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Sensitivity to previous irinotecan treatment does not predict the efficacy of combination chemotherapy with cetuximab plus irinotecan for wild-type *KRAS* metastatic colorectal cancer

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ABSTRACT

The aim of this study was to evaluate the association of sensitivity to previous irinotecan-based chemotherapy with efficacy of cetuximab plus irinotecan therapy in metastatic colorectal cancer (MCRC) patients with wild-type *KRAS*. We analysed a pooled data set consisting of data from 87 MCRC patients from two previous phase II studies ($n = 60$) and a group given off-protocol treatment ($n = 27$) following irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapy. Overall objective response rate to cetuximab plus irinotecan was 28.7%, median progression-free survival (PFS) was 5.3 months, and median overall survival was 12.2 months. Objective response rate did not significantly differ between patients with a favourable response to previous irinotecan ($n = 23$), stable disease ($n = 38$), or progressive disease ($n = 26$), with observed rates of 29.2%, 31.6%, and 23.1%, respectively. Additionally, the non-parametric Spearman rank correlation coefficients (ρ) between the PFS of previous irinotecan-based chemotherapy and that of cetuximab plus irinotecan were quite low ($\rho = 0.067$ and 0.057 in patients with previous irinotecan as first- and second-line therapies, respectively). Although exploratory nature and small sample size may be limitations of this study, these findings indicate that the efficacy of irinotecan plus cetuximab in MCRC patients with wild-type *KRAS* did not differ by previous sensitivity to irinotecan.

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1. Introduction

Cetuximab, a recombinant human/mouse chimeric monoclonal IgG1 antibody that specifically targets the epidermal growth factor receptor (EGFR), significantly improves the prognosis for metastatic colorectal cancer (MCRC) compared to best supportive care alone as a third-line treatment.[1] Furthermore, the BOND-1 study, which examined over 300 patients with irinotecan-pretreated MCRC, demonstrated that combining cetuximab with irinotecan results in higher response rates and longer progression-free survival (PFS) than cetuximab alone (22.9% vs. 10.8%, respectively).[2] Based on these results, cetuximab plus irinotecan has become one of the standard chemotherapies in MCRC patients after failure with 5-fluorouracil (5-FU), oxaliplatin, and irinotecan.[3] Although the BOND-1 study also suggested that cetuximab may restore chemosensitivity to irinotecan in MCRC patients with irinotecan-refractory disease,[2] to our knowledge, only one study has reported the relationship between the efficacies of previous irinotecan-based chemotherapy and cetuximab plus irinotecan for MCRC.[4] Notably, neither this study[4] nor the BOND-1 study[2] evaluated *KRAS* status, which may have affected treatment response, on the basis of several retrospective findings that the indications for cetuximab are limited to MCRC patients with wild-type *KRAS*.[5–9]

Here, we examined the association of sensitivity to previous irinotecan-based chemotherapy with outcomes after cetuximab plus irinotecan treatment in MCRC patients with wild-type *KRAS* using a pooled data set consisting of data from two phase II studies[10,11] and a group of other eligible patients who had received off-protocol treatment.

2. Patients and methods

2.1. Patients

We previously conducted two phase II studies to prospectively evaluate the effectiveness and safety of combination chemotherapy with weekly cetuximab plus irinotecan[10] or biweekly cetuximab[11] in the treatment of MCRC patients with wild-type *KRAS* who had experienced progression after irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapy. The primary end-point was response rate, and the tumour response was assessed objectively every 8 weeks according to the Response Evaluation Criteria in Solid Tumours (RECIST ver. 1.0) guidelines. Eligibility criteria and treatment schedules for these two phase II studies were as described previously.[10,11] In brief, patients with metastatic colorectal adenocarcinoma with wild-type *KRAS*, which was defined as the *KRAS* gene without mutations in codons 12 and 13, were eligible. *KRAS* status was evaluated in each institution using either cycleave PCR genotyping (Aichi Cancer Center Hospital)[12,13] or a direct sequencing method (BML, Tokyo, Japan). Patients were also required to have radiographically confirmed disease progression during previous chemotherapy using irinotecan or within three months after the last chemotherapy dose, and treatment failure (defined as disease progression/discontinuation due to toxicity) within six months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy. In the weekly regimen, cetuximab was administered initially at 400 mg/m^2 followed by weekly 250 mg/m^2 infusions. In the biweekly regimen, cetuximab was administered at 500 mg/m^2 biweekly. In both regimens, irinotecan was administered biweekly at a dose ranging from 100 to 150 mg/m^2 as the same dose as that given during their most recent irinotecan based therapy.[14,15] The studies were approved by the institutional review board of each participating centre, and were registered in the UMIN clinical trial registry (UMIN000001838 and UMIN000001951). Additionally, the present study also included other patients who fulfilled the inclusion criteria of the above phase II studies and had been similarly treated with cetuximab plus irinotecan off-protocol. This exploratory study was also approved by the institutional review board of each participating centre.

Details of patient characteristics prior to the initiation of chemotherapy were obtained from the attending physician. Objective tumour response of previous chemotherapy was also assessed according to the RECIST ver. 1.0 guidelines. PFS associated with previous chemotherapy was measured from the beginning of treatment to the date of progression. Written informed consent was obtained from each patient prior to treatment administration.

2.2. Statistical methods

The purpose of the present study was to evaluate the association between several prognostic factors including previous efficacy of irinotecan-based chemotherapy, and clinical outcomes after cetuximab plus irinotecan treatment. The clinical outcomes consisted of objective response rate, PFS, and overall survival (OS). Objective responses were evaluated according to the RECIST criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). PFS was measured from the initiation of cetuximab plus irinotecan treatment to the occurrence of progression or death without evidence of progression. OS was defined as the interval between the date of initiation of cetuximab plus irinotecan and the date of death or last follow-up, and was estimated using the Kaplan–Meier method.

The objective response rates to cetuximab plus irinotecan were compared according to the responses of previous irinotecan-based chemotherapy. Distribution of results was assessed by the Fisher exact test, and survival curves were compared by the log-rank test. The correlation between PFS of previous irinotecan-based chemotherapy and PFS or OS of cetuximab plus irinotecan was evaluated using the non-parametric Spearman rank correlation coefficient (ρ). Since PFS of irinotecan-based chemotherapy may differ based on treatment lines, the non-parametric correlation analysis was stratified by treatment line (i.e., first- or second-line). The correlation between the interval from the last dose of previous irinotecan to initiation of cetuximab plus irinotecan (i.e., irinotecan-free interval) and PFS was also evaluated.

Prognostic factors associated with PFS and OS were evaluated using uni and multivariate Cox proportional hazard modelling. Associations were expressed as hazard ratios (HRs) and 95% confidence intervals (95% CIs). Factors included in the uni- and multivariate analyses were age (<65 vs. >65 years), gender (male vs. female), ECOG PS (0–1 vs. 2), number of metastatic sites (1–2 vs. 3 or more), pathological type

(moderately or well-differentiated adenocarcinoma vs. poorly differentiated adenocarcinoma), previous use of bevacizumab (yes vs. no), duration of previous chemotherapy (<median vs. >median), response to oxaliplatin-based chemotherapy (CR/PR vs. SD vs. PD), PFS associated with oxaliplatin-based chemotherapy (<median vs. >median), cause of discontinuation of oxaliplatin (disease progression vs. others), response to irinotecan-based chemotherapy (CR/PR vs. SD vs. PD), PFS associated with irinotecan-based chemotherapy (<median vs. >median), and dose of irinotecan (100 vs. 125 vs. 150 mg/m^2). As the PFS of irinotecan- and oxaliplatin-based chemotherapies may have differed by treatment line, median PFS of these chemotherapies was calculated with stratification by treatment line (i.e., first- or second-line). Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were two-sided, and *P* values <0.05 were considered to be statistically significant.

3. Results

3.1. Patient characteristics

The present analysis was conducted between September 2008 and August 2010 in 87 patients, consisting of 60 patients in phase II clinical trials and 27 patients administered an off-protocol treatment (Table 1). Forty-nine patients (56%) received a weekly regimen of cetuximab, while the other 38 patients (44%) received a biweekly regimen, with all patients receiving biweekly irinotecan. All patients had received two or more prior chemotherapy regimens, with a median interval from initiation of first-line chemotherapy to initiation of cetuximab plus irinotecan treatment of 22.0 months (range, 6.4–50.4). Prior oxaliplatin-containing regimens included FOLFOX (infusional and bolus 5-FU with oxaliplatin) in 85 patients (98%), XELOX (capecitabine plus oxaliplatin) in 1 patient (1%), and

Table 1 – Patient characteristics.

Characteristic		No. (*n* = 87)	%
Median age, (years)		62 (29–81)	
Gender	Male	57	66
	Female	30	34
ECOG PS	0	31	36
	1	50	57
	2	6	7
Origin	Colon	50	57
	Rectum	37	43
Pathology[a]	Wel/mod	80	92
	Poorly	7	8
No. of disease sites	1 or 2	51	59
	3 or more	36	41
Prior colorectomy	Yes	78	90
	No	9	10
Duration of prior CTx for advance disease (months)	Median	22.1	–
Previous use of BV	Yes	65	75
	No	22	25
Response to oxaliplatin-based 1st-line (*n* = 60)	CR/PR/SD/PD	0/32/19/9	–
PFS (months)	Median	7.3	–
Response to oxaliplatin-based 2nd-line (*n* = 27)	CR/PR/SD/PD	0/2/17/8	–
PFS (months)	Median	5.6	–
Response to irinotecan-based 1st-line (*n* = 27)	CR/PR/SD/PD	1/13/10/3	–
PFS (months)	Median	11.5	–
Response to irinotecan-based 2nd-line (*n* = 60)	CR/PR/SD/PD	0/9/28/23	–
PFS (months)	Median	5.0	–
Irinotecan-free interval (months)	Median	3.4	
Cetuximab regimen	Weekly	49	56
	Biweekly	38	44

CR, complete response; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease.

[a] Pathology of MCRC was categorised as either moderately or well-differentiated (Wel/mod) or poorly differentiated adenocarcinoma.

Table 2 – Response to cetuximab plus irinotecan according to response to previous irinotecan use.

Response to previous irinotecan	Response to irinotecan plus cetuximab				
	CR/PR	SD	PD	NE	ORR (%)
CR/PR (*n* = 23)	7	10	4	2	29.2
SD (*n* = 38)	12	19	6	1	31.6
PD (*n* = 26)	6	10	7	3	23.1

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

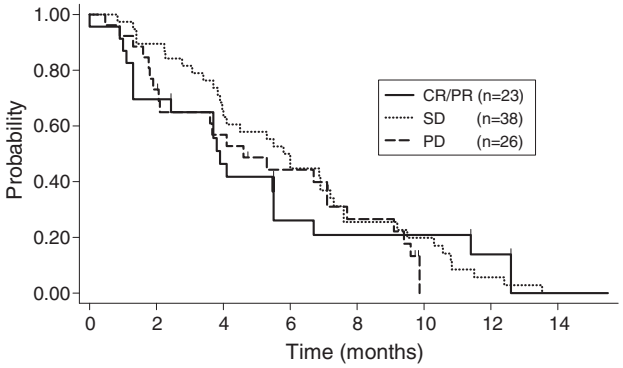

Fig. 1 – Progression-free survival (PFS) after treatment with cetuximab plus irinotecan according to objective response to previous irinotecan-based chemotherapy. Kaplan–Meier curve for median PFS of patients with either complete or partial response to previous irinotecan (CR/PR, *n* = 23), stable disease (SD, *n* = 38) or progressive disease (PD, *n* = 26) was 4.1, 5.8, and 4.6 months, respectively, with no significant differences detected between the three groups.

S-1 plus oxaliplatin in 1 patient (1%). Prior irinotecan-containing regimens included FOLFIRI (infusional and bolus 5-FU with irinotecan) in 64 patients (74%), irinotecan monotherapy in 11 patients (13%), S-1 plus irinotecan in 8 patients (9%), and irinotecan plus hepatic arterial infusion chemotherapy of 5-fluorouracil in 4 patients (<1%). Sixty patients received oxaliplatin-based therapy prior to irinotecan-based therapy, while the other 27 received these therapies in reverse sequence. Bevacizumab had been previously administered to 65 patients (75%) prior to cetuximab plus irinotecan. All patients discontinued prior irinotecan-based chemotherapy due to disease progression. Prior oxaliplatin-based regimen was discontinued due to disease progression in 64 patients and adverse events (predominantly sensory neuropathy) in 23 patients. The objective responses and median PFS of previous chemotherapies are summarised in Table 1. Among all patients, the median irinotecan-free interval period was 3.4 months (range, 0.5–41.1). The median values were used as cut-off thresholds to classify patients by each respective variable.

3.2. *Treatment outcomes and efficacy of cetuximab plus irinotecan*

The median number of cetuximab administrations for the weekly and biweekly regimens were 16 (range, 2–47) and 8 (range, 2–24), respectively. Irinotecan was administered at doses of 100, 125, and 150 mg/m^2 in 18, 26, and 43 patients, respectively. The average dose intensity of irinotecan was 67 mg/m^2/week. Treatment was discontinued in 79 patients due to disease progression (n = 70), toxicity (n = 6), curative surgery (n = 1), and loss to follow-up (n = 2). The median follow-up period was 17.9 months (range, 4.0–26.4), and 8 patients continued to receive protocol treatment at the time of analysis.

Among the 87 MCRC patients, one patient achieved CR, 23 patients experienced PR, and 40 had SD, as evaluated using the RECIST criteria. Sixteen patients had PD, while six patients were not evaluable for treatment response due to either symptomatic deterioration (n = 3) or treatment withdrawal due to toxicity (n = 3) prior to radiological response evaluation. The overall response rate was 28.7% (95% CI, 19.5–39.4) and the disease control rate (CR + PR + SD) was 73.6% (95% CI, 63.0–82.4). The median PFS was 5.3 months (95% CI, 3.9–6.7) and median OS was 12.2 months (95% CI, 9.4–16.5), with 42 patients still alive at the end of the study.

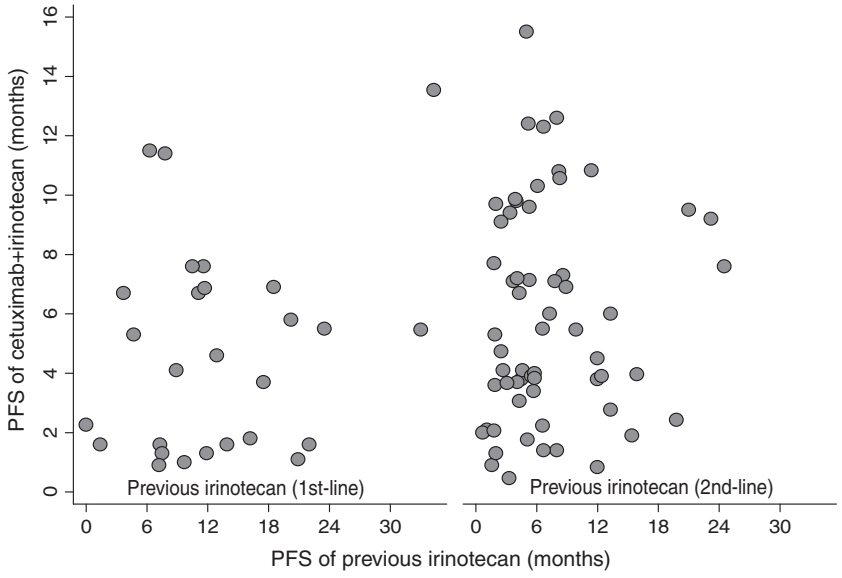

Fig. 2 – Progression-free survival (PFS) for cetuximab plus irinotecan based on PFS for two treatment lines of previous irinotecan. PFS of previous irinotecan (*x*-axis) and PFS of irinotecan plus cetuximab (*y*-axis) were plotted in each patient. The Spearman correlation coefficient between previous PFS of irinotecan and PFS of cetuximab plus irinotecan was ρ = 0.067 in patients with previous irinotecan as first-line and ρ = 0.057 in patients with previous irinotecan as second-line, with no significant correlation was found.

3.3. Response to previous irinotecan and clinical outcome

We next evaluated the relationship between response to previous irinotecan-based chemotherapy and clinical outcomes following cetuximab plus irinotecan treatment. The objective response rates to cetuximab plus irinotecan for patients with either a favourable response (CR or PR) to previous irinotecan ($n = 23$), SD ($n = 38$), or PD ($n = 26$) were 29.2%, 31.6%, and 23.1%, respectively (Table 2), with no significant differences detected between the three groups ($P = 0.74$). In addition, no significant differences were observed for PFS among patients by response to previous irinotecan, SD, or PD, who exhibited median values of 4.1 (95% CI, 1.6–6.7), 5.8 (95% CI, 3.9–7.2), and 4.6 months (95% CI, 2.1–7.1), respectively (Fig. 1). Further, no significant differences by previous response were observed in OS (data not shown).

3.4. PFS of previous irinotecan and clinical outcome

To determine if the PFS of previous irinotecan-based chemotherapy influenced the PFS of cetuximab plus irinotecan treatment, non-parametric correlation analyses were performed by stratifying MCRC patients by first- and second-line treatment regimens (Fig. 2). Almost no correlation was observed between previous PFS for irinotecan and PFS for cetuximab plus irinotecan, regardless of the treatment line of chemotherapy ($\rho = 0.067$ and 0.057 in patients with previous irinotecan as first- and second-line therapies, respectively). A similar tendency was observed for OS, with only a low correlation detected between the first- and second-line treatments ($\rho = 0.12$ and 0.19, respectively).

3.5. Irinotecan-free interval and clinical outcome

The relationship between the length of the irinotecan-free interval in MCRC patients and clinical outcomes following cetuximab plus irinotecan treatment was evaluated by non-parametric correlation analysis. Almost no correlation was observed between the irinotecan-free interval and either PFS ($\rho = 0.15$; Fig. 3) or OS ($\rho = 0.001$) for cetuximab plus irinotecan.

3.6. Uni and multivariate analyses for PFS and OS

The results of the uni and multivariate analyses for PFS and OS are summarised in Tables 3 and 4, respectively. Previous responses and PFS of irinotecan-based chemotherapy had no significant impact on PFS and OS after cetuximab plus irinotecan.

4. Discussion

In this study, we evaluated the relationship between sensitivity to previous irinotecan-based chemotherapy and efficacy of cetuximab plus irinotecan in MCRC patients with wild-type *KRAS* in whom prior chemotherapy consisting of irinotecan, oxaliplatin, or fluoropyrimidine had failed. Our results indicate that sensitivity to previous irinotecan-based chemotherapy has no association with clinical outcomes of subsequent irinotecan plus cetuximab treatment. Therefore, irinotecan plus cetuximab should be considered for irinotecan-refractory MCRC patients with wild-type *KRAS* regardless of previous irinotecan sensitivity.

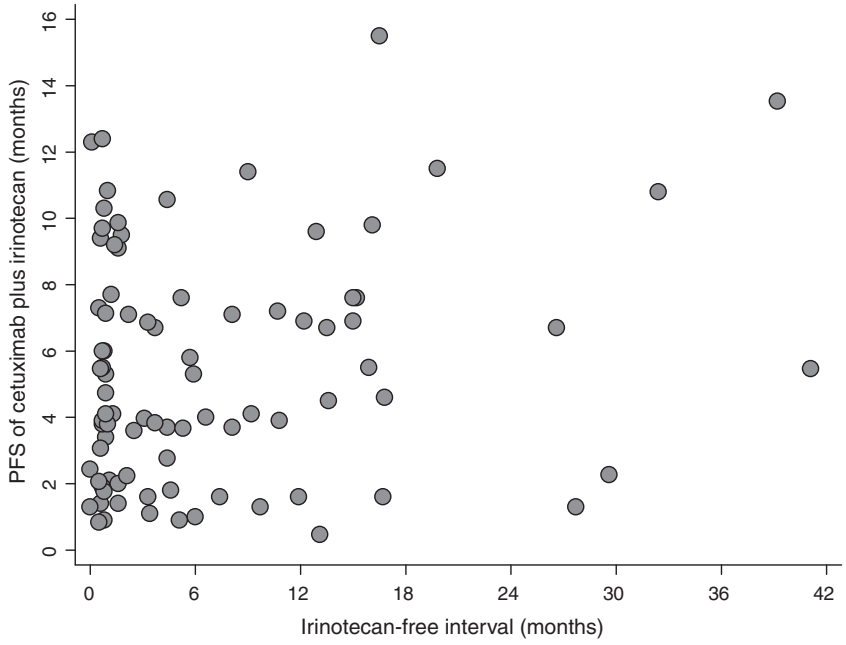

Fig. 3 – Relationship between progression-free survival (PFS) for cetuximab plus irinotecan and irinotecan-free interval. Irinotecan-free interval (*x*-axis) and PFS of irinotecan plus cetuximab (*y*-axis) were plotted in each patient. The Spearman correlation coefficient between irinotecan-free interval and PFS of cetuximab plus irinotecan was $\rho = 0.15$, with no significant correlation was found.

Table 3 – Univariate analysis for PFS and OS.

Characteristic	Cut off	*n*	Univariate for PFS			Univariate for OS		
			HR	95% CI	*P* value*	HR	95% CI	*P* value*
Age	65<	50	ref	–	–	ref	–	–
	65>	74	1.15	0.73–1.80	0.54	1.06	0.59–1.91	0.84
Gender	Male	57	ref	–	–	ref	–	–
	Female	30	1.16	0.72–1.89	0.54	1.36	0.74–2.52	0.32
PS	0	31	ref	–	–	ref	–	–
	1	50	1.31	0.81–2.14	0.27	1.41	0.72–2.78	0.32
	2	6	2.26	0.86–5.99	0.1	3.96	1.38–11.3	0.01
Pathology[a]	Wel/mod	80	ref	–	–	ref	–	–
	Poorly	7	2.61	1.18–5.81	0.018	1.69	0.61–4.76	0.31
No. of disease sites	1 or 2	20	ref	–	–	ref	–	–
	3 or more	36	1.31	0.83–2.09	0.24	1.96	1.08–3.54	0.03
Duration of prior CTx for advanced disease	<Median	43	ref	–	–	ref	–	–
	>Median	44	0.55	0.35–0.87	0.01	0.59	0.33–1.08	0.09
Previous use of BV	Yes	65	1.4	0.82–2.37	0.21	0.85	0.45–1.61	0.62
	No	22	ref	–	–	ref	–	–
Previous oxaliplatin response	CR/PR	34	ref	–	–	ref	–	–
	SD	36	1.25	0.76–2.06	0.38	1.38	0.72–2.66	0.33
	PD	17	1.66	0.89–3.12	0.11	1.67	0.71–3.95	0.24
PFS of oxaliplatin–based CTx	<Median	44	ref	–	–	ref	–	–
	>Median	43	0.76	0.49–1.21	0.27	0.64	0.35–1.17	0.15
Cause of oxaliplatin discontinuation	Progression	64	ref	–	–	ref	–	–
	Other	23	0.78	0.46–1.31	0.35	0.91	0.48–1.74	0.78
Previous irinotecan response	CR/PR	23	ref	–	–	ref	–	–
	SD	38	1.07	0.60–1.89	0.82	0.86	0.43–1.72	0.67
	PD	26	1.27	0.60–1.89	0.47	0.9	0.41–1.99	0.79
PFS of irinotecan-based CTx	<Median	43	ref	–	–	ref	–	–
	>Median	44	1.07	0.68–1.67	0.77	0.87	0.48–1.57	0.64
Cetuximab regimen	Weekly	49	ref	–	–	ref	–	–
	Biweekly	38	1.02	0.65–1.62	0.92	1.08	0.58–2.04	0.79

BV, bevacizumab; CI, confidence interval; CR, complete response; CTx, chemotherapy; HR, hazard ratio; OS, overall survival; PD, progressive disease PFS, progression-free survival; PR, partial response; PS, performance status; ref, reference; SD, stable disease.

[a] Pathology of MCRC was categorised as either moderately or well-differentiated (Wel/mod) or poorly differentiated adenocarcinoma

* *P* values <0.05 were considered to be statistically significant (underlined values).

Table 4 – Multivariate analysis for PFS and OS.

Characteristic	Cut off	Multivariate for PFS			Multivariate for OS		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Response to previous irinotecan CTx	CR/PR	ref	–	–	ref	–	–
	SD	1.07	0.58–1.98	0.58	0.97	0.46–2.03	0.93
	PD	1.33	0.66–2.67	0.66	0.99	0.39–2.49	0.99
PFS of previous irinotecan CTx	<Median	ref	–	–	ref	–	–
	>Median	1.35	0.85–2.27	0.21	1.01	0.52–1.95	0.98

Adjusted by: age, gender, PS, pathology, number of disease sites, duration of CTx, previous bevacizumab use, response and PFS of oxaliplatin-based CTx, dose of irinotecan Abbreviations: CI, confidence interval; CR, complete response; CTx, chemotherapy; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; ref, reference; SD, stable disease.

In the BOND-1 study,[2] which established a strategy to reintroduce irinotecan plus cetuximab for irinotecan-refractory MCRC, no subset analysis was performed according to previous response to irinotecan. Since cetuximab is effective without irinotecan for MCRC, we speculated that it would be meaningful to determine which patients might benefit by the reintroduction of irinotecan. Although several non-randomised trials have examined cetuximab plus irinotecan for irinotecan-pretreated MCRC[10,11,16–19], to our knowledge only Tahara et al. have reported the efficacy of this combination chemotherapy and response to previous irinotecan.[4] Their phase II study evaluated weekly cetuximab plus irinotecan for patients with MCRC and found that response rates were significantly higher in patients who had achieved a positive response to prior irinotecan treatment than in those who had not (60.0% vs. 20.7%, respectively). However, *KRAS* status was not evaluated in this study. As *KRAS* status is a strong predictive marker for cetuximab-based chemother-

apy, it may have contributed to the observed differences in response rates. Here, therefore, we restricted our analysis to patients with wild-type *KRAS* tumours. Results showed no significant correlation between the efficacy of previous irinotecan-based chemotherapy and clinical outcomes following subsequent cetuximab plus irinotecan treatment. In addition, the overall response rate of 28.1% (18/67) in patients without a positive response to previous irinotecan (SD, 38 patients; and PD, 26 patients) was relatively high compared with the rates of 12.8–17% observed in previous studies of EGFR monoclonal antibody monotherapy in a similar setting of wild-type *KRAS* MCRC.[5,20] Our results suggest that combining irinotecan with cetuximab may improve the outcomes of MCRC, even in patients who did not respond to prior irinotecan-based chemotherapy.

Recently, several biomarkers and clinical factors other than *KRAS* were reported as predictive markers of chemotherapy using EGFR antibodies such as cetuximab or panitumumab.[21] Although the response and disease control rates in the present study for wild-type *KRAS* MCRC were relatively higher than those of previous prospective studies in a similarly pretreated setting without consideration of *KRAS* genotype[2,16–19], efficacy is still not sufficient, and further investigation to identify MCRC patients most likely to benefit from EGFR antibody treatment appears necessary. This need is highlighted by the fact that nearly all patients experienced progression of MCRC after cetuximab plus irinotecan treatment, even after they achieved a significant response to the combined chemotherapy. Further clinical research aimed at improving MCRC treatment outcomes should focus on acquired resistance to cetuximab-based chemotherapy.

Several limitations of the study warrant mention. First, previous treatment regimens, including those of irinotecan, varied among patients. Second, the sequence of oxaliplatin- and irinotecan-based chemotherapies was not consistent. However, limiting the analysis to patients who received first-line oxaliplatin-based chemotherapy followed by second-line FOLFIRI ($n = 50$) produced nearly identical results (data not shown). Third, the moderate sample size of this study necessitates confirmation of these results in a large cohort study.

In conclusion, our exploratory analysis of a pooled data set from two previous phase II studies and off-protocol treatment of MCRC patients revealed that sensitivity to previous irinotecan-based chemotherapy had no impact on clinical outcomes after cetuximab plus irinotecan treatment. Irinotecan plus cetuximab is similarly effective for MCRC patients with wild-type *KRAS* who experience disease progression after irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapies regardless of previous irinotecan sensitivity.

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Conflict of interest statement

None declared.

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