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Propensity Score Analysis of Regorafenib Versus Trifluridine/Tipiracil in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapy (REGOTAS): A Japanese Society for Cancer of the Colon and Rectum Multicenter Observational Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. This study compared the efficacy of regorafenib and trifluridine/tipiracil (TFTD) in patients with metastatic colorectal cancer (mCRC) who are refractory to standard chemotherapy, because despite their clinical approval, it still remains unclear which of these two drugs should be used as initial treatment.

Materials and Methods. The clinical data of patients with mCRC who were treated with regorafenib or TFTD and those of drug-naive patients, between June 2014 and September 2015, were retrospectively collected from 24 institutions in Japan. Overall survival (OS) was evaluated using the Cox's proportional hazard models based on propensity score adjustment for baseline characteristics.

Results. A total of 550 patients (223 patients in the regorafenib group and 327 patients in the TFTD group) met all criteria. The median OS was 7.9 months (95% confidence interval [CI], 6.8–

9.2) in the regorafenib group and 7.4 months (95% CI, 6.6–8.3) in the TFTD group. The propensity score adjusted analysis showed that OS was similar between the two groups (adjusted hazard ratio [HR], 0.96; 95% CI, 0.78–1.18). In the subgroup analysis, a significant interaction with age was observed. Regorafenib showed favorable survival in patients aged <65 years (HR, 1.29; 95% CI, 0.98–1.69), whereas TFTD was favored in patients aged ≥65 years (HR, 0.78; 95% CI, 0.59–1.03).

Conclusion. No significant difference in OS between regorafenib and TFTD was observed in patients with mCRC. Although the choice of the drug by age might affect survival, a clearly predictive biomarker to distinguish the two drugs should be identified in further studies. *The Oncologist* 2018;23:7–15

Implications for Practice: Previous studies of patients with metastatic colorectal cancer refractory to standard chemotherapy had demonstrated that both regorafenib and trifluridine/tipiracil could result in increased overall survival compared with placebo, but there are no head-to-head trials. This large, multicenter, observational study retrospectively compared the efficacy of regorafenib and trifluridine/tipiracil in 550 patients with metastatic colorectal cancer refractory to standard chemotherapy who had access to both drugs. Although no difference in overall survival was found between the two drugs in adjusted analysis using propensity score, regorafenib showed favorable survival in patients aged <65 years, whereas trifluridine/tipiracil was favored in patients aged ≥65 years in the subgroup analysis.

INTRODUCTION

The development of novel drugs for metastatic colorectal cancer (mCRC) has progressed, and the median overall survival (OS) from first-line chemotherapy has reached 30 months [1–3]. Advances in later-line chemotherapy, as well as upfront chemotherapies with oxaliplatin-containing and irinotecan-containing regimens in combination with angiogenesis inhibitors or anti-epidermal growth factor receptor (anti-EGFR) antibody in patients with wild-type *RAS*, have significantly contributed to the improvement of the OS duration [4].

Survival benefits of salvage chemotherapy have been demonstrated by both regorafenib and trifluridine/tipiracil (TFTD) treatments. Regorafenib, which is a multimolecular targeted drug inhibiting angiogenesis and apoptosis [5], has shown to improve OS compared with placebo in patients with mCRC refractory to standard chemotherapy in a randomized phase III trial (CORRECT) [6]. The median OS was 6.4 months in the regorafenib group and 5.0 months in the placebo group (hazard ratio [HR] 0.77; 95% confidence interval [CI], 0.64–0.94; $p = .0052$). The improvement of OS after treatment with TFTD, a thymidine-based nucleic acid analogue and tipiracil hydrochloride [7], compared with placebo, has been confirmed in a global randomized phase III trial (RECOURSE) including patients with mCRC refractory to standard chemotherapy [8]. The median OS was 7.1 months in the TFTD group and 5.3 months in the placebo group (HR 0.68; 95% CI, 0.58–0.81; $p < .001$). Based on the results of these pivotal trials, the usage of regorafenib and TFTD was approved in Japan in March 2013 and 2014, respectively. Although the eligible patients can receive both drugs individually, it remains unclear which drug should be used first because of a lack of head-to-head randomized trials.

The aim of this study was to compare the efficacy between regorafenib and TFTD in patients with mCRC refractory to standard chemotherapy, who had access to both drugs, to determine whether a further prospective comparative trial should be conducted.

MATERIALS AND METHODS

Patient Population

This study was registered with the University Hospital Medical Information Network (number UMIN000020416). With approval from the Ethics Committee of each participating institution, we retrospectively collected the clinical data of patients with mCRC who received either regorafenib or TFTD between June 2014 and November 2015. The requirement for informed consent was waived because of the retrospective design of this study. The patients' follow-up was until September 2016.

Main eligibility criteria were as follows: (a) histologically confirmed colorectal adenocarcinoma, (b) no prior treatment with regorafenib and TFTD, (c) previous treatment with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and anti-EGFR antibody (if the patients had tumor with wild-type *KRAS/NRAS*), (d) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and (f) adequate organ function. After clinical data collection and blinded assessment, we excluded patients who could receive only a specific drug treatment, either regorafenib or TFTD, because of comorbidity and/or medical history.

Endpoints and Statistical Analysis

The primary endpoint was OS, defined as the time from the start of study treatment to death from any cause. Secondary endpoints included best response rate and disease control rate according to the Response Evaluation Criteria in Solid Tumors version 1.1; progression-free survival (PFS), defined as the time from the start of study treatment to disease progression or death from any cause; time to treatment failure (TTF), defined as the time from the start of study treatment to the termination from any cause or disease progression; time to ECOG PS ≥2, defined as the time from the start of study treatment to decision of an ECOG PS ≥2; and safety according to the Common Terminology Criteria for Adverse Events version 4.0.

The primary analysis was performed using the Cox's proportional hazard model including treatment group and propensity score for all patients (the observational dataset). A 1:1 matching using the propensity score (propensity score-matched dataset) was performed as a sensitivity analysis. Patients in the two groups were matched by a difference of propensity score within 0.05. Propensity score was calculated with a multivariable logistic regression model including 20 prognostic variables (supplemental online Table 1). The predictive factor for OS was explored using subgroup analyses and interaction tests. The clinical outcomes, including OS, PFS, TTF, and time to ECOG PS
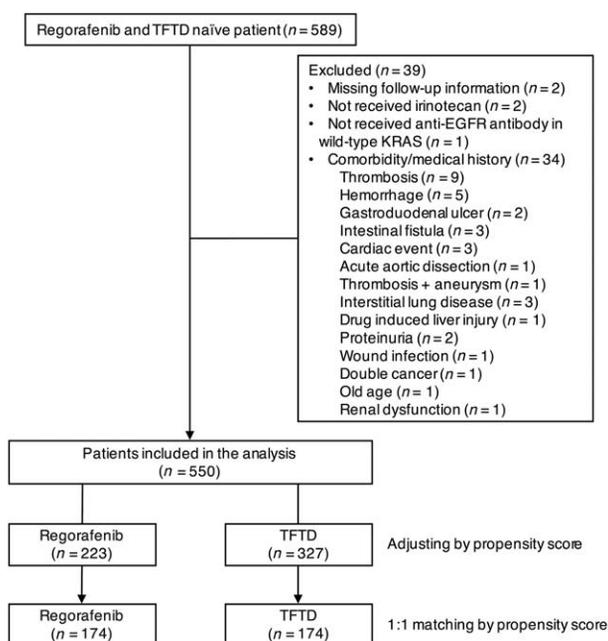
Figure 1. Patient selection flow diagram.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; TFTD, trifluridine/tipiracil.

≥2, were evaluated using the Kaplan-Meier method. Continuous and categorical variables were presented as median (interquartile range: 25%–75%) and number (proportion) of patients, respectively. Statistical tests were two-sided with 5% significant level. All analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html).

RESULTS

Patients

The number of patients who met all criteria for inclusion in the analysis was 550, including 223 patients in the regorafenib group and 327 patients in the TFTD group (Fig. 1). Thirty-four patients among excluded patients had comorbidity or medical history, such as thrombosis, hemorrhage, and cardiac events. Several characteristics, including primary tumor site, bone metastasis, number of metastatic organ sites, and initial dose reduction, were imbalanced between the two groups (Table 1). Regarding the decision of the therapeutic drug, the physician's choice was more frequent in the regorafenib group, whereas the patient's request was more frequent in the TFTD group ($p < .001$). The rate of initial dose reduction was higher in the regorafenib group than in the TFTD group (20% vs. 5%;

Table 1. Comparison of patients' characteristics between regorafenib and TFTD groups in the observational dataset

Characteristics	Regorafenib (n = 223) n (%)	TFTD (n = 327) n (%)	p value
Age, years			
Median (IQR)	64 (31–84)	64 (29–86)	.77
≥65 years	107 (48)	156 (48)	.95
Sex			.43
Male	126 (57)	197 (60)	
Female	97 (43)	130 (40)	
BMI, kg/m^2			
≥18.5 kg/m^2	194 (87)	267 (82)	.10
ECOG PS			.13
0	95 (43)	128 (39)	
1	121 (54)	176 (54)	
2	7 (3)	23 (7)	
Primary tumor site			.029
Right[a]	60[c] (27)	62[c] (19)	
Left[b]	163 (73)	265[d] (81)	
Surgery on primary tumor			.83
Yes	176 (79)	255 (78)	
Histological grade			.60
Well- and moderately-differentiated adenocarcinoma	197 (88)	297 (91)	
Other adenocarcinoma	17 (8)	19 (6)	
Missing	9 (4)	11 (3)	
RAS status			.80
Mutant	109 (49)	161 (49)	
Missing	6 (3)	6 (2)	
Metastatic organ site			
Liver	141 (63)	201 (61)	.72
Dissemination	37 (17)	73 (22)	.10
Bone	8 (4)	45 (14)	<.001

(continued)

Table 1. (continued)

Characteristics	Regorafenib (n = 223) n (%)	TFTD (n = 327) n (%)	p value
Number of metastatic organ site(s)			.004
1	60 (27)	75 (23)	
2	106 (48)	124 (38)	
≥3	57 (26)	128 (39)	
Intolerable drug			
Any drugs	63 (28)	112 (34)	.16
Fluoropyrimidine	7 (3)	19 (6)	.16
Oxaliplatin	56 (25)	87 (27)	.77
Irinotecan	9 (4)	27 (8)	.054
Bevacizumab	13 (6)	29 (9)	.25
Anti-EGFR antibody	3 (1)	12 (4)	.12
Prior regimens			.60
≥3	106 (48)	164 (50)	
Duration from initiation of first-line chemotherapy			.92
≥18 months	163 (73)	241 (74)	
Platelets at baseline			.18
≥400 × 10^3/μL	7 (3)	20 (6)	
Missing	2 (1)	1 (0.3)	
Baseline serum albumin			.71
≤3.5 g/dL	95 (43)	149 (46)	
Missing	7 (3)	8 (2)	
Baseline serum AST			.67
≥40 IU/L	62 (28)	95 (29)	
Missing	2 (1)	1 (0.3)	
Baseline CRP			.89
≥1.0 mg/dL	100 (45)	141 (43)	
Missing	6 (3)	10 (3)	
Baseline serum CEA			.64
≥5.0 μg/L	196 (88)	292 (89)	
Missing	2 (1)	5 (2)	
Decision of therapeutic drug			<.001
Patient's request	27 (12)	104 (32)	
Physician's choice	183 (82)	182 (56)	
Comorbidity or others	4 (2)	21 (6)	
Unknown	9 (4)	20 (6)	
Initial dose reduction			
Yes	45 (20)	17 (5)	<.001
Reasons for initial dose reduction			.54
General health deterioration	11 (24)	6 (35)	
Adverse event (prior chemotherapy)	4 (9)	3 (18)	
Unknown	14 (31)	4 (24)	
Others	16 (36)	4 (24)	

[a]Including cecum, ascending colon, and transverse colon.
[b]Including descending colon, sigmoid colon, and rectum.
[c]One patient with cecal and sigmoid colonic cancers in the regorafenib group and one patient with cecal and transverse colonic cancers in the TFTD group.
[d]Two patients with descending and sigmoid colonic cancers and one patient with sigmoid colonic and rectal cancers in the TFTD group.
Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CEA, carcinoembryonic antigen; CRP, C reactive protein; ECOG PS, European Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IQR, interquartile range; RAS, rat sarcoma; TFTD, trifluridine/tipiracil.
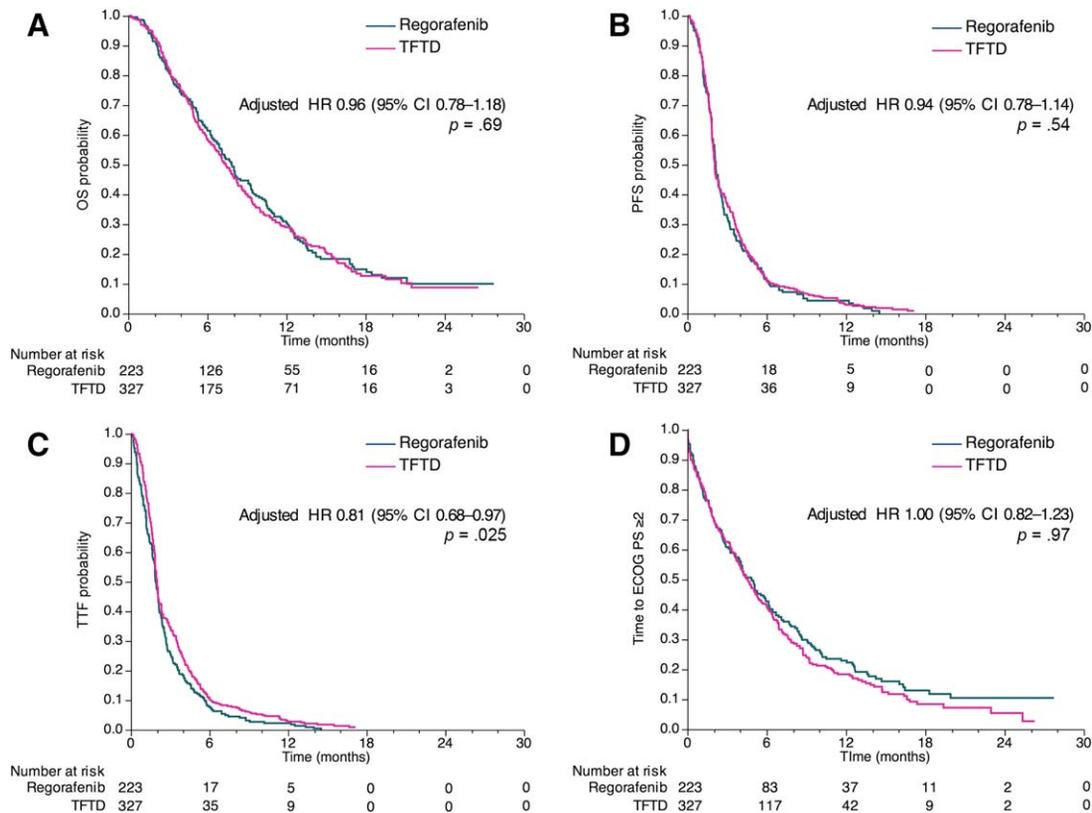
Figure 2. OS, PFS, TTF, and time to ECOG PS ≥2 for patients who were treated with regorafenib versus TFTD in the observational dataset. Kaplan-Meier curves for OS (A), PFS (B), TTF (C), and time to ECOG PS ≥2 (D). Adjusted HRs were calculated using the propensity score.
   Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFTD, trifluridine/tipiracil; TTF, time to treatment failure.

$p < .001$). The median follow-up time was 17.6 months in the regorafenib group and 17.3 months in the TFTD group.

Efficacy

Events of death were observed in 171 patients (77%) in the regorafenib group and 247 patients (76%) in the TFTD group. The median OS was 7.9 months (95% CI, 6.8–9.2) in the regorafenib group and 7.4 months (95% CI, 6.6–8.3) in the TFTD group (Fig. 2A and supplemental online Table 2). There was no significant difference between the two groups (unadjusted HR of TFTD to regorafenib, 1.03; 95% CI, 0.85–1.26; $p = .75$). In the propensity score adjusted analysis for OS, similar results were observed between the two groups (adjusted HR, 0.96; 95% CI, 0.78–1.18; $p = .69$). Moreover, the PFS and time to ECOG PS ≥2 were similar between the two groups (adjusted HR, 0.94 and 1.00, respectively), although the TTF was longer in the TFTD group than in the regorafenib group (adjusted HR, 0.81; 95% CI, 0.68–0.97; $p = .025$; Fig. 1B–1D and supplemental online Table 2). Among patients with target lesions (212 patients in the regorafenib group and 307 patients in the TFTD group), no complete responses were observed and partial response was found in 3 patients (1%) who received TFTD. Lastly, the disease control rate was similar between the two groups (32.1% in the regorafenib group vs. 29.6% in the TFTD group, $p = .56$).

Subgroup Analyses

In the observational dataset, statistical significance was observed only between the interaction of treatment and

patient's age (p value for interaction = .012; Fig. 3A). Specifically, regorafenib showed favorable survival in patients aged <65 years (HR, 1.29; 95% CI, 0.98–1.69), whereas TFTD was favored in patients aged ≥65 years (HR, 0.78; 95% CI, 0.59–1.03; Fig. 3B). The median OS in the patients aged <65 years and patients aged ≥65 years was 10.4 months (95% CI, 8.0–12.3) and 6.2 months (95%, CI 4.9–7.4) among the regorafenib group, respectively. The median OS in those patients was 7.0 months (95% CI, 5.8–8.6) and 7.7 months (95% CI, 6.5–8.6) among the TFTD group, respectively.

Safety and Toxicity

Incidence of grade 3 or more hematologic toxicities was higher in the TFTD group than in the regorafenib group (39% vs. 13%; $p < .001$), particularly the incidence of neutropenia (33% vs. 3%; $p < .001$; Table 2). In contrast, incidence of grade 3 or more nonhematologic toxicities was higher in the regorafenib group than in the TFTD group (47% vs. 13%: $p < .001$), particularly the incidence of hand-foot skin reaction (20% vs. 0%; $p < .001$). Liver dysfunction was observed in 12% of patients in the regorafenib group, and one of them died because of liver failure. Treatment-related death was observed in four patients (2%) of the regorafenib group and two patients (1%) of the TFTD group.

Discontinuation of Study Treatment and Post-Treatment

Discontinuation of study treatment because of treatment-related toxicities was higher in the regorafenib group than in
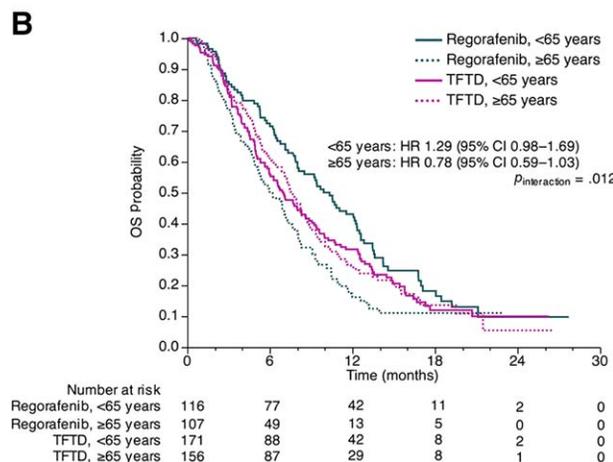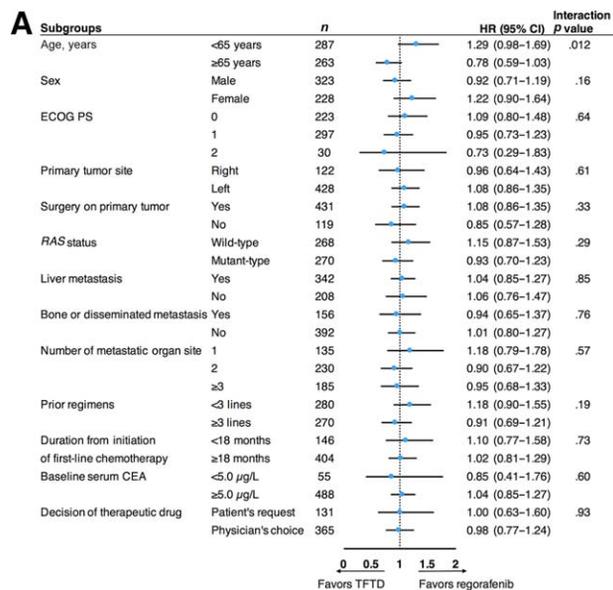
Figure 3. Subgroup analyses of OS in the observational dataset. Forest plots with HRs for overall survival **(A)**. Kaplan-Meier curves for OS according to age <65 years and ≥65 years **(B)**.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; RAS, rat sarcoma; TFTD, trifluridine/tipiracil.

Table 2. Comparison of the frequency of treatment-related grade ≥3 adverse events in ≥3% of patients in the observational dataset

Event	Regorafenib (n = 223) n (%)	TFTD (n = 327) n (%)	p value
Hematologic toxicities			
Any	30 (13)	128 (39)	<.001
Neutropenia	6 (3)	107 (33)	<.001
Anemia	11 (5)	35 (11)	.018
Thrombocytopenia	14 (6)	11 (3)	.14
Nonhematologic toxicities			
Any	104 (47)	41 (13)	<.001
Fatigue	7 (3)	8 (2)	.61
Anorexia	10 (4)	18 (6)	.69
Febrile neutropenia	0	9 (3)	.013
Hypertension	13 (6)	0	<.001
Hand-foot skin reaction	44 (20)	0	<.001
Liver dysfunctions[a]	27 (12)	1 (0.3)	<.001
Skin disorders[b]	8 (4)	1 (0.3)	.004

[a]Including AST increase, ALT increase, total-bilirubin increase, and ALP increase.
[b]Including erythema multiforme and Stevens-Johnson syndrome.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; TFTD, trifluridine/tipiracil.

significant difference in OS was observed between the two groups (adjusted HR, 1.02; 95% CI, 0.81–1.30; p = .85; supplemental online Fig. 1A and supplemental online Table 4). Progression-free survival, TTF, and time to ECOG PS ≥2 were also similar to those in the observational dataset (supplemental online Fig. 1B–1D and supplemental online Table 3). The HRs for PFS, TTF, and time to ECOG PS ≥2 were 0.92 (p = .47), 0.80 (p = .036), and 1.02 (p = .85), respectively. In the subgroup analysis, HRs by age were similar to those in the observational dataset, although they were not statistically significant (p value for interaction = .18; supplemental online Fig. 2 and supplemental online Table 5). Incidence of grade 3 or more toxicities and the details of discontinuation of study treatment and posttreatment were also similar to those in the observational dataset (supplemental online Tables 6 and 7). In a post hoc analysis, the median OS in patients who received the two drugs was 10.8 months (95% CI, 9.3–12.6) in the regorafenib group and 9.5 months (95% CI, 9.2–12.1) in the TFTD group (p = .53).

DISCUSSION
We demonstrated that regorafenib and TFTD have similar efficacy in patients with mCRC refractory to standard chemotherapy using propensity score analysis. These drugs have been approved for clinical use in the U.S., Europe, and Japan. However, limited data comparing the efficacy and safety of regorafenib and TFTD are available in patients with mCRC refractory to standard chemotherapy [9, 10]. We performed a large observational study to determine the necessity of randomized trials in comparing the efficiency of two regimens; similar OS between regorafenib and TFTD has been observed in a cross-trial comparison [6, 8].

To reduce the bias for a retrospective study, we used propensity score analysis. Nevertheless, no significant differences in OS between the two groups were observed, either in the

the TFTD group (24% vs. 7%; p < .001), whereas the proportion of patients who had ECOG PS ≥2 at discontinuation was similar between the two groups (p = .93; Table 3). The crossover rate was higher in the regorafenib group than in the TFTD group (60% vs. 40%; p < .001). The proportion of patients who were treated with any other chemotherapies except regorafenib and TFTD was higher in the TFTD group than in the regorafenib group (12% vs. 5%; p = .004). In a post hoc analysis, the median OS in patients who received the two drugs was 10.5 months (95% CI, 9.2–12.2) in the regorafenib group and 9.4 months (95% CI, 8.3–10.7) in the TFTD group (p = .53).

Sensitivity Analysis
One hundred seventy-four patients in each group were matched by propensity score. Patients' characteristics were well-balanced between the two groups, except the initial dose reduction (p < .0001; supplemental online Table 3), and no

Table 3. Comparison of discontinuation of study treatment and post-study treatment outcomes between regorafenib and TFTD in the observational dataset

Outcome measures	Regorafenib (*n* = 223) *n* (%)	TFTD (*n* = 327) *n* (%)	*p* value
Discontinuation of study treatment	223 (100)	321 (98)	
Reason for discontinuation of study treatment			<.001
Disease progression	168 (75)	296 (92)	
Treatment-related toxicities	54 (24)	21 (7)	
Others	1 (0)	4 (1)	
Post-study treatment outcomes			
ECOG PS at discontinuation			.93
0 + 1	152 (70)	217 (68)	
≥2	68 (30)	104 (32)	
Subsequent chemotherapy			
Any chemotherapies	144 (65)	160 (50)	<.001
Regorafenib	2 (1)	121 (38)	NE
TFTD	131 (59)	0	NE
Others	11 (5)	39 (12)	.004
Crossover between both drugs[a]	134 (60)	127 (40)	<.001

[a]Crossover includes patients who were treated with both regorafenib and TFTD in any lines.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluated; TFTD, trifluridine/tipiracil.

propensity score-adjustment or propensity score-matching analyses (HR, 0.96 and 1.02, respectively). The HR for OS was consistently close to 1.00 in all analyses. Although there were no significant differences in the PFS and tumor response between the two groups, the TTF was shorter in the regorafenib group than in the TFTD group because the termination by treatment-related toxicities was more frequent in the regorafenib group. In fact, incidence of grade 3 or more nonhematologic toxicities associated with regorafenib was consistent with the results of the CORRECT trial [6]. We adopted time to ECOG PS ≥2 as a surrogate of quality of life assessment because regorafenib-related toxicities might be associated with decreased quality of life. However, time to ECOG PS ≥2 was similar between the two groups. In addition, similar proportion of patients with ECOG PS ≥2 at the study treatment discontinuation was observed between the groups. These results suggest that regorafenib-related toxicities did not affect progression of their conditions during treatment and at the discontinuation.

The efficacy outcomes of the two drugs reproduced the results of previous respective pivotal trials, despite the real-world setting of this study, because the participants had access to both drugs [6, 8]. In fact, the proportion of patients who received subsequent chemotherapies after regorafenib or TFTD was higher than that in the pivotal trials (65% vs. 26% in the CORRECT trial and 50% vs. 42% in the RECOURSE trial). However, one fourth of those patients, who were treated with TFTD, received any other chemotherapy except regorafenib. The majority of the subsequent chemotherapies were oxaliplatin-containing or anti-EGFR antibody-containing regimens (data not shown), which have been conducted in previous phase II trials; these regimens were used following a rechallenge strategy [11, 12]. The efficacy of regorafenib after failure of TFTD or vice versa is uncertain and should be determined in a future trial.

In the subgroup analysis for OS, including propensity score-adjustment and propensity score-matching analysis, regorafenib

was a favorable trend of OS in the younger patients, whereas TFTD was in the elderly patients. The reasons for this difference are unclear, but similar trends were observed in the subgroup analysis of the pivotal trials. Although the OS was significantly longer in the regorafenib group patients than in the placebo group patients among those aged <65 years (HR, 0.72), no significant difference was observed in the OS between the two groups among patients aged ≥65 years (HR, 0.86) [13]. In contrast, the OS was significantly longer in the TFTD group than in the placebo group, both among patients aged <65 years (HR, 0.74) and those aged ≥65 years (HR, 0.62) [14]. In our study, the difference in OS seemed to be higher in the regorafenib group than in the TFTD group. It might be that regorafenib tolerance decreased in elderly patients compared with younger patients, whereas TFTD tolerance was similar between the two age groups examined. These results are consistent with clinical impression; however, they should be confirmed in a prospective trial because the subgroup analysis has a bias.

This study has several limitations. Firstly, as a retrospective observational study, it is characterized by bias. To reduce it, patients were enrolled after the two drugs were approved in Japan, and an adjusted analysis using propensity score was established for the patients without comorbidity and/or medical history who had to receive a specific drug treatment. Secondly, all patients who were enrolled in our study were Japanese. However, no ethnic differences between Japanese and Western patients were observed in either of the pivotal trials [6, 8, 15]. Finally, the patients whose dosage was reduced at the initiation dose were included. The initial dose reduction of regorafenib was reported as one of the prognostic factors in a previous prospective observational study [16]. Nevertheless, in this study, the initial dose reduction was not included as a propensity score because no variability was observed before the treatment. A post hoc analysis was established using the propensity score,

including the initial dose reduction; however, the results were similar to those in the primary analysis (data not shown).

Clinical predictive markers to distinguish the two drugs were not identified in our study. Because clinical outcomes did not differ between unadjusted and adjusted populations in an analysis adjusted for patients' characteristics, it is premature to conduct a superiority randomized trial. Novel genetic or metabolic predictive biomarkers will be needed for a physician to decide the appropriate drug for initiating treatment patients with mCRC. Respective predictive biomarkers have been analyzed in previous reports [17, 18]; however, no clear biomarkers that could distinguish the two drugs have been found.

Conclusion

Regorafenib and TFTD showed a similar effect on the OS of patients with mCRC refractory to standard chemotherapy in the real-world setting, on both unadjusted and adjusted analyses. Although the choice of the drug by age might affect survival, a clearly predictive biomarker to distinguish the two drugs should be identified in further studies.

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:
Martha M. Kirstein, Ansgar Lange, Anne Prenzler et al. Targeted Therapies in Metastatic Colorectal Cancer: A Systematic Review and Assessment of Currently Available Data. *The Oncologist* 2014;19:1156–1168.

Implications for Practice:
Introduction of targeted agents in treatment algorithms of patients with metastatic colorectal cancer (mCRC) has significantly improved median overall survival. Emerging therapeutic options are available for patients with mCRC in 2014. This article reviews and assesses the available phase II and III data in order to elucidate the best combination and sequence modalities of targeted therapies in patients with mCRC.