Efficacy and Safety of Regorafenib or TAS-102 in Patients with Metastatic Colorectal Cancer Refractory to Standard Therapies

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Abstract. *Background: Regorafenib and TAS-102 are novel antitumor agents for patients with metastatic colorectal cancer (mCRC) whose disease has progressed after standard therapies. In randomized trials, regorafenib and TAS-102 prolonged survival in patients with mCRC. However, the appropriate selection of regorafenib or TAS-102 in treatment strategy has not yet been established. Patients and Methods: We performed a retrospective analysis, between March 2013 and July 2015, on the efficacy and safety of regorafenib or TAS-102. Results: Thirty-seven patients with mCRC treated with regorafenib or TAS-102 were included. Of these 37 patients, 23 first received regorafenib and 14 received TAS-102. The median progression-free survival and overall survival were 3.0 and 5.8 months, respectively, in the regorafenib group and 2.1 and 6.3 months, respectively, in the TAS-102 group. Drug-related adverse events (AEs) and grade ≥3 AEs were 23 (100%) and 10 (43.5%), respectively, in the regorafenib group and 13 (92.9%) and 2 (14.3%), respectively, in the TAS-102 group. The most frequent grade ≥3 AEs were hepatotoxicity (17.4%) and hand-foot syndrome (13.0%) in the regorafenib group, and neutropenia (14.3%) in the TAS-102 group. In subgroup analysis, the median overall survival was 11.5 months in patients receiving crossover treatment with regorafenib to TAS-102, and 7.6 months in those receiving crossover treatment with TAS-102 to regorafenib. Conclusion: Our results showed that regorafenib and TAS-102 have comparable efficacy but different toxicity profiles in patients with mCRC. Both are considered new salvage treatment options. Differences in the toxicity profiles between the two treatments will help in choosing regorafenib or TAS-102.*

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According to the World Health Organization's most current statistics, colorectal cancer (CRC) is one of the most common types of cancer in the world (1). Surgical resection is considered to offer a potential cure to patients with CRC; however, approximately a quarter of patients present with synchronous metastases, and up to 50% of patients will develop metastases during the course of their disease (2, 3). Standard therapy for metastatic disease generally consists of fluoropyrimidine-based chemotherapy plus either oxaliplatin or irinotecan combined with anti-vascular endothelial growth factor (VEGF) therapy or anti-epidermal growth factor receptor (EGFR) therapy (2-5). However, because many patients maintain good performance status (PS) and might be candidates for further therapy, additional options are needed for patients who have disease progression despite having received all currently available standard therapies. Recently, a major interest in clinical research is the development of new molecules that may be active in this specific setting, with the aim to further improve the outcome of patients with refractory metastatic colorectal cancer (mCRC).

Regorafenib is a novel oral multi-kinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumor angiogenesis [VEGF receptors 1-3, and tyrosine kinase with immunoglobulin-like and epidermal growth factor-like homology domain 2 (TIE2)], oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and the tumor microenvironment [platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR)] (6). Two randomized phase III trials showed that regorafenib significantly prolonged survival compared with best supportive care (BSC) (7, 8). On the basis of the results of the CORRECT trial, regorafenib was approved for the

treatment of mCRC that has progressed on standard therapies by the US Food and Drug Administration (FDA) in September 2012 and by the Japanese Ministry of Health, Labor, and Welfare in March 2013.

TAS-102 is an orally administered combination of a thymidine-based nucleic acid analog, trifluridine and a thymidine phosphorylase inhibitor (TPI), tipiracil hydrochloride, at a molar ratio of 1:0.5. Trifluridine is the active antitumor component of TAS-102, and its triphosphate form is incorporated into DNA in tumor cells (9). The incorporation into DNA is thought to contribute to the antitumor effect of trifluridine (10, 11). TPI is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades trifluridine (12). In the randomized, J-003 phase II trial conducted in Japan, TAS-102 monotherapy showed a survival benefit over BSC in patients with mCRC after failure of standard chemotherapies (13). TAS-102 has improved progression-free survival (PFS) and overall survival (OS), with a favorable safety profile, in the global phase III RECOURSE trial conducted in patients with refractory mCRC or who were intolerant to standard therapies (14). TAS-102 was first approved in Japan in March 2014 and by the FDA in September 2015.

These randomized trials suggested that both regorafenib and TAS-102 could improve the outcomes of patients with unresectable mCRC after failure of standard chemotherapies (7, 8, 13, 14). On the basis of these results, regorafenib and TAS-102 are considered new treatment options for the salvage line. However, the appropriate selection of regorafenib or TAS-102 has not yet been established. Thus, we performed a retrospective analysis of the efficacy and safety of regorafenib and TAS-102 in patients with mCRC refractory to standard chemotherapies.

Patients and Methods

Patient selection. This retrospective analysis included patients who had histologically-confirmed, unresectable, mCRC, received at two or more prior regimens of standard chemotherapy, had an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2 and had adequate organ function. This retrospective analysis was approved by the Institutional Review Board of our institution (Approved number 15144).

Treatment. gorafenib was administered at 160 mg once daily on days 1-21 of every 28-day cycle. TAS-102 was administered at 35 mg/m^2 orally, twice daily, on days 1-5 and 8-12 of every 28-day cycle. Treatment was continued until patients had confirmed disease progression, unacceptable toxicity, withdrew consent, or stopped treatment at the investigator's discretion if felt to be clinically indicated.

Assessments. Patient characteristics, adverse events (AEs), treatment compliance, treatment response, and PFS and OS were analyzed retrospectively, with the data collected from medical records at Osaka University. The tumor response rate was defined as the proportion of patients with complete (CR) or partial (PR) responses, and the disease control rate (DCR) was defined as the proportion of patients with a best response of CR or PR or stable disease (SD); assessment of SD had to be made after at least 6 weeks. Tumor response and progression were radiologically assessed by investigators with the Response Assessment in Solid Tumors (RECIST) criteria (version 1.1) (15). Patients underwent safety assessments during every cycle, including collection of information about AEs and laboratory changes (hematology, clinical chemistry, and urinalysis). We graded AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (16).

Statistical analysis. Continuous variables were compared using Kruskal–Wallis. Discrete variables, expressed as the number and percentage, were compared using the x^2 test or Fisher exact test, when appropriate. PFS was defined as duration from the start of regorafenib or TAS-102 to the first recorded occurrence of oncologist-assessed disease progression. OS was defined as the duration of time from the start of regorafenib or TAS-102 to death from any cause. Survival curves were generated using the Kaplan–Meier method, and differences in survival were evaluated with the logrank test. JMP pro version 11 (SAS Institute, Cary, NC, USA) was used for this analysis. *p*-Values of less than 0.05 were considered to indicate statistical significance.

Results

Patients' baseline characteristics. Between March 2013 and July 2015, 37 patients with mCRC who were treated with regorafenib or TAS-102 were included in the analysis. All patients had received prior chemotherapy regimens containing fluoropyrimidines, oxaliplatin, and irinotecan. Of these patients, 23 received regorafenib and 14 received TAS-102. Table I shows the patients' baseline characteristics. More patients in the TAS-102 group had a poor ECOG PS than those in the regorafenib group (p=0.02), and fewer patients in the TAS-102 group had received previous anti-VEGF treatment than those in the regorafenib group (p=0.05). Baseline characteristics in patients with wild-type KRAS status were similar in both groups (52.2% and 64.3%). All patients had previously received an anti-EGFR monoclonal antibody. After disease progression, six (26.1%) patients received further TAS-102 in the regorafenib group, and eight (57.1%) received further regorafenib in the TAS-102 group (p=0.08). The median duration of follow-up was 5.5 months in the regorafenib group and 6.1 months in the TAS-102 group (Table II).

Efficacy. Table II shows the tumor responses. No patient in either group had a CR or PR. Disease control was achieved in seven (30.4%) out of 23 patients in the regorafenib group and four (28.6%) out of 14 patients in the TAS-102 group.

The median PFS was 3.0 months [95% confidence interval (CI)=1.64 to 4.52 months] in the regorafenib group

Table I. *Patient baseline characteristics (n=37).*

Variable	Regorafenib group (n=23)	TAS-102 group (n=14)	*p*-Value
Age			0.18
Median (range), years	59 (37-83)	66 (44-80)	
Gender, n (%)			0.31
Male	12 (52.2)	10 (71.4)	
Female	11 (47.8)	4 (28.6)	
ECOG PS, n (%)			0.02
0	10 (43.5)	1(7.2)	
1	13 (56.5)	10 (71.4)	
2	0 (0.0)	3 (21.4)	
KRAS, n (%)			0.51
Wild-type	12 (52.2)	9 (64.3)	
Mutation	11 (47.8)	5 (35.7)	
Primary site, n (%)			0.49
Colon	13 (56.5)	10 (71.4)	
Rectum	10 (43.5)	4 (28.6)	
Metastatic sites, n			
Liver	15	9	
Lung	12	9	
Lymph node	3	7	
Peritoneal dissemination	2	2	
Bone	3	4	
Other	0	0	
Previous anti-EGFR treatment, n (%)	12 (52.2)	9 (64.3)	0.51
Previous anti-VEGF treatment, n (%)	23 (100)	10 (71.4)	0.05
Post-treatment use of regorafenib or TAS-102, n (%)	6 (26.1)	8 (57.1)	0.08

ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Table II. *Efficacy and safety.*

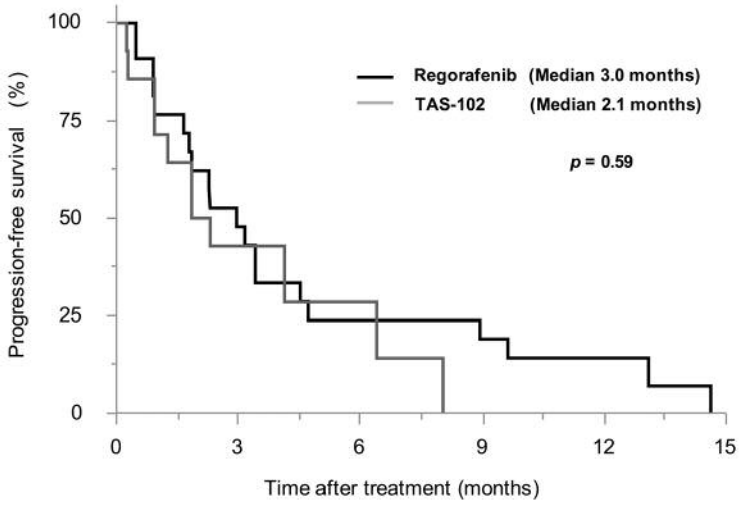
Variable	Regorafenib group (n=23)	TAS-102 group (n=14)
Efficacy		
RR (CR+PR), n (%)	0 (0.0)	0 (0.0)
DCR (CR+PR+SD), n (%)	7 (30.4)	4 (28.6)
CR, n (%)	0 (0.0)	0 (0.0)
PR, n (%)	0 (0.0)	0 (0.0)
SD, n (%)	7 (30.4)	4 (28.6)
PD, n(%)	16 (69.6)	10 (71.4)
Median PFS (95% CI), months	3.0 (1.64-4.52)	2.1 (0.92-6.39)
Median OS (95% CI), months	5.8 (3.70-11.7)	6.3 (3.21-9.93)
Median follow up, months	5.5	
Safety		
Initial dose, median (mg)	160	110
Median (range) no. of treatment cycles	3 (1-16)	3 (1-9)
Median (range) duration of treatment, months	2.3 (0.1-14.7)	2.1 (0.2-8.0)
Required dose reductions, n (%)	15 (65.2)	2 (14.3)
Reason for treatment discontinuation, n (%)		
Disease progression	14 (60.9)	12 (85.7)
AEs	6 (26.1)	2 (14.3)
Other	3 (13.0)	0 (0.0)

RR, Response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval; AEs, adverse events.

and 2.1 months (95% CI=0.92 to 6.39 months) in the TAS-102 group (Table II, Figure 1). The median OS was 5.8 months (95% CI=3.70 to 11.7 months) in the regorafenib group and 6.3 months (95% CI=3.21 to 9.93 months) in the TAS-102 group (Table II, Figure 2). The OS rate in the regorafenib and the TAS-102 groups were 45.0% and 47.4% at 6 months, and 19.3% and 0.0% at 12 months, respectively (Figure 2). Results of the subgroup analysis for PFS and OS are shown in Table III. The median PFS was 4.7 months (95% CI=2.13 to 14.7 months) in patients who received crossover treatment with regorafenib to TAS-102, and 3.7 months (95% CI=0.92 to 8.03 months) in patients who received crossover treatment with TAS-102 to regorafenib. The median OS was 11.5 months (95% CI=5.47 months to not reached) and 7.6 months (95% CI=2.98 to 11.5 months), respectively.

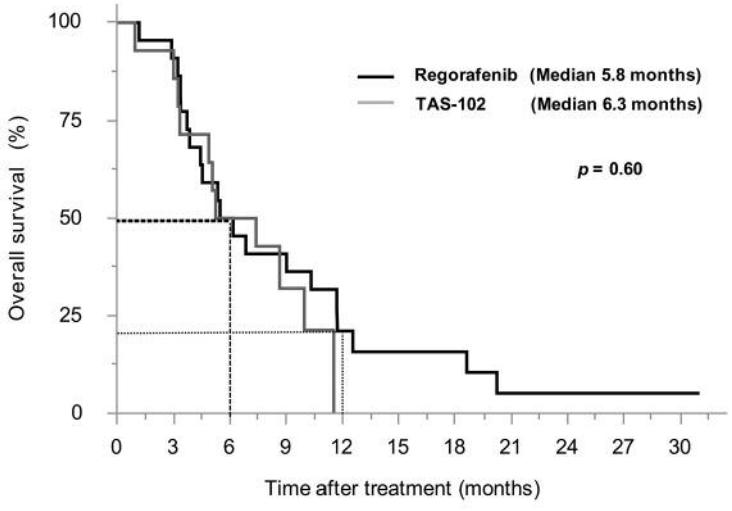
Safety and AEs. Patients given regorafenib received a median daily dose of 160 mg. The median daily dose of TAS-102 was 110 mg. The median duration of treatment was 2.3 (range=0.1-14.7) months in the regorafenib group and 2.1 (range=0.2-8.0) months in the TAS-102 group (Table II). Dose or schedule modifications were required in 15 out of 23 patients (65.2%) receiving regorafenib and two out of 14 patients (14.3%) receiving TAS-102 (Table II). AEs were the most common reason for dose modification. Drug-related AEs led to permanent discontinuation in six (26.1%) patients receiving regorafenib and two (14.3%) patients receiving TAS-102 (Table II). In both groups, the most frequent reason for treatment discontinuation was radiological disease progression (Table II).

Table IV shows drug-related AEs. Drug-related AEs occurred in 23 (100%) patients in the regorafenib group and 13 (92.9%) patients in the TAS-102 group. Drug-related grade 3 or more AEs occurred in 10 (43.5%) patients receiving regorafenib and two (14.3%) patients receiving TAS-102. No patient in either group had a treatment-related death. The most frequent regorafenib-related AEs of grade 3 or more were hand-foot syndrome (HFS) and hepatotoxicity. On the other hand, the most frequent TAS-102-related AE of grade 3 or more was neutropenia.



Number at risk					
Regorafenib	23	11	5	4	2
TAS-102	14	6	2	0	0

Figure 1. *Kaplan–Meier curves for progression-free survival in patients receiving regorafenib or TAS-102.*



Number at risk											
Regorafenib	23	20	11	9	4	3	3	1	1	1	1
TAS-102	14	13	8	3	0	0	0	0	0	0	0

Figure 2. *Kaplan–Meier curves for overall survival in patients receiving regorafenib or TAS-102.*

Discussion

In this analysis, we describe the different toxicity profiles of regorafenib and TAS-102, which could have contributed to the improved PFS and OS in patients with mCRC in whom standard therapies had failed. Additionally, the OS benefit in patients who received crossover treatment between the two drugs was significantly larger than that in the patients who received only one of the drugs.

The tumor response in this analysis was similar between the two treatment groups. No patient had a CR or PR in either group. The DCR was 30.4% in the regorafenib group and

Table III. *Efficacy of the two drugs in subgroup analysis.*

Variable	Regorafenib group		TAS-102 group	
	Regorafenib only (n=17)	Crossover to TAS-102 (n=6)	TAS-102 only (n=6)	Crossover to regorafenib (n=8)
Efficacy				
Median PFS (95% CI), months	2.3 (0.89-3.41)	4.7 (2.13-14.7)	1.5 (0.23-6.39)	3.7 (0.92-8.03)
Median OS (95% CI), months	4.5 (3.34-10.3)	11.5 (5.47-NR)	5.3 (0.92-8.62)	7.6 (2.98-11.5)
Median follow-up, months	4.5	11.4	5.3	6.7
Median (range) no. of treatment cycles	2.0 (1-11)	11.0 (1-24)	2.0 (1-6)	3.0 (1-9)
Median (range) duration of treatment, months	1.8 (0.1-9.6)	4.1 (0.6-14.6)	1.5 (0.2-6.4)	2.8 (0.9-8.0)

PFS, Progression-free survival; OS, overall survival; CI, confidence interval; AEs, adverse events; NR, not reached.

Table IV. *Drug-related adverse events.*

	Regorafenib group (n=23)		TAS-102 group (n=14)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any event, n (%)	23 (100)	10 (43.5)	13 (92.9)	2 (14.3)
Clinical adverse event, n (%)				
Fatigue	4 (17.4)	0 (0.0)	8 (57.1)	0 (0.0)
Hand-foot syndrome	14 (60.9)	3 (13.0)	1 (7.1)	0 (0.0)
Diarrhea	2 (8.7)	0 (0.0)	2 (14.3)	0 (0.0)
Anorexia	6 (26.1)	0 (0.0)	4 (28.6)	0 (0.0)
Voice changes	4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	11 (47.8)	1 (4.3)	0 (0.0)	0 (0.0)
Oral mucositis	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash or desquamation	6 (26.1)	1 (4.3)	1 (7.1)	0 (0.0)
Nausea/vomiting	2 (8.7)	0 (0.0)	4 (28.6)	0 (0.0)
Fever	9 (39.1)	0 (0.0)	1 (7.1)	0 (0.0)
Cough	5 (21.7)	0 (0.0)	1 (7.1)	0 (0.0)
Alopecia	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Taste neuropathy	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sensory neuropathy	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pain, abdomen	2 (8.7)	0 (0.0)	1 (7.1)	0 (0.0)
Laboratory abnormalities, n (%)				
Neutropenia	0 (0.0)	0 (0.0)	2 (14.3)	2 (14.3)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (13.0)	1 (4.3)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	8 (34.8)	1 (4.3)	0 (0.0)	0 (0.0)
Hepatotoxicity	12 (52.2)	4 (17.4)	1 (7.1)	0 (0.0)
Hyperammonemia	2 (8.7)	2 (8.7)	0 (0.0)	0 (0.0)
Increased in creatinine level	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)
Proteinuria	9 (39.1)	0 (0.0)	1 (7.1)	0 (0.0)

28.6% in the TAS-102 group. The DCR found in this analysis was less in both groups than that in found in previous clinical trials (Table II and V) (7, 8, 13, 14). Although the reasons for the differences were unclear, the difference in the timing of the imaging tests might explain this. In clinical trials, imaging tests such as computed tomography scans are performed regularly every 6 or 8 weeks. However, in clinical practice, the timing of imaging tends to be prolonged, and disease progression may be seen before SD is confirmed. The PFS and OS were similar in both treatment groups in our analysis and were consistent with that of previous clinical trials (Tables II and V) (7, 8, 13, 14). These results indicate that regorafenib or TAS-102 could have contributed to the improved PFS and OS in patients with mCRC after failure of standard treatments.

Table V. *Randomized phase II and III trials with regorafenib or TAS-102 in patients with metastatic colorectal cancer.*

Study	Phase	Treatment	No. of patients	ORR (%)	DCR (%)	Any grade (grade ≥3) AEs (%)	Median PFS (months)	Median OS (months)
Grothey *et al*. (7)	III randomized (2:1)	Regorafenib	505	0.0	41.0	93.0 (54.0)	1.9	6.4
		Placebo	255	0.0	15.0	61.0 (16.0)	1.7	5.0
				p=NA	*p*<0.0001		HR=0.49 (95% CI=0.42-0.58) *p*<0.0001	HR=0.77 (95% CI=0.64-0.95) *p*=0.0052
Li *et al*. (8)	III randomized (2:1)	Regorafenib	136	4.0	51.0	97.0 (54.0)	3.2	8.8
		Placebo	68	0.0	7.0	46.0 (15.0)	1.7	6.3
				p=NA	*p*<0.0001		HR=0.31 (95% CI=0.22-0.44) *p*<0.0001	HR=0.55 (95% CI=0.40-0.77) *p*=0.0016
Yoshino *et al*. (13)	II randomized (2:1)	TAS-102	112	0.9	44.0	– (19.0)	2.0	9.0
		Placebo	57	0.0	11.0	– (9.0)	1.0	6.6
				p=NA	*p*<0.001		HR=0.41 (95% CI=0.28-0.59) *p*<0.0001	HR=0.56 (95% CI=0.39-0.81) *p*=0.0011
Mayer *et al*. (14)	III randomized (2:1)	TAS-102	534	1.6	44.0	98.0 (69.0)	2.0	7.1
		Placebo	266	0.4	16.0	93.0 (52.0)	1.7	5.3
				p=0.29	*p*<0.001		HR=0.48 (95% CI=0.41-0.57) *p*<0.001	HR=0.68 (95% CI=0.58-0.81) *p*<0.001

ORR, Overall response rate; DCR, disease control rate; AEs, adverse events; HR, hazard ratio; CI, confidence interval; NA, not available; PFS, progression-free survival; OS, overall survival.

The AEs reported in this analysis were mostly consistent with the known safety profiles of regorafenib and TAS-102 in previous clinical trials (7, 8, 13, 14, 17, 18). In our analysis, AEs of grade 3 or more were more frequent in the regorafenib group than in the TAS-102 group. Hepatotoxicity and HFS were the most frequently observed clinically meaningful AEs (grade ≥3) in patients treated with regorafenib, occurring in 17.4% and 13.0% of patients, respectively, while neutropenia was the most frequently observed clinically meaningful AE (grade ≥3) in patients treated with TAS-102, occurring in 14.3%. In the regorafenib group, although the proportion of patients with hepatotoxicity of grade 3 or more was higher than that in the CORRECT trial (7), few patients had fatigue or diarrhea of grade 3 or more. In the TAS-102 group, few patients had serious AEs compared with those in the RECOURSE trial (14), although neutropenia was the main AE. Corresponding to the higher rate of AEs observed in the regorafenib group than in the TAS-102 group, dose modifications due to AEs were more frequent in the regorafenib group than in the TAS-102 group (65.2% *vs*. 14.3%, Table II). The toxic effects of TAS-102 were generally mild and manageable compared with regorafenib. Interestingly, despite a higher proportion of AEs and the number of patients discontinuing treatment because of toxic effects in the regorafenib group compared to the TAS-102 group, the duration of treatment was similar in the two groups. Thus, early and proactive prophylaxis and management of AEs, especially HFS and liver function test abnormalities (which were the most common AEs needing treatment modifications), are important to ensure that patients are able to remain on treatment with regorafenib.

The availability of both regorafenib and TAS-102 has not yet been evaluated. In our analysis, a lower proportion of patients were treated with TAS-102 after regorafenib than patients treated with regorafenib after TAS-102. One reason might be that the approval times of the two drugs were different in Japan. Regorafenib was approved in March 2013 and TAS-102 in March 2014. For this reason, some patients with disease progression after regorafenib treatment could not receive TAS-102. Another reason might be the different toxicity profiles of the two drugs. Regorafenib might worsen the quality of life of patients because of the higher incidence of grade 3 or more AEs in the regorafenib group than those treated with TAS-102. Additionally, our subgroup analysis showed that the OS benefit in patients who received crossover treatment with both drugs was significantly larger than that in patients who only received one of the two drugs (Table III). These data suggest that the strategy to maximize the availability of both drugs can prolong the OS in this poor prognostic setting.

In the future, the detection of potential predictive or prognostic biomarkers, or the evaluation of combination therapy with other cytotoxic and biological drugs in patients

with mCRC refractory to standard therapies is warranted (19). A retrospective biomarker analysis during the CORRECT trial showed that regorafenib seemed to be consistently associated with a clinical benefit in patient subgroups based on *KRAS* and *PIK3CA* mutational status and protein biomarker concentrations (20). In the TAS-102 trials, there was no correlation between the efficacy of TAS-102 and two potential biomarkers: thymidine kinase 1 and thymidine phosphorylase (21). To date, no predictive biomarkers of benefit or resistance to TAS-102 have been found. Secondly, some preclinical and clinical studies have shown that the combination of regorafenib or TAS-102 and various chemotherapeutic and targeted agents demonstrated synergistic effects and might provide a promising salvage therapy for patients with refractory mCRC (22-26). Thus, combination therapy might maximize the benefit derived from regorafenib or TAS-102 in patients with mCRC.

Our analysis has several important limitations (*e.g.* a retrospective analysis conducted at a single institution, small number of patients, heterogeneity of characteristics, and no biomarkers tested except KRAS) and selection bias may have affected our results. However, this is the first report to directly compare the efficacy and safety of regorafenib and TAS-102.

In conclusion, our results showed that regorafenib and TAS-102 have comparable efficacy and different toxicity profiles in patients with mCRC. These two drugs can be regarded as new options for the salvage line. The differences in toxicity profiles, tolerability to previous treatments, comorbidities, and patient's preferences between the two treatments will help in choosing either regorafenib or TAS-102. Additionally, our findings suggest that the strategy to maximize the availability of both drugs could prolong the OS in this poor prognostic setting.

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None.

Conflicts of Interest

The Authors have declared that no conflict of interest exists in regard to this study.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global Cancer Statistics, 2012. CA Cancer J Clin *65*: 87-108, 2015.

2 Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Köhne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S and Cervantes A: ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol *23*: 2479-516, 2012.

3 Miyamoto Y, Watanabe M, Sakamoto Y, Shigaki H, Murata A, Sugihara H, Etoh K, Ishimoto T, Iwatsuki M, Baba Y, Iwagami S, Yoshida N and Baba H: Evaluation of the necessity of primary tumor resection for synchronous metastatic colorectal cancer. Surg Today *44*: 2287-2292, 2014.

4 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): colon cancer. Version 2. 2016. http://www.nccn.org/professionals/physician_gls/ pdf/colon.pdf. Accessed 26 Jan 2016. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): rectal cancer. Version 2. 2016. http://www.nccn.org/professionals/physician_gls/ pdf/rectal.pdf. Accessed 26 Jan 2016.

5 Saeki H, Emi Y, Kumashiro R, Otsu H, Kawano H, Ando K, Ida S, Kimura Y, Tokunaga E, Oki E, Morita M, Shimokawa M and Maehara Y: Impact of second-line and later cetuximab-containing therapy and KRAS genotypes in patients with metastatic colorectal cancer: a multicenter study in Japan. Surg Today *44*: 1457-1464, 2014.

6 Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH and Zopf D: Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer *129*: 245-255, 2011.

7 Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo controlled, phase 3 trial. Lancet *381*: 303-312, 2013.

8 Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW; CONCUR Investigators: Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol *16*: 619-629, 2015.

9 Fujiwara Y and Heidelberger C: Fluorinated pyrimidines. XXXVII. The incorporation of 5-trifluoromethyl-2-deoxyuridine into the deoxyribonucleic acid vaccinia virus. Mol Pharmacol *6*: 281-291, 1970.

10 Emura T, Suzuki N, Yamaguchi M, Ohshimo H and Fukushima M: A novel combination antimetabolite, TAS-102, exhibits antitumor activity in FU-resistant human cancer cells through a mechanism involving FTD incorporation in DNA. Int J Oncol *25*: 571-578, 2004.

11 Suzuki N, Nakagawa F, Nukatsuka M and Fukushima M: Trifluorothymidine exhibits potent antitumor activity *via* the induction of DNA double-strand breaks. Exp Ther Med *2*: 393-397, 2011.

12 Fukushima M, Suzuki N, Emura T, Yano S, Kazuno H, Tada Y, Yamada Y and Asao T: Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2'-deoxyribonucleosides. Biochem Pharmacol *59*: 1227-1236, 2000.

13 Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T and Ohtsu A: TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double- blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol *13*: 993-1001, 2012.

14 Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med *372*: 1909-1919, 2015.

15 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

16 US Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Washington, DC: US Department of Health and Human Services, 2010.

17 Strumberg D, Scheulen ME, Schultheis B, Richly H, Frost A, Büchert M, Christensen O, Jeffers M, Heinig R, Boix O and Mross K: Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. Br J Cancer *106*: 1722-1727, 2012.

18 Yoshino T, Komatsu Y, Yamada Y, Yamazaki K, Tsuji A, Ura T, Grothey A, Van Cutsem E, Wagner A, Cihon F, Hamada Y and Ohtsu A: Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Invest New Drugs *33*: 740-750, 2015.

19 Salvatore L, Rossini D, Moretto R, Cremolini C, Schirripa M, Antoniotti C, Marmorino F, Loupakis F, Falcone A and Masi G: *TAS-102* for the treatment of metastatic colorectal cancer. Expert Rev Anticancer Ther *15*: 1283-1292, 2015.

20 Tabernero J, Lenz HJ, Siena S, Sobrero A, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Yoshino T, Goldberg RM, Sargent DJ, Wagner A, Laurent D, Teufel M, Jeffers M, Grothey A and Van Cutsem E: Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. Lancet Oncol *16*: 937-948, 2015.

21 Komatsu Y, Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Baba H, Tsuji A, Yamaguchi K, Muro K and Ohtsu A: The Value of Thymidine Kinase 1 (*TK1*) and Thymidine Phosphorylase (*TP*) Expression as Predictive Factors With the Treatment Efficacy of *TAS-102*, a Novel Antitumor Agent, in Patients (pts) With Metastatic Colorectal Cancer (mCRC). Eur J Cancer *47(Suppl 1)*: S-421, 2011.

22 Marks EI, Tan C, Zhang J, Zhou L, Yang Z, Scicchitano A and El-Deiry WS: Regorafenib with a fluoropyrimidine for metastatic colorectal cancer after progression on multiple 5-FU-containing combination therapies and regorafenib monotherapy. Cancer Biol Ther 16:1710-1719, 2015.

23 Napolitano S, Martini G, Rinaldi B, Martinelli E, Donniacuo M, Berrino L, Vitagliano D, Morgillo F, Barra G, De Palma R, Merolla F, Ciardiello F and Troiani T: Primary and acquired resistance of colorectal cancer to anti-EGFR monoclonal antibody can be overcome by combined treatment of regorafenib with cetuximab. Clin Cancer Res *21*: 2975-2983, 2015.

24 Lu CY, Yeh YS, Huang CW, Ma CJ, Yu FJ and Wang JY: FOLFIRI and regorafenib combination therapy with dose escalation of irinotecan as fourth-line treatment for patients with metastatic colon cancer according to UGT1A1 genotyping. Onco Targets Ther *7*: 2143-2146, 2014.

25 Emura T, Murakami Y, Nakagawa F, Fukushima M and Kitazato K: A novel antimetabolite, TAS-102 retains its effect on FU-related resistant cancer cells. Int J Mol Med *13*: 545-549, 2004.

26 Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y and Ohtsu A: Phase I study of *TAS-102* and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs *33*: 1068-1077, 2015.

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