

# Trifluridine/Tipiracil and Regorafenib in Patients with Metastatic Colorectal Cancer: A Retrospective Study at a Tertiary Oncology Center

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

**Key Words.** Metastatic colorectal cancer • Trifluridine/tipiracil • Regorafenib • Antineoplastic agent

## ABSTRACT

**Background.** Trifluridine/tipiracil (FTD/TPI) and regorafenib prolong survival for patients with refractory metastatic colorectal cancer (mCRC); limited comparative effectiveness data exist.

**Materials and Methods.** A retrospective, longitudinal cohort study of patients with mCRC who initiated FTD/TPI or regorafenib (index therapy) between 2012 and 2017 at a U.S. tertiary oncology center, Dana-Farber Cancer Institute, was conducted. Using best tumor response assessments, real-world overall response rates (rwORR) and disease control rates (rwDCR) were described and analyzed using logistic regression. Survival rate was examined for each month after index therapy using Kaplan-Meier. Overall survival (OS) was assessed using Cox proportional hazards models. Subgroup analyses among patients with index therapy as second- or third-line were performed.

**Results.** One hundred twenty-six and 95 patients were treated with FTD/TPI or regorafenib as index therapy,

respectively. Patients treated with FTD/TPI versus regorafenib had a better response (rwORR 52.5% vs. 34.2%; adjusted odds ratio [OR] = 2.6; all  $p$  value <.05; rwDCR 64.2% vs. 46.1%; adjusted OR = 2.5; all  $p$  value <.05). Similar findings were observed for FTD/TPI versus regorafenib as second- or third-line therapy (rwORR 54.8% vs. 25.9%; adjusted OR = 4.1; all  $p$  value <.05; rwDCR 69.0% vs. 37.0%; adjusted OR = 4.9; all  $p$  value <.05). A greater proportion of patients treated with FTD/TPI versus regorafenib survived at 3 months (86.2% vs. 73.4%;  $p$  value = .016) and 4 months (79.6% vs. 65.8%;  $p$  value = .017). Adjusted OS hazard ratio for FTD/TPI versus regorafenib was 0.80,  $p$  value = .157.

**Conclusion.** Patients treated with FTD/TPI had better tumor response and disease control than patients treated with regorafenib. Subgroup analysis in second- or third-line suggests that early use of FTD/TPI may have clinical benefits. *The Oncologist* 2021;26:e2161–e2169

**Implications for Practice:** In this retrospective cohort study, patients with refractory metastatic colorectal cancer treated with trifluridine/tipiracil (FTD/TPI) were significantly less likely than those treated with regorafenib to have dose modifications and more likely to have higher real-world objective response rate (rwORR) and real-world disease control rate (rwDCR) while treated. Patients treated with FTD/TPI versus regorafenib had significantly higher odds of having rwORR or rwDCR in adjusted analyses. Monthly survival rates were higher overall in patients treated with FTD/TPI versus regorafenib in the first 6 months of follow-up, particularly at months 3 and 4. This study offers insight into patients' treatment experience in real-world clinical settings.

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## INTRODUCTION

Systemic therapy for metastatic colorectal cancer (mCRC) generally begins with chemotherapy regimens involving a fluoropyrimidine in combination with either oxaliplatin or irinotecan [1]. Biologic agents are often added to these cytotoxic backbones. Specifically, chemotherapy may be combined with monoclonal antibodies targeting the vascular endothelial growth factor pathway, such as bevacizumab, or the epidermal growth factor receptor, namely cetuximab or panitumumab; this latter class of antibodies is only effective in patients with RAS and BRAF-wild-type tumors [2].

Two oral agents have been studied and approved for mCRC that has progressed on the above therapies [2]. Regorafenib is an oral multikinase inhibitor approved by the U.S. Food and Drug Administration in 2012 [3] based on the results of the phase III CORRECT trial, comparing regorafenib with placebo in patients with previously treated mCRC who had progressed beyond their last available standard therapy [4]. The trial demonstrated a significant improvement in overall survival (OS) among patients receiving regorafenib compared with those receiving placebo (median OS, 6.4 vs. 5.0 months; hazard ratio [HR], 0.77;  $p$  value = .005) [4]. Trifluridine/tipiracil (FTD/TPI) is an oral chemotherapy agent consisting of a cytotoxic component, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil. FTD/TPI was approved in 2015 for the same population of patients for whom regorafenib was approved [5]; this approval was based on the results of the phase III RECURSE trial, which compared FTD/TPI with placebo in patients with mCRC who had received at least two prior standard chemotherapy regimens [6]. This study showed a significant improvement in OS among patients treated with FTD/TPI compared with placebo (median OS, 7.1 vs. 5.3 months; HR, 0.68;  $p$  value <.001) [6].

However, real-world evidence of clinical outcomes for patients treated with regorafenib and FTD/TPI is lacking. This information is important given regorafenib and FTD/TPI have equivalent indications and routes of administration. This retrospective comparative effectiveness study used data collected from electronic medical records (EMRs) and a clinical database at a tertiary oncology center to evaluate and compare the impact of FTD/TPI versus regorafenib on clinical outcomes such as tumor response and survival among patients with mCRC who had progressed on or were intolerant to previous lines of therapies. In addition, dosing patterns and dose modifications for these therapies as well as clinical conditions while being treated were assessed.

## MATERIALS AND METHODS

### Study Design and Study Population

This was a retrospective, longitudinal cohort study using data from EMRs and a clinical database at Dana-Farber Cancer Institute. The center's Institutional Review Board granted approval for this study. Data for this study included longitudinal information on patient demographic and disease characteristics, treatment types, oncology-specific

evaluations for tumor response, survival, and clinical conditions while on treatment as documented in physician notes.

Eligible patients had a biopsy-confirmed adenocarcinoma of the colon or rectum when at least 18 years of age, had confirmed metastatic disease, had initiated FTD/TPI or regorafenib treatment for mCRC, and had at least one visit at the study center. As depicted in supplemental online Figure 1, the index date was defined as the date of prescription of the first of FTD/TPI or regorafenib (index therapy). The baseline period was defined as the 6-month period preceding the index date. The follow-up period was defined as the time from the index date to the end of data availability (earliest of death, last visit at center, discharge to hospice, or end of study).

Data on demographic and clinical characteristics during the baseline period were collected and included primary cancer site, sites of metastases, genetic mutation status, comorbidities, and Likert pain score, which is based on a 10-point scale with 0 indicating no pain, 5 indicating moderate pain, and 10 indicating worst pain. Data also included treatment prior to the index therapy such as prior surgery, number of prior treatment regimens, and type of systemic therapies for mCRC. Treatment patterns in the follow-up period were assessed, including patient and clinical setting characteristics associated with index therapy, the line of the index therapy, dosing and dose modifications of the index therapy, and treatments after index therapy. Clinical endpoints as available in the EMR and clinical database were assessed in the follow-up period and included real-world best tumor response during the course of treatment with index therapy, which was based on information from both clinician assessment from notes as well as radiographic assessments from imaging reports. Best tumor response assessments during the treatment period were used to compute real-world overall response rate (rwORR) (i.e., proportion of patients who responded) and real-world disease control rate (rwDCR) (i.e., proportion of patients who had responded or a stable disease response at least 6 weeks after the index date). This approach differs from tumor response assessments in clinical trials that are performed at regular intervals. However, this real-world best tumor response assessment approach has been used in other observational settings [1, 7, 8]. OS was defined as the time between index date and death. The incidence of select clinical conditions while on treatment (e.g., hand-foot syndrome, rash or desquamation, general pain, fatigue, weight loss, increased aspartate aminotransferase [AST], increased alkaline phosphatase [ALP], hyperbilirubinemia, lymphocytopenia, neutropenia, thrombocytopenia, and febrile neutropenia) was assessed after the initiation of FTD/TPI or regorafenib therapy. Dose intensity was calculated as the mean daily dose of active treatment days. The relative dose intensity was defined as the ratio of dose intensity to recommended dose where recommended dose is 35 mg/m<sup>2</sup> twice daily for FTD/TPI and 160 mg daily for regorafenib.

### Statistical Analysis

The treatment groups of interest in the study were identified for analysis based on the index therapy (i.e., whether

the patient first received FTD/TPI or regorafenib following an mCRC diagnosis). Descriptive statistics were calculated using frequencies and proportions for categorical variables and means, SDs, and medians for continuous variables. Differences between patients by index therapy were compared using Pearson  $\chi^2$  tests (or Fisher's exact tests) for categorical variables, while continuous variables were compared using Wilcoxon rank-sum tests. Logistic regression models adjusting for potential baseline confounders that were prespecified a priori (i.e., gender, age, baseline Likert pain score, time from mCRC diagnosis to start of therapy, line of therapy) were performed to report the odds ratio (OR) and 95% confidence intervals (CIs) for rwORR and rwDCR.

Median OS and survival rates for each month after index therapy initiation were calculated using Kaplan-Meier analysis, in which patients who did not have an event were censored at the date of last follow-up; the log-rank test was employed to determine whether survival rates were different between patients who first initiated with FTD/TPI versus regorafenib as their index therapy. Cox proportional hazards models adjusting for potential baseline confounders that were prespecified a priori (i.e., gender, age, baseline Likert pain score, time from mCRC diagnosis to start of therapy, line of therapy) were used to compare OS between patients initiating different index therapy; HR and 95% CIs were estimated. The incidence of each clinical condition was estimated using multivariable Poisson regression models adjusted for relevant demographic covariates.

Planned subgroup analyses for patients who initiated the index therapy as second- or third-line mCRC treatment were performed. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## RESULTS

Between April 2012 and December 2017, 126 patients were prescribed FTD/TPI, and 95 patients were prescribed regorafenib as their index therapies. Baseline patient demographic and clinical characteristics are presented in Table 1. A higher proportion of patients treated with FTD/TPI had Eastern Cooperative Oncology Group performance status 1 (46.8% vs. 32.6%;  $p$  value = .033), and the mean Likert pain score was higher in the FTD/TPI arm (0.9 vs. 0.3;  $p$  value = .007) with a lower proportion of FTD/TPI patients reporting no pain compared with regorafenib patients (79.8% vs. 92.6%;  $p$  value = .009). A higher proportion of patients treated with regorafenib had a left-sided primary colon tumor (57.4% vs. 44.0%;  $p$  value = .049). Characteristics of index therapy and patients at initiation of index therapy are described in Table 2. Patients who were first prescribed regorafenib versus FTD/TPI were more likely to be treated with this therapy during the early years of the study. The median follow-up for patients first treated with FTD/TPI and regorafenib was 7.1 and 6.3 months, respectively. Similar proportions of patients in both groups had surgery prior to index therapy (FTD/TPI: 65.1% vs. regorafenib: 75.8%;  $p$  value = .086) and surgery for resection of primary cancer site (FTD/TPI: 61.9% vs. regorafenib: 73.7%;  $p$  value = .065). Median relative dose intensity was significantly higher for patients initiating

treatment with FTD/TPI versus regorafenib (FTD/TPI: 1.0 vs. regorafenib: 0.8;  $p$  value < .001). Twenty percent more patients with FTD/TPI as index therapy had no dose modifications compared with patients with regorafenib as index therapy (84.0% vs. 64.1%;  $p$  value < .001). Patients in both groups had a median of 3.0 pharmacologic regimens prior to index therapy; preindex and postindex therapies were comparable in both groups (supplemental online Table 1). Among 63 patients with FTD/TPI as index therapy that had a postindex therapy, 16 (25.4%) switched to regorafenib and 13 (20.6%) had both chemotherapy and biological therapy. Among 40 patients with regorafenib as index therapy that had a postindex therapy, 12 (30.0%) switched to FTD/TPI and 8 (20.0%) had a chemotherapy and biological therapy.

Best real-world tumor response results are presented in Table 3. One hundred twenty (95.2%) patients with FTD/TPI as index therapy and 76 (80.0%) of those with regorafenib as index therapy had a clinician reported tumor response during the treatment period. Patients with FTD/TPI versus regorafenib as index therapy were more likely to respond to treatment (rwORR 52.5% vs. 34.2%;  $p$  value = .012) and achieve disease control (rwDCR 64.2% vs. 46.1%;  $p$  value = .013) based on best tumor response during the treatment period. Among patients who initiated index therapy as second- or third-line therapy, patients with FTD/TPI versus regorafenib were more likely to respond to treatment (rwORR 54.8% vs. 25.9%;  $p$  value = .018) and achieve disease control (rwDCR 69.0% vs. 37.0%;  $p$  value = .009). In the adjusted analyses, patients treated with FTD/TPI as index therapy had better tumor response and disease control compared with patients treated with regorafenib (rwORR OR, 2.57; 95% CI, 1.38–4.80; and rwDCR OR, 2.52; 95% CI, 1.36–4.68). Similarly, in the subgroup analyses of patients treated with index therapy as only second- or third-line mCRC treatments, patients treated with FTD/TPI had better tumor response and disease control compared with patients treated with regorafenib (rwORR OR, 4.11; 95% CI, 1.32–12.79; and rwDCR OR, 4.86; 95% CI, 1.57–15.04). Among all patients, most patients treated with FTD/TPI and regorafenib discontinued treatment because of disease progression (FTD/TPI: 85.2% vs. regorafenib: 77.9%;  $p$  value = .162). Patients treated with FTD/TPI versus regorafenib had less discontinuation because of toxicity/intolerance (8.2% vs. 24.2%;  $p$  value < .001).

Among patients who had FTD/TPI as their index therapy, 95 (75.4%) died (91 because of colon or rectal cancer) compared with 84 (88.4%) (79 died because of colon or rectal cancer) among those with regorafenib as their index therapy ( $p$  value = .015). Median OS was 7.5 months (95% CI, 6.0–8.8) versus 7.1 months (95% CI, 5.0–8.2) for all patients treated with FTD/TPI versus regorafenib. In the subgroup analyses of patients treated with index therapy as only second- or third-line mCRC treatments, patients treated with FTD/TPI versus regorafenib had a median OS of 7.7 months (95% CI, 4.4–11.5) versus 5.1 months (95% CI, 2.9–7.9), which was not significantly different. However, at each month of follow-up for the first 6 months, monthly survival was greater among patients who had initiated FTD/TPI versus regorafenib in the overall population and in

**Table 1.** Demographic and clinical characteristics among patients with FTD/TPI and regorafenib as index therapy

Demographic characteristics	FTD/TPI, <i>n</i> = 126	Regorafenib, <i>n</i> = 95	<i>p</i> value
Age at index date, mean ± SD (median), yr	56.6 ± 11.1 (55.0)	58.7 ± 11.7 (57.0)	.190
Race/ethnicity, <i>n</i> (%)			
White	107 (84.9)	85 (89.5)	.321
Black	5 (4.0)	3 (3.2)	.999
Hispanic or Latino	3 (2.4)	3 (3.2)	.999
Asian/Pacific Islander	6 (4.8)	2 (2.1)	.471
Unknown/not sure	5 (4.0)	2 (2.1)	.702
Gender, <i>n</i> (%)			
Female	69 (54.8)	43 (45.3)	.162
Male	57 (45.2)	52 (54.7)	.162
Clinical and disease characteristics			
Body mass index, mean ± SD (median), kg/m <sup>2</sup>	27.2 ± 6.5 (26.2)	28.3 ± 7.2 (25.9)	.235
ECOG performance status, <i>n</i> (%)			
0 Fully active	34 (27.0)	24 (25.3)	.773
1 Restricted in physically strenuous activity	59 (46.8)	31 (32.6)	.033 <sup>a</sup>
2 Require bed rest during <50% of waking day	5 (4.0)	3 (3.2)	1.000
3 Require bed rest during ≥50% of waking day	1 (0.8)	1 (1.1)	1.000
4 Completely disabled	0 (0.0)	0 (0.0)	
Unknown	27 (21.4)	36 (37.9)	.007 <sup>a</sup>
Likert pain score available, <i>n</i> (%)	124 (98.4)	94 (98.9)	
Mean ± SD	0.9 ± 2.2	0.3 ± 1.3	.007 <sup>a</sup>
Primary cancer site, <i>n</i> (%)	125 (99.2)	94 (98.9)	
Colon	98 (78.4)	80 (85.1)	.208
Left side	55 (44.0)	54 (57.4)	.049 <sup>a</sup>
Right side	38 (30.4)	24 (25.5)	.429
Side unspecified	5 (4.0)	2 (2.1)	.701
Rectum	27 (1.6)	13 (13.8)	.141
Rectosigmoid	0 (0.0)	1 (1.1)	.429
Number of metastases at mCRC diagnosis, mean ± SD (median)	2.1 ± 1.1 (2.0)	2.0 ± 0.9 (2.0)	.750
Genetic mutation status, <i>n</i> (%)			
<i>KRAS</i>	90 (71.4)	61 (64.2)	.916
Mutated	48 (53.3)	32 (52.5)	
Wild type	42 (46.7)	29 (47.5)	
<i>NRAS</i>	22 (17.5)	2 (2.1)	1.000
Mutated	5 (22.7)	0 (0.0)	
Wild type	17 (77.3)	2 (100.0)	
<i>BRAF</i>	71 (56.3)	49 (51.6)	.647
Mutated	4 (5.6)	1 (2.0)	
Wild type	67 (94.4)	48 (98.0)	

<sup>a</sup>*p* value <.05.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FTD/TPI: trifluridine/tipiracil; mCRC, metastatic colorectal cancer.

the subgroup analyses of patients who initiated index therapy as only second- or third-line mCRC treatments. Specifically, patients who initiated FTD/TPI versus regorafenib had significantly greater survival rates at months 3 and 4 in the overall population and at months 2, 3, and 4 in the subgroup (Table 4). In the adjusted OS analysis controlling for gender, age, baseline Likert pain score, time from mCRC diagnosis, and index therapy after third-line of therapy in Table 5,

patients treated with FTD/TPI versus regorafenib had similar risk of death (HR, 0.80; 95% CI, 0.59–1.09). In the subgroup analyses of only second- or third-line mCRC treatments, patients treated with FTD/TPI versus regorafenib had similar risk of death (HR, 0.60; 95% CI, 0.36–1.02).

Incidences of clinical conditions observed during index treatment are presented in supplemental online Figure 2. The occurrence of nonhematological clinical conditions was

**Table 2.** Characteristics of index therapy treatment

Treatment characteristics	FTD/TPI, <i>n</i> = 126	Regorafenib, <i>n</i> = 95	<i>p</i> value
Year of treatment initiation, <i>n</i> (%)			
2012	1 (0.8)	16 (16.8)	<.001 <sup>a</sup>
2013	1 (0.8)	22 (23.2)	<.001 <sup>a</sup>
2014	0 (0.0)	27 (28.4)	<.001 <sup>a</sup>
2015	44 (34.9)	14 (14.7)	<.001 <sup>a</sup>
2016	49 (38.9)	7 (7.4)	<.001 <sup>a</sup>
2017	31 (24.6)	9 (9.5)	.004 <sup>a</sup>
Time from mCRC diagnosis to start of therapy mean ± SD (median), mo	34.0 ± 25.1 (27.8)	31.3 ± 19.4 (29.2)	.863
Follow-up time from index therapy mean ± SD (median), mo	9.2 ± 6.7 (7.1)	8.5 ± 7.6 (6.3)	.157
Treatment setting, <i>n</i> (%)			
Clinical trial	4 (3.2)	0 (0.0)	.136
Standard of care	116 (92.1)	95 (100.0)	.006 <sup>a</sup>
Compassionate use	5 (4.0)	0 (0.0)	.072
Unknown	1 (0.8)	0 (0.0)	
Line of index therapy, <i>n</i> (%)			
2nd	8 (6.3)	4 (4.2)	.487
3rd	39 (31.0)	29 (30.5)	.946
4th	36 (28.6)	22 (23.2)	.365
5th	26 (20.6)	22 (23.2)	.652
6th plus	17 (13.5)	18 (18.9)	.271
Patients with dosing information, <i>n</i> (%)	119 (94.4)	92 (96.8)	
First prescription dose, mean ± SD (median), mg/day	118.9 ± 27.3 (120.0)	142.2 ± 76.5 (160.0)	
Dosing patterns, patient level			
Dose intensity, mean ± SD (median), mg/day	117.5 ± 25.9 (120.0)	132.3 ± 66.9 (120.0)	.010 <sup>a</sup>
Label recommended dose, mean ± SD (median), mg/day	130.8 ± 20.0 (130.4)	160.0 ± 0.0 (160.0)	
Relative dose intensity, mean ± SD (median)	0.9 ± 0.2 (1.0)	0.8 ± 0.4 (0.8)	<.001 <sup>a</sup>
Patients with no dose modifications, <i>n</i> (%)	100 (84.0)	59 (64.1)	<.001 <sup>a</sup>
Dose modifications per patient, mean ± SD	0.2 ± 0.5	0.4 ± 0.6	.001 <sup>a</sup>

<sup>a</sup>*p* value <.05.

Abbreviations: FTD/TPI, trifluridine/tipiracil; mCRC, metastatic colorectal cancer.

**Table 3.** Unadjusted real-world tumor response among patients with FTD/TPI vs. regorafenib as index therapy

Unadjusted real-world tumor response	All patients			Among patients in 2L and 3L of treatment		
	FTD/TPI, <i>n</i> = 126	Regorafenib, <i>n</i> = 95	<i>p</i> value	FTD/TPI, <i>n</i> = 47	Regorafenib, <i>n</i> = 33	<i>p</i> value
Patients with physician assessed tumor response, <i>n</i> (%)	120 (95.2)	76 (80.0)		42 (89.4)	27 (81.8)	
Real-world best tumor responses						
Real-world overall response rate, <i>n</i> (%)	63 (52.5)	26 (34.2)	.012 <sup>a</sup>	23 (54.8)	7 (25.9)	.018 <sup>a</sup>
Stable disease	30 (25.0)	22 (28.9)	.542	11 (26.2)	9 (33.3)	.523
≥6 weeks after index date	14 (11.7)	9 (11.8)	.970	6 (14.3)	3 (11.1)	.999
Progressive disease	27 (22.5)	28 (36.8)	.029 <sup>a</sup>	8 (19.0)	11 (40.7)	.049 <sup>a</sup>
Real-world disease control rate, <i>n</i> (%)	77 (64.2)	35 (46.1)	.013 <sup>a</sup>	29 (69.0)	10 (37.0)	.009 <sup>a</sup>

<sup>a</sup>*p* value <.05.

Abbreviations: 2L, second line; 3L, third line; FTD/TPI, trifluridine/tipiracil.



**Table 4.** Kaplan-Meier estimates of survival among patients with FTD/TPI vs. regorafenib as index therapy

Time period after index date	Proportion of patients that survived					
	All patients			Among patients in 2L and 3L of treatment		
	FTD/TPI, <i>n</i> = 126	Regorafenib, <i>n</i> = 95	<i>p</i> value	FTD/TPI, <i>n</i> = 47	Regorafenib, <i>n</i> = 33	<i>p</i> value
1 month	98.4%	94.7%	.126	97.9%	97.0%	.808
2 months	92.0%	84.1%	.071	95.7%	78.8%	.021 <sup>a</sup>
3 months	86.2%	73.4%	.016 <sup>a</sup>	84.6%	66.7%	.045 <sup>a</sup>
4 months	79.6%	65.8%	.017 <sup>a</sup>	75.6%	54.5%	.034 <sup>a</sup>
5 months	64.2%	60.1%	.275	58.7%	51.5%	.275
6 months	58.9%	55.5%	.313	51.1%	48.5%	.420
Median OS (95% CI), mo	7.5 (6.0–8.8)	7.1 (5.0–8.2)	.312	7.7 (4.4–11.5)	5.1 (2.9–7.9)	.073

<sup>a</sup>*p* value < .05.

Abbreviations: 2L, second line; 3L, third line; CI, confidence interval; FTD/TPI, trifluridine/tipiracil; OS: overall survival.

**Table 5.** Multivariable Cox proportional hazards model for overall survival

	All patients ( <i>n</i> = 217)		Among patients in 2L and 3L of treatment ( <i>n</i> = 79)	
	Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Index therapy (ref: regorafenib)	0.80 (0.59–1.09)	.157	0.60 (0.36–1.02)	.057
Gender (ref: male)	1.43 (1.05–1.94)	.023 <sup>a</sup>	1.44 (0.86–2.41)	.169
Age at start of index therapy	1.01 (1.00–1.03)	.072	1.01 (0.99–1.03)	.457
Baseline Likert pain score	1.09 (1.01–1.18)	.027 <sup>a</sup>	1.07 (0.94–1.22)	.306
Time from mCRC diagnosis to start of therapy (months)	0.99 (0.98–1.00)	.017 <sup>a</sup>	0.99 (0.97–1.01)	.239
Index therapy after 3L of therapy (ref: ≤ 3L)	1.05 (0.75–1.46)	.780		

<sup>a</sup>*p* value < .05.

Abbreviations: 2L, second line; 3L, third line; CI, confidence interval; mCRC, metastatic colorectal cancer.

lower for patients with FTD/TPI as index therapy versus patients with regorafenib as index therapy; this was particularly true for the incidence of a hand-foot syndrome diagnosis (incidence rate ratio [IRR] 0.06; 95% CI, 0.01–0.27). The occurrence of hematological clinical conditions was higher among patients with FTD/TPI versus regorafenib as index therapy, and particularly for the incidence of a neutropenia (IRR 5.35; 95% CI, 2.01–14.21).

## DISCUSSION

In this retrospective study at a tertiary oncology center, we examined real-world treatment outcomes among patients with mCRC treated with FTD/TPI or regorafenib to supplement and contextualize clinical trial results. We found patients treated with FTD/TPI had better tumor response and disease control compared with patients who first initiated treatment with regorafenib. There was a noticeable difference between the tumor response rates previously described for FTD/TPI and regorafenib and the real-world outcomes seen in our analysis [4, 6, 8–19]. Other observational studies for FTD/TPI have reported overall response rates slightly higher than that reported in the clinical trial and variable disease control rates (DCRs). This study assessed tumor response based on information from both clinician notes as well as radiologist assessments in imaging

reports. These assessments involved individual or group interpretation of scan findings and measurements and were not necessarily bound by the RECIST used to determine tumor response in clinical trials. Furthermore, this study examined tumor response in a real-world setting where scans are not performed at regular time intervals, so assessing response at fixed time points is not possible in most real-world analyses. Therefore, best tumor response in this study was reported over the course of the patient's treatment with the index therapy, similar to other observational studies [1, 7, 8, 11, 14], rather than at fixed time points like in clinical trials [4, 6]. The DCR reported in the current study was the proportion of patients with a complete or partial response or stable disease at 6 weeks; for other observational studies, it was not clear whether the stable disease had to be measured at 6 weeks to qualify for disease control. Overall, this study's tumor response results may have limited comparability to other studies' results because of differences in underlying tumor response definitions.

There were differences between this observational study and other published studies in study eligibility criteria that could also contribute to the observed differences in tumor response. In the CORRECT trial, patients had to have been treated with standard therapies available within the country they resided; 49% of trial patients treated with

regorafenib had at least four prior lines of treatment [4]. For the RECURSE trial, patients were required to have at least two prior regimens of standard chemotherapy; 60% of FTD/TPI-treated patients in the trial had at least four prior lines of therapy [6]. The current study had no such requirements regarding prior therapy because this was a real-world study that more closely reflects clinical practice and experience. Although the proportion of patients with at least four lines of prior therapy was similar for regorafenib-treated patients (42.1%) to that in the trial [4], the proportion was lower for FTD/TPI-treated patients (34.9%) in this observational study versus that in the RECURSE trial [6]. Because regorafenib was approved in 2012 [3] and FTD/TPI was approved in 2015 [5], the current study had more patients treated with regorafenib versus FTD/TPI in earlier years (2012–2014) than later years (2015–2017). As a result, patients who were treated with regorafenib in the earlier years of the study may have had the opportunity for more lines of therapy than FTD/TPI patients and did not have the opportunity to be prescribed FTD/TPI. However, there were no significant differences in the line of therapy that the index treatment was received or type of therapy received preindex therapy (e.g., chemotherapy, biological therapy). An analysis of a compassionate use program of FTD/TPI-treated patients showed that patients who were less heavily pretreated had better efficacy than those who were fully pre-treated [20]. This could in part explain the higher response rate for FTD/TPI in the current study relative to what was reported in the RECURSE trial. In addition, a large proportion of patients in the current study had a left-sided primary colon tumor (57.4% and 44.0% of patients treated with regorafenib vs. FTD/TPI, respectively), whereas the proportion of patients with left-sided colorectal cancer in the clinical trials is unknown [4, 6]. Some studies suggest that patients with left-sided colorectal cancer may be more responsive to conventional and/or targeted treatments [21], which could help explain the differences in tumor response rates between the clinical trials and the current study, especially for patients treated with regorafenib in whom the majority had left-sided primary colon tumor. Although clinical trials are important for providing evidence on the relative efficacy and safety of treatments in controlled settings, real-world analyses are important as they report results from a wider range of patients who are treated with the therapies of interest.

Similar median OS for patients receiving FTD/TPI and those receiving regorafenib was observed (median OS, 7.5 months; 95% CI, 6.0–8.8; and 7.1 months; 95% CI, 5.0–8.2, respectively); however, patients who initiated FTD/TPI versus regorafenib had significantly greater survival rates at months 3 and 4 of follow-up. The similarity in survival between patients receiving FTD/TPI and those receiving regorafenib in this study is consistent with the findings from another retrospective study conducted in Japan [15]. The survival rates seen for FTD/TPI- and regorafenib treated patients in this study were similar to those reported in the CORRECT and RECURSE trials [4, 6], respectively. In the CORRECT trial comparing regorafenib with placebo, survival rate at 6 months for patients treated with regorafenib was 52.5% [4] (similar to

55.5% in this study's arm of patients treated with regorafenib). In the RECURSE trial comparing FTD/TPI with placebo, survival rate at 6 months for patients treated with FTD/TPI was approximately 60% [6] (similar to 58.9% in this study's arm of patients treated with FTD/TPI).

Because of similar survival for FTD/TPI- and regorafenib treated patients, clinical decision-making between these agents centers primarily on their tolerability profiles. This is particularly relevant in this population, in which either treatment may not yield a clinical benefit in half of treated patients [12]. Our current study demonstrated that hematologic clinical conditions observed during the treatment period were more common and nonhematologic clinical conditions less common among patients treated with FTD/TPI compared with those treated with regorafenib. This is a pattern consistent with their registration trials and subsequent studies [4, 6, 13]. In this study, the incidence of hand-foot syndrome was significantly higher in patients receiving regorafenib whereas neutropenia and lymphocytopenia were significantly higher in patients receiving FTD/TPI. Similarly, a retrospective study of the efficacy and safety of regorafenib and FTD/TPI found that hand-foot syndrome was more frequent in patients receiving regorafenib versus FTD/TPI [22]. A retrospective analysis of 83 patients with mCRC treated with FTD/TPI under the Expanded Access Program in the U.S. and 92 patients in Japan showed that 46.3% experienced chemotherapy-induced neutropenia at 1 month after initiating treatment [23]. Interestingly, in that analysis, patients who developed chemotherapy-induced neutropenia at 1 month had significantly longer OS [23]. The authors of that study suggested that neutropenia after treatment initiation may be an important predictive biomarker of clinical outcomes for patients treated with FTD/TPI; they also postulated that the presence or absence of neutropenia might merit changes in dosing or schedule for patients and in the development of future clinical trials [23].

These clinical conditions observed during treatment may also impair the ability to continue with the planned dose of treatment. Different dosing schedules have been studied for regorafenib as its prominent toxicities, such as hand-foot syndrome and fatigue, can significantly impact tolerability [24]. The phase II regorafenib dose-optimisation (ReDOS) study compared starting patients at 80 mg daily and escalating the dose weekly if tolerated to the standard starting dose of 160 mg daily versus starting patients at 160 mg; this study also investigated preemptive use of topical clobetasol for hand-foot syndrome [24]. No significant difference was seen in progression-free survival or OS between those patients in the dose-escalation group and the standard-dosing group [24]. A greater proportion of patients in the dose-escalation group started their third planned cycle of treatment. Based on these findings, weekly dose escalation was felt to be a viable alternative for regorafenib dosing.

In our study, patients treated with FTD/TPI had significantly fewer dose modifications per patient than those treated with regorafenib. Similarly, a significantly higher percentage of FTD/TPI patients did not require any dose modifications over the course of their treatment. Thus, the relative dose intensity was significantly higher in the FTD/TPI

group than in the regorafenib group. The median starting dose for regorafenib was 160 mg daily, suggesting that providers had not generally chosen to preemptively dose reduce regorafenib. Of note, the ReDOS trial results were presented in 2018 and published in 2019 [24], after the patients captured in our analysis had initiated their index treatment.

In the absence of clear predictive biomarkers for treatment with either FTD/TPI or regorafenib in mCRC, we identified subgroups of patients that have been studied previously. Among patients that initiated index therapy as second- or third-line therapy, patients with FTD/TPI versus regorafenib as index therapy had significantly higher rwORR and rwDCR and significantly better survival at 2, 3, and 4 months of follow-up, which suggests that early use of FTD/TPI may have clinical benefits.

There are some limitations of the current study to note. With an analysis of nonrandomized treatment groups, unmeasured confounding and potential biases (e.g., selection bias) could account for observed associations. For OS, we attempted to reduce such bias by adjusting for potential confounders. Missing data in any study may bias study results if the missingness is not completely random. No corrections for multiple comparisons were made to avoid increasing type II error for nonsignificant associations [25–27]. In addition, patients that received regorafenib versus FTD/TPI as index therapy were more likely to be treated earlier in the study, which could bias results, although there were no significant differences in follow-up time. For the evaluation of best response, approximately 5% of the FTD/TPI-treated patients and 20% of the regorafenib-treated patients did not have evaluations, which could bias results. In contrast to clinical trials with protocol-specified definitions of clinical events, assessments of progression and clinical response in retrospective studies of real-world clinical practice may not be made consistently across patients and across physicians. Furthermore, the median age of patients at index treatment initiation was 55.0 years for FTD/TPI and 57.0 years for regorafenib, so we could not thoroughly assess outcomes among patients under 50 years in whom the rate of colon cancer is growing [28]. Lastly, only one clinical center was included in this study.

## CONCLUSION

Despite these limitations, the current study used detailed clinical and treatment data to assess clinical outcomes for a population of patients with mCRC treated with FTD/TPI and regorafenib. This real-world retrospective study showed that rwORR and rwDCR rates among FTD/TPI-treated

patients were significantly higher than regorafenib treated patients based on best tumor response reported while being treated with index therapy. Patients treated with FTD/TPI versus regorafenib also had higher likelihood of tumor response and disease control in adjusted analyses. The study found that patients treated with FTD/TPI compared with patients treated with regorafenib had higher survival rates in the 6 months following index therapy and had similar adjusted OS. Analysis of clinical conditions during treatment is consistent with clinical studies.

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## DISCLOSURES

**Mei S. Duh:** Analysis Group, Inc. (E), Taiho Oncology, Inc. (RF); **Victoria E. Barghout:** Taiho Oncology, Inc. (C/A); **Lynn Huynh:** Analysis Group, Inc. (E), Taiho Oncology, Inc. (RF); **Mihran A. Yenikomshian:** Analysis Group Inc. (E), Taiho Oncology, Inc., Pfizer, Novartis, Merck, GlaxoSmithKline; **Kimmie Ng:** Seattle Genetics, BiomX, Array Biopharma (SAB), X-Biotix Therapeutics (C/A), Cancer Research UK, Colorectal Cancer Alliance, Pharmavite, Evergrande Group, Janssen, Revolution Medicines, Genentech (RF); **Charles S. Fuchs:** Agios, Amylin Pharmaceuticals, AstraZeneca, Bain Capital, CytomX Therapeutics, Daiichi-Sankyo, Eli Lilly & Co., Entrinsic Health, Evolveimmune Therapeutics, Genentech, Merck, Taiho, Unum Therapeutics (C/A), CytomX Therapeutics (SAB), CytomX, Entrinsic Health, Evolveimmune Therapeutics (OI), Amylin Pharmaceuticals, Eli Lilly & Co. (ET), Genentech, Roche (E). The other authors indicated no financial conflicts.

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