that the surgical morbidity and mortality were almost similar between surgery alone and surgery following the neoadjuvant chemotherapy; however, the surgical procedures were less than D2 in most cases in the UK study and were not accurately described in the French study.[8,12] Only one European phase III study has compared D2 alone and D2 following the neoadjuvant chemotherapy. In that study, the overall morbidity was higher and injury of major blood vessels was more frequent in the neoadjuvant group than in the surgery alone group.[13]

Generally, chemotherapy acts for tumor tissue and induces variety changes of both tumor and stroma including necrosis, inflammation, and fibrosis, which makes D2 surgery difficult.[14] Although experienced surgeons may complete D2 after neoadjuvant chemotherapy safely as reported in several Japanese phase II studies of single arm, surgical complication is unavoidable.[15–18] Accidental in jury of major blood vessels during surgery may cause lethal complication. If risk factor for complications is clarified, it becomes possible to determine appropriate indication and surgical procedure considering the balance between the risk and the benefit.

Previously, only Fujitani et al. reported that age greater than 60 years and high body mass index were significant risk factors for overall complications in 71 patients who received gastrectomy following induction chemotherapy and preoperative chemoradiotherapy in the retrospective analysis of M.D. Anderson Cancer Center.[19] However, their report was based on a retrospectively collected data in which most patients received induction chemoradiotherapy. Complication was not determined following Clavien-Dindo classification. Moreover, surgical procedure had not been strictly limited to D2.

The purpose of the present study is to identify risk factors of postoperative complications after D2 surgery following neoadjuvant chemotherapy. This study was conducted as an exploratory analysis of a prospective, randomized, Phase II trial of neoadjuvant chemotherapy.

PATIENTS AND METHODS

The patients who received neoadjuvant chemotherapy and D2 gastrectomy as a protocol treatment in the phase II trial were examined in this study. The details of this trial were described in the previous report.[20,21] Briefly, key eligibility included clinical T2-3/N+ or clinical T4aN0 in case of scirrhous or junction tumors, clinical T2-3 with nodal metastasis to the major branched artery, clinical T4aN+, clinical T4b, para-aortic nodal metastases, or resectable minimal peritoneal metastases confirmed by laparoscopy. Staging laparoscopy was mandatory to diagnose peritoneal metastasis. Eligible patients were randomized to two courses of S-1 plus cisplatin, four courses of S-1 plus cisplatin, two courses of Paclitaxel plus cisplatin, or four courses of Paclitaxel plus cisplatin. The sample size was calculated to be 60–80 in a total considering a statistical power of approximately 0.8.

Neoadjuvant Chemotherapy

In S-1 plus cisplatin regimen, S-1 80 mg/m^2 was given orally twice daily for the first 3 weeks of a 4-week cycle and cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle as described previously.[20,21] In Paclitaxel plus cisplatin regimen, Paclitaxel 60 mg/m^2 and cisplatin 25 mg/m^2 were administered on days 1, 8, and 15 as 1 course, repeated every 4 weeks.[20,21] Neoadjuvant chemotherapy was discontinued if there was documented disease progression, unacceptable toxicity, or withdrawal of consent.

Surgery

During 2–6 weeks after completion of neoadjuvant chemotherapy or when the tumors progressed during the treatment, patients proceeded to surgery. R0 resection was aimed by gastrectomy with standard D2 lymphadenectomy.[2] Para-aortic nodal dissection or combined resection of small part of the peritoneum or adjacent organs are permitted for the curative intent but more invasive surgery, such as pancreaticoduodenectomy or Appleby's surgery are not. When macroscopically curative surgery was achieved, protocol treatment was terminated.

Evaluation

Clinical diagnosis of T and N was determined by thin-slice CT with 5- to 7-mm thickness or multidetector low CT following Habermann's method.[22] T1 tumors were defined as those that could not be found on the images or those with focal thickening of the inner layer with a visible outer layer of the gastric wall and a clear fat plane around the tumor. T2-3 tumors were defined as those with focal or diffuse thickening of the gastric wall with transmural involvement and a smooth outer border of the wall or only a few small linear strands of soft tissue extending into the fat plane involving less than one-third of the tumor extent. T4a tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent or wide reticular strands surrounding the outer border of the tumor. T4b tumors were defined as those with obliteration of the fat plane between the gastric tumor and the adjacent organ or invasion of an adjacent organ. Regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter. Progression of tumors was evaluated by the 14th edition of the Japanese Gastric Cancer Classification.[2] Clinical response of the lymph node was evaluated by

version 1.0 of the Response Evaluation Criteria for Solid Tumors.[23] The surgical complications were assessed and classified according to the Clavien–Dindo classification.[24] The incidence of reoperation and the length of hospital stay also were recorded. Operative mortality was defined as postoperative death from any cause within 30 days after surgery or during the same hospital stay.

Statistical Analysis

A uni- and multivariate logistic regression analyses was performed to identify risk factors for morbidity. Comparisons between the two groups were analyzed by chi-square test. In the multivariate analysis, we fitted linear regression models. To select a model, we used backward elimination. All statistical tests were two-sided, and significance was set at $P < 0.05$.The SPSS software package (v11.0 J Win, SPSS, Chicago, IL) was used for all statistical analyses.

Ethical Review

The COMPASS phase II trial had been approved in all institutions and confirmed to all patients who registered to this trial. This exploratory analysis was attached to the COMPASS phase II trial.

RESULTS

Patient's Characteristics

Between October 2009 and July 2011, a total of 83 patients were registered to the COMPASS trial. Among them, 69 patients received the neoadjuvant chemotherapy and D2 gastrectomy. On the other hands, 14 patients did not receive gastrectomy because curative D2 surgery was not possible. Six patients did not receive surgery based on the CT findings, two received bypass surgery because of the stenosis of the primary lesion, and six underwent palliative D1 surgery due to bleeding or stenosis. Characteristics of 69 patients before neoadjuvant chemotherapy are shown in Table 1. The operative details are shown in Table 2. The background factors and operative procedures were well balanced between the two regimens.

Operative Morbidity and Mortality

Postoperative complications were found in 18 among 69 patients (26.1 %). No surgical mortality was observed. Details of complications are shown in Table 3. Pancreatic fistula was found in 13 % in all grades and in 1.4 % in grade 3 or more, anastomotic leakage was 4.3 % in all grades and in 2.9 % in grade 3 or more, and abdominal abscess was 4.3 % in all grades and in 1.4 % in grade 3 or more. No patient required reoperation. No mortality was observed.

Risk Factors for Operative Morbidity

Risk factors for surgical morbidity were analyzed by uni- and multivariate analyses using clinical factors determined before the enrollment of the study. The results are summarized in Table 4. Among these, creatinine clearance (CCr) $\leq$ 60 ml/min ($P = 0.016$) was identified as sole significant independent risk factor for overall morbidity. Median value of CCr (range) was 54 ml/min (42–60 ml/min) in patients with creatine clearance $\leq$60 ml/min and 78 ml/min (61–143 ml/min) in patients with creatine clearance >60 ml/min. Table 5 shows the details of the complications after D2 gastrectomy between the two groups. Occurrence of pancreatic fistula was significantly different between the two groups. Pleural effusion was tended to be higher in patients with creatine clearance $\leq$60 ml/min compared with patients with creatine clearance >60 ml/min.

DISCUSSION

This is the first report to evaluate the risk factors for morbidity of D2 gastrectomy after neoadjuvant chemotherapy (NAC) in patients with gastric cancer. The present study demonstrated that creatinine clearance (CCr) was the only independent risk factor for surgical complications. Therefore, careful attention is required in patients with low CCr when surgeons consider D2 gastrectomy after NAC.

In this study, creatinine clearance (CCr) was the only independent risk factor for surgical complications in the patients who received D2 gastrectomy after NAC. Generally, impaired renal function had the decreased immunity, decreased ability of wound healing, prolonged fluid retention, and anemia.[25] Prolonged fluid retention may cause peripheral edema, ascites, and pleural effusion. In the present study, pleural effusion was tended to be high in patients with low CCr. Moreover, the patients with low CCr had more pancreatic fistula than those with high CCr. However, previous reports demonstrated that renal function was not selected as risk factor for primary surgery.[26,27] Renal function is related with clearance of anticancer drug, such as Cisplatin (CDDP).[28] High concentration of CDDP in the patients with low CCr may cause more tissue damage than those with high CCr, which may be related to complications.[14] Moreover, median value of CCr in patients with low CCr was 54 ml/min, which suggested that their renal function was not severely disturbed. Exact mechanisms for CCr as a risk factor should be clarified in the future.

TABLE 1 Patient's characteristics

	S-1 + Cisplatin	Paclitaxel + Cisplatin	Total
Patients number	34	35	69
Male/female	23/11	26/9	49/20
Age (yr), median (range)	66 (32–79)	66 (44–77)	66 (32–77)
Performance status 0/1	34/0	34/1	68/1
BMI (kg/m^2), median (range)	21.1 (16.9–25.2)	21 (15.9–27)	21 (15.9–27)
Creatinine clearance (ml/min), median (range)	74.8 (42–120.4)	75.3 (47–143)	75 (42–143)
Clinical T factor 3/4a/4b	2/29/3	4/30/1	6/59/4
Clinical N factor 0/1/2	5/24/5	7/26/2	12/50/7
Metastasis status			
Negative	32	31	63
Cytology positive	2	4	6
Peritoneal metastasis	0	0	0
Esophagus invasion			
Negative	24	23	47
Positive	10	12	22
Macroscopic tumor type			
0	0	1	1
1	1	4	5
2	9	10	19
3	16	15	31
4	3	3	6
5	5	2	7
Pathologic tumor type			
Differentiated	14	15	29
Undifferentiated	20	20	40
Actual course of neoadjuvant chemotherapy			
1	2	1	3
2	21	16	37
3	1	2	3
4	10	16	26
Clinical response			
Complete response	1	0	1
Partial response	14	10	24
Stable disease	18	24	42
Progression disease	1	1	2

In the present study, age was a marginally significant risk factor in the univariate analysis but not in the multivariate analysis. Elderly patients often have comorbidities and age-related physiological problems, such as organ dysfunction. Fujitani et al. also demonstrated that age was one of risk factor for complications in patients who received gastrectomy following induction chemoradiotherapy.[19] Several reports showed that age was a risk factor for surgical complication for primary gastric cancer surgery.[26,27] Dutch phase III trial comparing D1 and D2 showed that age older than 65 years was a significant risk factor for hospital death and overall complications.[26] Kohn reported that many organ function decreases linearly after 30 years old.[29] Actually, the elderly patients had higher risk with 32 % than that of the nonelderly with 10.5 %. On the other hand, among the elderly, patients with high CCr had 25 % of morbidity, whereas those with low CCr had very high risk with 83.3 %. Thus, surgical risk could be well separated by combining CCr. CCr was significantly correlated with age ($r = -0.468$ and $P = 0.000$ by Pearson's correlation coefficient) in this cohort. CCr was significantly related with age in this cohort ($r = -0.468$,

TABLE 2 Operative details

	S-1 + Cisplatin	Paclitaxel + Cisplatin	Total
Gastrectomy			
Total	25	27	52
Distal	9	8	17
Esophagogastrectomy, yes/no	10/24	12/23	22/47
Splenectomy, yes/no	16/18	22/13	38/31
Pancreatectomy, yes/no	0/34	2/33	2/67
Bulsectomy, yes/no	3/31	7/28	10/59
Mediastinal lymphadenectomy			
None	34	34	68
Transhiatal	0	1	1
Blood loss (ml), median (range)	430 (60–1300)	440 (70–1990)	440 (60–1990)
Operation time (min), median (range)	242 (155–422)	262 (172–381)	254 (155–422)

TABLE 3 Details of complications

	Grade 1	Grade 2	Grade 3a/3b	Grade 4a/4b	Grade 5
Pancreatic fistula	4	4	1/0	0	0
Abdominal abscess	0	2	1/0	0	0
Anastomotic leakage	0	1	2/0	0	0
Pneumonia	1	0	0	0	0
Postoperative bleeding	1	2	1/0	0	0
Wound abscess	0	1	0	0	0
Anastomotic stenosis	0	1	0	0	0
Pleural effusion	2	0	0	0	0

$P = 0.000$ by Pearson's correlation coefficient). Morbidity rate was related with CCr in the elderly patients (11/44 in the patients with high CCr and 5/6 in those with low CCr), but the relationship was uncertain in the nonelderly patients (2/17 in the patients with high CCr and 0/2 in those with low CCr) because of small numbers. Generally, CCr decreases in the elderly patients. A value of CCr as a risk factor may be in the elderly patients.

In the primary D2 surgery, splenectomy and body mass index (BMI) were reportedly identified as the most significant independent risk factors.[26,30] However, splenectomy was not a risk factor both in uni- and multivariate analyses in the present study. This may be due to the difference of tumor progression and the effect of neoadjuvant chemotherapy. In the present study, most patients had clinical nodal metastases. Nodal dissection itself may become difficult due to fibrotic changes after neoadjuvant chemotherapy, which may increase the minimal risk due to spleen-preserving surgery up to the high risk observed in splenectomy. More, BMI was not an independent risk factor in this study, in contrast to JCOG9501 trial in which BMI >25 kg/m^2 was a significant risk factor for major surgical complications.[31] This discrepancy may be attributed to lower incidence of BMI > 25 kg/m^2. The proportion of patients BMI > 25 kg/m^2 was 7.2 % (5/69) in the present series as opposed to 14.7 % (77/523) in the JCOG9501 trial.

The present study has some limitations. First, sample size was relatively small, although this study is an exploratory analysis of prospective, multicenter, randomized phase II study. Second, our results would not be applicable for the different cohort, which has different tumor stage. Different risk factor may be selected if other cohort has relatively early disease for which prophylactic nodal dissection is enough. Third, the present study used the clinical data before the study entry other than the clinical response. We considered that surgical difficulties depended on the tumor progression before the chemotherapy. On the other hand, CCr or body mass index may change after chemotherapy. Although the CCr just before surgery was not collected in this study, CCr would be not changed or worsened in most cases. Body weight may decrease in some cases after chemotherapy. Thus, our results would underestimate the impact of CCr as risk factor but not overestimate. Forth, optimal cutoff values were unknown. In this study, we used the 60 ml/min as the cutoff value of CCr and 60 years as the cutoff value of age. Distribution, median, and average of the CCr of all patients were 41.0–143.0 ml/min, 73.15 ml/min, and 78.3 ± 19.1 ml/min. CCr of 60 ml/min was lower limit to guarantee the "unimpaired renal function" and was selected as one of the stratification factors in this trial. Therefore, we used the 60 ml/min as the cutoff value of CCr. Median age

TABLE 4 Univariate and multivariate analyses of risk factors for complications

Factors	No	No. of complications	Univariate analysis		Multivariate analysis	
			Relative risk	*P*	Relative risk	*P*
Age (yr)				0.086		
<60	19	2	1.000			
≥60	50	16	4.000 (0.823–19.44)			
Gender				0.19		
Female	20	3	1.000			
Male	49	15	2.499 (0.635–9.828)			
Body mass index				0.496		
<25	64	16	1.000			
≥25	5	2	2.000 (0.306–13.061)			
Type of gastrectomy				0.782		
Distal gastrectomy	17	4	1.000			
Total gastrectomy	52	14	1.197 (0.334–4.295)			
Splenectomy and/or pancreatomy				0.615		
Yes	38	9	1.000			
No	31	9	1.318 (0.449–3.871)			
Bulsectomy				0.761		
No	59	15	1.000			
Yes	10	3	1.257 (0.288–5.49)			
Clinical response				0.785		
SD-PD	44	11	1.000			
CR-PR	25	7	1.167 (0.385–3.5133)			
Clinical tumor invasion				0.674		
T4a	63	16	1.000			
T3	6	2	1.469 (0.245–8.794)			
Clinical lymph node metastasis				0.155		
N (−)	12	1	1.000			
N (+)	57	17	4.675 (0.559–39.113)			
Clinical esophagus invasion				0.562		
No	47	12	1.000			
Yes	22	6	1.094 (0.348–3.436)			
Clinical stage				0.587		
IV	6	1	1.000			
II or III	63	17	1.848 (0.201–16.974)			
Chemotherapy regimen				0.246		
Paclitaxel + Cisplatin	35	7	1.000			
TS-1 + Cisplatin	34	11	1.913 (0.639–5.727)			
Chemotherapy course				0.754		
3–4	29	7	1.000			
1–2	40	11	1.192 (0.398–3.573)			
Creatinine clearance (ml/min)				0.022		0.016
>60	61	13	1.000		1.000	
≤60	8	5	6.154 (1.297–29.197)		8.666 (1.487–50.509)	

of all the patients was 66 (range 32–79) years in this trial. Previously, Fujitani et al. demonstrated that age was one of risk factor for complications in patients who received gastrectomy following induction chemoradiotherapy.[19] In that report, they set the cutoff value as 60 years. Therefore, we set the cutoff value as 60 years in this study. Appropriate cutoff value should be determined in the other validation studies.

TABLE 5 Operative morbidity between CCr $\leq$ 60 ml/min and CCr > 60 ml/min

	CCr $\leq$ 60 ml/min (n = 8)		CCr > 60 ml/min (n = 61)		P
	No. of patients	(%)	No. of patients	(%)	
Pancreatic fistula	4	50	5	8.2	0.004
Abdominal abscess	1	12.5	2	3.3	0.215
Anastomotic leakage	0	0	3	4.9	0.814
Pneumonia	0	0	1	1.6	0.715
Postoperative bleeding	0	0	4	6.6	0.906
Wound abscess	0	0	1	1.6	0.715
Anastomotic stenosis	0	0	1	1.6	0.715
Pleural effusion	1	12.5	1	1.6	0.085

In summary, low CCr was a significant risk factor for surgical complications in D2 gastrectomy after NAC. Careful attention is required for these patients when surgeons consider D2 gastrectomy after NAC.

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CONFLICT OF INTEREST None declared.

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A Prospective Observational Study to Examine the Relationship between Quality of Life and Adverse Events of First-line Chemotherapy Plus Cetuximab in Patients with *KRAS* Wild-type Unresectable Metastatic Colorectal Cancer: QUACK Trial

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We have planned a multicentre prospective study to examine the relative impact of the efficacy and adverse events of cetuximab plus first-line chemotherapy on the quality of life in Japanese patients with *KRAS* wild-type unresectable colorectal cancer. The Dermatology Life Quality Index and the European Organization for Research Treatment of Cancer *Quality of Life Questionnaire Core 30 will be used to assess dermatology-specific and health-related quality of life. The severity of adverse events will be assessed by using the National Cancer Institute Common Terminology Criteria for adverse Events ver. 4.0.* The endpoints will be the following associations: adverse events, including skin toxicity and quality of life; efficacy and skin toxicity; efficacy and quality of life; and skin-related quality of life and health-related quality of life. A total of 140 patients are considered to be appropriate for inclusion in this study. The results of this study will provide more information to both patients and physicians regarding the practical use of cetuximab and its impact on *quality of life* in patients with unresectable colorectal cancer in Japan. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000010985.

Key words: quality of life – colorectal cancer – cetuximab

INTRODUCTION

Colorectal cancer (CRC) remains a major clinical challenge and is the second most common cancer and fourth leading cause of cancer-related death worldwide (1). Although CRC screening programmes including faecal occult blood test and colonoscopy have facilitated mortality reduction by removing precursor lesions and enabling diagnosis at an early stage (2), many patients have locally advanced or metastatic disease at the time of diagnosis.

Cetuximab (Erbitux®, Merck Serono, Darmstadt, Germany and Bristol-Myers Squibb, USA) is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of the epidermal growth factor receptor (EGFR) and induces anti-tumour effects by competitively inhibiting ligand-induced EGFR tyrosine kinase activation (3). Cetuximab initially showed efficacy against irinotecan-refractory and EGFR-positive metastatic CRC (4) and was approved by the US Food and Drug Administration (FDA) in 2004. However, genetic mutations of

KRAS, a downstream component of the EGFR signalling pathway, were found as biomarkers for cetuximab resistance (5), and the indication for cetuximab was amended to include *KRAS* wild-type metastatic CRC by the FDA in 2009. In the randomized Phase III CRYSTAL study, first-line FOLFIRI plus cetuximab provided a significant survival advantage over FOLFIRI alone for the treatment of *KRAS* wild-type metastatic CRC (23.5 vs. 20.0 months; hazard ratio 0.796; $P < 0.0094$) (6). Similar results were observed in the randomized Phase II OPUS study (7). Additionally, the pooled analysis of the CRYSTAL and OPUS studies demonstrated that the addition of cetuximab to first-line chemotherapy led to significant improvements in overall survival (OS; hazard ratio 0.81; $P = 0.0062$), progression-free survival (PFS; hazard ratio 0.66; $P < 0.001$) and overall response rate (ORR; odds ratio 2.16; $P < 0.0001$) (6). On the basis of these pivotal findings, the European Society for Medical Oncology guidelines recommended cetuximab plus FOLFIRI or FOLFOX as one of the standard first-line treatment regimens for patients with metastatic CRC (8).

While advances in treatment have been associated with increasing rates of survival, they are also associated with increased rates of long-term adverse events (9). Therefore, for patients with never resectable CRC who are asymptomatic or without imminent symptoms and at limited risk for rapid deterioration, the aim of therapy is to prevent tumour progression and prolong life while maintaining quality of life (QoL) (8). Importantly, incorporating the patient's perspective, including their values and priorities about treatment can assure personalized and appropriate shared decision making because those patients require information not only related to survival estimated, but also regarding HRQoL in the treatment (10,11). In the CRYSTAL study, the administration of FOLFIRI plus cetuximab was associated with significantly more severe skin toxicity (19.7 vs. 0.2%), including acne-like rash, dry skin, paronychia, infusion-related reactions (2.5 vs. 0%) and diarrhoea (15.7 vs. 10.5%) than administration of FOLFIRI alone (12). Of note, skin toxicity was generally observed during the early treatment phase and developed in >80% of patients receiving cetuximab (4), resulting in a restriction of daily activities, independence, patient satisfaction and compliance (13). Indeed, skin toxicity adversely affected skin-related QoL based on the Dermatology Life Quality Index (DLQI) (14). On the other hand, the severity of skin toxicity could predict the clinical benefit of cetuximab (15–17), and addition of cetuximab to FOLFIRI enhanced earlier symptom relief for patients symptomatic at baseline (18). Furthermore, the inverse relationships between global health status (GHS)/QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and cetuximab were frequently reported in patients treated as later-lines, who have more symptoms and lower baseline GHS/QoL scores with the further tumour progression than those treated as first-line, and likely to gain improvements in GHS/QoL corresponding to the tumour response (7,19). In contrast to improvements of GHS/QoL in later-lines treatment, adverse events may negate the positive efficacy obtained from cetuximab treatment in patients with relatively higher baseline GHS/QoL scores in first-line treatment (18). Thus, the relative impact between the efficacy and toxicity of cetuximab on health-related QoL (HRQoL) has not been resolved, especially in first-line treatment, and the cetuximab-related adverse event with the greatest negative impact on HRQoL remains unclear. Therefore, further research is needed to clarify these issues.

In Japan, the efficacy and safety of cetuximab plus irinotecan for the treatment of irinotecan-refractory and EGFR-positive metastatic CRC were confirmed in a Phase II study (20), and subsequently, cetuximab received approval in Japan in 2008. In a Japanese post-marketing surveillance analysis of 2006 patients between September 2009 and January 2009, the profiles and incidence of cetuximab-related adverse events were not different from previous reports from other countries (21). However, 99% of these patients received cetuximab as second or further-line treatment, therefore, the clinical efficacy and safety of cetuximab as first-line treatment in Japan remain unclear. Based on this background information, we have planned a prospective observational study to examine the relative impact of the efficacy and adverse events of cetuximab plus first-line chemotherapy on QoL in Japanese patients with *KRAS* wild-type unresectable CRC. The results of this study will provide more information regarding the practical use of cetuximab and its impact on QoL in patients with *KRAS* wild-type unresectable CRC. The relevant information for overall burden and efficacy of treatment will facilitate treatment decision making for both patients and physician.

This study has been conducted in accordance with the Declaration of Helsinki and Ethics Guidelines for Clinical Research by the Ministry of Health, Labor, and Welfare Ministry in Japan. Informed consent will be obtained from all patients before registration. The study protocol was approved by the institutional review board or ethics committee of each participating institution and was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000010985 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000012842&language=E) on July 19, 2013.

STUDY PROTOCOL

Objectives

The purpose of this study is to examine the relative impact of the efficacy and adverse events of first-line treatment including cetuximab on QoL in Japanese patients with *KRAS* wild-type unresectable CRC.

Study Setting

The study setting is a multi-institutional prospective observational study. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000010985

Endpoints and Assessments

The endpoints are the following associations: adverse events and QoL; efficacy and skin toxicity; efficacy and QoL; and skin-related QoL using DLQI and HRQoL using EORTC QLQ-C30.

The severity of adverse events will be assessed using the National Cancer Institute Common Terminology Criteria for adverse Events ver. 4.0 (22). The outcomes of treatment efficacy include ORR, time to treatment failure (TTF), PFS and OS. Treatment response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (23). TTF is defined as the time from registration to the time of treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death. PFS is defined as the time from registration to the time of progression after first-line treatment initiation or death from any cause. OS is defined as the time from registration to the time of death or last contact.

The EORTC QLQ-C30, a cancer-specific self-administered core questionnaire, will be used to assess HRQoL because it is valid and reliable in the advanced cancer setting, including CRC (24–26). This 30-item questionnaire contains five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a GHS/QoL and six single scales assessing additional symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact) (25). The response categories will include 'not at all', 'a little bit', 'somewhat', 'quite a bit' and 'very much', with response scores ranging from 1 to 4. The total scores range from 0 to 100 after linear transformation. Higher scores for the functional and GHS/QoL scales will indicate a higher level of functioning and a better HRQoL, respectively. Higher scores in the symptom scales will represent a higher level of symptoms.

The DLQI, a skin-specific self-administered questionnaire, will be used to assess skin-related QoL and contains 10 questions covering 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment). The total scores range from 0 to 30, with higher scores indicating greater QoL impairment (14,27,28).

Eligibility Criteria

Patients with unresectable CRC who satisfy the inclusion criteria and do not meet the exclusion criteria as described below will be recruited as subjects.

Inclusion Criteria

(1) Patients with unresectable CRC who plan to be treated with cetuximab plus first-line chemotherapy (FOLFIRI or mFOLFOX6)
(2) Not confirmed mutation in *KRAS* codon 12 or 13
(3) At least one measurable lesion according to the RECIST ver.1.1
(4) No prior chemotherapy (adjuvant chemotherapy more than 6 months prior to enrolment is allowed)
(5) Aged 20 years or older
(6) Eastern Cooperative Oncology Group performance Status 0–2
(7) Adequate organ function
(8) Life expectancy >3 months
(9) Negative hepatitis B surface antigen
(10) Agreement of contraception
(11) Written informed consent
(12) Ability to answer the QoL questionnaires

Exclusion Criteria

(1) Serious bone marrow suppression
(2) Serious sensory disturbance
(3) A history of mental disturbances or cerebrovascular attack
(4) Previous radiotherapy against evaluable lesions
(5) Severe stenosis of primary site or primary tumour resection within 4 weeks (colostomy within 2 weeks) prior to enrolment
(6) Serious drug hypersensitivity or a history of drug allergy
(7) Uncontrolled hypertension, diabetes or hypercalcemia
(8) Severe liver cirrhosis or hepatic dysfunction
(9) Severe renal dysfunction
(10) Interstitial pneumonia, pulmonary fibrosis or high-grade pulmonary emphysema
(11) Active infection
(12) A history of severe heart disease
(13) Brain metastases
(14) Massive pleural effusion, ascites or pericardial effusion
(15) Uncontrolled diarrhoea
(16) Active concomitant malignancy
(17) Pregnancy, possible pregnancy or nursing
(18) Judged inappropriate for the study by their physicians

Registration

Any medical institution that would like to participate should contact the Epidemiological and Clinical Research Information Network (ECRIN). Interested institutions will receive registration forms from the ECRIN. Registered patients will be treated with FOLFIRI plus cetuximab or mFOLFOX6 plus cetuximab as determined by a physician in clinical practice.

Treatment Methods

The FOLFIRI plus cetuximab regimen will consist of cetuximab (initial 2 h infusion of 400 mg/m^2 followed thereafter by a weekly 1 h infusion of 250 mg/m^2) with concurrent l-leucovorin (2 h infusion of 200 mg/m^2) and irinotecan (90 min infusion of 150 mg/m^2), followed by 5-fluorouracil (5-FU; intravenous bolus of 400 mg/m^2 followed by a 46 h continuous infusion of 2400 mg/m^2 every 14 days). mFOLFOX6 plus cetuximab will consist of cetuximab (initial 2 h infusion of 400 mg/m^2 followed thereafter by a weekly 1 h infusion of 250 mg/m^2) with concurrent l-leucovorin (2 h infusion of 200 mg/m^2) and oxaliplatin (2 h infusion of 85 mg/m^2),

followed by 5-FU (intravenous bolus of 400 mg/m^2 followed by a 46 h continuous infusion of 2400 mg/m^2 every 14 days). Treatment will be continued until disease progression or occurrence of unacceptable toxicity.

Follow-up

Disease progression and occurrence of new diseases will be monitored by abdominal computed tomography (CT), thoracic CT or magnetic resonance imaging at pre-chemotherapy (baseline) and every 8 weeks during the treatment period. Safety will be assessed by monitoring adverse events using physical and laboratory examinations. The survey sheets, including safety, efficacy and compliance with treatment, will be collected at registration and after 4, 8, 16 and 24 weeks. In addition, patient outcome will be investigated 2 years after study initiation and 1 year after accrual of the last patient. The QoL assessments will be performed at baseline and after 2, 4, 8, 16 and 24 weeks using EORTC QLQ-C30 and DLQI. A window of 2 weeks around each follow-up QoL assessment time point will be accepted. If the patient does not complete the study treatment, the last QoL assessment will be performed at the time of judgment of the study termination.

Statistical Methods

The association of adverse events with QoL will be analyzed using a linear mixed-effects model, including covariates such as baseline QoL scores, time since the start of chemotherapy, and grade of adverse events at each time point of QoL assessment. The association between efficacy (TTF, PFS and OS) and skin toxicity will be analyzed using the Cox proportional hazard model with skin toxicity as a time-dependent explanatory variable. The association between treatment response and skin toxicity will be analyzed using the Mantel extension test with a contingency table.

The sample size was calculated as 128 patients to assess the association between GHS/QoL in EORTC QLQ-C30 and skin toxicity with a one-sided significance level of 0.025 and a power of 80% based on the hypothesis that the degree of deterioration in GHS/QoL due to Grade 2 or higher skin toxicity, a clinically relevant event, is 50% of the standard deviation because that Grade2 or higher skin toxicity showed a trend toward a decreased GHS/QoL scores using EORTC QLQ-C30 in first-line treatment (18,29), and that the incidence was ~55% in a Japanese post-marketing surveillance of cetuximab (21). The total sample size to be accrued has been set at 140 to account for potential dropout and ineligible cases.

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Conflict of interest statement

Kensei Yamaguchi has received speaker honoraria from Chugai, Bristol-Myers Squibb and Merck Serono. Hirofumi Fujii has received speaker honoraria from Bristol-Myers Squibb and Merck Serono. Atushi Sato received honoraria from Chugai and Yakult. The other authors also declare no conflict of interest.

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Multicenter Phase II Study of Second-line Cetuximab plus Folinic Acid/5-Fluorouracil/Irinotecan (FOLFIRI) in *KRAS* Wild-type Metastatic Colorectal Cancer: The FLIER Study

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Abstract. *Background: This study was the first multicenter phase II study of cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in KRAS wild-type mCRC as a second-line treatment in Japan including BRAF and PIK3CA genotyping. Patients and Methods: Tumors of 112 pre-registered patients were genotyped for KRAS, BRAF, and PIK3CA. The primary study end-point was response rate, and secondary end-points were progression-free survival (PFS), overall survival (OS), and safety. Results: Sixty-seven patients (59.8%) were EGFR-positive and KRAS wild-type. The mean age of the enrolled patients (n=60) was 62.6 years (range=37-82 years). The response rate was 31.7% and stable disease was observed in 53.3%. No objective response was observed in patients with BRAF or PIK3CA mutations. The median PFS and OS were 7.4 and 18.2 months, respectively. Grade-3/4 adverse events were leucopenia (26.7%), neutropenia (43.3%), paronychia (10.0%), fissure (10.0%) and acne-like rash (5.0%). Conclusion: Second-line cetuximab plus FOLFIRI was effective and well-tolerated.*

Colorectal cancer is the fourth most common cancer worldwide, and the number of patients affected by this disease continues to steadily grow (1-3). It is estimated that approximately 92,000 new cases of colorectal cancer are diagnosed each year in Japan (4). Infusion of folinic acid, 5-fluorouracil (5-FU) and irinotecan is known as the FOLFIRI regimen and is one of the standard first- and second-line chemotherapeutic regimens for patients with metastatic colorectal cancer (mCRC). The FOLFIRI regimen has been shown to be more effective than infusion of 5-FU with folinic acid-only (LV5FU2 or AIO regimen) in terms of response rate (FOLFIRI: 41% *vs.* LV5FU2/AIO: 23%), time-to-progression (TTP) (FOLFIRI: 6.7 *vs.* LV5FU2/AIO: 4.4 months), and median survival time (MST) (FOLFIRI: 17.4 *vs.* LV5FU2/AIO: 14.1 months) as first-line treatment (5). Cetuximab is a human/mouse chimeric monoclonal antibody of the immunoglobulin G1 (IgG1) subclass that targets the epidermal growth factor receptor (EGFR), inhibiting EGFR signaling and producing antitumour effects by competing with ligands at the EGFR (6-7). Cetuximab, administered alone or in combination with irinotecan, showed efficacy in the treatment of patients with EGFR-positive mCRC, who were refractory to irinotecan (8). Subsequent studies confirmed the efficacy and safety of cetuximab alone or in combination with chemotherapy (9, 10). Based on the results

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Key Words: Colorectal cancer, *KRAS*, FOLFIRI, cetuximab, Japanese.

of these studies and a Japanese phase II clinical study (14), in which cetuximab was administered in combination with irinotecan in 39 patients with EGFR-positive mCRC refractory to irinotecan, in July 2008, cetuximab was approved for second-line and later treatment for EGFR-positive mCRC in Japan.

Genetic features of the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (*KRAS*) have been reported to predict patient response to cetuximab (11,13). The CRYSTAL (cetuximab combined with irinotecan in first-line therapy for mCRC) study reported the impact of *KRAS* mutation on outcome in patients receiving FOLFIRI, with or without cetuximab (12). This study evaluated a total of 1,063 patients from the original intention-to-treat (ITT) population of 1,198 patients. The KRAS-evaluable population had similar overall outcomes and characteristics to the ITT population. Patients with KRAS wild-type tumors benefited significantly from the addition of cetuximab to FOLFIRI. The response rate and median progression-free survival (PFS) in the cetuximab/FOLFIRI arm for patients with *KRAS* wild-type were 57.3% and 9.9 months, respectively. This rate was significantly better than the outcomes obtained with FOLFIRI alone, which was associated with a response rate of 39.7% and a median PFS of 8.4 months. Patients with *KRAS* mutations did not benefit from the addition of cetuximab, showing response rates of 31.3% and 36.1% and a median PFS of 7.7 months and 7.4 months in the FOLFIRI-alone and cetuximab/FOLFIRI arms, respectively. The overall survival (OS) also significantly improved with cetuximab/FOLFIRI in patients with wild-type KRAS (median OS of 23.5 months *vs.* 20.0 months for FOLFIRI alone). OS was reduced in patients with mutated *KRAS*, irrespective of cetuximab administration (16.2 months for FOLFIRI/cetuximab *vs.* 16.7 months for FOLFIRI-alone) (15). These studies demonstrated that cetuximab plus FOLFIRI as first-line therapy produced significant survival benefits for patients with mCRC. However, there are few reports on the efficacy and safety of cetuximab-plus-FOLFIRI as second-line therapy. In the National Comprehensive Cancer Network (NCCN) guideline (2014, version 2) (16), the recommended second-line chemotherapies for patients with wild-type *KRAS* initially treated with FOLFOX (folinic acid, 5-FU, and oxaliplatin) or capecitabine and oxaliplatin (CapeOx) regimens are FOLFIRI or irinotecan, with or without cetuximab or another EGF antibody, panitumumab.

The efficacy and safety of cetuximab in combination with FOLFIRI have not, therefore, been adequately reported. The objectives of the present study were to determine the efficacy of cetuximab-plus-FOLFIRI treatment as a second-line chemotherapy for mCRC in patients with wild-type *KRAS*, and to evaluate the safety profile of the specific treatment.

Patients and Methods

Patients. All patients included in this study provided written informed consent. Those included had histologically-proven, unresectable mCRC with at least one measurable lesion, according to the response evaluation criteria in solid tumors (RECIST) (17). They had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and adequate organ function for study treatment. All patients were 20 years old or more and had a life expectancy of at least three months. They had previously received at least one regimen of oxaliplatin-containing chemotherapy, at least 28 days prior to the first study treatment. For inclusion in the study, each patient's primary or metastatic tumor tissue needed to have immunohistochemically-confirmed EGFR expression and *KRAS* wild-type sequences at codons 12 and 13. Each of the patients included in the study had previously had surgery and tumour samples had been stored.

Analysis of tumor EGFR expression. The paraffin-embedded tissues fixed in 10% neutral buffered formalin were cut at 4 μm thickness. Immunostaining of sections was performed using the EGFR pharmDx™ kit (Dako, Glostrup, Denmark) according to the instructions of the manufacturer. EGFR expression was defined as membranous immunohistological brown staining of tumour cells. Positivity for EGFR expression was taken as any membranous staining above background level, whether this was complete or incomplete circumferential staining. The primary tumor was considered positive when 1% of tumor cells had membranous staining.

Tumor KRAS, BRAF and PIK3CA genotype analyses. DNA extraction was performed using a QIAamp DNA FFPE Tissue kit (QIAGEN, Tokyo, Japan) according to the manufacturer's instructions. Mutation of *KRAS* at codons 12 and 13, *BRAF* at codon 600, *PIK3CA* at exons 9 and 20 were determined by direct sequencing as previously described (18). Briefly, each region was amplified by PCR using: *KRAS* primer set (forward, F: ACCTTATGTGT GACATGTTCTAATATAG, reverse, R: GAATGGTCCTGCACCA GTAA); *BRAF* primer set (F: TCAT AATGCTTGCTCTGA TAGGA, R: GGCCAAAAATTTAATCAGTG GA), *PIK3CA* primer sets (9F: GCTTTTTCTGTAAATCATCTGTG, 9R:CTGAGATCAGCCA AATTCAGT, 20F: ACATTCGAAAGACCC TAGCC, 20R: GCAA TTCCTATGCAATCGGTC) and Taq polymerase with 3'-exonuclease activity (Ex Taq; Takara, Tokyo, Japan). Purified PCR products were used as a template for cycle sequencing reactions using a BigDye terminator v3.1 cycle sequencing kit (AppliedBiosystems, Foster City, CA, USA), and the reaction products were applied to an ABI 3500 Genetic Analyser (Applied Biosystems).

Study design. This phase II, multicenter, open-label, single-arm study was conducted in Japan. The study protocol was approved by the Institutional Review Board at each study site. Patients received cetuximab in combination with a FOLFIRI regimen. The initial dose of cetuximab was administered as a single intravenous infusion over 2 h at 400 mg/m^2, followed by weekly 1-h infusions at 250 mg/m^2. Prior to cetuximab treatment, patients received an anti-histamine and a corticosteroid to reduce the risk of infusion reaction.

Study end-points and assessments. The primary end-point of this study was the response rate, determined using the RECIST criteria (version 1.0). The secondary end-points were disease control rate (DCR), PFS, and OS. PFS was determined from the day of study

Table I. *Patient demographics and characteristics at baseline.*

Characteristic	All Patients N=60
Gender	
Male	39 (65.0%)
Female	21 (35.0%)
Age (years)	
Mean (SD)	62.6 (9.8)
Median	62
Minimum	37
Maximum	82
Tumour site	
Colon	34 (56.7%)
Rectum	26 (43.3%)
ECOG PS	
0	54 (90.0%)
1	6 (10.0%)
Metastasis	
Liver	38 (63.3%)
Lung	23 (38.3%)
Other	17 (28.3%)
Prior chemotherapy	
FOLFOX + bevacizumab	32 (53.3%)
FOLFOX	14 (23.3%)
FOLFOX + cediranib/placebo	11 (18.3%)
Other	3 (5.0%)

FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin.

enrolment to the last study contact date when patients were alive and had not shown disease progression. OS was calculated from the day of study enrolment to death. Safety end-points included the incidence and severity of adverse events (AEs). AEs were graded based on the National Cancer Institute common terminology criteria for AEs (version 3.0) (19).

Statistical analysis. All analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA). Frequency counts and percentages are provided for categorical variables. Response rate and DCR were reported as a proportion of the study population, with 95% binomial confidence intervals (CI). Continuous variables were summarized using mean, median, standard deviation (SD), and range. Survival curves were drawn by the Kaplan–Meier method and a 95% CI for the median survival time was constructed using a Greenwood formula.

The target sample size of 50 patients to investigate treatment response effects was based on expected and threshold response rates of 16% and 4%, respectively, with α=0.05 (one-sided), β=0.1, and binomial distribution.

Results

Patients' characteristics. From December 2008 to November 2009, a total of 112 patients were pre-registered. Of these, 45 were excluded (40.2%) as they had *KRAS* mutations (37 in codon 12, 8 in codon 13). The most frequent *KRAS* mutation was GGT→GAT at codon 12.

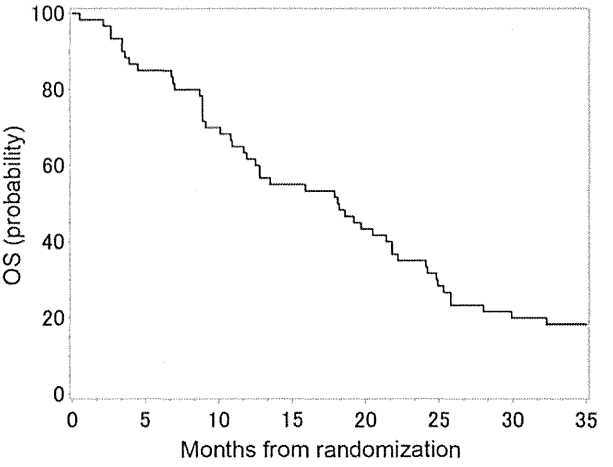

Figure 1. *Therapeutic effects: Progression-free survival (PFS) curve. CI: Confidence interval, MST: median survival time.*

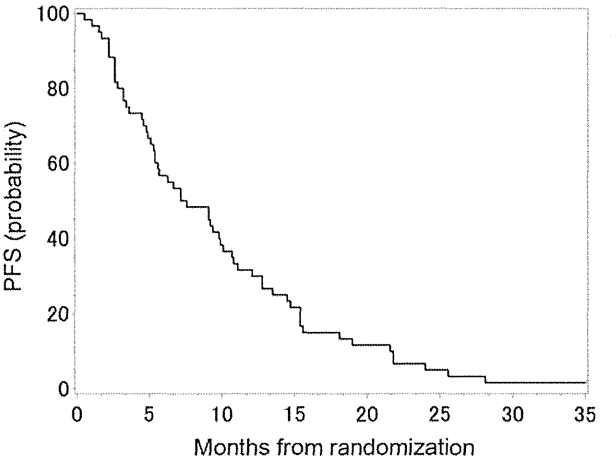

Figure 2. *Therapeutic effects: Overall survival (OS) curve. CI: Confidence interval, MST: median survival time.*

Sixty patients satisfied the inclusion criteria and were enrolled. The patient demographic characteristics are shown in Table I. The median patient age was 62 years (range=37-82 years), and 65% were male. The median follow-up period was 39.7 months. Fifty-four (90%) and six (10%) patients had an ECOG PS of 0 and 1, respectively. Thirty-two (53.3%) of the 60 patients had received bevacizumab-plus-FOLFOX therapy before registering in this study. Twenty-nine patients (63.3%) had liver metastasas. *BRAF* and *PIK3CA* mutations were present in three (5.0%) and two (3.3%) tumors, respectively.

Efficacy. Out of the 60 patients enrolled in the study, 19 (31.7%; 95% CI=20.3-45.0%) had a complete or partial

Table II. *Patient genotype and response to therapy.*

	All (n=60)	*BRAF/PIK3CA*	
		WT (n=55)	MT (n=5)
Tumour response, n (%)			
CR	1	1	0
PR	18	18	0
SD	32	31	1
PD	8	4	4
NE	1	1	0
Response rate(%; 95% CI)	19/60 (31.7%; 20.3-45.0)	19/55 (34.5%; 22.2-48.6)	0/5 (0)
Disease control rate, n (%; 95% CI)	51/60 (85.0%; 73.4-92.9)	50/55 (90.9%; 80.1-97.0)	1/5 (20%; 0.5-71.6)

WT, Wild-type; MT, mutant; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

response, and 51 (85.0%; 95% CI=73.4-92.9%) had a complete or partial response to therapy, or stable disease, as determined by the investigators. For the comparison with the threshold 4% response rate, the one-sided *p*-value was <0.0001. In addition, the response rate and DCR in individuals with wild-type *BRAF* and *PIK3CA* tumors was 34.5% (95% CI=22.2-48.6%) and 90.9% (95% CI=80.1-97.0%), respectively (Table II).

The median PFS and OS were 7.4 months (95% CI=5.3-10.1 months) and 18.2 months (95% CI=11.7-21.8 months), respectively (Figures 1 and 2). Patients with *BRAF* mutations (n=3) showed tumor enlargement of 85.6%, 50.9%, and 12%, and those with *PIK3CA* mutation (n=2) also showed tumor enlargement of 44.0% and 4.0% (Figure 3).

Safety. Thirty-nine patients (65.0%) withdrew from the cetuximab plus FOLFIRI therapy due to progression of disease, two (3.3%) withdrew due to AEs, and 17 (18.3%) withdrew for other reasons. No patient died within 28 days of the last dose of the study medication. All 60 patients experienced at least one AE during the study, most of which were mild to moderate in severity.

The most common grade 3/4 AEs with FOLFIRI-plus-cetuximab were neutropenia (43.3%), leukopenia (26.7%), and vomiting (5.0%). The only cetuximab-related grade 3/4 AEs were fissure (10.0%), paronychia (10.0%), and acne-like rash (5.0%) (Table III).

Table III. *Adverse events of grade 3 or more in all patients.*

	Grade 3 (n)	Grade 4 (n)	Grade 3/4 (%)
Leucopenia	14	2	26.7%
Neutropenia	14	12	43.3%
Anaemia	1	0	1.7%
Nausea	1	0	1.7%
Vomiting	3	0	5%
Anorexia	2	0	3.3%
Diarrhoea	1	0	1.7%
Acne-like rash	3	0	5%
Fissure	6	0	10%
Paronychia	6	0	10%
Hypomagnesaemia	0	0	0%

Discussion

The present FLIER study was the first to prospectively estimate the efficacy of cetuximab-plus-FOLFIRI as a second-line treatment for mCRC in Japanese patients with wild-type *KRAS*. FOLFIRI-plus-cetuximab was well-tolerated as a second-line treatment in this study and showed antitumour activity in patients with mCRC. *KRAS* mutation rates of 37.0% and 37.7% have been reported by large-scale studies (20,21). The *KRAS* mutation rates found in this study (40.2%) were therefore similar to those of these previous reports.

In the present study, the response rate was 31.7%. Objective response rates ranging from 17-23% (22-24) have been reported in patients receiving FOLFIRI regimens, and rates of 4-8% (24, 25) have been reported in patients receiving other irinotecan-based therapies (including patients with both wild-type and mutant *KRAS* tumours). Our response rate was, therefore, higher than that in any previous study of FOLFIRI alone. In addition, all five patients with *BRAF* and *PIK3CA* mutations showed tumor enlargement, hence the response rate and DCR in individuals with wild-type *BRAF* and *PIK3CA* tumours was 34.5% and 90.9%, respectively. This result was concordant with the previous reports (26).

In the present study, the median PFS and OS were 7.6 and 19.5 months in patients with wild-type *KRAS*, which were also higher than those previously reported for patients receiving FOLFIRI regimens after failure of oxaliplatin-based therapies (PFS range=3.7-4.7 months; OS range=9.3-

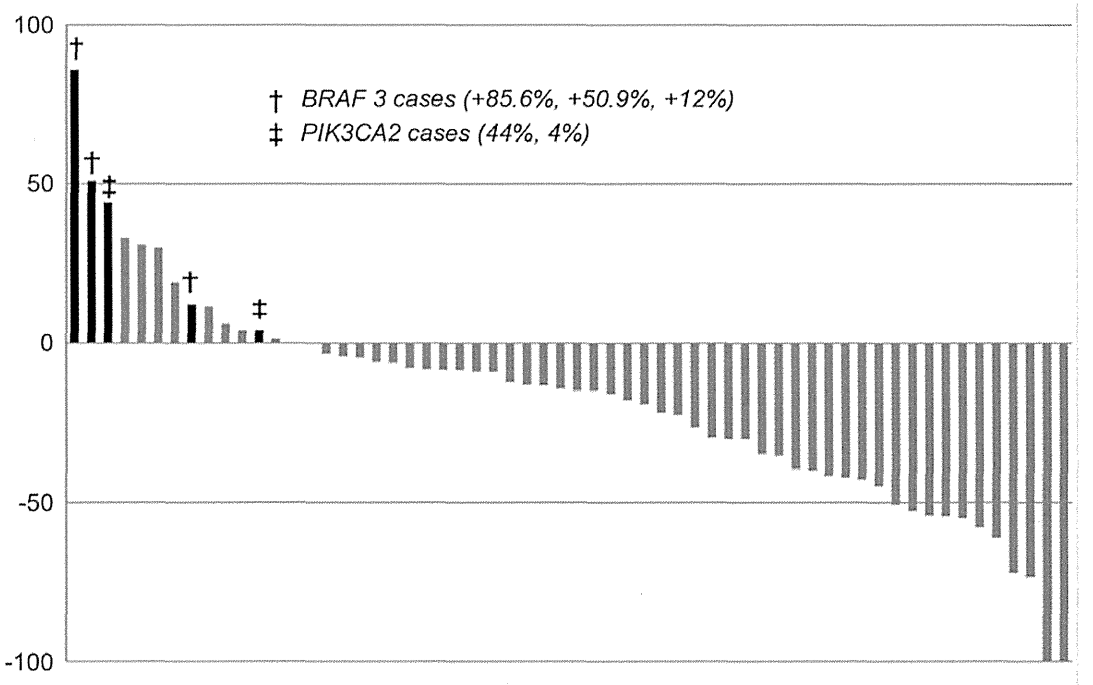

Figure 3. *Waterfall plot of tumour shrinkage, grouped by BRAF, and PI3KCA mutation status. Each column shows the rate of shrinkage. Pts, Patients; dagger/columns, BRAF mutation; double dagger/columns, PI3KCA mutation.*

10.5 months) (22-24). Thus, addition of cetuximab to FOLFIRI as second-line therapy provided additional benefit to mCRC patients with wild-type *KRAS* tumours.

A recent prospective analysis evaluated the effect of tumor *KRAS* genotype on the efficacy of second-line panitumumab-plus-FOLFIRI in a phase II, open-label, single-arm study of patients with mCRC (PRECEPT study) (27). That study showed a lower response rate (23%), shorter PFS (6.5 months, 95% CI=4.8-8.3 months) and OS (12.5 months, 95% CI=9.8-19.0 months) in patients with wild-type *KRAS* mCRC, compared to the findings obtained in our study. Patients in that study had received first-line treatment with bevacizumab-plus-oxaliplatin-based chemotherapy. In the present study, patients had received prior treatment with bevacizumab plus FOLFOX (n=32, 53.3%); FOLFOX-alone (n=14, 23.3%); FOLFOX-plus-cediranib or placebo (n=11, 18.3%), and others (n=3, 5.0%). Second-line irinotecan-based chemotherapy is commonly used in mCRC after first-line oxaliplatin-based chemotherapy. A recent randomised phase III study (TML; ML18147) reported the effects of second-line bevacizumab-plus-chemotherapy in mCRC patients who were previously treated with bevacizumab-plus-chemotherapy (28). This TML study showed a 5.4% response rate, PFS of 5.7 months, and OS of 11.2 months. Thus, cetuximab can be a highly effective second-line treatment, even in patients already treated with bevacizumab.

A phase II study of second-line bevacizumab-plus-FOLFIRI was also conducted in patients with mCRC (AVASIRI trial) (29). That study reported a similar response rate (32%), PFS (11.6 months, 95% CI=6.9-16.4 months), and OS (21.4 months, 95% CI=12.0-30.8 months) to those of the present study. This indicated that treatment with an antibody against either EGFR (cetuximab), or an antibody against vascular endothelial growth factor (VEGF, bevacizumab) warrants further validation in a large-scale study.

Recently, the results of an open-label randomised controlled trial comparing irinotecan plus oral S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate; IRIS) with FOLFIRI as second-line chemotherapy for mCRC were reported. This study showed that the IRIS treatment resulted in a PFS that was not inferior to that associated with FOLFIRI treatment in patients receiving second-line chemotherapy for mCRC (30).

In the present study, the major common haematological grade 3/4 AEs were neutropenia (43.3%) and leukopenia (26.7%). Grade 3/4 acne-like rash and diarrhea were observed in only 5.0% and 1.7% of the patients, respectively. No patients in the present study exhibited any levels of hypomagnesaemia. A previous study of second-line panitumumab plus FOLFIRI in patients with wild-type *KRAS*

reported grade 3/4 AEs of neutropenia (23%), skin-related toxicities (28%), diarrhea (14%), and hypomagnesaemia (8%). Moreover, grade 3/4 AEs of neutropenia (64%), leukopenia (16%), and diarrhea (8%) were reported following second-line bevacizumab-plus-FOLFIRI. In both of these studies as well as in the present study, high rates of neutropenia were found, with moderate to severe neutropenia occurring in nearly in over one-third of all patients. These findings, taken together with the results of the present study, also emphasize the need to proactively manage skin toxicities (31) and hypomagnesaemia (32) in patients receiving antibody to EGFR.

In summary, the FLIER study was the first study to prospectively estimate the efficacy of cetuximab-plus-FOLFIRI treatment in patients with wild-type *KRAS* receiving second-line treatment for mCRC in Japan. FOLFIRI-plus-cetuximab was well-tolerated and had antitumour activity as second-line therapy in patients with mCRC.

Conclusion

The present study was the first multicentre prospective phase II study of second-line cetuximab plus FOLFIRI for patients with wild-type *KRAS* mCRC in Japan. The *KRAS* mutation rate in the pre-registered study population was comparable to that reported by previous studies. Cetuximab plus FOLFIRI was well-tolerated and had antitumour activity as a second-line therapy in patients with wild-type *KRAS* mCRC, producing a treatment response rate of 31.7% and PFS of 7.4 months.

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Letter to the Editor

"Palliative Hemodialysis" in the Context of End-of-Life Care for Dialysis Patients

Dear Editor,

This report highlights a new concept on better management of end-of-life care for dialysis patients who are in the terminal phase of their renal disease.

CASE REPORT

A 76-year-old man with advanced lung cancer with metastasis in the liver was admitted to our hospital to receive palliative care for the terminal phase of his cancer. He had also been receiving hemodialysis. On the 97th day after admission he developed anorexia and his physical condition deteriorated. As a consequence he asked us to discontinue dialysis as he considered it was a burden to him. We explained that dialysis was an essential life-sustaining therapy and therefore it was difficult to stop the treatment without adequate discussion. Based on his physical status and the fact that he only had a short life expectancy we asked his preference for end-of-life treatment that included withdrawal (WD) from dialysis. We considered that WD was an acceptable option for care in his case, although we also informed him of the risk that his life expectancy would be shortened if he chose this option. As a result he decided on a resuscitation preference (i.e., do not resuscitate), although he was confused and reluctant to clearly state his opinion on WD. His family also agreed with his decision. We concluded that he was probably afraid of suffering life-threatening symptoms such as respiratory distress, which inevitably occurs following WD of dialysis. After careful consideration, we concluded that intermittent or shortened regular dialysis to reduce the burden of hemodialysis was a suitable option. We defined this treatment option as "palliative hemodialysis". When the patient desired to skip the scheduled dialysis this was accepted, and when he wished to finish a dialysis session, this was also permitted. We also supplied single-needle-dialysis to reduce the pain of needle insertion. "Palliative hemodialysis" was continued for 23 days and the patient died peaceful and with dignity on the 120th hospital day.

DISCUSSION

It is necessary to recognize that hemodialysis may sometimes be a burden for severely ill dialysis patients due to the pain of inserting the fistula needle and the stress of keeping still during the treatment (1). Recently, some reports have highlighted the importance of patient-centered medicine (2).

Palliative hemodialysis that we have described in this case study may be consistent with this concept. An example in another field includes palliative radiation therapy, which is performed currently to minimize distress symptoms such as continuous pain of cancers (3). It is obviously beneficial for patients if better end-of-life care is initiated, and accordingly nephrologists need to take care when considering the decision-making process (4).

In conclusion, a new concept of palliative hemodialysis may be worth considering in hemodialysis patients who are unable to state their preference for end-of-life care because of dementia or persistent disturbances of consciousness due to cerebrovascular disorders. We consider it is important for nephrologists to show considerable interest in improving end-of-life care for patients.

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