

A Phase 2 Clinical Trial of Panitumumab Monotherapy in Japanese Patients with Metastatic Colorectal Cancer

Kei Muro¹, Takayuki Yoshino^{2,3}, Toshihiko Doi³, Kuniaki Shirao⁴, Hiroya Takiuchi⁵, Yasuo Hamamoto⁶, Hiroyuki Watanabe⁷, Bing-Bing Yang⁸ and Daisuke Asahi⁷

¹Aichi Cancer Center Hospital, Nagoya, ²Shizuoka Cancer Center, Shizuoka, ³National Cancer Center Hospital East, Chiba, ⁴National Cancer Center Hospital, Tokyo, ⁵Osaka Medical College, Osaka, ⁶Tochigi Cancer Center, Utsunomiya, ⁷Takeda Bio Development Center Ltd, Tokyo, Japan and ⁸Amgen Inc., Thousand Oaks, CA, USA

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Objective: Panitumumab, a fully human monoclonal antibody targeting epidermal growth factor receptor (EGFR), has antitumor activity and an acceptable safety profile in patients with metastatic colorectal cancer (mCRC). This Phase 2 study evaluated efficacy, pharmacokinetics and safety of panitumumab in Japanese patients with mCRC who developed progressive disease during or after fluoropyrimidine, irinotecan and oxaliplatin chemotherapy.

Methods: Eligible patients had histologically proven colorectal adenocarcinoma and EGFR tumor expression in $\geq 1\%$ of tumor cells by immunohistochemistry. Patients received panitumumab 6 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) by independent central review. Secondary endpoints included progression-free survival (PFS), overall survival (OS), pharmacokinetic parameters and incidence of adverse events.

Results: Fifty-two patients received at least one dose of panitumumab. Seven patients had partial responses for a confirmed ORR of 13.5% (95% CI: 5.6, 25.8). Median PFS was 8.0 weeks (95% CI: 7.4, 11.4) and median OS was 9.3 months (95% CI: 7.1, 12.8). Panitumumab pharmacokinetics were consistent with prior studies in Japanese and non-Japanese patients. The most common treatment-related adverse events (all, worst grade 3) were acne (81%, 2%), dry skin (62%, 0%), rash (46%, 2%), paronychia (33%, 2%), pruritus (33%, 0%) and hypomagnesemia (33%, 0%). No adverse event of infusion reaction was reported by the investigators.

Conclusions: Panitumumab monotherapy was active in Japanese patients with chemotherapy-refractory mCRC, with pharmacokinetic and safety profiles similar to those seen in prior studies.

Key words: panitumumab – pharmacokinetics – colorectal neoplasms – metastases – drug toxicity

INTRODUCTION

Cancer is one of the leading causes of death in Japan, and the incidence of colorectal cancer (CRC) has been increasing (1). In Japan, 131 438 new cases (87 825 colon cancers and 43 613 rectal cancers) and 55 070 deaths are anticipated in 2010 (2). Of newly diagnosed patients with CRC, 15–25% of the patients have metastatic disease (3) and 50% or more of the patients who are initially diagnosed with localized disease ultimately develop metastatic CRC (mCRC) (4).

Expression of the epidermal growth factor receptor (EGFR) is frequently associated with malignant transformation in carcinomas, including CRC (5,6). Currently, there are two anti-EGFR monoclonal antibodies, panitumumab and cetuximab, that are approved in the USA and Europe for the treatment of mCRC. Tumor expression of EGFR is a labeling requirement for both drugs (7,8).

Panitumumab is a fully human, monoclonal antibody with high affinity ($K_D = 5 \times 10^{-11}$ M) for EGFR (7). Efficacy, pharmacokinetics and safety of panitumumab have been tested in Japanese patients with solid tumors (9). In that study, patients received panitumumab at doses of 2.5 mg/kg

For reprints and all correspondence: Kei Muro, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi, Japan. E-mail: kmuro@aichi-cc.jp

once weekly, 6.0 mg/kg every 2 weeks (Q2W) and 9.0 mg/kg every 3 weeks as monotherapy. All responders in that study (4 patients of 18 enrolled) had advanced CRC. The study described here extends the evaluation of panitumumab in Japanese patients with mCRC.

PATIENTS AND METHODS

STUDY DESIGN AND ELIGIBILITY CRITERIA

This was a multicenter, open-label, single-arm, Phase 2 clinical study in Japanese patients with mCRC who developed disease progression during or after prior fluoropyrimidine, irinotecan and oxaliplatin chemotherapy. The study was approved by Institutional Review Boards at all study sites.

Panitumumab (derived from Chinese hamster ovary cells on a 12 kl production scale) was supplied at a concentration of 20 mg/ml in 10 ml vials (Amgen Inc., Thousand Oaks, CA, USA). Panitumumab was administered by intravenous infusion using a 0.22 μ m in-line filter at a dose of 6.0 mg/kg Q2W over approximately 60 min. This dose of panitumumab was selected based on pharmacokinetic modeling, which indicated that 6.0 mg/kg Q2W would maintain a trough serum concentration at or above that necessary to achieve EGFR saturation levels while providing a convenient Q2W dosing. This dose has also been tested and deemed to be tolerable in a small study of Japanese patients (9).

Patients received panitumumab until they developed progressive disease or were unable to tolerate treatment. Patients who discontinued treatment for any reason underwent a safety follow-up visit. All patients were followed for 24 months after the first panitumumab infusion at approximately 3-month intervals to assess survival.

Eligible patients were men and women >20 years old who provided written informed consent. All patients had a pathologic diagnosis of colorectal adenocarcinoma with documented radiographic evidence of progressive disease during or after the most recent regimen with fluoropyrimidine, irinotecan and oxaliplatin. To ensure adequate exposure to prior chemotherapy, average dose-intensity of irinotecan (≥ 50 mg/m²/week) and oxaliplatin (≥ 30 mg/m²/week) was required. Patients were also required to have: unidimensionally measurable disease (≥ 20 mm in at least one dimension); an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and EGFR expression on $\geq 1\%$ of evaluated tumor cells. EGFR expression was determined by immunohistochemistry using the EGFR pharmDX™ kit (DakoCytomation, Carpinteria, CA, USA) and all tests were performed at a central laboratory (Esoterix Clinical Trials Services BVBA, Mechelen, Belgium).

STUDY ENDPOINTS

Efficacy endpoints included the objective response rate (ORR; primary endpoint), time to response, duration of

response, duration of stable disease, time to treatment failure, progression-free survival (PFS) time and overall survival (OS; secondary endpoints). Time to treatment failure was calculated as the time from the date of enrollment to the date a decision was made to end the treatment period for any reason. Panitumumab pharmacokinetic endpoints included the area under the concentration–time curve (AUC); maximum ($C_{\max}$) and minimum ($C_{\min}$) observed concentrations; and half-life during the dosing interval ($t_{1/2}$). Safety endpoints included incidence of all adverse events; changes in laboratory values and vital signs; and the incidence of anti-panitumumab antibody formation and infusion reactions.

ASSESSMENTS

Patients were evaluated for tumor response according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) at weeks 8, 12, 16, 24, 32, 40 and 48 and every 8 weeks thereafter until disease progression. Tumor responses were confirmed no less than 4 weeks after the criteria for response were first met. In addition to investigators' assessments, radiographic scans of all patients were reviewed by a central reviewer.

Predose serum samples for pharmacokinetic analyses were collected from a subset of patients and at 0.5, 24, 96, 168 and 240 h after completion of the first infusion and within 0.5 h before and 0.5 h after completion of infusions at Weeks 3, 5 and 7 and every 8 weeks thereafter. An additional sample was collected during the safety follow-up visit. A validated immunoassay with electrochemiluminescence detection was used to measure panitumumab concentrations in the serum samples (10). Pharmacokinetic assays were performed by Amgen Inc.

Serum samples to test for anti-panitumumab antibodies were collected before panitumumab infusion at Weeks 1, 7 and 23, and during the safety follow-up visit. This study utilized the same validated assays to detect the potential presence of anti-panitumumab antibodies as has been used in previous panitumumab clinical trials (11). An ELISA assay and a Biacore™ assay were used for screening, and a cell-based bioassay was used to detect neutralizing antibodies. Anti-panitumumab antibody assays were performed by Amgen Inc.

A retrospective analysis of tumor *KRAS* status was performed. DNA extracted from archived paraffin-embedded tumor tissue was analyzed for mutant *KRAS* sequences using a K-RAS Mutation Test Kit (DxS Ltd, Manchester, UK) that used allele-specific real-time polymerase chain reaction (12). *KRAS* assessments were performed by HistoGeneX (Antwerpen, Belgium).

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 with the exception of skin or nail toxicities, which were graded using the modified Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

STATISTICAL ANALYSES

Efficacy and safety analyses were conducted on the Full Analysis Set, which comprised all patients who had received at least one infusion of panitumumab. The Pharmacokinetics Analysis Set included all patients who received panitumumab and had evaluable serum data.

Mean values and standard deviations (SDs) are provided for continuous endpoints and frequency and percentage distributions are provided for discrete data. The ORR and its two-sided 95% confidence interval (CI) (13) were calculated. Survival time (progression-free and overall), time-to-event and duration endpoints are summarized with Kaplan–Meier curves and two-sided 95% CIs.

RESULTS

DEMOGRAPHICS

Of 98 patients who were screened, 53 patients were enrolled in six study sites in Japan. The most common reasons for screen failure were: tumor was EGFR-negative, EGFR expression was not diagnostic, and insufficient dose-intensity of irinotecan or oxaliplatin. One patient did not receive panitumumab because of disease progression clinically judged by the investigator, and 52 patients received at least one dose of panitumumab and were included in the Full Analysis Set. Forty-nine (94%) patients ended treatment because of disease progression, one (2%) patient withdrew consent and no patient withdrew from the study because of adverse events. Two patients remained with the study at the time of data cut-off (12 April 2007). Baseline demographic and clinical characteristics are summarized in Table 1.

PANITUMUMAB EXPOSURE

The median number of infusions per patient was 6 (range: 2–20 infusions). The median average weight-adjusted dosage of panitumumab was 6.04 mg/kg and the median weight-adjusted cumulative dosage was 35.5 mg/kg (range: 12.1–113.8 mg/kg).

EFFICACY

Objective responses were observed in seven patients for a rate of 13.5% (95% CI: 5.6, 25.8) by central radiographic image review. All seven responders had a partial response and no patient had a complete response. Seventeen (33%) and 26 (50%) patients had stable disease and progressive disease, respectively. Two (4%) patients could not be evaluated for objective response because of withdrawn consent for one patient and lack of confirmation of response in the other patient. Similar to results from central assessment, the ORR was 15.4% (8 of 52 patients; 95% CI: 6.9, 28.1) based on the investigators' assessments. Twenty-three (44%) and 19

Table 1. Patient demographics and disease characteristics at baseline

Characteristic	All patients (N = 52)
Male sex, n (%)	34 (65)
Age, median years (minimum, maximum)	59.0 (23, 77)
Primary diagnosis, n (%)	
Colon cancer	30 (58)
Rectal cancer	22 (42)
ECOG performance status, n (%)	
0	29 (56)
1	23 (44)
2	0
Prior chemotherapy, n (%)	
1 line	0
2 lines	27 (52)
≥3 lines	25 (48)
Cells with EGFR membrane staining, n (%)	
1% to <10%	30 (58)
10–35%	16 (31)
>35%	6 (12)
Highest membrane staining intensity, n (%)	
1+ (weak)	29 (56)
2+ (moderate)	14 (27)
3+ (strong)	9 (17)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

(37%) patients had stable disease and progressive disease, respectively.

The median time of follow-up for all 52 patients was 26.1 weeks (range: 5.4–42.0 weeks). The mean time to response in the seven responders was 7.6 weeks (95% CI: 6.1, 9.1) and the median duration of response was 16.2 weeks (95% CI: 16.1, 24.1). The median duration of stable disease was 15.0 weeks (95% CI: 11.4, 16.3). The median time to treatment failure was 11.4 weeks (95% CI: 8.4, 15.0). At the time of data cut-off, the median PFS was 8.0 weeks (95% CI: 7.4, 11.4) (Figure 1). The median OS was 9.3 months (95% CI: 7.1, 12.8).

Objective responses were also analyzed by EGFR expression (percentage of EGFR-positive cells and staining intensity) and grade of skin-related toxicity (Table 2). No correlation was observed between panitumumab efficacy and percentage of tumor cell membrane staining. All responders had grade 2 or 3 skin-related adverse events.

Tumor samples for retrospective *KRAS* testing were available for testing from only 16 patients in this study; however, data for 8 Japanese patients with mCRC enrolled in a prior Phase 1 panitumumab study (9) were also available. In a pooled analysis of these 24 patients, 14 (58%) had wild-type *KRAS* and 10 (42%) had mutated *KRAS*. Four (17%) patients

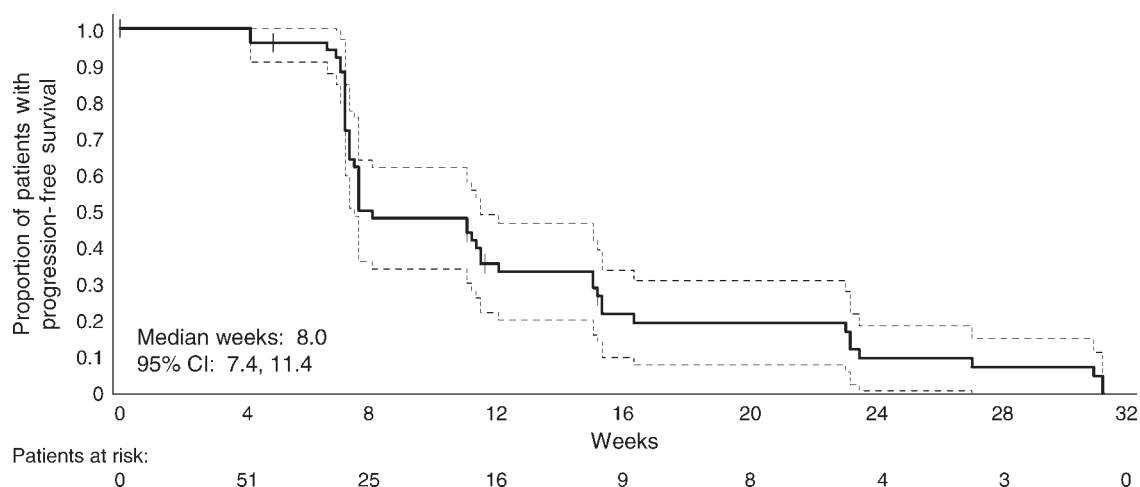


Figure 1. Progression-free survival (PFS) based on central assessment. The Kaplan–Meier curve of PFS for all patients ($N = 52$) is shown. Dashed lines represent 95% CI and censored patients are designated by vertical lines.

Table 2. Objective response and progression-free survival by EGFR tumor cell membrane staining and skin toxicity per central independent radiographic review

Category	<i>n</i>	Objective response		Progression-free survival Median time weeks (95% CI) ^c
		Patients responding, ^a <i>n</i> (%)	Rate % (95% CI) ^b	
EGFR staining				
1% to <10%	30	4 (13)	13.3 (3.8, 30.7)	8.0 (7.4, 11.4)
10% to 35%	16	3 (19)	18.8 (4.1, 45.7)	7.4 (7.1, 23.0)
>35%	6	0	0 (0, 45.9)	11.2 (7.6, 15.0)
EGFR intensity				
1+ (weak)	29	4 (14)	13.8 (3.9, 31.7)	7.6 (7.3, 11.1)
2+ (moderate)	14	1 (7)	7.1 (0.2, 33.9)	12.0 (7.1, 15.3)
3+ (strong)	9	2 (22)	22.2 (2.8, 60.0)	11.4 (7.6, 23.4)
Maximum grade ^d of skin toxicity				
Grade 1	8	0	0 (0, 36.9)	7.6 (4.1, 7.6)
Grade 2	41	6 (15)	14.6 (5.6, 29.2)	11.0 (7.4, 12.0)
Grade 3	3	1 (33)	33.3 (0.8, 90.6)	15.0 (7.1, 23.0)

CI, confidence interval; *n*, number of patients; EGFR, Epidermal growth factor receptor.

^aPatients with a complete response or partial response.

^bCI for objective response rate were calculated based on the *F* distribution method (13).

^cCI for progression-free survival were calculated based on a sign test (25).

^dGrades based on the National Cancer Institute Common Toxicity Criteria version 2.0 with the exception of skin or nail toxicities, which were graded using the modified Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

had a partial response to panitumumab therapy; all of these patients had tumors expressing wild-type *KRAS*. Median (95% CI) PFS was 13.2 (8.0, 23.1) weeks in patients with wild-type *KRAS* and 7.3 (7.1, 7.6) weeks in patients with mutated *KRAS* in their tumors.

PHARMACOKINETICS

Serum samples for pharmacokinetic analyses were collected from 20 patients who received panitumumab 6 mg/kg Q2W.

After the first panitumumab dose, the mean (SD) $C_{\max}$ was 113 (36.1) $\mu\text{g/ml}$ and the mean (SD) $C_{\min}$ was 15.4 (8.5) $\mu\text{g/ml}$; during the first dosing interval, the mean AUC (SD) was approximately 640 (174) $\mu\text{g day/ml}$ and the mean (SD) $t_{1/2}$ was 5.6 (2.0) days. After multiple panitumumab administrations, the mean (SD) steady-state concentrations based on data from the third dose and beyond were 31.7 (21.3) mg/ml before infusion and 146 (34.6) mg/ml immediately after infusion; these values were 2.0- and 1.3-fold higher, respectively, than the corresponding value after the first administration.

SAFETY

All patients had at least one adverse event and most patients (98%) had at least one adverse event that was considered by the investigator to be possibly related to treatment with panitumumab. No patient discontinued the study because of an adverse event. Most adverse events were grade 1 or 2. Thirteen (25%) patients had an adverse event with a worst grade of 3, and three (6%) patients had events with a worst grade of 4. The most common grade 3 adverse events were anorexia ($n = 4$) and hypophosphatemia ($n = 3$). Five grade 4 adverse events occurred in three patients, including anemia, fatigue, abnormal hepatic function, hepatic failure and hyperuricemia. One patient had a grade 5 event that was attributed to disease progression within 30 days of the last dose of panitumumab.

Most treatment-related events were grade 1 or 2, and skin-related events were most common (Table 3). One patient had a grade 3 serious adverse event of deep vein thrombosis. No grade 4 or higher treatment-related adverse event was reported. Fifty-one (98%) patients had treatment-related skin

toxicities. The most common skin toxicities were acne (81%), dry skin (62%), rash (46%), paronychia (33%), pruritus (33%), nail disorder (15%) and erythema (13%). Three (4%) patients had grade 3 treatment-related skin toxicities (acne, rash and paronychia). In a Kaplan–Meier analysis of skin toxicities, the median time to first toxicity was 6 days (95% CI: 5, 7) and the median time to most severe toxicity was 9 days (95% CI: 7, 13).

Grade 3 or 4 laboratory toxicities were seen in 12 (23%) patients; 11 (21%) patients had grade 3 and 1 (2%) patient had a grade 4 laboratory toxicity. Nineteen patients had grade 1 and two patients had grade 2 hypomagnesemia. Non-transient anti-panitumumab antibodies were seen in two (4%) patients; these patients did not have any severe or serious adverse events. Serum antibodies from these two patients did not exhibit neutralizing activity.

There were no investigator-reported adverse events of infusion reactions in this study. In a conservative *post hoc* analysis of adverse event terms (categories of acute infusion reaction/cytokine release syndrome and allergic reaction/hypersensitivity occurring on the day of infusion and resolving the same day or the day after the infusion), potential infusion reactions were reported in 6 (12%) patients, yielding a per-infusion incidence of 7/367 (2%). All potential infusion reactions were grade 1 and included pyrexia ($n = 3$), vomiting ($n = 1$), hypertension ($n = 1$) and fatigue ($n = 1$).

Table 3. Treatment-related adverse events^a occurring in $\geq 10\%$ of patients

Adverse event, ^b n (%)	All patients ($N = 52$)	
	All grades	Grade 3
Patients with any treatment-related adverse event	51 (98)	6 (12) ^c
Skin toxicities	51 (98)	3 (6)
Acne	42 (81)	1 (2)
Dry skin	32 (62)	0
Rash	24 (46)	1 (2)
Pruritis	17 (33)	0
Paronychia	17 (33)	1 (2)
Nail disorder	8 (15)	0
Erythema	7 (13)	0
Hypertrichosis	5 (10)	0
Hypomagnesemia	17 (33)	0
Fatigue	13 (25)	0
Stomatitis	12 (23)	0
Anorexia	11 (21)	1 (2)
Diarrhea	8 (15)	0
Vomiting	7 (13)	0
Constipation	5 (10)	0
Decreased weight	5 (10)	0

^aThe investigator considered there to be a reasonable possibility that the event may have been caused by panitumumab.

^bAdverse events were coded using the MedDRA dictionary version 9.0. Grades based on the National Cancer Institute Common Toxicity Criteria version 2.0 with the exception of skin or nail toxicities, which were graded using the modified Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

^cThe remaining treatment-related grade 3 events not included in the table were anemia ($n = 1$) and hypophosphatemia ($n = 1$).

DISCUSSION

The ORR (13.5%) in this study of panitumumab in Japanese patients with mCRC was similar to rates reported in prior studies in non-Japanese patients (11,14,15). Consistent with results from prior studies that examined the relationship between level of EGFR expression and efficacy of anti-EGFR monoclonal antibodies (15–19), no apparent correlation was observed between panitumumab efficacy and percentage of tumor cell membrane EGFR staining. These observations suggest that EGFR staining may not identify patients who are more likely to respond to anti-EGFR antibody therapy, and patients should not be denied this treatment based on EGFR testing. Patients with grade 2 or 3 skin-related adverse events had higher response rates and longer PFS than patients with grade 1 events. These findings are consistent with studies associating skin toxicity with response to anti-EGFR antibodies (15–17,19).

The presence of mutated *KRAS* in tumors has been seen to be a negative predictor of response to anti-EGFR monoclonal antibody therapies (12,20). In a pooled analysis (21) of patients with available *KRAS* status in this study and a prior Phase 1 study in Japanese patients with mCRC (9), all patients who had a response to panitumumab had tumors that expressed wild-type *KRAS*. Although a comparison of efficacy between Japanese patients with tumors expressing wild-type *KRAS* and those with mutated *KRAS* is not conclusive because of the small sample size, our findings are

consistent with other panitumumab (12) and cetuximab studies (22).

The pharmacokinetic profile of patients who were tested in this study was similar to those from prior studies in Japanese patients (23) and non-Japanese patients (24). At the 6 mg/kg Q2W dose and schedule, steady-state concentrations are attained by the third infusion.

Similar to observations in prior clinical trials of the anti-EGFR monoclonal antibodies (15–17,19), the most common adverse events reported in this study were skin-related. The skin reactions were primarily mild to moderate in severity. Only 6% of skin-related adverse events were severe (grade ≥ 3) compared with $\sim 16\%$ in prior studies (7).

In conclusion, this Phase 2 study examined the effects of panitumumab in Japanese patients with mCRC who developed disease progression or relapsed while on or after prior fluoropyrimidine, irinotecan and oxaliplatin chemotherapy. Results from this study indicate that panitumumab at a dose of 6 mg/kg Q2W was well tolerated and exhibited clinically meaningful antitumor activity in this patient population. The pharmacokinetic and safety profiles were similar to those observed in previous non-Japanese panitumumab clinical studies.

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Conflict of interest statement

None declared.

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