Curr Colorectal Cancer Rep (2017) 13:325–333
DOI 10.1007/s11888-017-0381-6

Treatment of Refractory Colorectal Cancer: Regorafenib vs. TAS-102

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Published online: 14 June 2017

Abstract
Purpose of Review This paper reviews the development, mechanism of action, clinical efficacy, and safety of regorafenib and TAS-102. Through this review, we aimed to help clinicians make an appropriate choice in patients who progressed after standard therapies.
Recent Findings Regorafenib and TAS-102 have shown superior survival results compared with placebo in refractory metastatic colorectal cancer (mCRC). In the phase III CORRECT study, regorafenib showed significant improvement in overall survival (OS) and progression-free survival (PFS). TAS-102 was associated with OS and PFS benefit as well in the phase III RECOURSE study. However, the toxicity profiles were quite different between the two agents.
Summary Regorafenib and TAS-102 are approved for the management of refractory mCRC. Optimal treatment sequence for using these two novel agents is not defined yet. Safety profiles and patient's condition should be considered before using these two agents in clinical settings. Further investigation is needed to identify the predictive biomarkers of both agents. These results will allow patients to benefit more from regorafenib and TAS-102.

Keywords Refractory colorectal cancer · Oral chemotherapy · Regorafenib · TAS-102 · Treatment selection · Biomarker

This article is part of the Topical Collection on *Systemic Therapies in Colorectal Cancer*

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Introduction

Colorectal cancer (CRC) is one of the most important public health issues and represents a major cause of cancer-related deaths worldwide [1–3]. Each year, nearly 1.36 million patients are diagnosed with CRC and almost 700,000 patients die from CRC [2]. Surgery is the curative treatment option for patients with resectable non-metastatic CRC; however, despite this curative surgery, approximately half of the patients eventually develop metastasis [2]. In patients with metastatic CRC, palliative chemotherapy remains as the current standard of care [4, 5].

The backbone of currently recommended chemotherapy is a combination of cytotoxic doublet using fluoropyrimidine with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) [4, 5]. After the development of biologic agents that target vascular endothelial growth factor (VEGF; bevacizumab, aflibercept, and ramucirumab) and epithelial growth factor receptor (EGFR; cetuximab or panitumumab), survival of patients with metastatic CRC has markedly improved up to 30 months [6–12]. Although some patients maintain good performance status after progression to above standard therapies, little option had been available for patients with resistance to standard treatment.

Fortunately, recent large phase III studies have demonstrated the efficacy of two novel agents (regorafenib and TAS-102) in patients with metastatic colorectal cancer (mCRC) who failed or were intolerant to standard treatment [13••, 14••]. Regorafenib and TAS-102 have shown superior survival data compared with placebo. Both drugs are oral agents, which is preferred by a large number of patients due to convenience [15, 16].

There is a lack of data that directly compares regorafenib with TAS-102 in terms of efficacy and safety. Moreover, it is not yet clear as to which drug is more effective among

different patient groups. In this review, we will examine the clinical efficacy and safety of the two novel drugs and provide some new determinants that could assist for proper patient selection.

Regorafenib

Regorafenib (Stivarga, Bayer) is an oral multitargeted tyrosine kinase inhibitor. Its chemical name is 4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate.

Preclinical Study

In vitro biochemical assays or cellular assays have shown that regorafenib potently inhibits vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), platelet-derived growth factor receptor (PDGFR)-ß, fibroblast growth factor receptor (FGFR)1, KIT, RET, RAF-1, and BRAF [17]. In a human colorectal xenograft model, regorafenib showed a significant tumor reduction [17]. In another preclinical study using patient-derived CRC models, regorafenib alone and in combination with irinotecan showed significant tumor growth inhibition and delayed time to tumor growth [18].

Phase I Studies

Mross et al. performed a first-in-human, phase I dose-escalation study that evaluated the safety, pharmacokinetic, pharmacodynamic, and efficacy profiles of regorafenib in patients with advanced solid tumors [19]. In this phase I study, 53 patients with advanced solid tumors refractory to standard treatment were enrolled into eight cohorts at dose levels from 10 to 220 mg daily. Five patients had dose-limiting toxicities (DLTs) in cycle 1 at the 220 mg dose level and two patients had DLTs at 160 mg. The recommended regorafenib dose was determined to be 160 mg once daily, given in cycles of 21 days on, 7 days off. The most common grade 3/4 adverse events (AEs) were hand-foot skin reaction (19%), hypertension (11%), diarrhea (8%), and rash/desquamation (6%).

Based on efficacy and safety data from dose-escalation study, 160-mg dose was investigated in the expanded cohort who had mCRC of same phase I study [20]. Thirty-eight patients (dose-escalation 15, extension 23) were enrolled in this study, and 27 patients were evaluated for tumor response. No patients had complete response (CR), one patient (4%) had a partial response (PR), and 19 patients (70%) had stable disease (SD). Median progression-free survival (PFS) was 107 days (95% CI, 66–161), and 13 patients had PFS of >100 days at the time of data cutoff. Another phase I study confirmed feasibility of 160 mg once daily in 15 Japanese patients and showed similar result to European study in terms of pharmacokinetics and safety profiles [21].

Phase III Studies

Based on the previous results, the CORRECT trial was conducted to evaluate the efficacy and safety of regorafenib in patients with mCRC that were refractory or intolerant to approved standard treatment [13••]. It was an international, randomized, placebo-controlled, phase III trial that enrolled 760 patients who were randomly assigned in a 2:1 ratio to either regorafenib (160 mg once daily, for the first 3 weeks of each 4-week cycle) or placebo. All patients received the best supportive care possible, and cross-over was not allowed during the study period. Patients were stratified according to previous *VEGF*-targeting treatments, time from diagnosis of metastatic disease, and geographic area. All patients in the CORRECT trial were previously heavily treated, having received prior treatment with fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab. Patients who had *KRAS* wild-type tumors were also treated with anti-*EGFR* therapies (cetuximab or panitumumab). All patients showed Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and almost half of the patients received four or more previous systemic chemotherapy. The primary endpoint was OS, which was significantly improved in regorafenib group compared to placebo group (median OS, 6.4 vs. 5.0 months; hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.64–0.94; $p = 0.0052$; Table 1). OS benefit was noted in most subgroups, and median PFS was also statistically longer in the regorafenib arm (1.9 vs. 1.7 months, HR 0.49; 95% CI 0.42–0.58; $p < 0.0001$). Objective response rate (ORR) was 1.0% vs. 0.4% ($p = 0.19$), and disease control rate (DCR; PR plus SD assessed at least 6 weeks after randomization) was 41 vs. 15% ($p < 0.0001$) with regorafenib versus placebo, respectively.

Based on the result of CORRECT trial, the US Food and Drug Administration (FDA) approved regorafenib on September 27, 2012 for treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-*VEGF* therapy, and, in cases of *KRAS* wild type, an anti-*EGFR* therapy [24].

In the CORRECT trial, 15% of the patients were Asian—of those, most of them were Japanese [13••]. Due to the unbalance in the study population, another study was conducted to evaluate regorafenib in a broader population of Asian patients with mCRC (CONCUR trial). The CONCUR trial was a randomized, double-blind, placebo-controlled, phase III trial, which enrolled patients in Korea, China, Hong Kong,

Table 1 Pivotal clinical trials of regorafenib and TAS-102

Reference	Study design	Treatment	*N*, patients	ORR (%)	DCR (%)	Median PFS (months)	HR for PFS	Median OS (months)	HR for OS
CORRECT trial (Grothey et al. [13••])	Phase III RCT (global)	Regorafenib	505	1.0	41	1.9	0.49 (95% CI 0.42–0.58; $p < 0.0001$)	6.4	0.77 (95% CI 0.64–0.94; $p = 0.0052$)
		placebo	255	0.4 ($p = 0.19$)	15 ($p < 0.0001$)	1.7		5.0	
CONCUR trial (Li et al. [22••])	Phase III RCT (Asia)	Regorafenib	136	4	51	3.2	0.31 (95% CI 0.22–0.44; $p < 0.0001$)	8.8	0.55 (95% CI 0.40–0.77; $p = 0.00016$)
		placebo	68	0 ($p = 0.045$)	7 ($p < 0.0001$)	1.7		6.3	
RECOURSE trial (Mayer et al. [14••])	Phase III RCT (global)	TAS-102	502	1.6	44	2.0	0.48 (95% CI 0.41–0.57; $p < 0.001$)	7.1	0.68 (95% CI 0.58–0.81; $p < 0.001$)
		placebo	258	0.4 ($p = 0.29$)	16 ($p < 0.001$)	1.7		5.3	
TERRA trial (Kim et al. [23••])	Phase III RCT (Asia)	TAS-102	271	1.0	44.1	2.0	0.43 (95% CI 0.34–0.54; $p < 0.001$)	7.8	0.79 (95% CI 0.62–0.99; $p = 0.035$)
		placebo	135	0 ($p = NA$)	14.6 ($p = NA$)	1.8		7.1	

DCR disease control rate, *HR* hazard ratio, *N* number, *NA* not available, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RCT* randomized controlled trial

Taiwan, and Vietnam [22••]. Patients were stratified by number of metastatic sites and time from diagnosis for metastatic disease. The CONCUR investigators also randomly assigned 204 patients at a 2:1 ratio (regorafenib 160 mg: placebo). The primary endpoint was OS, which was also significantly better in regorafenib group than in placebo group (median OS, 8.8 vs. 6.3 months; HR 0.55; 95% CI 0.40–0.77; $p = 0.00016$), consistent with the results of the CORRECT trial. PFS was also significantly longer in patients treated with regorafenib (median PFS, 3.2 vs. 1.7 months; HR 0.31; 95% CI 0.22–0.44; $p < 0.0001$). Survival outcomes were better in the CONCUR trial than in the CORRECT trial, which might have been due to difference of eligibility criteria. Prior targeted agent such as bevacizumab, cetuximab, and panitumumab was mandatory in the CORRECT trial, but not in CONCUR trial. Only about 60% of patients in the CONCUR trial had been treated with targeted agents, whereas all patients in the CORRECT trial were previously treated with targeted agents. Interestingly, subgroup analysis showed that OS benefit of regorafenib was greater in patients who were not exposed to targeted therapy than those who were (HR 0.31; 95% CI 0.19–0.53). Benefit in those receiving previous targeted therapy was similar to that observed in CORRECT (HR 0.77, 95% CI 0.64–0.94). Though it was a pre-planned analysis, it should be interpreted with caution.

TAS-102

TAS-102 (Lonsurf, Taiho Oncology) is a combination drug that consists of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5. FTD (2′-deoxy-5-(trifluoromethyl) uridine) is an antineoplastic thymidine-based nucleoside analog first developed in the early 1960s [25]. FTD shows antitumor activity by inhibition of thymidylate synthase (TS), and when TS is inhibited, the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) is blocked, leading to DNA damage and cell death [26–28]. Phase I/II study of FTD monotherapy showed antitumor activity in breast cancer and colon cancer, but its toxicity profile was not acceptable [29]. In addition, the half-life of FTD is too short (about 18 min) for use as an anticancer agent [30].

TPI (5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1H,3H)-dione monohydrochloride) inhibits thymidine phosphorylase (TP), an enzyme that degrades FTD to its metabolite [30]. Thus, TPI is effective in inhibiting FTD degradation and increasing the bioavailability of FTD [31]. Using a xenograft model, Emura et al. found that combination of FTD and TPI was effective for maintaining adequate plasma concentration of FTD, and the optimum ratio of FTD to TPI was 1:0.5 M, which yielded high antitumor activity and low toxicity [32].

Preclinical Study

In vitro study using 5-fluorouracil (5-FU)-resistant CRC cell line demonstrated that TAS-102 has a significantly higher antitumor activity than intravenous 5-FU or continuous 5-FU infusion treatments [33]. In a preclinical study using a mouse model of human CRC, TAS-102 markedly inhibited the number of liver metastasis [34].

Phase I Study

Several phase I studies were conducted to determine the maximal tolerated dose (MTD), DLTs, and optimal dosing schedule [35–39]. Based on the results of encouraging preclinical studies, Hong et al. performed a phase I study of TAS-102 in patients with advanced or metastatic solid tumor refractory to standard therapy [35]. 50 mg/m^2/day was selected as the MTD when administered daily for 14 days, followed by a 1-week rest, and bone marrow toxicity was the primary DLT. Other phase I studies determined the optimal treatment dose as once daily or three times a day every 3 or 4 weeks [36, 37].

An additional dose-escalation phase I study was performed in Japan to determine the MTD and DLTs in patients with advanced solid tumors [38]. In this study, TAS-102 was administered twice daily on days 1–5 and days 8–12 in a 28-day cycle, and 21 patients were enrolled (n = 18, CRC) into five cohorts at 15 to 35 mg/m^2 twice daily. The recommended TAS-102 dose was determined to be 35 mg/m^2 twice daily in this treatment schedule. The most common grade 3/4 AEs were predominantly hematologic AEs: neutropenia (42.9%), leucopenia (33.3%), and anemia (33.3%). No patients had CR or PR, and 11 patients (52.4%) had SD.

A previous phase I study conducted in patients with metastatic breast cancer in the USA identified 25 mg/m^2 twice daily as the MTD [40]. Because phases I and II studies in Japanese populations showed that a higher dose (35 mg/m^2 twice daily) was feasible [38, 41•]. Bendell et al. evaluated the safety of TAS-102 in Japanese recommended dose (RD) and in US patients with mCRC [39]. Twenty-seven patients with mCRC were enrolled; DLT was not observed in cohort 1 (30 mg/m^2 twice daily), whereas it was observed in one of the nine patients in cohort 2 (35 mg/m^2 twice daily). In this study, RD was also determined 35 mg/m^2 twice daily as same dose of Japanese trial [38]. The dose of TAS-102 is determined by the body surface area (BSA). TAS-102 is available as two strengths of tablet: 15 and 20 mg. When BSA is 2.3 or higher, the dose is capped at 80 mg BID.

Phase II Study

Japanese investigators conducted a double-blind, randomized, placebo-controlled phase II trial to evaluate the efficacy and safety of TAS-102 in patients with unresectable mCRC who were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin [41•]. They randomly allocated 169 patients, in a 2:1 ratio, to either TAS-102 plus best supportive care (BSC) or placebo plus BSC. TAS-102 was administered 35 mg/m^2 twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. Treatment with TAS-102 showed an OS benefit of 2.4 months (median OS, 9.0 vs. 6.6 months; HR 0.56; 95% CI 0.39–0.81; p = 0.0011).

Phase III Studies

The phase III RECOURSE study enrolled 800 eligible patients with mCRC whose cancer were refractory to standard chemotherapy or intolerant to those treatments [14••]. Patients were randomly assigned at a 2:1 ratio to receive TAS-102 (35 mg/m^2 twice daily in the same treatment schedule as used in the previous phase II study [41•]) or placebo. Patients were stratified by *KRAS* mutation status, time from diagnosis of metastatic disease, and geographic area. The patients were required to receive at least two prior standard chemotherapies with each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and anti-*EGFR* monoclonal antibodies (cetuximab or panitumumab). Approximately 60% of patents received four or more prior anticancer regimens. All but one patient and all but two patients with *KRAS* wild-type tumors had received bevacizumab and anti-*EGFR* antibody, respectively. Regorafenib became available during the course of the study, and 18% patients were then pretreated with regorafenib. The primary endpoint was OS, which was significantly improved in the TAS-102 group than in the placebo group (median OS, 7.1 vs. 5.3 months; HR 0.68; 95% CI 0.58–0.81; $p < 0.001$). The OS benefit with TAS-102 was observed in all pre-specified subgroups. Median PFS was also statistically longer with TAS-102 (2.0 vs. 1.7 months; HR 0.48; 95% CI 0.41–0.57; $p < 0.001$). ORR was 1.6 vs. 0.4% (p = 0.29) and DCR (PR plus SD assessed at least 6 weeks after randomization) was 44 vs. 16% ($p < 0.001$) with TAS-102 vs. placebo.

Based on the result of the RECOURSE study, FDA approved TAS-102 on September 22, 2015 for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-*VEGF* biological therapy, and, in cases of *RAS* wild-type, an anti-*EGFR* therapy [42].

Like the CONCUR study, the TERRA study was conducted to confirm the efficacy and safety of TAS-102 in a broader Asian population with mCRC with or without exposure to targeted therapy [23••]. It was a randomized, double-blind, placebo-controlled phase III study of TAS-102 in Asian patients in Korea, China, and Thailand. Patients were stratified by *KRAS* mutation status and geographic area. Approximately half of the patients had received prior targeted therapy. The study showed similar results with RECOURSE study. TAS-

102 treatment showed an improvement in OS (median OS, 7.8 vs. 7.1 months; HR 0.79; 95% CI 0.62–0.99; $p = 0.0035$) and PFS (median PFS, 2.0 vs. 1.8 months; HR 0.43; 95% CI 0.34–0.54; $p < 0.001$). Pre-specified subgroup analysis of OS showed a favorable trend for TAS-102 in most subgroups. A higher benefit was observed in RECOURSE compared with TERRA in terms of OS (HR 0.68 vs. 0.79). Benefit of OS in TERRA was similar to that of Japanese population in RECOURSE (HR 0.76). Cross-trial comparisons should be interpreted with caution because several factors such as prior targeted therapy exposure, post-study treatment, and sample size might affect the results.

Safety

Treatment-related AEs of regorafenib and TAS-102 in the pivotal phase III trials are shown in Table 2. AEs of both drugs are generally manageable, but the toxicity profiles are quite different. Therefore, it is important for oncologists to be aware of what AE is expected to occur in those receiving regorafenib or TAS-102.

The most common grade 3/4 adverse events observed in regorafenib group in CORRECT were hand-foot skin reaction (HFSR; 17 vs. <1%), fatigue (9.6 vs. 5.1%), diarrhea (7.2 vs. 1%), hypertension (7 vs. 1%), and rash/desquamation (6 vs. 0%) when compared to placebo group. Most AEs occurred during the early treatment cycle (cycle 1 or 2). Generally, these toxicity profiles in CONCUR trial were similar to CORRECT except for HFSR [22••]. Notably, HFSR of any grade was higher in Asian than in non-Asian patients (74 vs. 47%). However, grade 3 HFSR was not different between two study populations.

Dose modification was carried out in 67 and 71% of patients (compared with 23 and 16% in the placebo arm) in CORRECT and CONCUR, respectively. Dose reduction and interruption were required in 38 and 61% of the patients in CORRECT, respectively. In CONCUR, 14% of patients discontinued due to AEs. The most frequent AEs requiring dose modification were dermatological and gastrointestinal events. However, regorafenib arm did not experience significantly worse quality of life measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) than placebo arm in CORRECT and CONCUR. Interestingly, these adverse events occurred mostly in the first cycle of treatment and became less prominent with subsequent cycles. Therefore, patient education is essential for adequate management of adverse events and frequent follow-up is needed during the first cycle. Owing to frequent dose modification and interruption, variations in dosing or interval scheduling are made without supporting evidences in clinical settings. ReDOS trial (NCT02368886), a randomized phase II study of lower dose regorafenib compared to standard-dose regorafenib in patients with mCRC, is ongoing to gather more evidence [43].

Unlike regorafenib, in the case of TAS-102, myelotoxicity was the DLT and the most common grade 3/4 AE was neutropenia in phase I studies [38, 39]. In the phase III RECOURSE study, grade 3/4 treatment-related AEs occurred in 69% of patients assigned to TAS-102 and 52% of patients assigned to placebo [14••]. The most frequent TAS-102-related AE of grade 3/4 was neutropenia (38% in TAS-102 vs. 0% in placebo), but there was relatively low incidence of febrile neutropenia (4 vs. 0%). TAS-102 had higher incidence of leukopenia (21 vs. 0%), anemia (18 vs. 3%), and thrombocytopenia (5 vs. <1%). Therefore, a patient should test complete blood count on day 15 of each cycle. Significant non-hematologic toxicities were uncommon. TAS-102 had higher incidence of nausea (48%) and vomiting (28%) of any grade, but severe (grade ≥3) nausea (2 vs. 1%) and vomiting (2 vs. <1%) were not common. Diarrhea of any grade was 32% (vs. 12%), but grade ≥3 was relatively low (3 vs. <1%). Delay of next cycle owing to AE occurred in 53% of patients receiving TAS-102, and dose reduction was necessary in 13.7% of patients. Treatment withdrawal due to AEs was observed in 19 (3.6%) patients in the TAS-102 group. The adverse events in TERRA were consistent with previous known safety profiles of TAS-102.

Treatment Selection and Biomarker

To date, there has not been any direct comparison of regorafenib and TAS-102 in clinical trial settings, and such studies are unlikely to be implemented in the near future. Therefore, a crucial issue that remains is determining the optimal sequence for using the two effective agents in refractory mCRC. Clues for this issue might be found through subgroup analyses of previous studies and retrospective studies. A non-randomized retrospective study evaluated the efficacy and safety of regorafenib and TAS-102 in Japanese population [44], which included a total of 200 patients whose baseline characteristics were similar. In this study, OS was not significantly different between regorafenib and TAS-102 (median OS, 6.7 months in regorafenib vs. 6.5 months in TAS-102; HR 1.01; 95% CI, 0.70–1.49; $p = 0.97$). Toxicity profiles of the two drugs were different, as shown in previous studies [13••, 14••, 23••, 45]. Interestingly, previous regorafenib or TAS-102 treatment had little effect on subsequent treatment with opposite drugs. In RECOURSE, 18% (17% in TAS-102 and 20% in placebo arm) received prior regorafenib administration before enrollment. Benefit of TAS-102 was maintained irrespective of prior regorafenib use in subgroup analysis (prior use of regorafenib: "Yes" subgroup HR 0.53 (95% CI 0.36–0.78) vs. "No" subgroup 0.47 (95% CI 0.39–0.56) [14••]. Therefore, patients' conditions and safety profiles should be taken into consideration when trying to optimize treatment sequence. Moreover, patient education and extensive discussion between patients and oncologists are crucial.

Table 2 Treatment-related adverse events of regorafenib and TAS-102

	Regorafenib in CORRECT trial (*N* = 500)		TAS-102 in RECOURSE trial (*N* = 533)	
	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)
Any event	93	54	98	69
Hematologic AE				
Neutropenia	NA	NA	67	38
Leukopenia	NA	NA	77	21
Anemia	7	3	77	18
Thrombocytopenia	13	3	42	5
Febrile neutropenia	NA	NA	4	4
Non-hematologic AE				
Anorexia	30	3	NA	NA
Nausea	14	<1	48	2
Vomiting	8	1	28	2
Decreased appetite	NA	NA	39	4
Fatigue	47	10	35	4
Diarrhea	34	7	32	3
Fever	10	1	19	1
Alopecia	7	0	NA	NA
Stomatitis	27	3	8	<1
Hand-foot skin reaction	47	17	2	0
Rash or desquamation	26	6	NA	NA
Hypertension	28	7	NA	NA
Hyperbilirubinemia	9	2	36	9

AE adverse event, *NA* not available

Notably, the first portion of survival curves overlaps in the four pivotal studies (CORRECT and CONCUR in regorafenib, RECOURSE and TERRA in TAS-102). Several efforts had been made to find the potential predictive biomarker in these groups. Unfortunately, biomarkers for predicting the efficacy of regorafenib and TAS-102 are yet to be established. Some researchers have suggested potential biomarkers for each drug. Tabernero et al. retrospectively analyzed the CORRECT study population to investigate the clinical activity of regorafenib using tumor mutational status or plasma protein levels [46]. The authors conducted correlative analyses of OS and PFS in patients who were enrolled in the CORRECT trial and found that high concentration of one of the plasma proteins, TIE-1, was associated with improved OS. Yoshino et al. investigated the association between thymidine kinase 1 (TK1) expression and efficacy of TAS-102 from previous phase II and phase III studies [47]. The authors measured TK1 expression in samples from 329 patients using immunohistochemistry and found that high expression of TK1 was associated with poor prognosis in the placebo group and was associated with improvement of OS in the TAS-102 group. In a randomized phase II trial of TAS-102, the drug showed efficacy irrespective of *KRAS* mutational status, while it seemed to be better in patients with *KRAS* mutation (median OS, 13.0 months in TAS-102 vs. 6.9 months in placebo; $p = 0.0056$) than those with *KRAS* wild-type (median OS, 7.2 vs. 7.0 months; $p = 0.191$) [41•]. The *KRAS* status, however, was not identified as a significant factor for determining survival in the following phase III RECOUSE trial [14••].

Several researchers investigated the role of imaging biomarker of 18-fluoro-deoxyglucose ([^{18}F]FDG) positron emission tomography (PET) or [^{18}F]fluorothymidin (FLT) PET in these two agents [48, 49]. Lee et al. investigated [^{18}F]FLT uptake in colon cancer cell lines and mouse xenograft models after TAS-102 administration [48]. Further study is needed to validate the role of [^{18}F]FLT in assessing pharmacodynamics of TAS-102. Also, there is an ongoing study using [^{18}F]FLT as a predictive imaging biomarker of treatment response to regorafenib (NCT02175095).

Conclusions

In summary, regorafenib and TAS-102 showed antitumor activity and survival advantage in patients with refractory mCRC in well-designed phase III clinical trials. Both drugs have been approved in similar treatment settings (refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan-based

chemotherapy, anti-*VEGF* therapy, and, if *RAS* wild-type, anti-EGFR therapy) and are used as oral agents. However, the toxicity profiles of the two drugs are very different, which should be considered for patient selection.

Several studies investigated few potential biomarkers, and more studies are currently ongoing to discover valid biomarker for efficacy of the two agents.

The following questions need to be addressed in order for these two agents to be applied further into clinical practice. Is there any role for earlier use of these agents? Could TAS-102 be a new backbone for combination treatment? Recently, immune checkpoint inhibitor is being investigated for use in microsatellite-instable and even in microsatellite-stable mCRC—is there any synergy of the two agents with immunologic drugs in mCRC? When we find the answer to these issues, regorafenib and TAS-102 will serve as solid pillars of colorectal cancer treatment.

Compliance with Ethical Standards

Conflict of Interest Jae Ho Jeong declares that he has no conflict of interest.

Yong Sang Hong declares that he has no conflict of interest.

Tae Won Kim has received research funding through grants from Bayer and Taiho.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Funding This study was supported in part by grants from the Asan Institute for Life Science (2015–414) and Korea Health 21 R&D Project, Ministry of Health and Welfare and Family Affairs (HI06C0868), Republic of Korea.

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- • Of importance
- •• Of major importance

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