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Panitumumab in Japanese Patients with Unresectable Colorectal Cancer: A Post-marketing Surveillance Study of 3085 Patients†

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Objective: Panitumumab was approved in Japan in April 2010 for the treatment of Kirsten rat sarcoma-2 virus oncogene wild-type unresectable and recurrent colorectal cancer. We conducted a post-marketing surveillance study to evaluate the safety and effectiveness of panitumumab.

Methods: After panitumumab was commercially available in Japan, all patients to be treated with panitumumab were enrolled. Data on baseline characteristics, treatment outcome, and incidence and severity of adverse drug reactions were collected.

Results: In total, 3091 patients were registered. In the safety analysis set ($n = 3085$), panitumumab was administered as monotherapy (40.7%) or combination therapy (59.4%). The median treatment duration was 113 days (range: 1–559 days), and 451 (14.6%) patients received panitumumab for $\geq$10 months. The overall incidence rate of adverse drug reactions was 84.1%, and the most common adverse drug reaction was skin disorders (78.4%). The incidence rates (all grades) of interstitial lung disease, infusion reaction, electrolyte abnormalities and cardiac disorders were 1.3% (mortality rate: 0.6%), 1.5, 19.3 and 0.2%, respectively. The median survival time of patients treated with panitumumab monotherapy as the third-line, or later, therapy was 10.3 months.

Conclusion: This post-marketing survey in clinical practice confirmed the safety and effectiveness of panitumumab. The benefit/risk balance for panitumumab in Japanese patients with unresectable colorectal cancer remains favorable.

Key words: colorectal cancer – panitumumab – post-marketing surveillance – safety

INTRODUCTION

Colorectal cancer is one of the most common cancers, representing the second (males; 9%) and third (females; 8%) most prevalent cancer in the USA (1), and the third overall leading cause of cancer-related death in the Western world (2). The past several decades have seen a dramatic increase in the incidence of colorectal cancer also in Japan (3); in 2008, age-standardized incidence rates in males and females in Japan were 41.7 and 22.8 cases per 100 000, with corresponding death rates of 15.2 and 8.9 per 100 000, respectively (4).

The introduction of monoclonal antibody-based therapy targeting epidermal growth factor receptor (EGFR) has provided new alternative treatment options for various types of malignancy, including colorectal cancer (5–8).

Panitumumab is a high-affinity, fully human IgG2 monoclonal antibody specific to the extracellular domain of EGFR (5,9). The clinical efficacy and tolerability of panitumumab have been well established in large, randomized, controlled clinical trials as monotherapy (10–13) or in combination with cytotoxic agents (14–17), in the first-, second- and third-line, or later, settings for patients with unresectable, advanced or recurrent colorectal cancer with wild-type Kirsten rat sarcoma-2 virus oncogene (*KRAS*). Panitumumab was first approved in the USA (September 2006) and European Union (EU) (December 2007) as monotherapy and for use in combination therapy in the EU (November 2011).

In Japan, panitumumab was approved (April 2010) for the treatment of wild-type *KRAS* gene unresectable, advanced and recurrent colorectal cancer as monotherapy, and for use in combination therapy in the first-, second- and third-line, or later, settings based on global clinical trials (10–12,14–17). The approval of panitumumab in Japan for use in combination therapy represents the first such approval in the world. However, because the number of Japanese individuals enrolled in the global clinical trials was relatively limited (13), the Japanese Ministry of Health, Labour and Welfare required the market authorization holders to conduct a post-marketing surveillance study, called All Cases Surveillance (18), as a condition of its approval to evaluate the safety and effectiveness of all Japanese patients treated with panitumumab. The main purpose of this study was to collect detailed information, particularly with regard to safety issues, on all panitumumab-treated patients; additionally, by evaluating a large number of patients, the study aimed to identify rare adverse drug reactions (ADRs), which are often undetectable in smaller clinical trials. The current paper reports the findings of the Japanese all cases surveillance study.

PATIENTS AND METHODS

This post-marketing surveillance study was planned to include all patients treated with panitumumab from the start date (15 June 2010) of its launch in Japan. To promote the appropriate use and evaluate safety information, a Vectibix Appropriate Use Committee, a Vectibix Safety Evaluation Committee and a Vectibix Interstitial Lung Disease (ILD) review subcommittee were organized. All reported ILD-like events were assessed individually by an ILD review subcommittee, comprising external experts in the field of radiology, pulmonology and medical oncology. Evaluation of ILD-like events was performed using computed tomography (CT) and X-ray imaging, and by assessment of clinical information. Completion of a specific registration form (Fig. 1), which reported patient characteristics and treatment information, was mandatory before panitumumab treatment was initiated. The registration period of this post-marketing surveillance was June 2010 to November 2010. Patients were carefully observed, and information during their clinical courses for 10 months (42 weeks), or until discontinuation of panitumumab for any reason, was collected through the pre-specified case report forms (CRFs). At the time of registration, a recommendation letter to stop initiating treatment with panitumumab was sent from the Vectibix Appropriate Use Committee to each attending doctor if at least one item on the dark gray zone of the registration form was checked (Fig. 1). Subsequently, the following information relating to clinical course was collected using CRFs: (1) patient background including prior chemotherapy and reason for its discontinuation/termination; (2) administration of panitumumab including its dose and date, premedication to prevent infusion reaction, concurrent medications and combined therapy; (3) laboratory tests including serum magnesium, calcium and potassium; (4) adverse events including time to onset, grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0, treatment, causality of panitumumab and recovery and (5) outcomes including disease progression, survival or death.

An ADR was defined as an adverse event for which a causal relationship with panitumumab could not be ruled out. ADRs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. With regard to toxicity, skin disorders, ILD, infusion reaction, electrolyte abnormalities and cardiac disorders were monitored with special interest. The effectiveness of panitumumab was assessed by overall survival, calculated using the Kaplan–Meier method. Overall survival time was defined as the time from the date of first administration of panitumumab to the date of death (regardless of the cause of death) or censored on the last date of survival (date of confirmation of survival as recorded in the CRF or, if there was no information regarding the date of confirmation of survival, the last date of panitumumab administration was used for calculation purposes).

This survey was initiated in June 2010 and the data lock point of the final analysis was set at 12 September 2012.

RESULTS

Patient Characteristics

During the registration period from June to November 2010, a total of 3091 patients were registered (completion of

History of severe hypersensitivity to the ingredients* of this drug.	□ No	□ Yes	

*Panitumumab, sodium chloride and sodium acetate.

Primary tumor	□ Colon/rectum (including RS)	□ Other ( )	
Purpose	□ Treatment of unresectable, advanced/recurrent cancer	□ Post-operative adjuvant therapy □ Other ( )	
***KRAS* genotype**	□ Wild	□ Not determinable	□ Mutant □ Not measured
Treatment stage (excluding post-operative adjuvant therapy)	□ First line	□ Second line	□ Third line or later

ECOG PS score	□ 0 □ 1 □ 2		□ 3	□ 4
History of or complication with interstitial pneumonia/pulmonary fibrosis	□ None	□ Interstitial pneumonia (□ Complication; □ History) □ Pulmonary fibrosis (□ Complication; □ History)		
Pregnancy/lactation status (for female patients)	□ No	□ Pregnant □ Lactating		
Concomitant chemotherapy planned	□ Yes→ □ FOLFOX □ No □ FOLFIRI	□ Chemotherapy other than FOLFOX and FOLFIRI ( )		□ Bevacizumab

If one or more boxes in the gray-shaded cells are checked, avoidance of administration is requested by the Takeda/Vectibix Appropriate Use Committee. If one or more boxes in the light gray-shaded cells (framed from a dark-black line) are marked, reassessment of administration is requested by the Takeda/ Vectibix Appropriate Use Committee.

Figure 1. Patient registration form—excerpt.

mandatory patient registration forms) from 1031 clinical institutes and departments in Japan. Of the 3091 registered patients, survey data were obtained for 3086 patients. The CRFs of five registered patients were not obtained despite repeated requests to physicians. Of these, 3085 patients were eligible for safety analysis; 1 patient was excluded from the safety analysis as no information was available regarding drug administration (Fig. 2).

Table 1 shows the clinical background of the 3085 patients at registration. While a *KRAS* test was attempted for all registered patients, it was not determined for 79 patients (2.6%) mainly due to the condition of the tissues. Despite a recommendation letter to stop, panitumumab was administered to three patients (0.1%) with mutant *KRAS* at each physician's discretion. The majority of patients (91.4%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1. Although the ECOG PS of 3080 patients was reported to be 0–2 at registration, 5 patients with PS 3 were registered despite requests for reassessment of administration. The general condition of 20 patients deteriorated to PS 3 or 4 before the administration of panitumumab. Therefore, patients with PS 3 (0.7%) or 4 (0.1%) were included in this surveillance. There were no other registered patients who met at least one item in the dark gray zone of the registration form (Fig. 1).

Panitumumab was used in the third-line, or later, setting for metastatic disease in 72.4% of patients, and previous anticancer treatment including adjuvant chemotherapy had been administered to 94.4% of patients, such as FOLFOX (79.1%), FOLFIRI (61.8%) and bevacizumab (monoclonal antibody, vascular endothelial growth factor-specific angiogenesis inhibitor; 68.5%); 29.7% of patients had received cetuximab (monoclonal antibody, EGFR antagonist) (duplicate counting).

Figure 3 shows treatment regimens administered and the status of administration (safety analysis set). At the start of panitumumab administration, 1254 (40.7%) patients received monotherapy and 1831 (59.4%) patients received combination chemotherapy. Combination therapy consisted (duplicate counting) of FOLFOX4 (3.6%), mFOLFOX6 (15.1%), FOLFIRI (33.9%), 5FU/l-LV (2.0%), CPT-11 (9.0%), S-1 + CPT-11 (1.3%) or other chemotherapy (3.1%). Of the 310 patients receiving first-line treatment, the majority (86.5%) received combination therapy, of which 193 patients received concomitant FOLFOX (62.3%). With regard to the use of panitumumab monotherapy in the first-line setting, primary physicians did not select combination chemotherapy considering

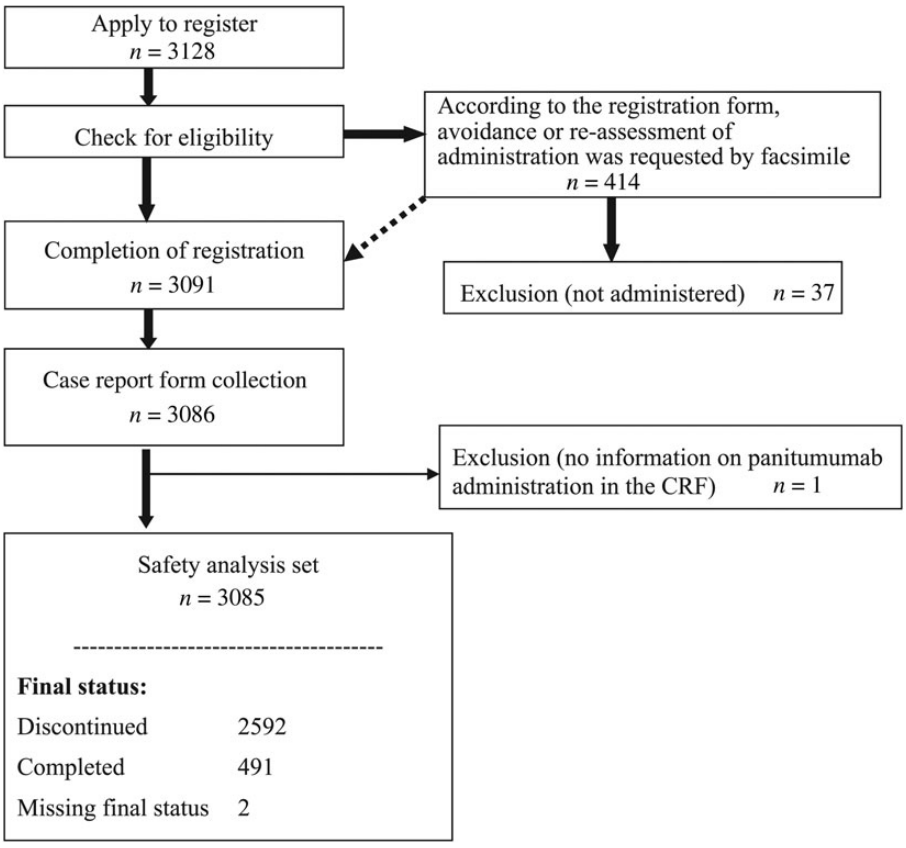


Figure 2. Patient registration in the panitumumab Japanese post-marketing surveillance study (safety analysis set).

various patient factors, such as age and general condition, because there is no limitation in the indication of panitumumab for combination or monotherapy in Japan. Combination therapy was administered in 394 of 543 (72.6%) patients as second-line treatment, of whom 276 (50.8%) received FOLFIRI. Almost half (47.6%) of the 2232 patients receiving third-line, or later, treatment were in the monotherapy group.

Treatment Course

The median period of treatment with panitumumab was 113.0 days (range: 1−559 days), with 14.6% of patients receiving panitumumab for >10 months.

Panitumumab was discontinued in 2592 (84.0%) patients in the safety analysis set ($n = 3085$). The main reasons for discontinuation (with some duplicate counting) were as follows: disease progression in 1903 (61.7%) patients, of which 1484 patients (78.0%) had confirmed disease progression by diagnostic imaging; occurrence of adverse events in 431 (14.0%) patients; patient refusal (190 patients; 6.2%); lack of patient hospital visits (30 patients; 1.0%) and other reasons (185 patients; 6.0%).

Safety Analysis

The overall incidence of ADRs in all grades was 84.1% (2595/3085 patients) (Table 2). The most common classification, according to the MedDRA system organ class (SOC), was 'skin and subcutaneous tissue disorders' (76.6%; 2364/3085) (Table 2), followed by 'infections and infestations' [(25.0%; 771/3085), which included paronychia (23.7%; 731/3085)], 'gastrointestinal disorders' (20.8%; 642/3085) and 'metabolism and nutrition disorders' (17.9%; 552/3085).

The incidence of ADRs in the monotherapy group ($n = 1254$) was 80.1% (1004/1254); 19.7% of these were ≥Grade 3 and 5.4% were classified as serious cases. In patients receiving combination therapy ($n = 1831$), 86.9% reported ADRs; 30.0% of these were ≥Grade 3 and 7.9% were serious cases. There were no major differences in the incidence of ADRs by combined regimens in the combination therapy group: FOLFOX (overall: 86.7%, ≥Grade 3: 29.3% and serious cases: 9.1%) and FOLFIRI (87.4, 29.8 and 8.1%, respectively).

A summary of safety data from the post-marketing surveillance study and panitumumab clinical trials (19) is presented in Table 3.

Skin Disorders

The overall incidence rate of 'major skin disorders' (which includes all related events) was 78.4% (≥Grade 3, 14.7%). Dermatitis acneiform occurred in 69.9% of patients (≥Grade 3, 10.5%), paronychia in 24.2% (≥Grade 3, 4.3%), dry skin in 21.7% (≥Grade 3, 2.1%) and pruritus in 4.8% (≥Grade 3,

Table 1. Patient demographics and baseline characteristics

	All patients ($n = 3085$)	
Baseline characteristic	Number	%
Gender		
Male	1965	63.7
Female	1120	36.3
Age (years)		
<65	1524	49.4
65–74	1058	34.3
≥75	503	16.3
Median (range) (years)	65.0 (18–90)	
KRAS status		
Wild	3003	97.3
Mutant	3	0.1
Not determinable[a]	79	2.6
Primary tumor type (duplicate counting)		
Colon	1860	60.3
Resected	1621	52.5
Unresected	239	7.8
Rectal	1244	40.3
Resected	1054	34.2
Unresected	189	6.1
Colorectal	3085	100.0
Resected	2661	86.3
Unresected	423	13.7
Treatment line[b]		
First-line	310	10.1
Second-line	543	17.6
Third-line or later	2232	72.4
ECOG performance status[c]		
0	1877	60.9
1	942	30.5
2	241	7.8
3	22	0.7
4	3	0.1
Past treatment regimens		
No	173	5.6
Yes (duplicate counting)	2911	94.4
FOLFOX	2439	79.1
FOLFIRI	1907	61.8
Bevacizumab	2113	68.5
Cetuximab	917	29.7

KRAS, Kirsten rat sarcoma-2 virus oncogene; ECOG, Eastern Cooperative Oncology Group; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan.
[a]Mainly due to the condition of tissue samples; reasonable attempts were made to determine the *KRAS* status for all patients.
[b]Treatment for metastatic or recurrent disease, excluding postoperative adjuvant chemotherapy from counting treatment lines.
[c]Specified PS immediately before panitumumab administration. Although 3080 patients were reported to be PS 0–2, the general condition worsened to PS 3 in 17 patients and to PS 4 in 3 patients.

0.4%). The median time from the first day of treatment to the onset of each of the major skin disorders was as follows: 15 days for dermatitis acneiform, 43 days for paronychia, 29 days for dry skin and 21 days for pruritus. Major skin disorders caused discontinuation of panitumumab in 7.0% (168/2419) of patients. The prevalence of skin disorders was similar with panitumumab monotherapy (74.7%; 937/1254) and panitumumab plus chemotherapy (80.9%; 1482/1831).

Electrolyte Abnormalities

Serum magnesium, calcium and potassium were checked at least once during treatment in 46.2% (1425/3085), 65.4% (2016/3085) and 92.5% (2855/3085) of the patients, respectively. The incidence rate of electrolyte abnormalities was 19.3% (596/3085), with that of ≥Grade 3 cases being 4.8% (149/3085). The respective incidence rates of hypomagnesemia, hypocalcemia and hypokalemia in patients for whom laboratory data for these three electrolytes were available were 36.5% (520/1425), 6.7% (136/2016) and 2.3% (67/2855). The incidence rate of hypomagnesemia in the overall population was 16.9% (520/3085), with that of ≥Grade 3 hypomagnesemia being 4.0% (123/3085). The median time to hypomagnesemia onset after panitumumab treatment initiation was 63 days in all cases: 39.5 days in patients who were treated with cetuximab immediately before panitumumab and 71 days in patients who were not. The incidence of hypomagnesemia and hypocalcemia peaked at 3–4 months after the start of panitumumab administration. Patients with low serum magnesium values also tended to have low serum calcium values.

Of 105 patients who experienced both hypomagnesemia and hypocalcemia, 42 patients had the same grade of hypomagnesemia and hypocalcemia; 42 and 21 patients compared to each other had higher grades of hypomagnesemia and hypocalcemia, respectively. Of 30 patients with ≥Grade 3 hypomagnesemia and hypocalcemia, 5 patients experienced relevant clinical symptoms accompanying electrolyte abnormalities: QTc prolongation (3 cases), rhabdomyolysis, paralysis, tetany and convulsion (1 case of each).

Infusion Reaction

Infusion reaction occurred in 1.5% (47/3085) of patients, with an incidence rate of Grade 3 or serious cases of 0.2% (6/3085). No Grade 4 cases, or deaths due to infusion reaction, were reported. Infusion reaction occurred at initial administration in 61.7% (29/47) of patients and in 14.9% (7/47) of patients at second administration, while the first infusion reaction occurred at the time of the third or later administration in the remaining 11 patients (with the latest infusion reaction occurring at the 21st administration). Panitumumab was administered to 70 patients who had past histories of infusion reaction due to cetuximab, following premedication and at reduced speed of infusion in almost all cases. Two of these patients (2.9%) experienced Grade 1 infusion reaction, while infusion reaction occurred in 9/847 (1.1%) patients without a history of infusion reaction to cetuximab administration.

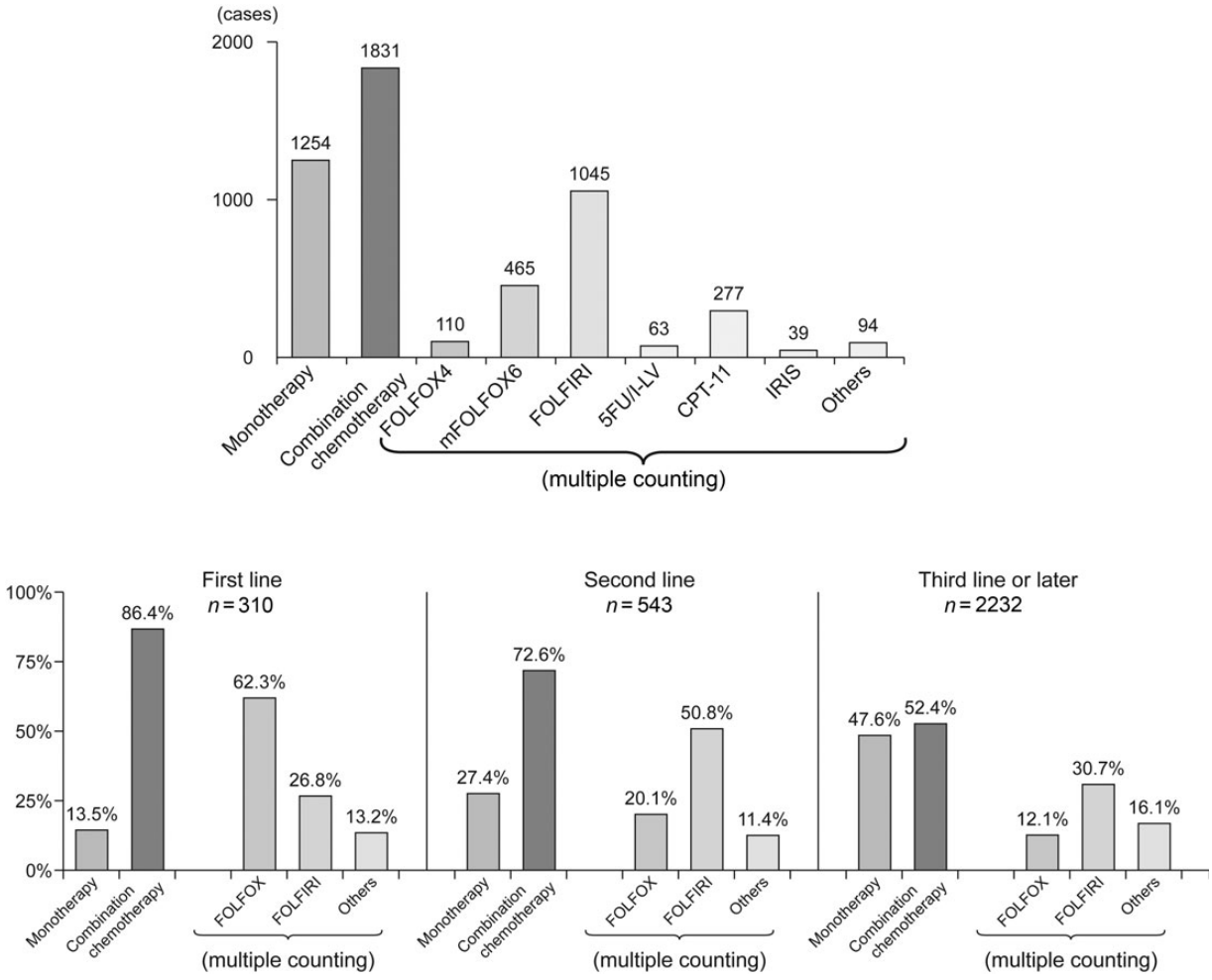


Figure 3. Treatment regimens and status of administration (safety analysis set).

Interstitial Lung Disease

Overall, the incidence rate of ILD was 1.3% (39/3085): 1.3% in monotherapy and 1.3% in combination therapy, resulting in a mortality rate of 0.6% (20/3085). Of the total ILD cases, 51.3% (20/39) were fatal. The time to onset of ILD varied (Table 4). As determined by CT imaging, diffuse alveolar damage (DAD) was observed in 46.2% (18/39) of patients and 15 of the 18 DAD cases were fatal. The remaining ILD cases were diagnosed as hypersensitivity pneumonia (9 cases) or organizing pneumonia (8 cases), with 4 unevaluable cases.

Cardiac Disorders

The incidence of cardiac disorders was 0.2% (7/3085), with death due to heart failure (Grade 5) reported in one patient. In this patient, treated with panitumumab and FOLFIRI, pancytopenia (not related to panitumumab) appeared on Day 23, followed by pneumonia (Day 28) and heart failure (Day 32).

Cases of Death

In total, 1135 deaths were recorded, and most of them were related to progression of colorectal cancer. However, in 25 (2.2%) patients, a relationship to panitumumab treatment could not be ruled out. Among these, the most common cause of death was ILD (20 patients, according to the evaluation of the ILD subcommittee).

Effectiveness

Figure 4 shows the Kaplan–Meier curve for overall survival based on 1062 patients in the safety analysis set who were receiving panitumumab monotherapy in the third-line, or later, setting.

The median overall survival time (95% confidence interval) was ~10.3 months (~9.0–11.8 months), with 56.6% censored cases.

DISCUSSION

The main objective of the current post-marketing surveillance study was to evaluate the safety of panitumumab in Japanese patients with unresectable colorectal cancer (and with the majority of patients possessing wild-type *KRAS* tumors) in clinical practice.

Table 2 Overall incidence of adverse drug reactions (ADRs) by system organ class (SOC)

	Any grade		≥Grade 3	
	n	%	*n*	%
All ADRs	2595	84.1	797	25.8
Skin and subcutaneous tissue disorders	2364	76.6	392	12.7
Infections and infestations	771	25.0	160	5.2
Gastrointestinal disorders	642	20.8	126	4.1
Metabolism and nutrition disorders	552	17.9	149	4.8
Investigations	204	6.6	74	2.4
General disorders and administration site conditions	111	3.6	29	0.9
Eye disorders	83	2.7	8	0.3
Nervous system disorders	68	2.2	18	0.6
Respiratory, thoracic and mediastinal disorders	63	2.0	28	0.9
Injury, poisoning and procedural complications	52	1.7	5	0.2
Blood and lymphatic system disorders	33	1.1	24	0.8
Hepatobiliary disorders	19	0.6	4	0.1
Renal and urinary disorders	12	0.4	7	0.2
Musculoskeletal and connective tissue disorders	10	0.3	2	0.1
Vascular disorders	9	0.3	2	0.1
Cardiac disorders	7	0.2	1	0.03

The overall incidence of ADRs was 84.1%, with skin disorders representing the most common classification (78.4%). Skin toxicity associated with panitumumab (and other EGFR antibodies) is well known (20). Indeed, the development of skin disorders, particularly rash, is considered to be a predictive factor for the efficacy of EGFR inhibitors (21,22). As reported previously with EGFR inhibitors (22,23), dermatitis acneiform (69.9%) was the most frequent skin disorder reported in the current study, occurring about 2 weeks after the initiation of panitumumab. In the current study, although major skin disorders such as dermatitis acneiform, paronychia, dry skin and pruritus occurred in 78.4% of patients, 93% of the patients who experienced skin disorders were able to continue panitumumab therapy.

The EGFR-signaling pathway potentially plays a pivotal role in regulating magnesium homeostasis, and, indeed, hypomagnesemia/magnesium has been shown in patients with colorectal cancer receiving EGFR-targeting antibodies (24). In the current study, 46.2% of patients were evaluated for serum magnesium, and Grade 3 or higher hypomagnesemia occurred in 4.0% of patients, with a shorter median time to onset in patients treated with cetuximab immediately prior to panitumumab (39.5 and 71 days, respectively), indicating that the total duration of exposure to an EGFR inhibitor is an important factor. From these findings, it is considered that the longer-term administration of anti-EGFR treatment worsens the severity of hypomagnesemia (24). However, in the present study, the incidence of hypomagnesemia and hypocalcemia peaked 3 and 4 months after the start of panitumumab administration, respectively. Moreover, the incidence of hypomagnesemia observed in the current post-marketing surveillance study is similar to that reported in a Phase II clinical trial of panitumumab in Japanese patients with metastatic colorectal cancer (13). Hypomagnesemia and associated hypocalcemia require special attention. Panitumumab therapy should be conducted with monitoring of blood electrolytes.

In the current study, almost all patients with prior experience of infusion reaction to cetuximab could receive panitumumab safely following premedication and with a reduced speed of infusion. Some reports have shown that panitumumab can be administered successfully in patients after a severe infusion reaction to cetuximab (25–29). On the other hand, post-marketing fatalities due to infusion reaction with panitumumab have been reported in patients with a history of severe cetuximab-related infusion reaction (30). Therefore, administration of panitumumab to patients with a history of infusion reaction to cetuximab is not currently recommended.

Pulmonary toxicity including drug-induced ILD represents an important adverse reaction that is associated with EGFR-targeted cancer therapy (31), with the potential to be fatal in some patients (32). We prospectively established an ILD subcommittee consisting of experts to accurately evaluate the incidence of ILD. Furthermore, in order to avoid panitumumab treatment, at the time of registration, a recommendation letter was issued to reconsider treatment with panitumumab if a patient had a history or complication of ILD

Table 3. Summary of safety data

Post-marketing survey in Japan	P-mab monotherapy ($n = 1254$)				Combination therapy ($n = 1831$)			
ADRs of special interest	All		≥Grade 3		All		≥Grade 3	
Skin disorders (SOC)	918	73.2%	118	9.4%	1446	79.0%	274	15.0%
Paronychia	272	21.7%	33	2.6%	459	25.1%	99	5.4%
Interstitial lung disease[a]	16	1.3%	—	—	23	1.3%	—	—
Infusion reaction	17	1.4%	1	0.1%	30	1.6%	5[b]	0.3%
Hypomagnesemia	257	20.5%	61	4.9%	263	14.4%	62	3.4%
Hypocalcemia	59	4.7%	16	1.3%	77	4.2%	26	1.4%
Cardiac disorders (SOC)	2	0.2%	0	0.0%	5	0.3%	1	0.1%

Clinical trials[c]	P-mab monotherapy[c] ($n = 1052$: KRAS WT)				P-mab + FOLFOX4[d] ($n = 322$: KRAS WT)				P-mab + FOLFIRI[e] ($n = 302$: KRAS WT)			
ADRs of special interest	All		≥Grade 3		All		≥Grade 3		All		≥Grade 3	
Skin disorders (SOC)	969	92.1%	130	12.4%	308	95.7%	110	34.2%	279	92.4%	101	33.4%
Paronychia	214	20.3%	12	1.1%	63	19.6%	11	3.4%	58	19.2%	9	3.0%
Interstitial lung disease	0	0.0%	0	0.0%	2	0.6%	2	0.6%	2	0.7%	2	0.7%
Infusion reaction	35	3.3%	5	0.5%	24	7.5%	8	2.5%	6	2.0%	1	0.3%
Hypomagnesemia	79	7.5%	22	2.1%	89	27.6%	19	5.9%	77	25.5%	8	2.6%
Hypocalcemia	11	1.0%	5	0.5%	14	4.3%	3	0.9%	14	4.6%	1	0.3%
Cardiac disorders (SOC)	10	1.0%	3	0.3%	7	2.2%	3	0.9%	6	2.0%	0	0.0%

P-mab, panitumumab.
[a]Based on the evaluation of the ILD review subcommittee.
[b]Including Grade-2 serious cases.
[c]Trial Nos: 20050216, 20040192, 20020408, 20030194, 20030167, 20030250, 20025405, 20030138, 20040116, 20030251, 20020375.
[d]Trial No: 2005203.
[e]Trial No: 2005181.

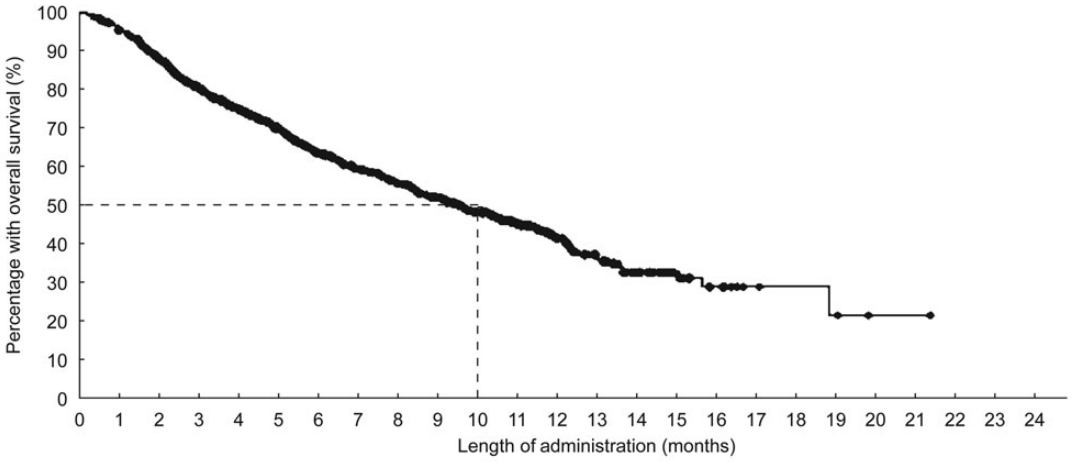
Table 4. Time to onset of interstitial lung disease (ILD)

	Time (months)											All
	≤1	≤2	≤3	≤4	≤5	≤6	≤7	≤8	≤9	≤10	>10	
ILD cases	8	4	11	1	4	5	0	3	2	0	1	39
Fatal cases	(6)	(2)	(4)	(0)	(2)	(2)	(0)	(1)	(2)	(0)	(1)	(20)

(Fig. 1). In the current post-marketing surveillance study of panitumumab, the overall incidence rate of ILD was 1.3%, with a mortality rate of 0.6%.The incidence of ILD was similar to that reported in a post-marketing survey of cetuximab in Japan (1.2%) (23). The ILD subcommittee carried out a full evaluation of ILD with panitumumab, concluding that the onset of ILD can occur at any time after the start of panitumumab administration and that there were no findings specific to panitumumab, either clinically or in CT imaging. The DAD type of ILD occurred in some cases, as with cetuximab and the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, and may be fatal. At present, no major differences in the incidence of ILD or in the rate of death due to ILD were found in comparison with cetuximab (23). Thus, ILD is one of the particular concerns with the use of panitumumab as well as other anti-EGFR drugs.

With regard to all panitumumab-related ADRs, there were no differences between its use as monotherapy or in combination therapy with cytotoxic agents, and the profile, incidences, onset and outcomes of these ADRs were very similar to those reported in previous clinical trials.

In contrast to the combination setting with chemotherapy regimens, the monotherapy setting represents the efficacy of panitumumab in clinical practice more accurately; therefore, patients treated with panitumumab monotherapy as a third-line or later therapy were selected for analysis of the effectiveness of panitumumab. The effectiveness of panitumumab, reported previously in clinical trials, was also confirmed in the current



Duration (months)	0	≤1	≤2	≤3	≤4	≤5	≤6	≤7	≤8	≤9	≤10	All
No. of patients	1062	999	890	756	637	535	440	368	325	281	227	—
Fatal cases	0	46	122	197	246	284	332	359	381	401	420	461
Censored cases	0	17	50	109	179	243	290	335	356	380	415	601

Figure 4. Overall survival ($n = 1062$) in patients receiving third-line, or later, therapy with panitumumab monotherapy.

post-marketing surveillance study. In a pivotal, Phase III, randomized, controlled study (15), the median overall survival time in the panitumumab group (wild-type *KRAS*) was ∼8.1 months (∼6.3−9.4 months) (11); data obtained from the present surveillance study exhibit a median overall survival of 10.3 months (56.6% censored cases).

Whilst acknowledging that post-marketing surveillance studies have some inevitable limitations (e.g. the lack of a control group) that differ from those in well-controlled, prospective clinical trials, it is recognized that post-marketing surveillance studies provide a information based on the general population (33). These factors result in greater external validity for post-marketing surveillance studies compared with well-controlled, randomized clinical trials (33). Despite these limitations, this large-scale, non-interventional study has some advantages. All patients treated with panitumumab were required to register before administration. Therefore, this surveillance study has minimum selection bias. This study also provides health-care professionals with valuable information on the safety and effectiveness of panitumumab based on real-world data.

In conclusion, the current post-marketing surveillance study in Japanese patients with unresectable colorectal cancer confirmed the safety profile and effectiveness of panitumumab that has been reported previously in clinical trials. No new safety signals were reported. It is considered that the benefit/risk balance for the use of panitumumab in patients with unresectable colorectal cancer remains favorable also in Japan.

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Conflict of interest statement

N.B., K.S., Y.K., K.H., A.G., N.Y., K.M., T.H., T.Y. and A.O. are members of the Vectibix Appropriate Use/Safety Evaluation Committee. N.B. has received a consultancy fee from Takeda, speaker honoraria from Takeda, Taiho and Yakult, and research funding from Takeda, Bristol-Myers Squibb, Merck Serono and Chugai. K.S. has received consultancy fees from Taiho, Chugai, Takeda and Merck Serono, speaker honoraria from Taiho, Chugai, Yakult, Bristol-Myers Squibb, Merck Serono, Kyowa Hakko Kirin, Takeda, Kaken, Johnson & Johnson, Toray, Aska and Bayer, a manuscript fee from Chugai, and a donation from Taiho, Chugai, Yakult, Bristol-Myers Squibb, Merck Serono, Kyowa Hakko Kirin,

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