Comparison of Panitumumab Plus Irinotecan and Cetuximab Plus Irinotecan for *KRAS* Wild-type Metastatic Colorectal Cancer

TOSHIFUMI YAMAGUCHI[1], SATORU IWASA[1], KENGO NAGASHIMA[2], NOBUAKI IKEZAWA[1], TETSUYA HAMAGUCHI[1], HIROKAZU SHOJI[1], YOSHITAKA HONMA[1], ATSUO TAKASHIMA[1], NATSUKO OKITA[1], KEN KATO[1], YASUHIDE YAMADA[1] and YASUHIRO SHIMADA[3]

[1]*Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan;*
[2]*Chiba University Hospital Clinical Research Center, Chiba, Japan;*
[3]*Department of Medical Oncology, Kochi Health Sciences Center, Kochi, Japan*

Abstract. *Background/Aim: Panitumumab and cetuximab are known to be effective treatments for KRAS wild-type metastatic colorectal cancer (mCRC). However, it remains unclear which of these two biologic agents confers the greatest benefit when combined with irinotecan in patients with KRAS wild-type mCRC previously treated with fluoropyrimidine, oxaliplatin and irinotecan. Patients and Methods: Data, from 139 patients who received panitumumab or cetuximab, in combination with irinotecan, for KRAS wild-type mCRC previously treated with fluoropyrimidine, oxaliplatin and irinotecan were analyzed. The efficacy and safety of panitumumab plus irinotecan was compared to that of cetuximab plus irinotecan. Results: Baseline characteristics of the panitumumab plus irinotecan (n=42) and cetuximab plus irinotecan (n=97) groups were similar. Among patients with measurable lesions, the response rate was 34% in the panitumumab plus irinotecan group and 20% in the cetuximab plus irinotecan group. Median progression-free survival (PFS) was 4.3 and 5.7 months in the panitumumab and cetuximab groups, respectively. Median overall survival was 13.6 months with panitumumab and 11.2 months with cetuximab. Conclusion: Panitumumab plus irinotecan was well-tolerated and displayed a similar level of efficacy to that of cetuximab plus irinotecan.*

Colorectal cancer (CRC) is the third most common type of cancer worldwide, with approximately one million new cases diagnosed annually (1). In Japan, CRC is the second most common type of cancer and the third leading cause of mortality (2). Irinotecan and oxaliplatin are widely used in combination with fluorouracil and leucovorin as either first- or second-line treatment for metastatic CRC (mCRC). Further advances have been achieved with the integration of novel biological agents targeting epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF). Cetuximab, a chimeric monoclonal antibody, and panitumumab, a fully human monoclonal antibody, are both directed against EGFR (3). It is well-established that the efficacy of these anti-EGFR antibodies is restricted to patients with *KRAS* wild-type tumors (4-8). Findings from the BOND study, that compared the efficacy of cetuximab plus irinotecan with that of cetuximab alone in mCRC refractory to irinotecan-based chemotherapy, suggest that the combination of irinotecan with an anti-EGFR antibody should be considered as standard treatment for *KRAS* wild-type mCRC (9). The disease control rate and time to progression were significantly better with cetuximab plus irinotecan compared to irinotecan alone. Moreover, results from the ASPECCT trial demonstrated that panitumumab was non-inferior to cetuximab for overall survival (OS) in the treatment of *KRAS* wild-type mCRC (10). Therefore, panitumumab plus irinotecan is widely used for the treatment of irinotecan-refractory mCRC in clinical practice.

This retrospective study compared the safety and efficacy of panitumumab plus irinotecan to that of cetuximab plus irinotecan in patients with *KRAS* wild-type mCRC refractory to fluorouracil, oxaliplatin and irinotecan.

Patients and Methods

Patients. This was a retrospective analysis of patients with *KRAS* wild-type mCRC who received irinotecan combined with either panitumumab or cetuximab following resistance to fluorouracil, oxaliplatin and irinotecan. Patients with *KRAS* wild-type mCRC,

Correspondence to: Satoru Iwasa, MD, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81 335422511, Fax: +81 335453567, e-mail: siwasa@ncc.go.jp

Key Words: Colorectal cancer, cetuximab, panitumumab, *KRAS*.

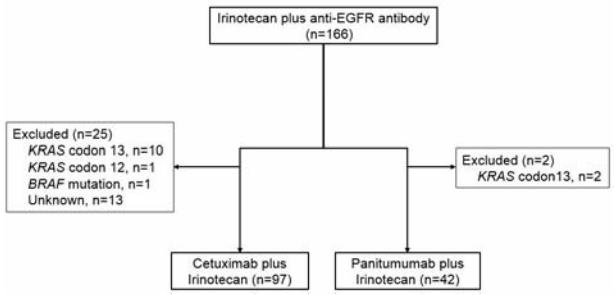


Figure 1. *Study flow.*

without *KRAS* mutations in codons 12 and 13, were eligible. Other inclusion criteria were as follows: >20 years old; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; previously treated with fluoropyrimidine, oxaliplatin and irinotecan; sufficient bone marrow function; and adequate hepatic and renal function. Patients with *BRAF* V600E mutation were excluded if the mutation status of this gene was known.

Treatment. Patients received irinotecan plus panitumumab or cetuximab (anti-EGFR antibody selection was at the physician's discretion) until disease progression or unacceptable toxicity. Cetuximab was administrated initially at a dose of 400 mg/m^2, followed by weekly infusions of 250 mg/m^2. Panitumumab was administrated at a dose of 6 mg/kg every 2 weeks. The dose level of irinotecan was selected by each physician according to the patient, based on prior toxicities experienced with twice-weekly irinotecan.

Evaluation and statistical analysis. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (11). Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

OS was calculated from the date of initiation of irinotecan plus anti-EGFR antibody to the date of death or the last follow-up visit. Progression-free survival (PFS) was calculated from the date of initiation of irinotecan plus anti-EGFR antibody treatment to the date of disease progression or death from any cause.

The median duration of follow-up and associated 95% confidence interval (CI) was calculated using the reverse Kaplan–Meier method.

Kaplan–Meier estimates were used to calculate survival probabilities, while the log-rank test was used to compare survival curves. To minimize selection bias, survival differences between each treatment group were evaluated by univariate and multivariate analyses using the Cox proportional hazard regression model and presented as the hazard ratio (HR) and 95% CI. Known prognostic factors for mCRC were systematically examined in analyses, and included treatment, prior bevacizumab use (no *versus* yes), age (≤65 *versus* >65 years), sex, ECOG PS (0-1 *versus* ≥2), alkaline phosphatase (≤300 *versus* >300), white blood cell counts (≤10,000 *versus* >10,000), histology (well differentiated type/moderately differentiated type *versus* Poorly-differentiated adenocarcinoma/Signet-ring cell carcinoma/Mucinous adenocarcinoma), number of metastatic sites (1 *versus* ≥2), location of primary site (left colon *versus* right colon) and presence of synchronous or metachronous disease.

Statistical analyses were performed using the SPSS statistical software package, version 22 (SPSS Inc., Chicago, IL, USA). *p*-Values <0.05 were considered to denote statistically significant differences.

Table I. *Patients' characteristics*.

Characteristic	Cetuximab plus irinotecan n (%)	Panitumumab plus irinotecan n (%)
Gender		
Male	67 (69%)	21 (50%)
Female	30 (31%)	21 (50%)
Age, year		
Median (range)	63 (29-79)	62 (33-81)
ECOG PS		
0	27 (28%)	10 (24%)
1	66 (68%)	30 (71%)
2	4 (4%)	2 (5%)
WBC		
≤10000	76 (78%)	39 (93%)
>10000	11 (11%)	3 (7%)
ALP		
≤300	31 (32%)	9(21%)
>300	66 (68%)	33 (79%)
Primary site		
Right colon	19 (20%)	6 (14%)
Left colon	78 (80%)	36 (86%)
Histological type		
tub	87 (90%)	39 (93%)
por/sig/muc	9 (9%)	3 (7%)
Unknown	1 (1%)	0
Disease status		
Synchronous	61 (63%)	24 (57%)
Metachronous	36 (37%)	18 (43%)
Site of metastasis		
Liver	67 (69%)	29 (69%)
Lung	64 (66%)	24 (57%)
Lymph node	31 (32%)	14 (33%)
Peritoneum	14 (14%)	4 (6%)
Bone	12 (12%)	
7 (17%)		
Others	9 (9%)	7 (17%)
Number of metastatic site		
1	26 (27%)	12 (29%)
≥2	71 (73%)	30 (71%)
Prior bevacizumab		
Present	66 (68%)	29 (69%)
Absent	31 (32%)	13 (31%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; WBC, white blood cell; ALP, alkaline phosphatase; well, well differentiated type; mod, moderately differentiated type; por, poorly differentiated adenocarcinoma; sig, Signet-ring cell carcinoma; muc, mucinous adenocarcinoma.

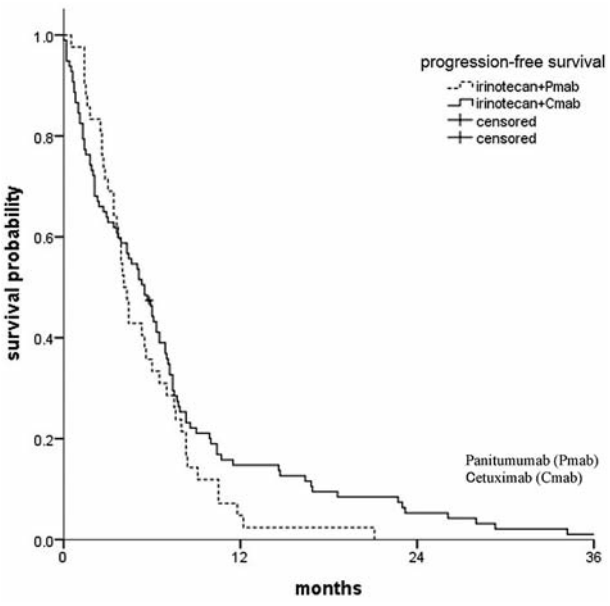


Figure 2. *Kaplan–Meier analysis of progression-free survival.*

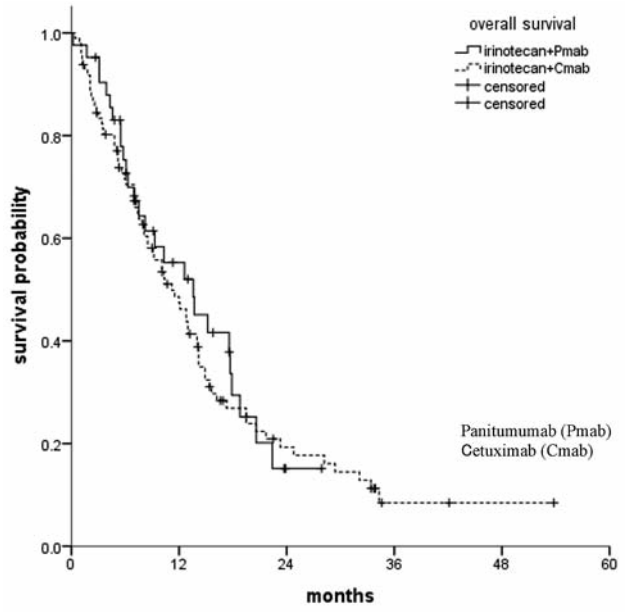


Figure 3. *Kaplan–Meier analysis of overall survival.*

Results

Patients' characteristics. Between October 2008 and December 2012, 166 consecutive patients with histologically confirmed, metastatic colorectal adenocarcinoma received irinotecan combined with panitumumab or cetuximab at the National Cancer Center Hospital, Tokyo, Japan. After the exclusion of 27 patients (14 with *KRAS* or *BRAF* mutations and 13 with unknown *KRAS* status), 139 patients were included in the final analysis (Figure 1). Patients' characteristics did not differ significantly between the panitumumab (n=42) and cetuximab (n=97) groups. Approximately 70% of patients in each treatment group had previously received bevacizumab (Table I).

Table II. *Response rate.*

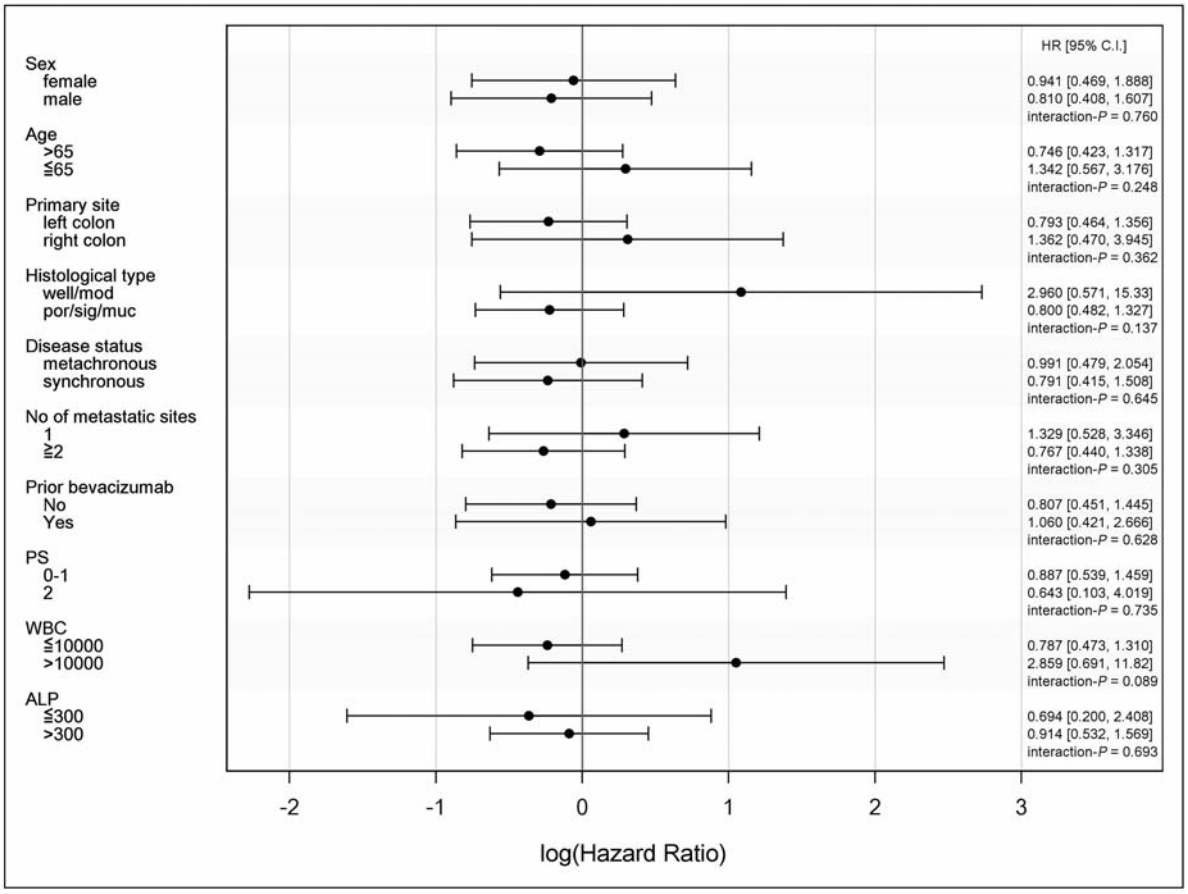
	Cetuximab plus irinotecan		Panitumumab plus irinotecan	
CR	0		0	
PR	18	(20%)	14	(34%)
SD	43	(47%)	15	(37%)
PD	27	(29%)	10	(24%)
NE	4	(4%)	2	(5%)
RR*	20% (95% CI: 12-29%)		34% (95% CI: 20-51%)	

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; RR, response rate; CI, confidence interval. *No confirmation.

Drug delivery and efficacy. Among the 31 patients with measurable lesions in the panitumumab plus irinotecan group, 14 achieved a partial response with an objective response rate of 34% (95% CI=20-51%). Among the 92 patients with measurable lesions in the cetuximab plus irinotecan group, 18 achieved a partial response and the objective response rate was 20% (95% CI=12-29%). No significant difference in response rate was observed between the two groups (Table II).

The relative dose intensity of the administered drugs was slightly lower in the panitumumab (78%) plus irinotecan (80%) group than in the cetuximab (87%) plus irinotecan (84%). Reasons for treatment discontinuation in the panitumumab and irinotecan groups were disease progression (n=36; 88% and n=82; 85%, respectively), toxicity (n=5; 10% and n=7; 7%, respectively) and other reasons (n=1; 2% and n=6; 6%, respectively).

At the time of data analysis, all patients, except for two, had experienced disease progression. The median duration of follow-up was 19.5 months in the panitumumab group and 33.7 months in the cetuximab group. Median PFS was 4.1 months (95% CI=3.4-4.7) and 5.5 months (95% CI=4.1-6.9) (Figure 2), whereas median OS was 13.6 months (95% CI=7.6-19.5) and 11.2 months (95% CI=8.1-14.3) (Figure 3) in the panitumumab and cetuximab groups, respectively, with no significant differences between the two groups for PFS



A multivariate interaction analysis of overall survival

Well, well differentiated type; mod, moderately differentiated type; por, poorly differentiated adenocarcinoma; sig, Signet-ring cell carcinoma; Muc, Mucinous adenocarcinoma; PS, performance status; WBC, white blood cell; ALP, alkaline phosphatase.

Figure 4. *A multivariate interaction analysis of overall survival.*

(HR=0.84; 95% CI=0.57-1.23) or OS (HR=1.11; 95% CI=0.71-1.73). Subset analysis suggested that the results were not influenced by interactions between the effect of each treatment and patient characteristics (Figure 4).

Subsequent chemotherapy (mainly re-introduction of oxaliplatin-based chemotherapy or an anti-EGFR antibody) was administered to 15 (36%) patients in the panitumumab plus irinotecan group, and 35 (36%) patients in the cetuximab plus irinotecan group, and all other patients received best supportive care, with no significant difference between the two groups.

Toxicity. Toxicity data are presented in Table III. In the panitumumab and cetuximab groups, more frequently observed adverse events were acneiform rash (90% and 82%, respectively) and paronychia (52% and 61%). All-grade hypomagnesemia was more frequently observed in panimumab plus irinotecan than in cetuximab plus irinotecan (43% and 23%). One patient receiving cetuximab experienced a grade 3 infusion-related reaction. No treatment-related deaths were observed in either group.

Discussion

In this study, the efficacy and safety of irinotecan plus panitumumab or cetuximab was retrospectively evaluated in patients with *KRAS* wild-type mCRC refractory to fluoropyrimidine, oxaliplatin and irinotecan. The results indicate that the combination of irinotecan with either panitumumab or cetuximab produces a similar level of efficacy, in terms of response rates, PFS and OS. Except for hypomagnesemia, there was no significant difference in

Table III. *Adverse events*.

Toxicity, n (%)	Cetuximab plus irinotecan				Panitumumab plus irinotecan			
	All grades		Grade 3/4		All grades		Grade 3/4	
Leucopenia	71	(73%)	18	(19%)	27	(64%)	6	(14%)
Neutropenia	62	(64%)	25	(26%)	26	(62%)	8	(19%)
Anemia	63	(65%)	8	(8%)	28	(67%)	4	(10%)
Thrombocytopenia	13	(13%)	2	(2%)	9	(21%)	0	
Nausea	34	(35%)	0		12	(29%)	1	(2%)
Anorexia	67	(69%)	3	(3%)	31	(74%)	3	(7%)
Diarrhea	45	(46%)	4	(4%)	20	(48%)	2	(5%)
Stomatitis	36	(37%)	1	(1%)	22	(52%)	1	(2%)
Rash acneiform	80	(82%)	3	(3%)	38	(90%)	1	(2%)
Paronychia	59	(61%)	5	(5%)	22	(52%)	1	(2%)
Hand foot syndrome	46	(47%)	4	(4%)	22	(52%)	0	
Alopecia	49	(51%)	-		27	(64%)	-	
Hypomagnesemia	22	(23%)	5	(5%)	18	(43%)	3	(7%)
AST elevation	60	(62%)	2	(2%)	28	(67%)	2	(5%)
ALT elevation	43	(44%)	1	(1%)	18	(43%)	2	(5%)
Infusion-related reaction	1	(1%)	1	(1%)	0		0	
Febrile neutropenia	4	(4%)	4	(4%)	1	(2%)	1	(2%)

AST, Aspartate transaminase; ALT, alanine aminotransferase.

toxicity between the two treatments. This suggests that either of the two anti-EGFR antibodies may be added to irinotecan for patients with *KRAS* wild-type mCRC refractory to fluoropyrimidine, oxaliplatin and irinotecan.

As described previously, in the BOND study, cetuximab plus irinotecan displayed superior efficacy to cetuximab alone for mCRC refractory to irinotecan, thus the combination of cetuximab with irinotecan has become standard treatment for irinotecan-refractory *KRAS* wild-type mCRC. Moreover, in the ASPECCT study, which enrolled patients with *KRAS* wild-type mCRC refractory to standard chemotherapy, panitumumab was non-inferior to cetuximab for OS. Therefore, panitumumab plus irinotecan has been considered as a treatment option, in addition to cetuximab plus irinotecan (9, 10).

Although the reason is unclear, hypomagnesemia was more frequent in the panitumumab plus irinotecan group (all grades; 43%) than the cetuximab plus irinotecan group (all grades; 23%) and this was also found in the ASPECCT study (all grades; 27%, panitumumab *vs*. 18%, cetuximab) (11). No infusion reactions were observed following panitumumab administration. This finding is consistent with previous reports concerning panitumumab and cetuximab, as well as the hypothesis that fully human monoclonal antibodies are less immunogenic than chimeric monoclonal antibodies (12-15).

Limitations of the present study include the small sample size, single-center population and retrospective, non-randomized design. Panitumumab or cetuximab was selected according to the physician's choice, which may have introduced a selection bias. Second, the differing characteristics of the patients in each group may have affected the results. Moreover, the reason for adding bevacizumab to previous chemotherapy was not documented and this cannot be excluded as a confounding factor. Third, regorafenib or TAS102, as salvage line chemotherapy, was not approved. Therefore, we think that subsequent chemotherapy does not impact OS in both groups. Finally, minor *RAS* mutations, other than *KRAS* exon 2, could not be excluded because a diagnostic kit was not commercially available.

Despite the retrospective nature being a major limitation, this study suggests that panitumumab plus irinotecan and cetuximab plus irinotecan exhibited similar efficacy and safety profiles in patients with *KRAS* wild-type mCRC refractory to fluoropyrimidine, oxaliplatin and irinotecan. Panitumumab plus irinotecan may be considered as a standard treatment option for patients with *KRAS* wild-type mCRC refractory to fluoropyrimidine, oxaliplatin and irinotecan.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

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