Trifluridine/Tipiracil and Regorafenib: New Weapons in the War Against Metastatic Colorectal Cancer

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Abstract: Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States. Approximately 20% of patients have metastatic disease at diagnosis, and a vast number of these patients die within 5 years. The advent of modern chemotherapeutics has improved median overall survival for these patients; nonetheless, we must keep striving for better outcomes. Trifluridine/tipiracil (TAS-102) and regorafenib are agents newly approved by the US Food and Drug Administration that show promise in the treatment of metastatic colorectal cancer. These drugs have the benefit of being formulated for oral administration and have different side effect profiles. These differences are important in the selection of the best therapy for each patient, especially if the patient is prone to a side effect that is unique to just one of the treatments. In this review, we discuss the mechanism of action, side effect profile, and clinical efficacy of trifluridine/tipiracil, and compare them with those of regorafenib. Future trials will evaluate the use of these drugs in earlier lines of therapy, alone and in combination with other agents. We now have 2 more agents in the arsenal against metastatic colorectal cancer and the future is looking brighter for patients, although we still have a long way to go.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States, and it is estimated that 49,190 people will die of this disease in 2016.[1] Roughly 20% of patients have evidence of metastatic disease at diagnosis, and only 13.1% of these patients will be alive 5 years after diagnosis.[2] However, with the advent of modern chemotherapeutics, the median overall survival (mOS) for patients with metastatic CRC (mCRC) has increased to 30 months and beyond.[3,4]

There are several first-line chemotherapy options for mCRC, which mostly include various combinations of fluoropyrimidines (leucovorin/5-fluorouracil [5-FU] or capecitabine)

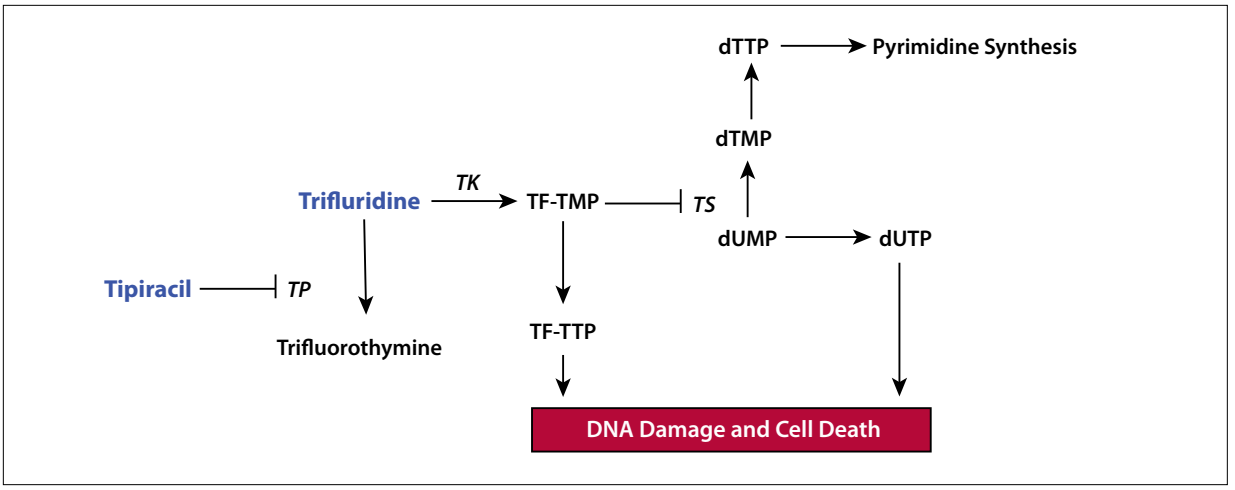

Figure. Mechanism of action of trifluridine and tipiracil.

Enzymes are italicized.

dTMP, 2'-deoxythymidine-5'-monophosphate; dTTP, 2'-deoxythymidine-5'-triphosphate; dUMP, 2'-deoxyuridine-5'-monophosphate; dUTP, 2'-deoxyuridine-5'-triphosphate; TF-TMP, trifluorothymidine monophosphate; TF-TTP, trifluorothymidine triphosphate; TK, thymidine kinase; TP, thymidine phosphorylase; TS, thymidylate synthase.

Adapted from Temmink OH et al. *Mol Cancer Ther.* 2010;9(4):1047-1057.[65]

with oxaliplatin and irinotecan (eg, leucovorin/5-FU/oxaliplatin [FOLFOX], leucovorin/5-FU/irinotecan [FOLFIRI], and leucovorin/5-FU/oxaliplatin/irinotecan [FOLFOXIRI]).[3,5-7] These regimens are frequently administered with biologic agents, such as the anti–vascular endothelial growth factor A (VEGF-A) monoclonal antibody bevacizumab (Avastin, Genentech) or the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab (Erbitux, Lilly) and panitumumab (Vectibix, Amgen), both of which are exclusively for patients with *RAS*–wild-type tumors.[8-10] Second-line treatment frequently consists of sequencing drugs that have not been used during frontline therapy, as well as other antiangiogenic agents, such as ziv-aflibercept (Zaltrap, Sanofi/Regeneron) and ramucirumab (Cyramza, Lilly), in combination with cytotoxic treatments.[11,12] Owing to the success of these numerous options, there is a growing population of patients with refractory mCRC who are candidates for further treatment. Thus, the need for efficacious—and ideally, less toxic—treatment options is increasing. Furthermore, some patients who maintain an adequate performance status will need to pursue even further lines of chemotherapy, and thus there is again a need for effective treatments with novel mechanisms of action.

Two newer agents—trifluridine/tipiracil (TAS-102; Lonsurf, Taiho Oncology) and regorafenib (Stivarga, Bayer)—are helping to fill these voids. The benefits of these drugs include their formulation for oral administration, their proven survival efficacy in the refractory setting, and side effect profiles that are distinct from each other and from other established therapies. In this review, we discuss the mechanism of action and clinical efficacy of trifluridine/tipiracil and compare them with those of regorafenib. In addition, we review ongoing clinical trials of trifluridine/tipiracil and regorafenib.

Pharmacology

TAS-102 is composed of trifluridine and tipiracil, 2 agents with very different but complementary activities. Trifluridine (5-trifluoro-2'-deoxythymidine) is a thymidine analogue that was initially synthesized by Heidelberger and colleagues more than 50 years ago.[13] This agent is phosphorylated to its monophosphate form, trifluridine monophosphate (TF-TMP), by thymidine kinase. TF-TMP in turn inhibits thymidylate synthase (TS), preventing the methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) to 2'-deoxythymidine-5'-monophosphate (dTMP), and interrupting pyrimidine synthesis (Figure).[14-17] Trifluridine monophosphate in cells is further enzymatically phosphorylated to the triphosphate form, trifluridine triphosphate (TF-TTP), which is also directly incorporated into DNA, causing strand breaks and cell death.[18,19] dUMP is phosphorylated to its triphosphate form (dUTP), and uracil is incorporated into DNA, leading to further DNA damage and cell death.[20,21]

Trifluridine monotherapy was moderately effective in phase 1 and 2 clinical trials (tumor shrinkage in 8 out of 23 breast cancers and 1 out of 6 colon cancers), but it had an unacceptable side effect profile.[22] Moreover, its pharmacokinetic profile and short plasma half-life

(<20 minutes) rendered trifluridine ill-suited for antitumor therapy.[23] These unfavorable characteristics led to the discontinuation of clinical trials of trifluridine monotherapy. A few years later, in 1980, the US Food and Drug Administration (FDA) approved trifluridine as an antiviral agent for use in keratoconjunctivitis and epithelial keratitis caused by herpes simplex virus (HSV) infections.[24,25]

Tipiracil (5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]-1H-pyrimidine-2,4-dione) inhibits thymidine phosphorylase (TP), the enzyme that degrades trifluridine into trifluorothymidine,[26] and this process increases the bioavailability of trifluridine. Trifluridine and tipiracil coadministration is necessary in order to maintain sufficient plasma concentrations of trifluridine when administered orally at a reasonable dose and schedule.[27] TP is also a known platelet-derived endothelial cell growth factor (PD-ECGF) and has angiogenic properties.[28-30] Thus, by inhibiting TP, tipiracil may have indirect antiangiogenic properties independent of its synergism with trifluridine.[26]

The combination of trifluridine and tipiracil was shown to be effective regardless of tumor sensitivity to fluoropyrimidines (eg, 5-FU and capecitabine).[31-34] This finding could be due to different mechanisms of action: 5-FU exerts its cytotoxic effect via inhibition of TS without being directly incorporated into DNA, whereas trifluridine is phosphorylated to form TF-TMP and TF-TTP and TF-TTP is incorporated into DNA, causing single- and double-stranded DNA breaks and DNA instability.[26,31,36] TF-TMP inhibits TS by binding directly to its active site at tyrosine 146.[16,17,35] Unlike 5-FU, trifluridine is also resistant to degradation by DNA glycosylase.[37] In preclinical models, trifluridine demonstrated activity against both 5-FU–sensitive and 5-FU–resistant cell lines.[32] Therefore, trifluridine and tipiracil are well suited for use in patients with mCRC that is refractory to standard 5-FU–based therapy.

Clinical Trials

Doi and colleagues[38] performed a phase 1 study of trifluridine/tipiracil in 21 Japanese patients with solid tumors that were refractory to standard chemotherapy (18 of the patients had CRC). Patients received trifluridine/tipiracil twice daily on days 1 to 5 and 8 to 12 of a 28-day cycle. Two patients had dose-limiting toxicities (DLTs) during the first cycle; one had grade 4 neutropenia, leukopenia, and thrombocytopenia at the 15 mg/m^2 twice-daily dose level, and the other had grade 4 neutropenia and leukopenia at the 35 mg/m^2 twice-daily dose level. Owing to increased rates of grade 3 or 4 neutropenia, the dose was not increased to more than 35 mg/m^2 twice daily, which became the recommended phase 2 dose. No patients had a complete response (CR) or partial response (PR), but 52.3% of patients had stable disease (SD). Median progression-free survival (mPFS) was 2.6 months, and mOS was 10.2 months. Taking only patients with mCRC into account, mPFS and mOS were 2.4 and 9.8 months, respectively.

Trifluridine/tipiracil was then evaluated in a phase 2 Japanese trial reported by Yoshino and colleagues[39] that demonstrated efficacy in patients with refractory mCRC. This double-blind study randomly assigned 172 patients with mCRC at a ratio of 2:1 to receive trifluridine/tipiracil (35 mg/m^2 twice daily by mouth on days 1 to 5 and 8 to 12 out of a 28-day cycle) or placebo. Patients were required to have had 2 or more lines of therapy and be refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin therapy. Median OS was significantly longer in the trifluridine/tipiracil arm (9.0 vs 6.6 months, hazard ratio (HR) for death, 0.56; 95% CI, 0.39-0.81; *P*=.0011), as was mPFS (2.7 vs 1.0 months; HR, 0.35; 95% CI, 0.25-0.50; *P*<.0001). As expected, treatment benefit with trifluridine/tipiracil was seen regardless of *KRAS* mutational status. However, patients with *KRAS* mutations had a longer mOS (mutant *KRAS*, 13.0 months with trifluridine/tipiracil vs 6.9 months with placebo [*P*=.0056]; wild-type *KRAS*, 7.2 months with trifluridine/tipiracil vs 7.0 months with placebo [*P*=.191]), although such a difference may have been due to the small sample size and incomplete assessment of *KRAS* status (12% of patients were not assessed). Grade 3/4 hematologic toxicities were common with trifluridine/tipiracil: neutropenia (50%), leukopenia (28%), anemia (17%), lymphopenia (10%), and thrombocytopenia (4%). Febrile neutropenia was relatively rare (4%). Nonhematologic grade 3/4 adverse events were uncommon: fatigue (6%), diarrhea (6%), nausea (4%), and vomiting (4%).

Because these studies were performed in a Japanese patient population, likely representing a distinct genotypic/phenotypic effect, a phase 1 study published by Bendell and colleagues[40] evaluated the safety, dose, and schedule of trifluridine/tipiracil in a Western population. Twenty-seven patients from 4 US centers received trifluridine/tipiracil using a 3+3 dose-escalation design, which adopted the same dosing schedule as that used in the prior Japanese trials. Ultimately, 3 patients received 30 mg/m^2 twice daily and 24 patients received 35 mg/m^2 twice daily (15 of these patients were part of an expansion cohort). No patient experienced a DLT at the first dose level and only 1 patient had a DLT at the second dose level (grade 3 febrile neutropenia). Although no patient in this study experienced a CR or PR, 17 patients did have SD for at least 6 weeks. Median PFS was 4.1 months (95% CI, 2.0-7.9) and mOS was 8.9 months (95% CI, 4.9-14.4). Neutropenia remained the most common toxicity, seen in

Table 1. Adverse Events Reported in the RECOURSE and CORRECT Trials

Adverse Events[a]	All Grades, Regorafenib, %	Grade 3/4, Regorafenib, %	All Grades, Trifluridine/ Tipiracil, %	Grade 3/4, Trifluridine/ Tipiracil, %
Any event	100	78	98	69
Hand-foot skin reaction	47	17	2	0
Rash	29	6	NR	NR
Fatigue	63	15	35	4
Hypertension	30	8	NR	NR
Diarrhea	43	8	32	3
Nausea	22	<1	48	2
Vomiting	8	1	28	2
Anorexia	47	5	NR	NR
Abdominal pain	24	5	21	2
Stomatitis	29	3	8	<1
Voice changes	32	0	NR	NR
Fever	28	2	19	1
Febrile neutropenia	NR	NR	4	4
Neutropenia	NR	NR	67	38
Leukopenia	NR	NR	77	21
Anemia	14	6	77	18
Thrombocytopenia	16	4	42	5
ALT increase	45	5	24	2
AST increase	65	6	30	4
TB increase	45	12	36	9
ALP increase	NR	NR	39	8

[a]Adverse events occurring in at least 5% of patients treated with regorafenib and at least 10% of patients treated with trifluridine/tipiracil.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CORRECT, Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer; NR, not recorded; RECOURSE, Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies; TB, total bilirubin.

Data from Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919[41,54] and Grothey A et al. *Lancet.* 2013;381(9863):303-312.[41,54]

78% of all patients, with grade 3/4 neutropenia seen in 70%. The recommended phase 2 dose was thus 35 mg/m^2 twice daily in both Japanese and Western populations.

These results were confirmed in the recently published international, double-blind, phase 3 RECOURSE trial (Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies), which again showed an OS benefit with trifluridine/tipiracil compared with placebo. Mayer and colleagues[41] randomly assigned 800 patients with refractory mCRC at a ratio of 2:1 to receive trifluridine/tipiracil or placebo. Patients were required to have had at least 2 prior regimens of standard chemotherapy and either tumor progression within 3 months of the last administration of chemotherapy or clinically significant adverse events from standard chemotherapy that prohibited the readministration of those therapies (ie, intolerance to fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab). If patients had *KRAS*–wild-type tumors, they must have also received either cetuximab or panitumumab.

Patients were stratified by *KRAS* mutational status, time from metastatic disease diagnosis to randomization (<18 months or ≥18 months), and geographic area (Japan, United States, Europe, or Australia). Median OS was 7.1 months in the trifluridine/tipiracil arm and 5.3 months in the placebo arm (HR, 0.68; 95% CI, 0.58-0.81; *P*<.001; mPFS was 2.0 and 1.7 months, respectively (HR, 0.48; 95% CI, 0.41-0.57; *P*<.001). Survival benefits with trifluridine/tipiracil were seen across all subgroups. Although the Japanese phase 2 study reported above showed increased survival for patients with *KRAS*-mutant tumors treated with trifluridine/tipiracil, mutational status did not play a significant role in survival outcomes when analyzed in this larger phase 3 study. The disease control rate (complete or partial response plus SD) was 44% with trifluridine/tipiracil compared with 16%

following placebo treatment (P<.001). It is noteworthy that 57% of patients had disease that had been refractory to fluoropyrimidine, which was administered as part of their last treatment regimen prior to study entry. Adverse events with trifluridine/tipiracil (Table 1) were similar to those seen in previous studies: grade 3/4 hematologic events included neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (5%), and febrile neutropenia (4%), and significant nonhematologic adverse events were uncommon.

During patient accrual into the RECOURSE study, regorafenib became available for the management of patients with previously treated colorectal cancer. Seventeen percent of the patients in the trifluridine/tipiracil group and 20% of those in the placebo group had received regorafenib prior to study enrollment. The clinical benefit associated with trifluridine/tipiracil was maintained regardless of prior treatment with regorafenib.[41]

The RECOURSE trial led to the FDA approval of trifluridine/tipiracil on September 22, 2015, for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic product, and—if *RAS*–wild-type—an anti-EGFR monoclonal antibody.[42] An updated survival analysis presented at the 2016 Gastrointestinal Cancers Symposium confirmed the OS benefit of trifluridine/tipiracil compared with placebo (mOS, 7.2 vs 5.2 months; HR, 0.69; 95% CI, 0.59-0.81; P<.0001). In addition, 1-year survival was significantly higher with trifluridine than with placebo (27.1% vs 16.6%).[43]

Alternative dosing schedules for trifluridine/tipiracil should be further investigated given the high incidence of grade 3/4 neutropenia (38% in the RECOURSE trial).[41] Phase 1 studies have examined once-daily administration of trifluridine/tipiracil on days 1 to 5 of a 3-week cycle, as well as divided dosing once, twice, or 3 times daily.[38,40,44-47] Although 35 mg/m^2 twice daily on days 1 to 5 and 8 to 12 of a 28-day cycle is the approved dose, and the RECOURSE protocol allowed 3 dose reductions in decrements of 5 mg/m^2, 53% of patients who received trifluridine/tipiracil on the trial still had to delay their second cycle by at least 4 days.[41] This finding indicates that for more than half of the patients treated, the bone marrow recovery period (days 13-27) was too short. Therefore, future studies should evaluate other dosing schedules to minimize treatment delays and dose de-escalations.

Trifluridine/tipiracil is supposed to be taken within 1 hour of completion of morning and evening meals, according to its package insert.[48] A pharmacokinetic study by Yoshino and colleagues[49] showed that the trifluridine C_{max}, and the tipiracil C_{max} and area under the curve (AUC), decreased by approximately 40% after a standard high-fat, high-calorie meal. The trifluridine AUC, however, was not decreased in the fed compared with the fasting state. Thus, because trifluridine is the clinically active agent, the efficacy of trifluridine/tipiracil should not be affected by food. According to the phase 1 study by Doi and colleagues,[38] trifluridine C_{max} correlated with neutropenia, so administering trifluridine/tipiracil in the postprandial state is recommended to lower trifluridine C_{max} and decrease the risk of neutropenia, without affecting the efficacy of TAS-102.

Regorafenib

Trifluridine/tipiracil is frequently compared with regorafenib, an oral multitargeted tyrosine kinase inhibitor. Both agents emerged on the market at a similar time and are indicated in the same line of therapy. Additionally, they have both been FDA-approved for mCRC refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if *RAS*–wild-type).[50] Although the actual target of regorafenib is unclear, this drug (with its active metabolites, M-2 and M-5) was shown to inhibit multiple potential sites of tumorigenesis, including KIT, RET, RAF1, BRAF, VEGF receptors 1 to 3, TIE2, DDR2, Trk2A, Eph2A, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), and demonstrated clinical activity in preclinical xenograft models of CRC.[50,51] A phase 1b study of regorafenib in 38 patients with refractory mCRC demonstrated a disease control rate of 74%.[52] Based on this trial, the recommended dose and schedule on the package insert is 160 mg/day for the first 21 days of a 28-day cycle, with 7 days off treatment at the end of every cycle, although many prescribers favor starting at lower doses and escalating doses based on tolerability (see discussion below).[53] The most common grade 3/4 adverse events seen in this trial were hand-foot skin reaction (32%), fatigue (11%), hypertension (11%), and desquamating rash (5%).

The phase 3 CORRECT trial (Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer) enrolled 760 eligible patients with mCRC and randomly assigned them at a ratio of 2:1 to receive regorafenib (160 mg daily for the first 21 days of a 28-day cycle) or placebo.[54] Patients were eligible if they were 18 years of age or older; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; had adequate bone marrow, liver, and renal function; and were refractory to standard therapy (all licensed treatments for mCRC, according to the patient's country of origin). Patients were stratified by prior treatment with anti-VEGF drugs, time since diagnosis of metastatic disease (≥18 months or <18 months), and geographic region. The primary endpoint was mOS, which was significantly longer in the regorafenib arm than in the placebo arm (6.4 vs 5.0 months; HR, 0.77; 95% CI, 0.64-0.94; P=.0052; Table 2). Median PFS also was statistically longer with regorafenib (1.9 vs 1.7 months; HR, 0.49; 95% CI, 0.42-

Table 2. Efficacy of Regorafenib and Trifluridine/Tipiracil

	Regorafenib	Placebo	*P* Value	Trifluridine/Tipiracil	Placebo	*P* Value
mOS	6.4 mo	5.0 mo	.0052	7.1 mo	5.3 mo	<.001
mPFS	1.9 mo	1.7 mo	<.0001	2.0 mo	1.7 mo	<.001
DCR	41%	15%	<.0001	44%	16%	<.001

DCR, disease control rate; mo, months; mOS, median overall survival; mPFS, median progression-free survival.

Data from Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919[41] and Grothey A et al. *Lancet.* 2013;381(9863):303-312.[54]

0.58; *P*<.0001). The disease control rate was 41% following regorafenib, compared with 15% following placebo treatment (*P*<.0001). Efficacy of regorafenib over placebo was seen across all subgroups except patients with existing primary disease in the colon and rectum (a relatively small group of only 44 patients). Common grade 3/4 adverse events in the regorafenib arm (Table 1) included hand-foot skin reaction (17%), fatigue (15%), hypertension (8%), diarrhea (8%), and rash (6%). Grade 3/4 liver test abnormalities were also reported in the regorafenib arm (elevations in alanine aminotransferase [5%], aspartate transaminase [6%], and bilirubin [12%]), and 1 fatal case of drug-induced liver injury was observed. The small phase 3 CONCUR trial (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) involved 204 Asian patients and confirmed a survival benefit of regorafenib over placebo in that population as well (mOS, 8.8 vs 6.3 months; HR, 0.55; 95% CI, 0.40-0.77; *P*=.00016).[55]

Dose reductions and delays of regorafenib should be managed based on protocol-specific dose modifications.[52,56,57] Dose de-escalation levels are 120 mg/day (dose level -1) and 80 mg/day (dose level -2). As an example, for the hand-foot skin reaction, the medication should be held until grade 1 or better is reached, according to the Common Terminology Criteria for Adverse Events (CTCAE). For a more severe reaction (grade 3), dosing should be held for at least 7 days, until grade 1 or better is achieved. Dose re-escalation is then often permitted, at the physician's discretion, of up to 160 mg/day.[57] Future studies should look at alternative treatment schedules (eg, 120 mg or perhaps 80 mg as a starting dose), which are already frequently used in clinical practice.[53]

A food-effect study enrolled 24 healthy men who received a single 160-mg dose of regorafenib on 3 separate occasions: when in a fasting state, with a high-fat meal, and with a low-fat meal.[50] Compared with the fasting state, a high-fat meal increased the mean AUC of regorafenib by 48% and decreased the mean AUC of its active M-2 and M-5 metabolites by 20% and 51%, respectively, whereas a low-fat meal increased the mean AUC of regorafenib, M-2, and M-5 by 36%, 40%, and 23%, respectively. It is thus recommended that regorafenib be taken once daily with food (a low-fat breakfast of less than 600 calories and less than 30% fat, according to the drug's package insert).[50]

Obviously, neither trifluridine/tipiracil nor regorafenib would be entirely suitable for patients unable to swallow and/or digest pills (eg, patients dependent on total parenteral nutrition owing to gastrointestinal obstruction or malabsorption).

How to Sequence Regorafenib and Trifluridine/Tipiracil

Trifluridine/tipiracil and regorafenib are now approved for the treatment of refractory mCRC; therefore, oncologists have to decide which agent to use first and how to sequence their choice with other drugs. Although both agents have an OS benefit, we often fail to incorporate them into treatment in favor of recycling prior lines of chemotherapy or other unproven approaches. Patient selection is vital because patients with good performance status, low tumor burden, and slower disease progression are likely to derive the most benefit from these drugs, whereas patients with poor performance status and rapidly progressive disease are less likely to benefit. Objective tumor response (CR or PR) is rarely observed with either drug: 1.6% with trifluridine/tipiracil in the RECOURSE trial, and 1.0% with regorafenib in the CORRECT trial.[41,54]

Regorafenib and trifluridine/tipiracil are similar in that they are novel oral drugs for use in refractory mCRC, with demonstrated efficacy when compared with placebo. However, their side effect profiles are markedly different. Regorafenib has high rates of hand-foot skin reaction, rash, hypertension, and fatigue, whereas trifluridine/tipiracil has high rates of hematologic events, notably neutropenia and leukopenia.

Consideration of these differences is important when selecting the best therapy for an individual patient, especially if that patient's tumor has recently progressed after cytotoxic chemotherapy and the patient has poor bone marrow function at baseline, has had severe hand-foot syndrome with prior capecitabine, or has severe fatigue. Head-to-head comparisons of the 2 drugs in terms of efficacy or safety have not been performed, and such studies are unlikely to occur

Table 3. Ongoing Clinical Trials of Regorafenib and Trifluridine/Tipiracil in Metastatic Colorectal Cancer

Title	Trial Identifier
Multi-Center, Randomized, Placebo-Controlled Phase II Study of Regorafenib in Combination With FOLFIRI Versus Placebo With FOLFIRI as Second-Line Therapy in Patients With Metastatic Colorectal Cancer	NCT01298570
A Two Arm Safety Study of Regorafenib Before or After SIR-Spheres® Microspheres (90Y) for the Treatment of Patients With Refractory Metastatic Colorectal Cancer With Liver Metastases	NCT02195011
Regorafenib Dose Optimization Study (ReDOS): A Phase II Randomized Study of Lower Dose Regorafenib Compared to Standard Dose Regorafenib in Patients With Refractory Metastatic Colorectal Cancer (mCRC)	NCT02368886
Phase Ib Study of the Combination Regorafenib With PF-03446962 in Patients With Refractory Metastatic Colorectal Cancer (REGAL-1 Trial)	NCT02116894
Combination Study of Panitumumab and Regorafenib in Advanced or Metastatic KRAS and NRAS Wild Type Colorectal Cancers	NCT02199223
Regorafenib in Metastatic Colorectal Cancer: An Exploratory Biomarker Study	NCT02402036
A Phase II Single-Arm Study of Regorafenib Maintenance Therapy in Patients With T3, T4 or Node-Positive Rectal Cancer Patients Who Completed Curative-Intent Treatment	NCT02287727
Phase II Study of Regorafenib in Good Performance Status Patients With Newly Diagnosed Metastatic Colorectal Adenocarcinoma	NCT02023333
A Randomized, Double-Blind Study of Ruxolitinib or Placebo in Combination With Regorafenib in Subjects With Relapsed or Refractory Metastatic Colorectal Cancer	NCT02119676
Identification of Predictive Biomarker of Regorafenib in Refractory Colorectal Cancer: A Prospective Explorative Study	NCT01996969
REBECCA: A Cohort Study of Regorafenib in the Real-Life Setting in Patients Previously Treated for Metastatic Colorectal Cancer	NCT02310477
An Open-Label Phase III Study of Regorafenib in Patients With Metastatic Colorectal Cancer (mCRC) Who Have Progressed After Standard Therapy (REGARD)	NCT01853319
An Uncontrolled, Open-Label Phase IIb Trial of Regorafenib in Subjects With Antiangiogenic-Naive and Chemotherapy-Refractory Advanced Colorectal Cancer	NCT02465502
Phase II Study of Regorafenib as Single Agent for the Treatment of Patients With Metastatic Colorectal Cancer (mCRC) With Any RAS or BRAF Mutation Previously Treated With FOLFOXIRI Plus Bevacizumab (PREVIUM)	NCT02175654
A Phase II Study of Single-Agent Regorafenib in the First Line Treatment of Frail and/or Unfit for Polychemotherapy Patients With Metastatic Colorectal Cancer (mCRC) (REFRAME)	NCT01875380
A Phase II Exploratory Study to Identify Biomarkers Predictive of Clinical Response to Regorafenib in Patients With Metastatic Colorectal Cancer Who Have Failed First-Line Therapy	NCT01949194
Regorafenib Monotherapy as Second-Line Treatment of Patients With RAS-Mutant Advanced Colorectal Cancer: a Multicentre, Single-Arm, Two-Stage, Phase 2 Study (STREAM)	NCT02619435
RECORA- Regorafenib in Patients With Metastatic Colorectal Cancer (mCRC) After Failure of Standard Therapy	NCT01959269
Phase I Study of TAS-102 and Radioembolization With 90Y Resin Microspheres for Chemo-Refractory Colorectal Liver Metastases	NCT02602327
A Phase I/II Study for the Safety and Efficacy of Panitumumab in Combination With TAS-102 for Patients With RAS Wild-Type Metastatic Colorectal Cancer Refractory to Standard Chemotherapy (APOLLON)	NCT02613221
An Open-Label, Multi-Center, Phase 2 Study of Switch Maintenance With TAS-102 Plus Bevacizumab Following Oxaliplatin or Irinotecan-Based Fluoropyrimidine-Containing Induction Chemotherapy in Patients With Metastatic Colorectal Cancer (ALEXANDRIA)	NCT02654639
Randomized, Double-Blind, Phase III Study of TAS-102 Versus Placebo in Asian Patients With Metastatic Colorectal Cancer Refractory or Intolerable to Standard Chemotherapies (TERRA)	NCT01955837
A Phase I Study of SGI-110 Combined With Irinotecan Followed by Randomized Phase II Study of SGI-110 Combined With Irinotecan Versus Regorafenib or TAS-102 in Previously Treated Metastatic Colorectal Cancer Patients	NCT01896856
A Multicenter Phase 1/2 Trial of TAS-102 With Bevacizumab for Metastatic Colorectal Cancer Refractory to Standard Therapies (C-TASK FORCE)	UMIN000012883 (completed, awaiting data)
Multicenter Phase 1b/2 Trial of Nintedanib With TAS-102 in Patients With Metastatic Colorectal Cancer (mCRC) Who Had Progression on or Were Intolerant to Standard Therapies (N-TASK FORCE)	UMIN000017114
Randomized Phase II Study of Regorafenib Followed by Cetuximab versus Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidine, Oxaliplatin, and Irinotecan (REVERECE)	UMIN000011294
A Phase I/II Study for the Safety and Efficacy of Panitumumab in Combination With TAS-102 for Patients With Wild-Type Metastatic Colorectal Cancer Refractory to Standard Chemotherapy (APOLLON)	UMIN000019876

in the future. If regorafenib and trifluridine/tipiracil are to be administered in sequence, data are yet to be provided regarding the order of administration (trifluridine/tipiracil followed by regorafenib or vice versa).

Predicting the efficacy of regorafenib or trifluridine/tipiracil is fraught with difficulty. Over time, biomarkers such as *KRAS* and *BRAF* mutations have helped guide therapeutic selection in mCRC, changing the treatment paradigm from a one-size-fits-all strategy to a tailor-made approach.[58] Ideally, novel predictive biomarkers will enable clinicians to make an informed decision regarding how to sequence regorafenib and trifluridine/tipiracil. Our institution has an ongoing biomarker discovery study in which we obtain tumor biopsies and peripheral blood samples at baseline and 2 weeks after starting regorafenib in order to carry out phosphoprotein, microRNA, and DNA mutational analyses (NCT02402036).[59]

It is worth noting that Kaplan-Meier curves drawn from data gathered in both the CORRECT and CONCUR studies suggest that different subgroups of patients might have differential responses to regorafenib treatment. In fact, a retrospective analysis using circulating tumor cell and tumor tissue DNA from patients treated with regorafenib in the CORRECT trial sought to identify biomarker subgroups that would clinically benefit from the drug. Patients treated with regorafenib appeared to benefit regardless of *KRAS* or *PIK3CA* mutation status, and regorafenib may further increase OS in patients with high serum concentrations of TIE1 (an angiopoietin receptor implicated in angiogenesis).[60] Other ongoing efforts are underway to identify patient subgroups through the identification and validation of biomarkers, and to refine the selection of patients likely to obtain benefit from regorafenib.[59] Additionally, given the activity of these agents in the refractory setting and their lack of overlapping toxicity, future studies may focus on the treatment of patients with refractory mCRC using trifluridine/tipiracil plus regorafenib combination therapy.

Furthermore, the favorable toxicity profile of trifluridine/tipiracil makes it an ideal partner for combination with other cytotoxic drugs (such as irinotecan[61,62] and oxaliplatin[63]) and targeted agents (such as bevacizumab[64]). Indeed, a number of such trials are ongoing, and the evaluation of trifluridine/tipiracil in earlier lines of therapy, conceivably in the maintenance (NCT02654639) or second-line settings, is forthcoming. Numerous other studies of trifluridine/tipiracil and regorafenib are listed in Table 3.

Conclusion

Trifluridine/tipiracil and regorafenib are 2 novel, FDA-approved agents that show promise in the treatment of refractory mCRC. Their use in earlier lines of therapy should certainly be investigated. We now have 2 more agents in the arsenal against mCRC, and the future is looking brighter for patients, although we still have a long way to go. Different treatment sequences and combinations should be researched, especially in clinical trials involving the use of precision medicine and other new therapies, such as immunotherapy.

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Dr Weinberg has no relevant disclosures. Drs Marshall and Salem both do consulting and research for Taiho and Bayer.

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