

## A Japanese Post-marketing Surveillance of Cetuximab (Erbitux®) in Patients with Metastatic Colorectal Cancer

Megumi Ishiguro<sup>1,2</sup>, Toshiaki Watanabe<sup>1,3</sup>, Kensei Yamaguchi<sup>1,4</sup>, Taroh Satoh<sup>1,5,6</sup>, Hideyuki Ito<sup>7</sup>, Taku Seriu<sup>8</sup>, Yuh Sakata<sup>1,9</sup> and Kenichi Sugihara<sup>1,2,\*</sup>

<sup>1</sup>Advisory Board for Proper Use of Cetuximab, <sup>2</sup>Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, Tokyo, <sup>3</sup>Department of Surgery, Teikyo University School of Medicine, Tokyo, <sup>4</sup>Department of Gastroenterology, Saitama Center Center, Saitama, <sup>5</sup>Department of Medical Oncology, Kinki University School of Medicine, Osaka, <sup>6</sup>Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Osaka, <sup>7</sup>Merck Serono Co., Ltd., Osaka, <sup>8</sup>Bristol-Myers K.K., Tokyo and <sup>9</sup>Department of Internal Medicine, Misawa Municipal Hospital, Aomori, Japan

\*For reprints and all correspondence: Kenichi Sugihara, Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. E-mail: k-sugi.srg2@tmd.ac.jp

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**Objective:** Cetuximab (Erbitux®) was approved for the treatment of metastatic colorectal cancer in Japan in 2008. To verify information on the safety in practical use of cetuximab, we conducted post-marketing surveillance in accordance with the conditions for approval.

**Methods:** All patients to be treated with cetuximab were enrolled by the central enrolment method. Data on treatment status, and incidence and severity of adverse drug reactions were collected. The target number of patients was 1800.

**Results:** A total of 2126 patients were enrolled from 637 institutions. Among 2006 patients analysed, 93.2% received cetuximab as third-line or later treatment. The median duration of treatment was 15.3 weeks, and 11.1% of patients received treatment for >48 weeks. The incidence of adverse drug reactions was 89.6%, of which  $\geq$  grade 3 was 21.5%. The incidence of infusion reactions was 5.7% (any grade), with 83.3% of them occurring at the first administration. The incidence of skin disorders was 83.7% (any grade), and the time to event varied for each skin disorder. The incidence of interstitial lung diseases was 1.2% (any grade). Diarrhoea and haematotoxicity scarcely occurred with cetuximab alone.

**Conclusions:** In this surveillance, the incidence and categories of adverse drug reactions are not distinct from previous reports. Although most patients received cetuximab as third-line or later treatment, treatment was maintained with a median duration of 15 weeks. Cetuximab treatment in practical use is considered to be well tolerated and clinically useful in Japanese patients with metastatic colorectal cancer.

*Key words:* colorectal cancer – cetuximab – post-marketing surveillance

### INTRODUCTION

Cetuximab (Erbitux®) is a human/mouse chimeric monoclonal immunoglobulin G<sub>1</sub> antibody that targets the epidermal

growth factor receptor (EGFR) to inhibit its signalling and shows anti-tumour effects by binding to EGFR competitively with ligands (1,2). Cetuximab, administered alone or in combination with irinotecan, showed efficacy in the treatment of

patients with EGFR-positive metastatic colorectal cancer (CRC) who are refractory to irinotecan (3). Subsequent studies confirmed the efficacy and safety of cetuximab alone or in combination with chemotherapy (4,5). Moreover, it was reported that *KRAS* status is a predictive marker of response to cetuximab (6–8).

Based on these studies and a Japanese phase II study (9) in which cetuximab was administered in combination with irinotecan in 39 patients with EGFR-positive metastatic CRC refractory to irinotecan, cetuximab was approved in Japan as second-line and later treatment for EGFR-positive metastatic CRC in July 2008.

In Japan, post-marketing surveillance (PMS) has been introduced to verify the safety and the clinical efficacy of medicines in practical use, and practice standards of PMS have been established under a ministerial order. As a condition of its approval, PMS of all patients receiving cetuximab during a certain period was requested by the Ministry of Health, Labour and Welfare.

In this report, treatment status and safety in the clinical use of cetuximab are examined based on prospectively aggregated PMS data.

## PATIENTS AND METHODS

### ENROLMENT

Following the launch of cetuximab on 19 September 2008, all patients to be treated with cetuximab were enrolled in advance using the central enrolment method. Patient information, including gender, age and treatment line, was collected from a company (Merck Serono Co., Ltd. and Bristol-Myers K.K.) prepared enrolment sheet. The company checked whether the patients met the following conditions for proper use upon approval: positive EGFR, no history of hypersensitivity to the components of the product, performance status (PS) 0–1, no interstitial lung diseases (ILDs) and refractoriness or intolerance to previous chemotherapy.

To detect adverse drug reactions (ADRs) with an incidence of 0.2% and a probability of at least 95%, and to complete the enrolment within 1 year after launch, the target number of patients was determined to be 1800.

### TREATMENT

In accordance with the statement on the package insert, the initial dose of cetuximab was administered at 400 mg/m<sup>2</sup> over 2 h followed by weekly infusions of 250 mg/m<sup>2</sup> over 1 h. As there were no data available on the efficacy and safety of cetuximab in combination with oxaliplatin-based regimens at the beginning of the surveillance in Japan, it was recommended to use irinotecan or FOLFIRI (folinic acid, fluorouracil and irinotecan) as a combination chemotherapy.

To reduce the risk of infusion reactions (IRs), pre-medication with antihistamines is recommended in the

‘precautions for use’ section on the package insert for cetuximab. Likewise, concomitant use of corticosteroid is also suggested to reduce the risk of IRs.

### MONITORING

The observation period was defined as the time between the first administration and the last administration of cetuximab. The case report forms including information of treatment status and ADRs filled out by physicians were collected three times (at Week 4, Week 8 and final administration).

### SAFETY EVALUATION

Severities of adverse events (AEs) were assessed mainly according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). As priority survey items, the incidence and severity of IRs, skin disorders, ILDs, electrolyte abnormalities including hypomagnesaemia, cardiotoxicity, gastrointestinal disorders, thrombosis/embolism, delayed wound healing and eye disorders (e.g. keratitis) were surveyed. AEs that the physicians and the company defined as being related to cetuximab treatment were analysed as ADRs.

### STATISTICAL ANALYSIS

All analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA). The incidences of ADRs, the number of treatment and duration of treatment were compared among patients characteristics and therapeutic factors using the  $\chi^2$  test, Fisher’s exact test, the Wilcoxon rank sum test or the non-paired *t*-test. *P* < 0.05 was considered to represent a statistically significant difference. The Kaplan–Meier method was used to calculate the cumulative incidence of ADRs.

## RESULTS

### PATIENT CHARACTERISTICS

Between 19 September 2008 and 5 January 2009, 2126 patients were enrolled from 637 institutions. Excluding 154 patients who did not receive cetuximab treatment, but including 34 who were treated with cetuximab outside of the enrolment condition, 2006 patients were included in the analysis. The cut-off date was set at 5 January 2010 (including patients continuing treatment).

The patient characteristics are shown in Table 1. The median age was 64 years (range, 18–87), the male/female ratio was 1:0.6 and 93.2% of patients received cetuximab as third-line or later treatment (Table 1). In this surveillance, *KRAS* testing was performed in 15%.

**Table 1.** Patient characteristics and clinical use

	<i>n</i>	%
<b>(A) Patient characteristics</b>		
Sex		
Male	1234	61.5
Female	772	38.5
Age		
<65 years	1032	51.4
≥65 years	971	48.4
Unknown	3	0.2
Tumour site (including overlapping sites)		
Colon	1235	61.6
Rectum	775	38.6
PS		
0	1370	68.3
1	630	31.4
2	2	0.1
Unknown	4	0.2
Treatment line		
Second line	133	6.6
Third line and later treatment	1869	93.2
Others	4	0.2
Previous chemotherapy		
(-)	3	0.2
(+)	2003	99.9
FOLFIRI	1510	75.3
FOLFOX	1854	92.4
5-FU/LV	370	18.4
Irinotecan	261	13.0
UFT/LV	337	16.8
Bevacizumab	923	46.0
Previous surgery		
(-)	81	4.0
(+)	1925	96.0
Previous radiation therapy		
(-)	1650	82.3
(+)	355	17.7
Unknown	1	0.0
EGFR-IHC		
Positive	1974	98.4
Negative	29	1.4
Not tested	3	0.2
KRAS status		
Wild	249	12.4
Mutant	53	2.6

**Table 1.** Continued

	<i>n</i>	%
Not tested	1691	84.3
Unknown	13	0.7
Comorbidity		
(-)	1019	50.8
(+)	974	48.6
Unknown	13	0.6
<b>(B) Clinical use</b>		
No. of treatments		
<4	253	12.6
4 to <16	900	44.9
16 to <32	524	26.1
32 to <48	255	12.7
≥48	74	3.7
Duration of treatment		
<4 weeks	276	13.8
4 to < 16 weeks	739	36.8
16 to <32 weeks	489	24.4
32 to <48 weeks	280	14.0
≥48 weeks	222	11.1
Cumulative dose		
<1500 mg/m <sup>2</sup>	435	21.7
1500 to <3000 mg/m <sup>2</sup>	493	24.6
3000 to < 9000 mg/m <sup>2</sup>	832	41.5
≥9000 mg/m <sup>2</sup>	236	11.8
Unknown	10	0.5
Combination chemotherapy		
(-)	460	22.9
(+)	1546	77.1
Irinotecan	1255	62.6
FOLFIRI	256	12.8
Others	35	1.7
Combination radiation therapy		
(-)	1943	96.9
(+)	59	2.9
Unknown	4	0.2
Pre-medication <sup>a</sup>		
No	14	0.7
Antihistamine alone	185	9.2
Corticosteroid alone	23	1.2
Antihistamine + corticosteroid	1783	88.9

PS, performance status; 5-FU, 5-fluorouracil; LV, leucovorin; UFT, tegafur-uracil; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry.  
<sup>a</sup>Excluded unknown (one patient).

Continued

STATE OF CLINICAL USE

In total, 77.1% of patients received cetuximab in combination with chemotherapy, and the rest received cetuximab alone. Almost all patients (99.3%) received pre-medication, and most of these (88.9%) were treated with both antihistamines and corticosteroids (Table 1).

The median duration of treatment was 15.3 weeks (range, 1–73.9), the median numbers of treatment was 13 (range, 1–61) and the median cumulative dose was 3255 mg/m<sup>2</sup> (range, 50.0–17 680.9). A total of 11.1% of patients continued cetuximab treatment for >48 weeks (Table 1). The number of treatment and the duration of treatment by patient characteristics are shown in Fig. 1. Treatment duration did not differ among treatment line. The number of treatment was significantly higher, and the duration of treatment was significantly longer in the patients with combination chemotherapy, wild *KRAS* tumours and skin disorders ( $P < 0.0001$ ).

SAFETY

The overall incidence of ADRs (any grade) was 89.6% ( $n = 1797$ ), and that of ADRs of  $\geq$ grade 3 was 21.5% ( $n = 432$ ) (Table 2). Among patient characteristics affecting the incidence of  $\geq$ grade 3 ADRs, significant differences were observed in the comorbidity (presence, 25.5% vs. none, 18.1%;  $P < 0.0001$ ) and combination chemotherapy (presence, 23.2% vs. none, 15.9%;  $P = 0.0006$ ). There were no significant differences by age (<65 years, 21.4% vs.  $\geq$  65 years, 21.6%;  $P = 0.91$ ).

Incidences of the priority survey items are shown in Table 2. IRs were observed in 5.7% of patients ( $n = 114$ ), whereas IRs  $\geq$ grade 3 were observed in 1.1% ( $n = 22$ ). Most IRs (83.3%;  $n = 95$ ), especially those of  $\geq$ grade 3 (20 out of 22) occurred at the first administration of cetuximab (Fig. 2). The median time to the onset of  $\geq$ grade 3 IRs was 10 min (range, 2 min to 8 h). Among the 22 patients with IRs of  $\geq$ grade 3, 21 developed IRs within 60 min after the start of administration. There were no differences in the incidence of IRs among pre-medication groups (data not shown).

Skin disorders were the most frequently observed ADRs, accounting for 83.7% of patients ( $n = 1679$ , any grade). In the seven categories grouped by symptom, dermatitis acneiform/rash ( $n = 1579$ , 78.7%) was observed most frequently, followed by dry skin ( $n = 442$ , 22.0%) and paronychia ( $n = 353$ , 17.6%). The cumulative incidence of each disorder over time after the start of administration of cetuximab is shown in Fig. 3. The median time to the onset of each skin disorder was 15 days for dermatitis acneiform/rash, 30 days for dry skin and 52 days for paronychia.

ILDs were observed in 1.2% of patients ( $n = 24$ ), and ILDs  $\geq$ grade 3 were reported in 0.7% ( $n = 15$ ). The outcomes included recovery in 2 patients, lower severity in 6 patients, non-recovery in 5 patients, death in 10 patients and unknown in 1 patient. The median time to onset of ILDs was 101 days (range, 17–431), indicating no certain tendency in time to onset of ILDs.

Electrolyte abnormalities (any grade, 11.5%;  $\geq$ grade 3, 1.2%) included hypomagnesaemia (10.8%), hypocalcaemia (0.5%), hyperkalaemia (0.4%), hypokalaemia (0.3%), hyponatraemia (0.2%), hypochloraemia (0.1%) and hypophosphataemia (0.1%). The median time to onset of

		No. of patients	No. of treatments	Median [range]	Duration of treatment Median (weeks)
Treatment line	2 <sup>nd</sup> line treatment	133	13	[1–54]	15.3
	3 <sup>rd</sup> line or later treatment	1,869	13	[1–61]	15.3
Combination chemotherapy	(–)	460	7	[1–55]	7.6
	(+)	1,546	15	[1–61]	8.1
	Irinotecan	1,255	14	[1–59]	7.6
	FOLFIRI	256	17	[1–61]	2.1
	Others	35	18	[1–55]	1.4
<i>KRAS</i> status	Wild-type	249	15	[1–58]	7.1
	Mutant type	53	9	[1–43]	11.1
	Not tested	1,691	13	[1–61]	5.3
	Unknown	13	15	[2–49]	3
Skin disorder	(–)	327	4	[1–51]	4.1
	(+)	1,679	15	[1–61]	18.0

Figure 1. Number and duration of treatment by patient characteristics. The bars show the median duration of the cetuximab treatment for each subgroup of patients. \* $P < 0.0001$  (the non-paired *t*-test).

hypomagnesaemia was 57 days (range, 3–418 days), and a higher rate of hypomagnesaemia was observed in patients undergoing long-term administration.

Cardiotoxicity was observed in 17 patients (0.9%) and cardiotoxicity  $\geq$  grade 3 was reported in 0.2% ( $n = 5$ ). Cardiotoxicity included myocardial infarction, cardiac failure, right cardiac failure and coronary spastic angina. All five patients with cardiotoxicity  $\geq$  grade 3 were treated with cetuximab plus irinotecan or FOLFIRI, and four patients died.

Other ADRs developed including diarrhoea (any grade, 15.1%;  $\geq$  grade 3 2.5%), leukopenia (4.3%; 2.0%) and neutropenia (2.8%; 2.2%). Leukopenia and neutropenia did not

occur in the cetuximab alone group, and the incidence of diarrhoea in this group was lower than that in the combination chemotherapy group (5.2 vs. 18.0%,  $P < 0.001$ ) (Fig. 4).

A total of 780 patients died during the surveillance period. Of these, a causal relationship with cetuximab could not be ruled out in 22 patients (1.1%). Of the 66 patients (3.3%) who died within 30 days, a causal relationship with cetuximab could not be ruled out in seven patients (0.4%).

**DISCUSSION**

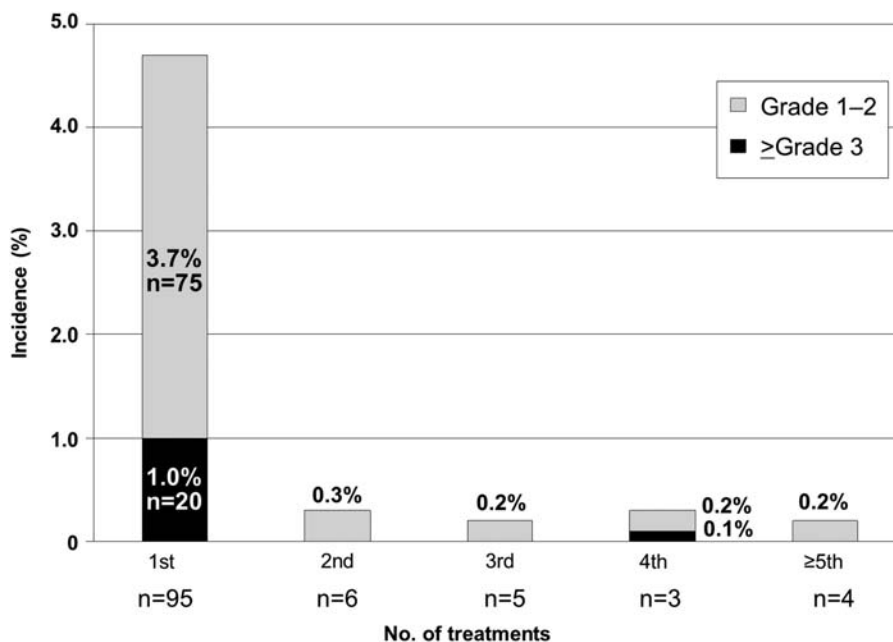
This report shows the results of a large-scale surveillance in which all patients treated with cetuximab were collected prospectively within a certain period after launch.

The incidence of ADRs in this surveillance (89.6%) was similar to that (93.0%) reported in the MABEL study, in which the efficacy and safety of the combination with irinotecan were studied in 1147 patients with EGFR-positive metastatic CRC refractory or intolerant to irinotecan (10), and that (100%) reported in a Japanese phase II study (9).

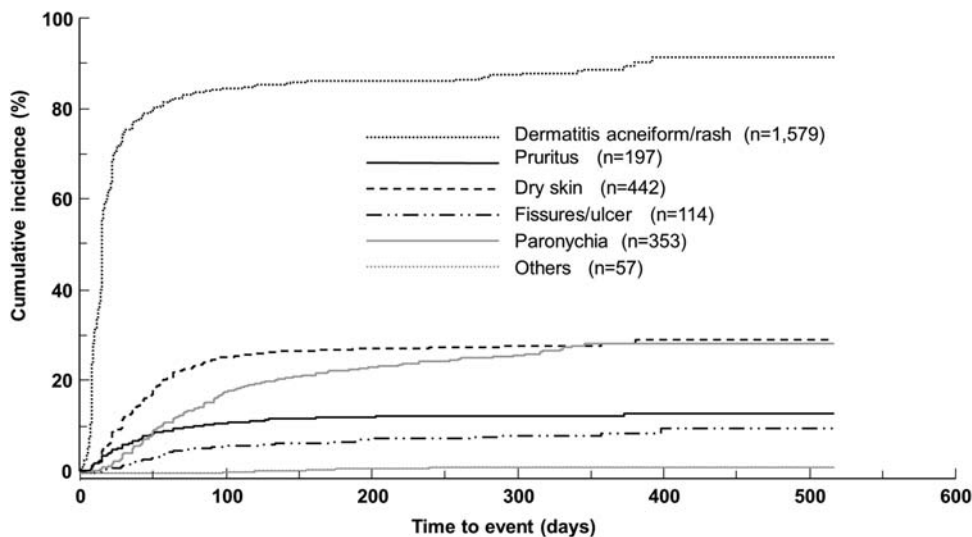
Because IRs occurred frequently at the first administration of cetuximab and most of the severe reactions occurred within 1 h after administration, careful observation during the first 1 h is therefore important in cetuximab treatment. It was reported that the incidence of IRs was decreased by administering antihistamine and corticosteroid as pre-medication (11). Accordingly, the Japanese package insert for cetuximab recommends pre-medication with an antihistamine (and corticosteroid), and 88.9% of patients received both pre-medications in this surveillance. So, the incidence

**Table 2.** Incidence of adverse drug reactions (ADRs)

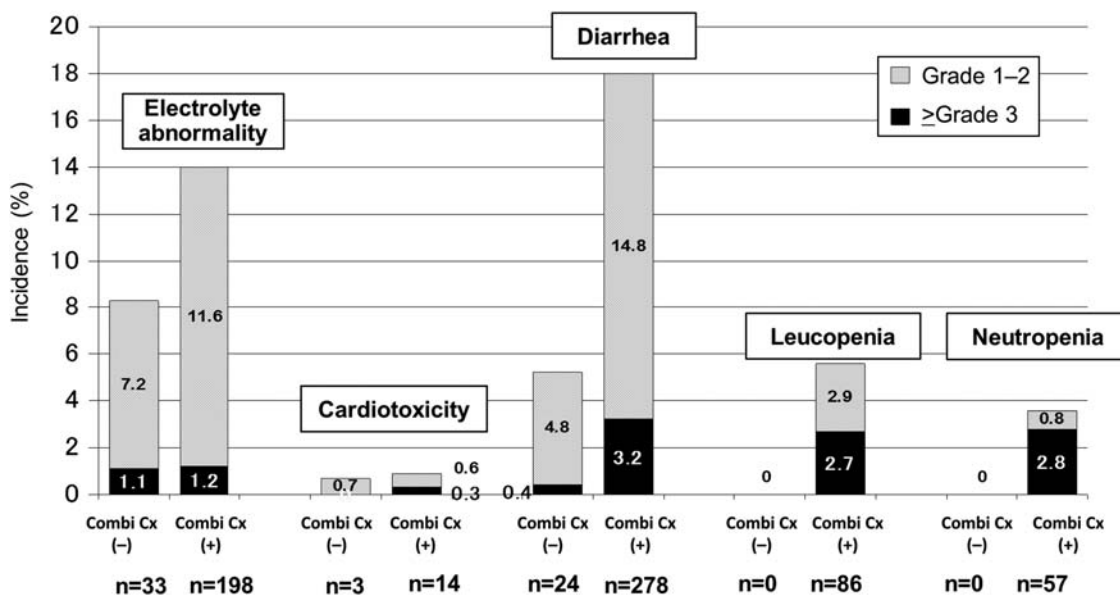
	Any grade		$\geq$ Grade 3	
	<i>n</i>	%	<i>n</i>	%
Overall incidence of ADRs	1797	89.6	432	21.5
Incidence of priority survey items				
Infusion reactions	114	5.7	22	1.1
Skin disorders	1679	83.7	212	10.6
Interstitial lung diseases	24	1.2	15	0.7
Electrolyte abnormalities including hypomagnesaemia	231	11.5	24	1.2
Cardiotoxicity	17	0.9	5	0.2
Gastrointestinal disorders	464	23.1	77	3.8
Thrombosis/embolism	11	0.6	8	0.4
Delayed wound healing	5	0.3	1	0.05
Eye disorders	53	2.6	1	0.05



**Figure 2.** Timing of infusion reactions (IRs). The bars show the incidence of IRs for each number of cetuximab treatments received. One patient with a grade 3 IR was excluded because the time to the onset of IR was unknown.



**Figure 3.** Cumulative incidence of skin disorders. The lines show the cumulative incidence of each skin disorder over time from the start of administration of cetuximab using the Kaplan–Meier methods. Skin disorders were divided into seven categories as grouped by symptoms, which is different from the counting based on the system organ class (SOC) classification of Medical Dictionary for Regulatory Activities Terminology (MedDRA).



**Figure 4.** The incidence of adverse drug reactions (ADRs) with/without combination chemotherapy. The bars show the incidence of ADRs in patients with/without combination chemotherapy. Combi Cx (-): patients receiving cetuximab alone. Combi Cx (+): patients receiving cetuximab in combination with chemotherapy.

of IRs in this report (5.7%) might be lower than that in the MABEL study (15.4%).

Skin disorders were the most frequent ADRs, and the time to event was different for each disorder similar to previous reports (12). The occurrence of skin disorders is considered a predictive factor for the efficacy of EGFR inhibitors (4,13), and it is important to manage skin disorders by considering the occurrence time of each symptom to continue the cetuximab treatment.

The incidence of ILDs in this surveillance (1.2%) was higher than that in the MABEL study (0.3%) (14). With other drugs, it has been suggested that the incidence of ILDs in Japanese patients is higher than that in Caucasian patients

(15,16). ILDs are often followed by serious outcomes including death, while no certain tendency in time of onset of ILDs was observed in this surveillance. Urgent consultation with a respiratory specialist and the introduction of corticosteroid pulse therapy should be considered when observing suspicious symptoms and/or images of ILDs.

The incidence of cardiotoxicity was low in this surveillance (0.9%), and all patients with cardiotoxicity  $\geq$  grade 3 were treated with irinotecan as combination chemotherapy. Cardiotoxicity has also been reported following fluorouracil treatment (17) and it is important to pay close attention when administering cetuximab in combination with these drugs.

Diarrhoea, leukopenia and neutropenia are frequently observed ADRs caused by cytotoxic anti-cancer drugs, but in this surveillance, they were rarely observed with administration of cetuximab alone. Based on this finding, cetuximab can be used safely in elderly patients and those receiving the drug as later-line treatment.

Although 93.2% of 2006 patients in this surveillance were treated in third-line or later treatment, the median duration of treatment was 15.3 weeks (range, 1–73.9), and 11.1% received long-term treatment >48 weeks, while that in the CO.17 study, in which cetuximab alone was administered to patients refractory or intolerant to fluorouracil, oxaliplatin and irinotecan, was 8.1 weeks (range, 1–60) (4). Based on these observations, cetuximab treatment is considered controllable and clinically effective in practical use in a later-line setting in Japan.

In addition, higher number of treatments and longer duration of treatment were observed in the patients with wild *KRAS* tumours and those who developed skin disorders. Treatment duration might be considered as a surrogate of the efficacy of treatment including cetuximab. Thus, it might indicate that these patients had obtained the clinical benefit from cetuximab treatment.

*KRAS* status has been reported to be a predictive factor of response to cetuximab since 2006 (6), and the indication for the use of cetuximab was changed to *KRAS* wild-type metastatic CRC in July 2008 by the European Medicines Agency, and in September 2009 by the US Food and Drug Administration. At the beginning of this surveillance, there was no description regarding *KRAS* status on the Japanese package insert for cetuximab, and *KRAS* testing was not covered by insurance. Therefore, only 15% ( $n = 263$ ) of the patients included in this surveillance had undergone *KRAS* testing. It is now recommended that *KRAS* testing, which has been covered by insurance since April 2010 in Japan, should be conducted before the administration of cetuximab.

## CONCLUSIONS

We conducted a prospective PMS in Japanese patients receiving cetuximab for the treatment of metastatic CRC. There was no notable difference in the profiles and incidence of ADRs compared with previous reports from other countries. Although >90% of the patients received cetuximab as third-line or later treatment, the treatment was maintained with a median duration of 15 weeks. Thus, cetuximab is considered well tolerated and clinically useful for Japanese patients.

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## Conflict of interest statement

Megumi Ishiguro received a consulting fee from Taiho Pharmaceutical Co., Ltd, and lecture honoraria from Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd and Yakult Honsha Co., Ltd; Toshiaki Watanabe received lecture honoraria from Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Yakult Honsha Co., Ltd, Takeda Pharmaceutical Company, Merck Serono Co., Ltd and Bristol-Myers K.K.; Taroh Satoh received lecture honoraria from Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Yakult Honsha Co., Ltd, Takeda Pharmaceutical Company, Daiichi Sankyo Company, Merck Serono Co., Ltd and Bristol-Myers K.K.; Yuh Sakata received lecture honoraria from Taiho Pharmaceutical Co., Ltd and Yakult Honsha Co., Ltd and a royalty from International Inc. Synergy; Kenichi Sugihara received lecture honoraria from Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Merck Serono Co., Ltd, Takeda Pharmaceutical Company, Bristol-Myers K.K. and Yakult Honsha Co., Ltd; Hideyuki Ito is an employee of Merck Serono Co., Ltd; Taku Seriu is an employee of Bristol-Myers K.K.

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