 (44)	99 (38)	61 (23)	461 (42)
Grade 3	1 (0.5)	8 (0.7)	9 (0.7)	2 (1.3)	12 (5.7)	0 (0)	5 (1.9)	30 (2.7)

Parameters	Asian Studies				Western Studies			
	J-PMS			MASCOT (n = 159)	EFC2962 (n = 209)	N9741 (n = 259)	EFC4584 (n = 268)	MOSAIC (n = 1108)
	PUT (n = 222)	PT (n = 1134)	Total (n = 1356)					
Skin Rash, No. (%)								
Any grade	8 (3.6)	38 (3.4)	46 (3.4)	1 (0.6)	6 (2.9)	34 (13)	42 (16)	12 (1.1)
Grade 3	0 (0)	2 (0.2)	2 (0.1)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)
Allergic Reaction, No. (%)								
Any grade	18 (8.1)	36 (3.2)	54 (4.0)	40 (25)	15 (7.2)	32 (12)	17 (6.3)	114 (10)
Grade 3	5 (2.3)	7 (0.6)	12 (0.9)	5 (3.1)	4 (1.9)	4 (1.5)	3 (1.1)	33 (3.0)
Interstitial Pneumonia, No. (%)								
Any grade	1 (0.5)	4 (0.4)	5 (0.4)	0 (0)	0 (0)	10 (3.9)	0 (0)	2 (0.2)
Grade 3	1 (0.5)	3 (0.3)	4 (0.3)	0 (0)	0 (0)	6 (2.3)	0 (0)	0 (0)

Abbreviations: J-PMS = Post Marketing Surveillance study; PT = previously treated with chemotherapy; PUT = previously untreated with chemotherapy.