Efficacy and Safety of TAS-102 in Clinical Practice of Salvage Chemotherapy for Metastatic Colorectal Cancer

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Abstract. *Background: TAS-102 is an anti-metabolite which demonstrated activity against multidrug-resistant advanced colorectal cancer. Its major toxicities are hematological disorders. Patients and Methods: Background, TAS-102 efficacy, toxicities and outcomes for patients with multidrug-resistant advanced colorectal cancer from six Institutions of the Kyushu Medical Oncology Group were retrospectively surveyed. Results: Forty-three patients, including fragile patients due to declining performance status and other comorbidities (37%) were analyzed. Efficacy was reflected in an objective overall response of 3%, median progression-free survival of 74 days (2.5 months) and median overall survival of 229 days (7.6 months). The most frequent Common Terminology Criteria for Adverse Events grade 3/4 adverse events were neutropenia (44%), leukopenia (26%) and anemia (23%). Febrile neutropenia was found in 7%. Sub-group analysis demonstrated an improved outcome on treatment with the sequence regorafenib–TAS-102. Conclusion: TAS-102 was safely administered to modestly fragile patients with equivalent efficacy to that for the non-fragile population. Further investigation of sequential treatment using regorafenib and TAS-102 is needed.*

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Colorectal cancer is the third most frequent cancer and the fourth most frequent cause of cancer-related death worldwide (1). In Japan in 2014, it ranked as second most frequent cause of cancer death (2). The overall survival (OS) of patients with advanced or recurrent colorectal cancer has been prolonged as new active drugs become available. These include several classes of agents: fluoropyrimidines, irinotecan, oxaliplatin, anti-epidermal growth factor receptor (EGFR) antibodies, and inhibitors of the vascular endothelium growth factor (VEGF) pathway. Using these agents, the median survivals reported by the latest clinical trials have been extended to 30 months (3).

TAS-102 is a combination of trifluridine and tipiracil at a molar ratio of 1:0.5 (4). Trifluridine, a thymidine-based nucleoside analog, inhibits cellular proliferation and causes cell death by incorporation of its triphosphorylated form to DNA. By combination with tipiracil, a thymidine phosphorylase inhibitor, the blood concentration of trifluridine can be sustained and it can remain active for longer in vivo. A placebo-controlled phase II study in Japan evaluated its efficacy and safety for patients with advanced or recurrent colorectal cancer resistant to or who were intolerable to oxaliplatin, irinotecan, fluoropyrimidines, bevacizumab and anti-EGFRs (5). The efficacy results were promising and its feasibility was favorable. A global placebo-controlled randomized phase III trial (RECOURSE) including 800 patients revealed its efficacy in overall survival [hazard ratio

(HR)=0.68] (6). Hematological adverse events were frequently observed in the TAS-102-treated group but the majority of adverse events were not severe. In Japan, TAS-102 was approved in 2014 following the national phase II study, and in the US and EU, approved in 2015 following the global phase III study.

Regorafenib, a small-molecule multi-targeted tyrosine kinase inhibitor, demonstrated quite similar efficacy to that of TAS-102 for the same group of patients (HR=0.77) (7). Its adverse events included skin toxicities, fatigue and, hypertension, amongst others. The agent was considered to be well tolerated in the global population, but required reconsideration in the Japanese sub-group. More frequent adverse events were observed in Japanese patients such as hand–food skin reaction and liver dysfunction (8). We reported the result of an observational study of Japanese practice that demonstrated a much higher frequency of liver dysfunction, including a case of grade 5 (severe) liver failure (9). These results indicate that careful patient selection is needed in the use of regorafenib, by means of performance status and background liver function, perhaps even to the subclinical extent of the residual function. Furthermore, the presumable ethnic differences of the metabolic pathways should be determined. The safety population of regorafenib has not been determined in the Japanese population and it might be smaller than that resulting from the inclusion criteria of the trial.

In Japan, these two drugs, TAS-102 and regorafenib, are now considered in salvage chemotherapy for patients with colorectal cancer resistant to or who are intolerable to conventional drugs. The clinical question is which of these two agents, with different indications, should be administered first? TAS-102 may be safely administered to more fragile patients than those included in the above-mentioned trials, such as patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 2, or any moderate organ dysfunction. Herein we report a retrospective survey of the efficacy and safety of TAS-102 in clinical practice including fragile patients, and an analysis of the difference of efficacy of regorafenib pre-treatment.

Patients and Methods

The present study retrospectively surveyed patients treated with TAS-102 with pathologically confirmed metastatic or recurrent colorectal adenocarcinoma, between May 26, 2014 and Jan 18, 2015. Forty-three patients were included from six institutes as follows: Department of Hematology and Medical Oncology, Kyushu University Hospital; Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center; Department of Medical Oncology, Hamanomachi Hospital; Department of Hematology and Oncology, Japan Community Healthcare Organization Kyushu Hospital; Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital and Department of Internal Medicine, Kyushu University Beppu Hospital. All the patients should be resistant or intolerable to conventional chemotherapeutic regimens including fluoropyrimidines, oxaliplatin, irinotecan and anti-EGFRs when the presence of wild-type *KRAS* exon 2 was confirmed.

The clinical information was obtained from medical records and included patient background, clinical course and outcome. TAS-102 standard dosing was planned at 35 mg/m^2 *bid* on days 1-5 and 8-12, and repeated in a 28-day cycle. The best therapeutic responses were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (10). Overall response rate (ORR) and disease control rate (DCR) were defined as the proportion of patients with complete response (CR) and partial response (PR), and the sum of those with CR, PR, stable disease (SD) and non-CR/non-progressive disease (PD) in the population, respectively. Progression-free survival (PFS) was defined as the interval from the initiation of TAS-102 to the date of tumor progression or death from any cause and OS as the interval between the initiation of the therapy and the date of death from any cause. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (11) and the most severe grades during chemotherapy were reported. The HR of survival and its 95% confidence interval (95% CI) in subgroup analyses was estimated with the Cox proportional hazards model.

The present study was carried out according to the regulations of the local Ethics Committee of each institution, the Declaration of Helsinki, and the Ethical Guidelines for Epidemiology Research 2013.

Results

Patients' characteristics and the prior treatments. Forty-three patients who were treated with TAS-102 were analyzed in this study (Table I). The median age of the patients was 63 years (range=38-85 years). Twenty-four patients were male and 19 were female. Most patients had an ECOG PS of 1 or more (30/43; 69.8%). *KRAS* exon 2 mutation was present in 18 patients (42%). More than three organs with metastatic disease were observed in 21 patients (49%), the major being lung (33, 77%) and liver (28 patients, 65%).

All patients had had prior chemotherapy consisting of fluoropyrimidine and oxaliplatin, and most had had irinotecan (39/43, 91%) (Table I). Cetuximab or panitumumab was administered to all patients with wild-type *KRAS* exon 2. Primary tumors were resected in 34 patients (79%) and liver metastases in 10 (23%). Among 43 examined patients, 16 (37%) were administered regorafenib prior to TAS-102. One patient discontinued regorafenib due to toxicity and 15 had progressive disease during regorafenib treatment. Twenty-seven patients were administered TAS-102 without regorafenib because of intolerance due to medical insufficiency (18 patients, 41%) and patients' preference (9 patients 21%).

Treatment, efficacy and toxicity of TAS-102 monotherapy. The median number of treatment cycles of TAS-102 was three (range=1-13). Most patients (86%) were treated with standard dose (Table II). Four patients were still under treatment at the time of data collection.

Table I. *Patients' characteristics*.

Characteristic (n=43)	Number	(%)
Gender		
Female	19	(44%)
Male	24	(56%)
Median age (range),years	63 (38-85)	
Performance status		
0	13	(30%)
1	26	(61%)
2	4	(9%)
KRAS exon 2 status		
Wild-type	24	(56%)
Mutant	18	(42%)
Unknown	1	(2%)
Primary site		
Right-sided colon	11	(26%)
Left-sided colon	18	(41%)
Rectum	14	(33%)
Metastatic site		
Liver	28	(65%)
Lung	33	(77%)
Lymph nodes	23	(53%)
Peritoneum	11	(26%)
Bone	7	(16%)
Brain	3	(7%)
Number of organs with metastases		
1-2	22	(51%)
3 or more	21	(49%)
Prior treatments		
Fluoropyrimidines	43	(100%)
Oxaliplatin	43	(100%)
Irinotecan	39	(91%)
Bevacizumab/ramucirumab**	32	(74%)
Cetuximab/panitumumab	24	(100%*)
Regorafenib	16	(37%)
Primary site resection	34	(79%)
Liver resection	10	(23%)
Reasons to prefer TAS-102		
Intolerant to regorafenib†	18	(42%)
(baseline liver toxicity)	(8)	
(baseline skin toxicity)	(4)	
(active wound)	(3)	
(other baseline comorbidity)	(3)	
Severe toxicity with regorafenib†	1	(2%)
Progression with regorafenib‡	15	(35%)
Patient preference‡	9	(21%)

*All wild-type for KRAS exon 2. **Ramucirumab indicates inclusion in the placebo-controlled trial of the drug. †Regarded as intolerant to regorafenib group; ‡regarded as regorafenib-tolerant group.

Table II. *Treatment with TAS-102*.

	Number	(%)
Initial dose		
Standard dose	37	(86%)
Initially reduced	6	(14%)
Median no. of cycles given (range)	3 (1-13+)	
Treatment modification		
Interruption, delay due to toxicities	20	(47%)
Dose reduction	14	(33%)
Reasons for discontinuation		
Progressive disease	34	(87%)
Adverse events	5	(13%)
treatment ongoing at data collection	4	

Table III. *Best objective responses*.

	Number	(%)
Best objective responses		
Complete response (CR)	0	(0)
Partial response (PR)	1	(3%)
Stable disease (SD)	10	(23%)
Progressive disease (PD)	27	(62%)
Non-CR/non-PD	2	(5%)
Not fully evaluated	3	(7%)
Response rate (CR+PR)	1	(3%)
Disease control rate (CR+PR+SD+non-CR/non-PD)	13	(33%)

Best objective responses to TAS-102 monotherapy according to RECIST ver. 1.1 was PD in the majority of cases (62%) (Table III). Three patients were not fully evaluated nor followed-up to assess efficacy. The ORR was 3% and DCR was 33%. The median PFS was 74 days (2.5 months) and median OS was 229 days (7.6 months) (Figure 1).

Hematological toxicities were frequently observed in the patients (Table IV). CTCAE grade 3 or more neutropenia occurred in 20 patients (44%), leukopenia in 11 (26%) and anemia in 10 (23%). Severe non-hematological toxicity was not frequently observed (all less than 10%), and febrile neutropenia only occurred in three cases (7%). Grade 3 ileus in two patients, hemorrhage in two and other severe adverse events were observed and were mostly related to progression of the primary disease.

In terms of subsequent treatments, 25 patients (58%) received best supportive care (Table V). Radiotherapy was performed in seven patients (16%), and re-introduction of anticancer agents such as fluoropyrimidines (6; 14%), and others in several cases. Regorafenib was administered to six patients (14%) after termination of TAS-102 treatment; three of them were previously recognized to be intolerant to regorafenib and recovered from this, whereas the other three patients preferred to receive TAS-102 treatment rather than regorafenib in the induction of salvage chemotherapy.

Sub-group analyses. KRAS mutational status: Efficacies of TAS-102 in the patient sub-groups by *KRAS* exon 2

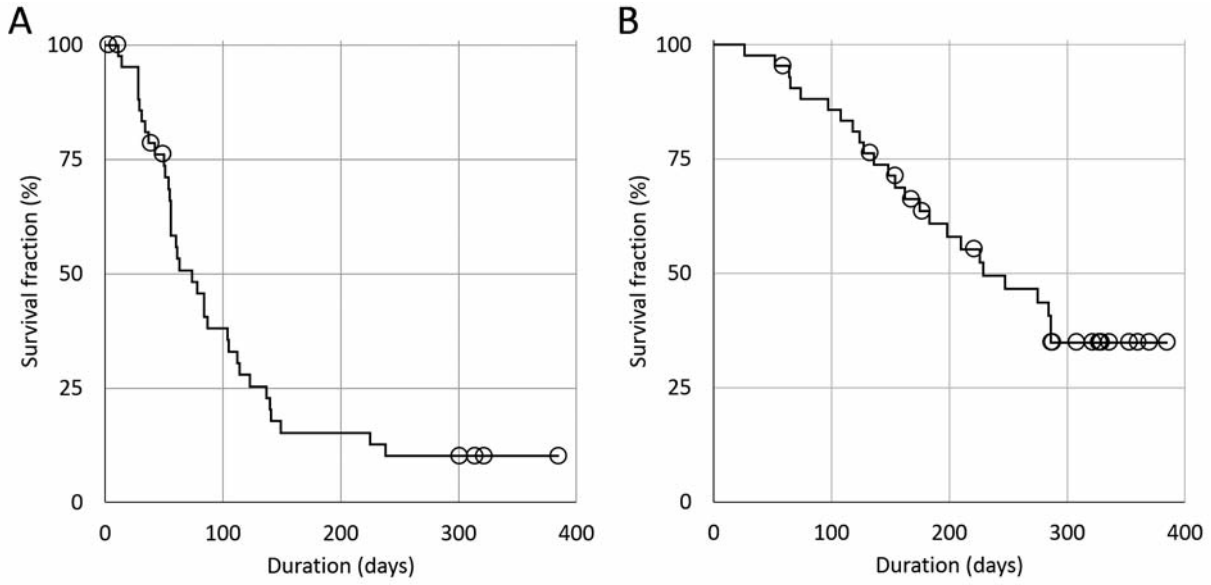

Figure 1. *Kaplan–Meier plots of progression-free survival (A) and overall survival (B) after TAS-102 monotherapy. Open circles indicate censored cases.*

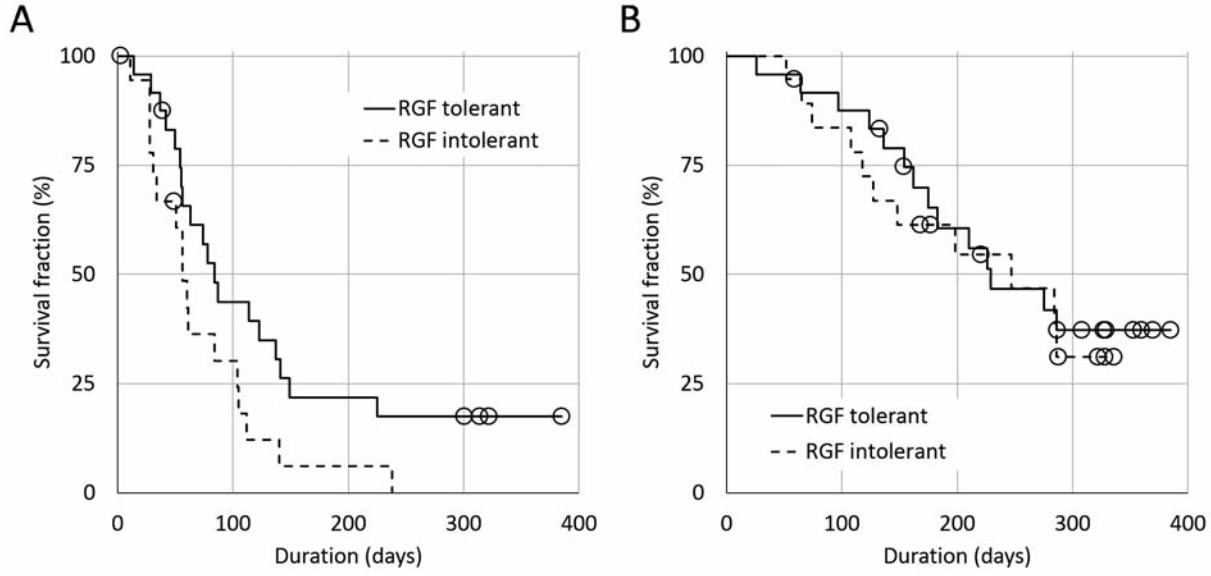

Figure 2. *Kaplan–Meier plots of PFS (A) and OS (B) of sub-groups by tolerance to regorafenib (RGF). Solid lines indicate tolerant to regorafenib and blocked lines intolerant. Open circles indicate censored cases.*

mutational status were compared. Efficacy tended to be better in the wild-type group compared to the group with *KRAS* mutation, with DCR of 45% *versus* 12%, median PFS of 2.9 *versus* 1.9 months (HR=0.81, 95% CI=0.42-1.60; p=0.53) and median OS of 9.5 *versus* 6.1 months (HR=0.68, 95% CI=0.31-1.53; p=0.35), respectively. Patient backgrounds were slightly more favorable in the group with wild-type KRAS because more patients with PS 2 were included in the groups with KRAS mutation (4% *versus* 16%, respectively).

Regorafenib tolerance and pre-treatment: Patients were divided into two groups by their tolerance to regorafenib at the initiation of salvage therapy. Fifteen patients who were fully

treated with regorafenib and nine patients who were offered regorafenib and TAS-102 and preferred the latter were designated as being tolerant, and the remaining patients were regarded as being intolerant, including 18 patients who were initially recognized as being intolerant to regorafenib and a patient who abandoned regorafenib due to severe adverse events. The median age, PS and number of metastatic organs were similar for both groups (Table VI). Median PFS, OS and DCR in the regorafenib-tolerant and -intolerant groups were 2.8 *versus* 1.9 months (HR=0.50, 95% CI=0.26-0.99; p=0.048), 8.2 *versus* 7.6 months (HR=0.85, 95% CI=0.38-1.91; p=0.68) and 39% *versus* 50%, respectively (Figure 2). The frequencies of severe toxicity were relatively higher in the regorafenib-tolerant group (Table VI).

The efficacy of TAS-102 in patients with and without pre-treatment with regorafenib (n=16 and 27, respectively) was also examined. In comparison of the patient groups, the regorafenib-pretreated group exhibited a trend for longer median PFS (4.6 *versus* 1.9 months, HR=0.33, 95% CI=0.15-0.68; p=0.0025), median OS (not reached *versus* 6.6 months, HR=0.49, 95% CI=0.19-1.14; p=0.10) (Figure 3) and a better DCR (43% *vs*. 27%; p=0.48) than the regorafenib-naïve group. From the point of view of salvage chemotherapy (whether regorafenib or TAS-102), the regorafenib-pretreated group corresponded to a strategy of treatment with regorafenib then TAS-102 (regorafenib-first strategy; n=16) and the regorafenib-naïve group included patients treated with a sequence of TAS-102 then regorafenib (n=6) and only with TAS-102 (n=21) (TAS-102-first strategy). The finding above subsequently resulted in much longer median OS from induction of salvage chemotherapy in the regorafenib-pretreated group than the other group (19.3 *vs*. 6.6 months; HR=0.13, 95% CI=0.03-0.41, p=0.0002). Comparing the backgrounds of these two groups (Table VII), PS was slightly better in regorafenib-pretreated group (PS 2: 6% in pretreated and 11% in the other group; p=0.68) and disease was much more metastatic in the pretreated group (57% *vs*. 44% had three or more organs with metastases; p=0.54). The median time from first-line chemotherapy to induction of salvage therapy was slight longer in the pretreated group (31.0 *vs*. 26.8 months; p=0.54).

Discussion

The present study demonstrated that the efficacy and toxicity of TAS-102 in clinical practice was equivalent to those in the RECOURSE trial (6). The median PFS (2.5 months) and OS (7.6 months) were comparable (2.0 and 7.1 months, respectively). A sub-group analysis of *KRAS* exon 2 mutational status indicated a comparably favorable outcome in the group with wild-type *KRAS*. The toxicity profile was also similar to that in the trial, and included mainly hematological toxicities such as neutropenia and anemia.

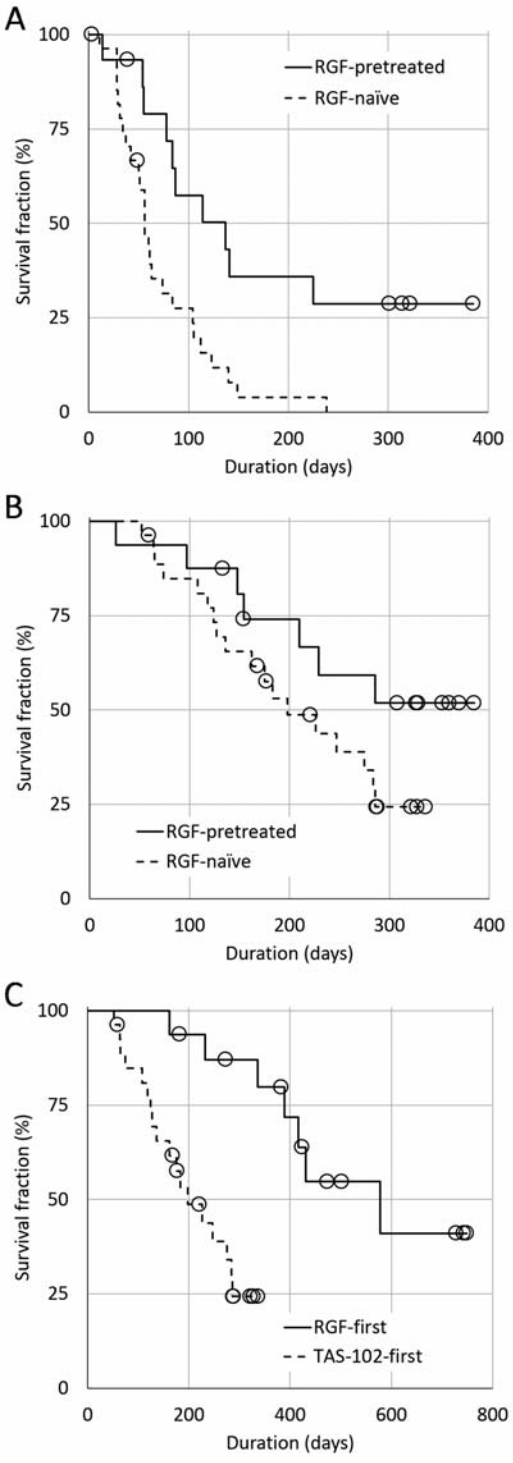

Figure 3. *Kaplan–Meier plots of progression-free survival (A) and overall survival (OS) (B) after TAS-102 monotherapy of the sub-groups of regorafenib (RGF)-pretreated and RGF-naïve patients. C: OS from induction of salvage therapy (either TAS-102 or RGF) of the subgroups of RGF-first strategy (corresponding to the RGF-pretreated group) and TAS-102-first strategy (RGF-naïve at TAS-102 induction, including patients treated with TAS-102 then RGF and only with TAS-102). Open circles indicate censored cases.*

Table IV. *Adverse events*.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Any grade (%)	Grade 3/4 (%)
Hematological						
Leukocytopenia	5	15	8	3	31 (72%)	11 (26%)
Neutropenia	4	7	15	5	31 (72%)	20 (44%)
Anemia	16	15	6	4	41 (95%)	10 (23%)
Thrombocytopenia	16	4	3	0	23 (53%)	3 (7%)
Non-hematological						
Diarrhea	5	3	0	0	8 (19%)	0
Nausea/vomiting	12	8	2	0	22 (51%)	2 (5%)
Anorexia	9	9	3	0	21 (49%)	3 (7%)
Infection	0	5	1	0	6 (14%)	1 (2%)
Febrile neutropenia	0	0	3	0	3 (7%)	3 (7%)
Albumin decrease	29	7	3	0	39 (91%)	3 (7%)
Creatinine increase	14	1	0	0	15 (35%)	0
Bilirubin increase	6	4	1	1	12 (28%)	2 (5%)
AST increase	24	8	2	0	34 (79%)	2 (5%)
ALT increase	22	3	2	0	27 (63%)	2 (5%)
ALP increase	21	9	4	0	34 (79%)	4 (9%)
Hyponatremia†			2	0		2 (5%)
Ileus†			3	0		3 (7%)
Hemorrhage†			2	0		2 (5%)
Other severe events†			2	0		

AST: Aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase. †Only severe events were reported.

Febrile neutropenia was not frequently observed (7%). Non-hematological toxicities included several severe events, but they were mostly related to the primary disease. It is noteworthy that this observational study included 16 patients (37%) who might not have been eligible for inclusion in the clinical trial because of comorbidities or declining performance status. Concerning such a fragile background, it is suggested that TAS-102 is also feasible in more patients other than those included in the trials, and that equivalent efficacy is expected.

On the other hand, regorafenib, another choice for salvage chemotherapy, has been reported to have severe toxicity. A subset analysis of the CORRECT trial (7), a randomized phase III trial comparing regorafenib *versus* placebo in the salvage setting, demonstrated more frequent toxicities in Japanese than in non-Japanese patients. In the CONCUR trial (12), the similarly designated trial of regorafenib in China and other Asian countries, higher toxicities than the non-Japanese subset of the CORRECT study were also reported. Our previous report on the efficacy and toxicity of regorafenib in clinical practice demonstrated more frequent and severe toxicities than these trials, including a fatal case of liver failure (9). We also reported that a reduced dose of regorafenib might have equivalent efficacy in the study. But a modification of drug dose with a prediction of toxicity remains difficult because the biological mechanisms of such an ethnic and individual difference in toxicity are not clear, so that a substantial proportion of patients cannot avoid severe toxicities. In Japanese practice, a careful selection of patients is required in the use of regorafenib, that is approved for salvage treatment of many patients with advanced and heavily treated colorectal cancer. It should be emphasized in the present study that an extended feasibility of TAS-102 is suggested and that the efficacy and safety did not decline in patients who were not ordinary clinically suitable for treatment with regorafenib.

Table V. *Subsequent treatments*.

Treatment	Number	(%)
Best supportive care only	25	(58%)
Radiotherapy	7	(16%)
Regorafenib	6	(14%)
(previously intolerant to regorafenib)	(3)	
(patient's preference for TAS-102 first)	(3)	
Fluoropyrimidine	6	(14%)
Irinotecan	2	(5%)
Oxaliplatin	2	(5%)
Bevacizumab	2	(5%)
Cetuximab/panitumumab	3	(7%)
Experimental drugs	4	(9%)

We also reported an improved efficacy of TAS-102 in the regorafenib-pretreated group. The regorafenib-pretreated group had longer median time from first-line chemotherapy to induction of salvage chemotherapy (31.0 months *vs*. 26.8

Table VI. *Patients' background and toxicity of TAS-102 for sub-groups by regorafenib tolerance at induction of salvage therapy.*

	Regorafenib tolerant (n=24)			Regorafenib intolerant (n=19)		
Median age (range), years	64 (45-85)			61 (38-80)		
Performance status, 0/1/2, %	29/63/8			32/57/11		
Number of organs with metastases: 1-2/≥3, %	38/62			68/32		
Maximum adverse event grade	G3	G4	G3/4	G3	G4	G3/4
Hematological	9	5	14 (58%)	6	3	9 (47%)
Non-hematological	11	1	12 (50%)	6	0	6 (32%)
Any	12	6	18 (75%)	9	3	12 (63%)

Table VII. *Patients' background for sub-groups by regorafenib pretreatment.*

	Regorafenib-pretreated (n=16)		Regorafenib-naïve (n=27)
Median age (range), years	61.5 (45-85)		64 (38-80)
Performance status: 0/1/2 (%)	38/56/6		26/63/11
Number of organs with metastases: 1-2/ ≥3, %	43/57		56/44
Median time from initial therapy to salvage induction, months	31.0		26.8
		δ=4.2	

δ: difference between the groups.

months in regorafenib-naïve group; δ=4.2 months), indicating that the group included patients with more indolent tumors and many patients responded to TAS-102. From the point of view of salvage therapy, the median OS from induction of salvage therapy was much longer in the regorafenib-pretreated group (regorafenib-first strategy) *versus* regorafenib-naïve group (TAS-102-first strategy) (19.3 months *vs*. 6.6 months, respectively; δ=12.7 months) and discussion is raised as to the better sequence of the two drugs: it is not clear which should be used first in salvage chemotherapy. As described above, these patient groups had different backgrounds of usage of the two drugs: all 16 patients treated with regorafenib first were then treated with TAS-102, and did not include those who were treated only with regorafenib. On the other hand, only six out of 27 patients treated with TAS-102 first were then treated with regorafenib. The former group obviously gained advantage from regorafenib monotherapy, but this does not fully explain the large difference because its median PFS was 2.2 to 3.2 months in previous reports (7, 9, 12). There remains speculation that the sequence of regorafenib then TAS-102 might lead to a better outcome, with the hypothesis of there being synergistic effects between the two drugs.

There is a hypothesis underlying the increased effect of TAS-102 after treatment with regorafenib. Combinations with tyrosine kinase inhibitors of VEGF signaling, including regorafenib, and cytotoxic agents were not clinically effective in colorectal cancer (13-15). But in a murine xenograft model, trifluridine was reported to be more concentrated in the tumor when administered with bevacizumab (16). Furthermore, the combination therapy of TAS-102 and bevacizumab demonstrated improved survival in phase I/II study: PFS at 16 weeks was 42.9% and median OS was 11.2 months (17). Inhibition of the VEGF pathway with bevacizumab might increase delivery of trifluridine to the tumor by normalizing angiogenesis. Regorafenib might act in a similar way to improve TAS-102 delivery.

Overall, TAS-102 is suitable for salvage chemotherapy because of its safety. But the results of our present study should be carefully interpreted because we carried out a single retrospective survey of a limited number of cases, that may lead to possible bias. Further study is needed to answer how TAS-102 and regorafenib should be implemented in the salvage treatment of colorectal cancer.

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Conflicts of Interest

Eishi Baba and Koichi Akashi are conducting research sponsored by Taiho Pharm. The other Authors declare that they have no conflict of interest.

References

1 International Agency for Research on Cancer. GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Geneva, Switzerland: World Health Organization, 2013.

2 Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Tokyo, Japan, 2015.

3 Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Mahoney MR, O'Neil BH, Shaw JE, Polite BN, Hochster HS, Atkins JN, Goldberg RM, Mayer RJ, Schilsky RL, Bertagnolli MM, Blanke CD, Cancer and Leukemia Group B (Alliance), SWOG, and ECOG: CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum. J Clin Oncol *32*: 5s, 2014 (suppl; abstr LBA3).

4 Tanaka N, Sakamoto K, Okabe H, Fujioka A, Yamamura K, Nakagawa F, Nagase H, Yokogawa T, Oguchi K, Ishida K, Osada A, Kazuno H, Yamada Y and Matsuo K: Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. Oncol Rep *32*: 2319-2326, 2014.

5 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 II trial. Lancet Oncol *13*: 993-1001, 2012.

6 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 and Ohtsu A; RECOURSE Study Group: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med *372*: 1909-1919, 2015.

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 and Laurent D; CORRECT Study Group: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase III trial. Lancet *381*: 303-312, 2013.

8 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.

9 Hirano G, Makiyama A, Makiyama C, Esaki T, Oda H, Uchino K, Komoda M, Tanaka R, Matsushita Y, Mitsugi K, Shibata Y, Kumagai H, Arita S, Ariyama H, Kusaba H, Akashi K and Baba E: Reduced dose of salvage-line regorafenib monotherapy for metastatic colorectal cancer in Japan. Anticancer Res *35*: 371-377, 2015.

10 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.

11 Cancer Therapy Evaluation Program, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf Last accessed 16th March 2016.

12 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 and 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 III trial. Lancet Oncol *16*: 619-629, 2015.

13 Argilés G, Saunders MP, Rivera F, Sobrero A, Benson A 3rd, Guillén Ponce C, Cascinu S, Van Cutsem E, Macpherson IR, Strumberg D, Köhne CH, Zalcberg J, Wagner A, Luigi Garosi V, Grunert J, Tabernero J and Ciardiello F: Regorafenib plus modified FOLFOX6 as first-line treatment of metastatic colorectal cancer: A phase II trial. Eur J Cancer *51*: 942-949, 2015.

14 Hecht JR, Trarbach T, Hainsworth JD, Major P, Jäger E, Wolff RA, Lloyd-Salvant K, Bodoky G, Pendergrass K, Berg W, Chen BL, Jalava T, Meinhardt G, Laurent D, Lebwohl D and Kerr D: Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol *29*: 1997-2003, 2011.

15 Hoff PM, Hochhaus A, Pestalozzi BC, Tebbutt NC, Li J, Kim TW, Koynov KD, Kurteva G, Pintér T, Cheng Y, van Eyll B, Pike L, Fielding A, Robertson JD and Saunders MP: Cediranib plus FOLFOX/CAPOX *versus* placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). J Clin Oncol *30*: 3596-3603, 2012.

16 Tsukihara H, Nakagawa F, Sakamoto K, Ishida K, Tanaka N, Okabe H, Uchida J, Matsuo K and Takechi T: Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. Oncol Rep *33*: 2135-2142, 2015.

17 Kuboki Y, NishinaT, Shinozaki E, Yamazaki K, Shitara K, Okamoto W, Kajiwara T, Matsumoto T, Tsushima T, Mochizuki N, Fukutani M, Nakamoto M, Hasegawa H, Sugama A, Nomura S, Sato A, Ohtsu A and Yoshino T: An investigator initiated multicenter phase I/II study of TAS-102 with bevacizumab for metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE). J Clin Oncol *33*: 2015 (suppl; abstr 3544).

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