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Chapter

Further Therapeutic Options in Heavily Pretreated Colorectal Cancer Patients

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Abstract

In this paper, currently available systemic treatment options (regorafenib, trifluridine/tipiracil, re-challenge chemotherapy, mitomycin C plus capecitabine) for pretreated patients with metastatic colorectal cancer are discussed and compared in terms of their efficacy and safety profiles. Treatment of these patients has remained a challenge for oncologists. The evidence from clinical trials is encouraging. Knowledge of response biomarkers and/or prognostic factors may be helpful in the identification of patients who could benefit most from the treatment. Adequate medication compliance can be achieved due to awareness of toxicity risk among both physicians and cancer patients and appropriate prevention and management of adverse events.

Keywords: metastatic colorectal cancer, regorafenib, trifluridine/tipiracil, re-challenge chemotherapy, mitomycin C plus capecitabine

1. Introduction

To this date, management of heavily pretreated patients with metastatic colorectal cancer, who present with good performance status and adequate organ function reserve, constituted a challenge for oncologists. However, two anticancer therapies dedicated for this specific group of patients became available nowadays. One of them is regorafenib, an oral inhibitor of protein kinases associated with angiogenesis. Another one is trifluridine/tipiracil (TAS-102), an orally administered combination of a thymidine-based nucleic acid analog, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. Treatment with both anticancer agents contributed to a significant improvement of overall survival (OS) and progression-free survival (PFS) in randomized III phase studies of Caucasian (CORRECT and TERRA) and Asian patients (CONCUR and RECOURSE). Recently, clinical benefits associated with administration of both drugs and good tolerability thereof were also confirmed in an observational study, REGOTAS. The aim of currently ongoing trials is to evaluate the efficacy and safety of regorafenib and TAS-102 combined with other anticancer drugs in metastatic colorectal cancer patients. While preliminary results of some of those studies seem promising, more evidence is needed to formulate any clinically relevant conclusions.

Another treatment option in metastatic colorectal cancer is re-induction of previously used chemotherapy with oxaliplatin- or irinotecan-based regimens.

Importantly, the time elapsed since completion of the primary treatment to the re-induction should not be shorter than 9 months. Finally, patients with metastatic colorectal cancer can receive chemotherapy with mitomycin C plus capecitabine. This generally neglected treatment option seems particularly reasonable in the case of countries in which regorafenib and trifluridine/tipiracil have been registered but are not reimbursed.

The aim of this review paper is to discuss the therapeutic options that could be used in metastatic colorectal cancer patients after three or more lines of systemic therapy.

2. Regorafenib

Regorafenib (BAY 73-4506) is a low-molecular-weight diphenylurea multikinase inhibitor of VEGFR1-3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, RAF-1, BRAF, and p38 MAP kinase for oral administration. This agent has been registered for patients with pretreated metastatic colorectal cancers and refractory gastrointestinal stromal tumors (GIST) [1, 2]. Regorafenib is administered at 160 mg daily (q.d.) for 3 weeks of each 4-week cycle (3 week *on*, 1 week *off*), until disease progression or drug intolerance, whichever first.

2.1 Trials

In a registration phase III trial, CORRECT (regorafenib monotherapy for previously treated metastatic colorectal cancer), 760 patients were randomized in a 2:1 ratio to receive regorafenib or placebo. The majority of patients were Caucasians (the study included only 111 Asians). Median OS turned out to be significantly longer in the regorafenib group than in the placebo group (6.4 vs. 5.0 months) [3]. In another randomized double-blind phase III trial, CONCUR, 204 patients with metastatic colorectal cancer after at least two lines of systemic therapy were randomized in a 2:1 ratio to receive regorafenib or placebo. All patients were Asians. Median OS in the regorafenib arm and placebo arm was 8.8 and 6.3 months, respectively. The results of this trial confirmed previous observations about the regorafenib efficacy. Toxicity profiles of regorafenib in both studies mentioned above were essentially similar [4]. However, these promising findings were not confirmed in another trial, PREVIUM, including patients with KRAS- or BRAF-positive metastatic colorectal cancer treated previously with FOLFOXIRI plus bevacizumab; median OS and median PFS in this group were 3.3 and 2.2 months, respectively [5].

2.2 Predictive markers

According to Komori et al., colorectal cancer patients who showed early decrease in carbohydrate antigen 19-9 (Ca19-9) levels had significantly longer PFS after regorafenib than individuals in whom this marker remained elevated (3.7 vs. 2.0 months). Multivariate analysis confirmed that early decrease in Ca19-9 level was a significant independent predictor of better response to regorafenib [6].

The authors of the CORRECT study analyzed an association between mutational status of the tumor and survival. The study demonstrated that the presence of KRAS-wild type and PIK3CA-wild type in primary tumor was a biomarker of PFS benefit [7]. In another study, conducted by Ma et al., the lack of EGFR expression turned out to be associated with longer PFS and OS (14 vs. 2.5 months and 19.7 vs. 9.6 months, respectively). While the presence of KRAS-wild type correlated with

longer OS, no significant association was found between this biomarker and PFS [8]. Furthermore, multivariate analysis documented prognostic value of tumor's location in the right or left side of the abdominal cavity, with better prognosis observed in the case of the left-sided malignancies [8].

RECIST 1.1 is an established instrument to assess a response to anticancer treatment based on radiologically determined cumulative diameter of target lesions. Cavitation of lung metastases assessed on CT scans at the baseline and at 8 weeks of regorafenib therapy seems to be a novel radiological predictor of PFS [9].

2.3 Toxicity

Adverse event (AE) profile of regorafenib is similar as in the case of other tyrosine multikinase inhibitors, and the AEs of this agent are generally manageable. The most common non-hematological toxicity, which may worsen patient's quality of life, is hand-foot skin reaction (HFSR) (54%) [10–12]. Hence, many patients who experienced this AE may require treatment modification [10]. Interestingly, the incidence of HFSR seems to vary by primary tumor type. According to literature, HFSR symptoms can be found in up to 50% of regorafenib-treated patients with hepatocellular carcinoma, 60.2% of individuals with GIST, and 46.6% of persons with metastatic colorectal cancer [11]. The second most common AE in regorafenib-treated patients is arterial hypertension. Based on the data from five clinical trials, the overall incidence of arterial hypertension in regorafenib-treated patients can be estimated at 44.4% and the incidence of high-grade (G3 and higher) hypertension at 12.5%. Similar to HFSR, the risk of this AE seems to vary according to tumor type [13].

Treatment with regorafenib may also contribute to all-grade hepatotoxicity (bilirubin, AST, ALT, and ALP elevation), an AE observed in approximately one-third of patients treated with this anticancer agent [14].

Other AEs frequently associated with regorafenib treatment are oral mucositis, fatigue, nausea, weight loss, and diarrhea [12, 15]. All-grade anorexia was shown to occur more often in patients who had been previously treated with tyrosine multikinase inhibitors. On the other hand, patients from this group less commonly presented with a high-grade AST elevation [12].

The incidence of hematologic toxicities, such as thrombocytopenia, anemia, neutropenia, and leukopenia, varies between 22% (thrombocytopenia) and 13% (leukopenia). However, high-grade (G3 or higher) hematologic toxicities are relatively rarely observed in regorafenib-treated patients [16].

2.4 Regorafenib combined with other anticancer agents

In a phase I study, regorafenib combined with an anti-VEGF inhibitor, cetuximab, provided a clinical benefit, defined as the presence of stable disease or partial response. However, these promising preliminary findings need to be verified in future studies [17].

Combination therapy with regorafenib and FOLFIRI produced highly promising results, with overall disease control rate (DCR), median PFS, and median OS equal to 58.5%, 6.0 and 12.0 months, respectively [8]. An objective response rate to regorafenib combined with modified FOLFOX (mFOLFOX6) as the first-line treatment was no better than that observed in historical controls, with 85.4% DCR and median PFS of 8.5 months [18]. Negative results, specifically the lack of either OS or PFS benefit, were obtained in a study investigating the efficacy and toxicity of regorafenib plus ruxolitinib, a Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway [19].

3. Trifluridine/tipiracil hydrochloride

TAS-102 is a new oral anti-metabolite drug, a 1:0.5 mixture of a thymidine-based nucleoside analog, alpha,alpha,alpha-trifluorothymidine (trifluridine: FTD), and thymidine phosphorylase inhibitor (tipiracil hydrochloride: TPI) [20–23]. FTD inhibits thymidylate synthase (TS), the key enzyme involved in DNA synthesis, whereas trifluridine incorporates into DNA via phosphorylation and initiates DNA fragmentation [20–22]. TPI enhances the exposure to FTD, improves its bioavailability, and increases the durability of response to this agent [24, 25]. Pre-exposure to 5-FU was shown to enhance FTD incorporation into DNA and to increase antitumor activity of this agent, as shown by lesser viability and proliferation of cancer cells [26]. TAS-102 proved to be effective in GI malignancies with inherent or acquired resistance to 5-FU, as well as in 5-FU-sensitive tumors [20, 21]. TAS-102 has recently been approved as the third-line treatment for adults with refractory metastatic colorectal cancer, patients with contraindications to currently available standard chemotherapy and biological therapy in the EU and USA, and individuals with unresectable advanced or recurrent colorectal cancer in Japan. The standard regimen is 35 mg/m^2 twice a day on days 1–5 and 8–12 of each 28-day cycle [24, 27].

3.1 Trials

The efficacy and safety of TAS-102 were a subject of a double-blind randomized phase II trial including Japanese patients with metastatic colorectal cancer. The patients were randomized in a 2:1 ratio to either TAS-102 or placebo arm. Median OS in the TAS-102 arm turned out to be longer than in the placebo arm (9.0 vs. 6.6 months). The most common AEs were hematologic toxicities, with grade 3 or 4 of neutropenia found in 50% of TAS-102-treated patients [28].

In a randomized double-blind phase III registration trial, TERRA, Asian patients with metastatic colorectal cancer who previously received at least two lines of systemic treatment were randomized in a 2:1 ratio to either TAS-102 or placebo group. The study confirmed the efficacy of TAS-102 in Asian population. Median OS in the TAS-102 arm was significantly longer than in the placebo group (7.8 vs. 7.1 months). Moreover, the TAS-102-treated patients had significantly lower mortality risk and significantly longer median survival follow-up time [29].

In a double-blind phase III registration trial, RECOURSE, 800 patients from Europe, North America, and Asia were randomly assigned to receive TAS-102 or placebo. PFS for the TAS-102 and placebo arm was 2.0 and 1.7 months, respectively. Patients from the TAS-102 arm had significantly longer median OS and significantly longer median time to worsening performance status (7.1 and 5.7 months, respectively) than individuals from the placebo arm (5.3 and 4.0 months, respectively). One-year OS rates for the TAS-102 and placebo arm were 27 and 18%, respectively [30]. Those promising results were further confirmed on a subgroup analysis; median OS for TAS-102-treated patients from the USA, Japan, EU, and Spain ranged between 6.5 and 7.8 months as compared with 4.3–6.7 months for the respective placebo arms, whereas median PFS in the TAS-102 and placebo groups amounted to 2.0–2.8 and 1.7–1.8 months, respectively [31, 32].

3.2 Predictors

Genetic polymorphisms in homologous recombination pathway seem to be a predictor of therapeutic response in metastatic colorectal cancer patients treated with TAS-102. According to Suenaga et al., TAS-102-treated patients with a combination of ENT1 rs760370, MATE1 rs2289669, and OCT2 rs316019 single-nucleotide

polymorphisms of genes involved in trifluridine metabolism and thymidine phosphorylase inhibitor excretion had significantly longer PFS and OS [33]. Also, single-nucleotide polymorphisms of genes involved in homologous recombination, such as ATM and XRCC3, could be predictive and prognostic markers in metastatic colorectal cancer treated with TAS-102. The TAS-102-treated patients who carried any G allele in ATM rs609429 polymorphism had significantly longer OS and nonsignificantly longer PFS than carriers of the C/C variant. Also, the presence of any A allele in XRCC3 rs861539 polymorphism was shown to be associated with significantly longer OS and PFS in TAS-102-treated patients [34].

Patients with ≥ grade 2 chemotherapy-induced neutropenia (absolute neutrophil count <1500/mm^3) at 1 month (CIN-1-month) of TAS-102 therapy had longer median PFS (3.0 vs. 2.4 months) and OS (14.0 vs. 5.6 months) than those without the neutropenia. The presence of neutropenia at 1 month of TAS-102 treatment and higher baseline CEA levels were identified as independent predictors of OS [35]. In another study, grade 3 or 4 CIN-1-month was shown to be associated with longer PFS than grade 0-2 CIN-1-month (4.3 vs. 2.0 months). Moreover, G3 or G4 neutropenia during the first cycle of TAS-102 therapy turned out to be associated with significantly higher DCR (72.2%) than grade 0–2 neutropenia (72.2 vs. 30.9%) [36]. Finally, a significant association was found between baseline creatinine clearance rate of less than 57.1 mL/min prior to TAS-102 administration and the incidence of G3 or G4 neutropenia after introduction of this agent [37].

Also, longer time elapsed since the onset of the first-line therapy to disease progression (more than 18 months) seems to be a predictor of better response to TAS-102 therapy. In one study, median PFS in TAS-102-treated patients with the time to progression exceeding 18 months was longer than in those who received the first-line therapy ≤18 months before (7 vs. 5 months) [38]. These findings were later confirmed in a meta-analysis conducted by Chen et al. [39].

Kwakman et al. identified KRAS-wild type tumor, good performance status (PS0 or PS1), and normal serum levels of lactate dehydrogenase and alkaline phosphatase as independent predictors of better response to TAS-102 treatment. All these factors correlated positively with longer OS. Patients with KRAS-wild type tumors had longer median OS than those with KRAS-mutated malignancies (6.9 vs. 4.9 months), and median OS in persons with ECOG PS0–1 turned out to be longer than in individuals with worse performance status (5.9 vs. 3.2 months) [40]. However, in a meta-analysis involving the data of 1318 patients who received TAS-102, OS was significantly longer than in the study mentioned above, regardless the KRAS mutation status. Furthermore, the treatment response was not influenced by the number of metastatic sites (1, 2, or more) [39]. Also, in a subgroup analysis of patients participating in the RECOURSE trial, neither OS nor PFS correlated with the KRAS status, as well as with patients' age and ethnicity [31].

ECOG performance status (PS0 or PS1), the number of metastatic sites (1 or 2), and the time elapsed since the diagnosis of the first metastasis (18 months or longer) were identified as prognostic factors in the RECOURSE trial; however, none of those factors turned out to be a predictor of therapeutic response [30].

3.3 Toxicity

Hematologic toxicities, including leukopenia, neutropenia, and anemia, and gastrointestinal toxicities, such as nausea/vomiting, diarrhea, and the loss of appetite, as well as fatigue of various grade, were the most frequent side effects observed in patients treated with trifluridine/tipiracil [40–45]. The most common grade 3/4 toxicity was myelosuppression (neutropenia, anemia, febrile neutropenia) [46]. In turn, cardiac ischemia seems to be one of the rarest AEs observed during the

therapy with TAS-102, which implies that this agent might constitute a reasonable option for patients with cardiovascular contraindications for 5-FU treatment [47].

Based on available evidence, TAS-102 seems to be a convenient, manageable, and safe agent to be used in daily clinical practice.

According to the data from the RECOURSE and J003 trials, severe AEs (SAEs) occurred in 27.7% of patients treated with TAS-102. In more than 50% of the patients, the toxicity necessitated a delay or interruption of TAS-102 therapy or dose reduction [41]. However, the incidence of SAEs and AEs leading to treatment discontinuation in TAS-102 and placebo arms was essentially similar, and fatal AEs turned out to be more common in the placebo group [41]. Furthermore, in an open-label expanded-access program, TAS-102 had similar safety profiles in older (≥65 years) and younger (<65 years) patients [48].

Finally, the occurrence of AEs had no significant impact on the quality of life and performance status of patients participating in the RECOURSE trial, even in those in whom TAS-102 had to be discontinued because of its toxicity [49].

3.4 TAS-102 combined with other anticancer drugs

In preclinical studies, TAS-102 combined with cytotoxic drugs (oxaliplatin, irinotecan) showed enhanced activity against recurrent and chemo-naïve colorectal cancers [50, 51]. Also, the regimes including TAS-102 and targeted therapies (cetuximab, panitumumab) or antiangiogenic agents (nintedanib, bevacizumab) were shown to be effective against colorectal cancer in preclinical studies [52, 53].

One phase I/II study demonstrated a promising efficacy and moderate toxicity of TAS-102 plus bevacizumab in patients with metastatic and refractory colorectal cancer [54].

The aim of currently ongoing **TR**iflUridine/tipiracil in **S**econd-line s**T**ud**Y** phase II/III study, the results of which will be available in 2022, is to determine DCR, response rate (RR), OS, PFS, safety profile, and time to treatment failure of trifluridine/tipiracil plus bevacizumab and irinotecan, fluoropyrimidine plus bevacizumab as the second-line treatments in patients with metastatic colorectal cancer who failed to respond to the first-line oxaliplatin-based therapy [55].

4. Regorafenib vs. TAS-102

An indirect comparison of regorafenib and TAS-102 based on published evidence from PubMed, Cochrane, and other databases suggests that these two agents did not differ in terms of PFS and OS benefit. However, regorafenib seems to produce all-grade toxicity more often than TAS-102 [56]. The most common forms of grade ≥3 toxicity found in regorafenib-treated patients were hepatotoxicity and palmar-plantar erythema, whereas individuals who received TAS-102 most often suffered from neutropenia [57, 58]. The similar efficacy of regorafenib and TAS-102 was confirmed in REGOTAS study (regorafenib vs. TAS-102 as salvage-line in patients with colorectal cancer refractory to standard chemotherapies: a multicenter observational study, UMIN 000020416) which showed no significant differences in OS and PFS of patients treated with one of those agents [59].

A subgroup analysis conducted within the framework of a retrospective study of Asian patients demonstrated that regorafenib was significantly more efficacious in individuals younger than 65 years, whereas TAS-102 provided greater OS benefit in persons aged 65 years or older [60]. Those findings are consistent with the results of the REGOTAS trial in which regorafenib-treated patients ≥65 years of age, with modified Glasgow Prognostic Score equal to 2 (GPS 2), had shorter OS and PFS

than individuals who received TAS-102 [59]. The same study identified modified GPS before later-line chemotherapy as the strongest predictor of OS in patients with metastatic colorectal cancer [59].

Nothing has been known about the efficacy and toxicity of TAS-102 in patients treated previously with regorafenib since publication of Kotani et al.'s study. In the latter study, median PFS in patients treated with regorafenib prior to TAS-102 implementation was 2.0 months as compared with 2.1 months in individuals with no history of regorafenib treatment, and median OS in these two groups was 4.7 and 6.2 months, respectively [61]. The toxicity of TAS-102, assessed based on the incidence of at least grade 3 side effects, was similar regardless of the study group [61]. The treatment sequence analysis demonstrated that TAS-102-treated patients had longer PFS and OS after a fluoropyrimidine-based therapy-free interval, 3.1 and 17.7 months, respectively, as compared with 2.2 and 8.1 months, respectively, in persons in whom TAS-102 was implemented immediately after the fluoropyrimidine-based therapy. However, no similar association was found between the efficacy of regorafenib and the time elapsed since fluoropyrimidine-based treatment discontinuation [62].

The prognosis seems to be also influenced by the sequence of regorafenib and TAS-102 administration. Median OS in patients who received crossover treatment with regorafenib followed by TAS-102 was 11.5 months, as compared with 7.6 months in individuals in whom first TAS-102 and then regorafenib were implemented [57].

5. Re-challenge chemotherapy

Another therapeutic option in heavily pretreated patients with metastatic colorectal cancer is re-challenge chemotherapy/re-initiation chemotherapy. Re-challenge chemotherapy is defined as the re-introduction of previously used chemotherapy with oxaliplatin or irinotecan-based regimens at least 9 months after the end of the initial exposure. Re-challenge chemotherapy constitutes an important option in patients who still present with good performance status and organ function reserve, especially in those in whom the initial chemotherapy was discontinued before progression of the disease (e.g., due to cumulative toxicities) [63–65]. Such approach did not shorten the period of the best supportive care and, more importantly, might prolong OS [65]. According to Chambers et al., clinical benefit rate (defined as the proportion of patients with partial response or stable disease) after re-challenge chemotherapy was 75.5% and time to progression equaled 6.5 months [63]. Moreover, re-challenge chemotherapy after regorafenib treatment seems to be a good strategy in heavily pretreated patients with metastatic colorectal cancer. According to literature, PFS after re-challenge chemotherapy varied between 0.5 and 3.5 months, and 6-month OS reached up to 27.3%. In some researchers' opinion, regorafenib could resensitize cancer patients to previously given chemotherapy, but this hypothesis still needs to be verified empirically [66].

Some authors reported the use of re-initiation chemotherapy or second re-challenge chemotherapy after the development of resistance, but none of these approaches is a standard of oncological treatment [63, 64].

6. Combination of capecitabine and mitomycin C (MMC)

MMC is a cytotoxic antibiotic which shows moderate efficacy when used as monotherapy in colorectal cancer patients. Upregulation of intra-tumoral

thymidine phosphorylase, an enzyme converting capecitabine to 5-FU, is the primary mechanism through which MMC acts synergistically to capecitabine [67]. According to literature, overall response rate in patients with metastatic colorectal cancer who received MMC (6 mg/m^2 intravenously on day 1 every 3 weeks) plus capecitabine (1000 mg/m^2 twice daily on days 1–14, followed by a 7-day treatment-free interval) ranged between 15.2 and 55.5% [68–72]. The majority of patients received previously two, three, or even four lines of anticancer therapy. Median PFS varied between 1.7 and 5.4 months [68–71, 74] and median OS between 5.4 and 13 months [68–72, 74]. While those results might be considered disappointing, it should be emphasized that all patients were pretreated with many lines of systemic therapy and had metastases in multiple locations.

With no doubt, the combination therapy with capecitabine and MMC is dedicated primarily for patients with cumulative side effects after previous treatment and/or contraindications to targeted therapies [70]. Furthermore, capecitabine plus MMC constitutes a good option of the best supportive care in patients who still maintain good performance status and organ efficiency, especially in countries in which regorafenib and TAS-102 have been registered but are not reimbursed.

Toxicity of capecitabine plus MMC combination is mild, acceptable, and easily manageable, and no significant hematological AEs have been reported thus far [71, 73–74]. The main non-hematological AEs documented in patients treated with this regimen are palmar-plantar erythema, nausea, diarrhea, and fatigue [71, 73–74].

7. Conclusions

Regorafenib and trifluridine/tipiracil have been authorized for the treatment of metastatic colorectal cancer, as the third or further therapy line. The patients are eligible for one of those treatments if they present with good performance status and adequate bone marrow, liver, and kidney function; hence, aside from clinical and molecular biomarker status, also those factors should be considered during patient qualification. While the toxicity of both anticancer agents is manageable, appropriate control of side effects requires clinical vigilance and good medication compliance. In some clinical situations, re-induction/re-challenge of previously given chemotherapy with oxaliplatin or irinotecan-based regimens and/or switching to mitomycin C plus capecitabine might be a reasonable option.

Conflict of interest

The author declares no conflict of interest.

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References

[1] Strumberg D, Schultheis B. Regorafenib for cancer. Expert Opinion on Investigational Drugs. 2012;**21**:879-889. DOI: 10.1517/13543784.2012.684752

[2] Crona DJ, Keisler MD, Walko CM. Regorafenib: A novel multitargeted tyrosine kinase inhibitor for colorectal cancer and gastrointestinal stromal tumors. The Annals of Pharmacotherapy. 2013;**47**:1685-1696. DOI: 10.1177/1060028013509792

[3] Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;**381**(9863):303-312. DOI: 10.1016/S0140-6736(12)61900-X

[4] Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2015;**16**:619-629. DOI: 10.1016/S1470-2045(15)70156-7

[5] Garcia-Alonso P, Benavides M, Falco E, Munoz A, Gomez A, Sastre J, et al. Single-agent regorafenib in metastatic colorectal cancer patients with any RAS or BRAF mutation previously treated with FOLFOXIRI plus bevacizumab (PREVIUM trial). The Oncologist. 2018;**23**:1271-e128. DOI: 10.1634/theoncologist.2018-0316

[6] Komori A, Taniguchi H, Hamauchi S, Masuishi T, Kito Y, Narita Y, et al. Serum CA19-9 response is an early predictive marker of efficacy of regorafenib in refractory metastatic colorectal cancer. Oncology. 2017;**93**:329-335. DOI: 10.1159/000479280

[7] Tabernero J, Lenz HJ, Siena S, Soobrero A, Falcone A, Ychou M, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: A retrospective, exploratory analysis of the CORRECT trial. The Lancet Oncology. 2015;**16**:937-948. DOI: 10.1016/S1470-2045(15)00138-2

[8] Ma CJ, Huang CW, Chang TK, Tsai HL, Su WC, Yeh YS, et al. Oncologic outcomes in metastatic colorectal cancer with regorafenib with FOLFIRI as a third- or fourth-line setting. Translational Oncology. 2018;**12**(3):502-512. DOI: 10.1016/j.tranon.2018.12.003

[9] Ricotta R, Verrioli A, Ghezzi S, Porcu L, Grothey A, Falcone A, et al. Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: Post hoc analysis of the CORRECT phase III trial (RadioCORRECT study). ESMO Open. 2017;**1**(6):e000111. DOI: 10.1136/esmoopen-2016-000111

[10] McLellan B, Ciardiello F, Lacouture ME, Segaert S, Van Cutsem E. Regorafenib-associated hand-foot skin reaction: Practical advice on diagnosis, prevention, and management. Annals of Oncology. 2015;**26**:2017-2026. DOI: 10.1093/annonc/mdv244

[11] Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: A meta-analysis. Investigational New Drugs. 2013;**31**:1078-1086. DOI: 10.1007/s10637-013-9977-0

[12] Yin X, Yin Y, Shen C, Chen H, Wang J, Cai Z, et al. Adverse events risk associated with regorafenib in the treatment of advanced solid tumors:

Meta-analysis of randomized controlled trials. OncoTargets and Therapy. 2018;**11**:6405-6414. DOI: 10.2147/OTT.S156760

[13] Wang Z, Xu J, Nie W, Huang G, Tang J, Guan X. Risk of hypertension with regorafenib in cancer patients: A systematic review and meta-analysis. European Journal of Clinical Pharmacology. 2014;**70**:225-231. DOI: 10.1007/s00228-013-1598-1

[14] Zhao B, Zhao H. Incidence and risk of regorafenib-induced hepatotoxicity. Oncotarget. 2017;**8**:84102-84111. DOI: 10.18632/oncotarget.21106

[15] Grothey A, George S, van Cutsem E, Blay JY, Sobrero A, Demetri GD. Optimizing treatment outcomes with regorafenib: Personalized dosing and other strategies to support patient care. The Oncologist. 2014;**19**:669-680. DOI: 10.1634/theoncologist.2013-0059

[16] Zhao B, Zhao H. Incidence and risk of hematologic toxicities in cancer patients treated with regorafenib. Oncotarget. 2017;**8**:93813-93824. DOI: 10.18632/oncotarget.21217

[17] Subbiah V, Khawaja MR, Homg DS, Amini B, Yungfang J, Liu H, et al. First-in-human trial of multikinase VEGF inhibitor regorafenib and anti-EGFR antibody cetuximab in advanced cancer patients. JCI Insight. 2017;**2**:90380. DOI: 10.1172/jci.insight.90380

[18] Argiles G, Saunders MP, Rivera F, Sobrero A, Benson A 3rd, Guillen Ponce C, et al. Regorafenib plus modified FOLFOX6 as first-line treatment of metastatic colorectal cancer: A phase II trial. European Journal of Cancer. 2015;**51**:942-949. DOI: 10.1016/j.ejca.2015.02.013

[19] Fogelman D, Cubillo A, Garcia-Alfonso P, Miron MLL, Nemunaitis J, Flora D, et al. Randomized, double-blind, phase two study of ruxolitinib plus regorafenib in patients with relapsed/refractory metastatic colorectal cancer. Cancer Medicine. 2018;**7**:5382-5393. DOI: 10.1002/cam4.1703

[20] Emura T, Murakami Y, Nakagawa F, Fukushima M, Kitazato K. A novel antimetabolite, TAS-102 retains its effect on FU-related resistant cancer cells. International Journal of Molecular Medicine. 2004;**13**:545-549

[21] Emura T, Suzuki N, Yamaguchi M, Ohshimo H, Fukushima M. A novel combination antimetabolite, TAS-102, exhibits antitumor activity in FU-resistant human cancer cells through a mechanism involving FTD incorporation in DNA. International Journal of Oncology. 2004;**25**:571-578

[22] Miyamoto Y, Lenz HJ, Baba H. A novel antimetabolite: TAS-102 for metastatic colorectal cancer. Expert Review of Clinical Pharmacology. 2016;**9**:355-365. DOI: 10.1586/17512433.2016.1133285

[23] Zaniboni A, Bertocchi P, Barni S, Petrelli F. TAS-102 (Lonsurf) for the treatment of metastatic colorectal cancer. A concise review. Clinical Colorectal Cancer. 2016;**15**:292-297. DOI: 10.1016/j.clcc.2016.06.003

[24] Burness CB, Duggan ST. Trifluridine/tipiracil: A review in metastatic colorectal cancer. Drugs. 2016;**76**:1393-1402. DOI: 10.1007/s40265-016-0633-9

[25] Lenz HJ, Stintzing S, Loupakis F. TAS-102, a novel antitumor agent: A review of the mechanism of action. Cancer Treatment Reviews. 2015;**41**:777-783. DOI: 10.1016/j.ctrv.2015.06.001

[26] Baba T, Kokuryo T, Yamaguchi J, Yokoyama Y, Uehara K, Ebata T, et al. Pre-exposure to fluorouracil increased trifluridine incorporation and enhanced its anti-tumor effect for

colorectal cancer. Anticancer Research. 2018;**38**:1427-1434

[27] Peeters M, Cervantes A, Moreno Vera S, Taieb J. Trifluridine/tipiracil: An emerging strategy for the management of gastrointestinal cancers. Future Oncology. 2018;**14**:1629-1645. DOI: 10.2217/fon-2018-0147

[28] Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: A double-blind, randomised, placebo-controlled phase 2 trial. The Lancet Oncology. 2012;**13**:993-1001. DOI: 10.1016/S1470-2045(12)70345-5

[29] Xu J, Kim TW, Shen L, Sriuranpong V, Pan H, Xu R, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: The TERRA study. Journal of Clinical Oncology. 2018;**36**:350-358. DOI: 10.1200/JCO.2017.74.3245

[30] Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. The New England Journal of Medicine. 2015;**372**:1909-1919. DOI: 10.1056/NEJMoa1414325

[31] Van Cutsem E, Mayer RJ, Laurent S, Winkler R, Gravalos C, Benavides M, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. European Journal of Cancer. 2018;**90**:63-72. DOI: 10.1016/j.ejca.2017.10.009

[32] Longo-Munoz F, Argiles G, Tabernero J, Cervantes A, Gravalos C, Pericay C, et al. Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients with metastatic colorectal cancer from Spain: Results of a subgroup analysis of the phase 3 RECOURSE trial. Clinical & Translational Oncology. 2017;**19**:227-235. DOI: 10.1007/s12094-016-1528-7

[33] Suenaga M, Schirripa M, Cao S, Zhang W, Yang D, Dadduzio V, et al. Potential role of polymorphisms in the transporter genes ENT1 and MATE1/OCT2 in predicting TAS-102 efficacy and toxicity in patients with refractory metastatic colorectal cancer. European Journal of Cancer. 2017;**86**:197-206. DOI: 10.1016/j.ejca.2017.08.033

[34] Suenaga M, Schirripa M, Cao S, Zhang W, Yang D, Murgioni S, et al. Genetic variants of DNA repair-related genes predict efficacy of TAS-102 in patients with refractory metastatic colorectal cancer. Annals of Oncology. 2017;**28**:1015-1022. DOI: 10.1093/annonc/mdx035

[35] Kasi PM, Kotani D, Cecchini M, Shitara K, Ohtsu A, Ramanathan RK, et al. Chemotherapy induced neutropenia at 1-month mark is a predictor of overall survival in patients receiving TAS-102 for refractory metastatic colorectal cancer: A cohort study. BMC Cancer. 2016;**16**:467. DOI: 10.1186/s12885-016-2491-y

[36] Hamauchi S, Yamazaki K, Masuishi T, Kito Y, Komori A, Tsushima T, et al. Neutropenia as a predictive factor in metastatic colorectal cancer treated with TAS-102. Clinical Colorectal Cancer. 2017;**16**:51-57. DOI: 10.1016/j.clcc.2016.07.005

[37] Yasue F, Kimura M, Usami E, Iwai M, Kawachi S, Mitsuoka M, et al. Risk factors contributing to the development of neutropenia in patients receiving oral trifluridine-tipiracil (TAS-102) chemotherapy for advanced/recurrent colorectal cancer. Die Pharmazie. 2018;**73**:178-181. DOI: 10.1691/ph.2018.7908

[38] Skuja E, Gerina-Berzina A, Hegmane A, Zvirbule Z, Vecvagare E, Purkalne G. Duration of previous treatment as a prognostic factor in metastatic colorectal cancer treated with trifluridine/tipiracil. Molecular and Clinical Oncology. 2018;**8**:699-702. DOI: 10.3892/mco.2018.1600

[39] Chen D, Wu YS, lin H, Wang Y, Li L, Zhang T. Efficacy and safety of TAS-102 in refractory metastatic colorectal cancer: A meta-analysis. Cancer Management and Research. 2018;**10**:2915-2924. DOI: 10.2147/CMAR.S174584

[40] Kwakman JJM, Vink G, Vestjens JH, Beerepoot LV, de Groot JW, Jansen RL, et al. Feasibility and effectiveness of trifluridine/tipiracil in metastatic colorectal cancer: Real-life data from the Netherlands. International Journal of Clinical Oncology. 2018;**23**:482-489. DOI: 10.1007/s10147-017-1220-0

[41] Falcone A, Ohtsu A, Van Cutsem E, Mayer RJ, Buscaglia M, Bendell JC, et al. Integrated safety summary for trifluridine/tipiracil (TAS-102). Anti-Cancer Drugs. 2018;**29**:89-96. DOI: 10.1097/CAD.0000000000000554

[42] Lee JJ, Chu E. Adherence, dosing, and managing toxicities with trifluridine/tipiracil (TAS-102). Clinical Colorectal Cancer. 2017;**16**:85-92. DOI: 10.1016/j.clcc.2017.01.003

[43] White T, Larson H, Minnella A, Hochster HS. Metastatic colorectal cancer: Management with trifluridine/tipiracil. Clinical Journal of Oncology Nursing. 2017;**21**:E30-E37. DOI: 10.1188/17.CJON.E30-E37

[44] Kasper S, Kisro J, Fuchs M, Muller C, Schulz-Abelius A, Karthaus M, et al. Safety profile of trifluridine/tipiracil monotherapy in clinical practice: Results of the German compassionate-use program for patients with metastatic colorectal cancer. BMC Cancer. 2018;**18**:1124. DOI: 10.1186/s12885-018-5063-5

[45] Overman MJ, Kopetz S, Varadhachary G, Fukushima M, Kuwata K, Mita A, et al. Phase I clinical study of three times a day oral administration of TAS-102 in patients with solid tumors. Cancer Investigation. 2008;**26**:794-799. DOI: 10.1080/07357900802087242

[46] Bendell JC, Rosen LS, Mayer RJ, Goldman JW, Infante JR, Benedetti F, et al. Phase 1 study of oral TAS-102 in patients with refractory metastatic colorectal cancer. Cancer Chemotherapy and Pharmacology. 2015;**76**:925-932. DOI: 10.1007/s00280-015-2850-4

[47] Vaflard P, Ederhy S, Torregrosa C, Andre T, Cohen R, Lopez-Trabada D. Fluoropyrimidines cardiac toxicity: 5-Fluorouracil, capecitabine, compound S-1 and trifluridine/tipiracil. Bulletin du Cancer. 2018;**105**:707-719. DOI: 10.1016/j.bulcan.2018.05.005

[48] Mayer RJ, Hochster HS, Cohen SJ, Winkler R, Makris L, Grothey A. Safety of trifluridine/tipiracil in an open-label expanded-access program in elderly and younger patients with metastatic colorectal cancer. Cancer Chemotherapy and Pharmacology. 2018;**82**:961-969. DOI: 10.1007/s00280-018-3686-5

[49] Van Cutsem E, Falcone A, Garcia-Carbonero R, Komatsu Y, Pastorino A, Peeters M, et al. Proxies of quality of life in metastatic colorectal cancer: Analyses in the RECOURSE trial. ESMO Open. 2017;**2**:e000261. DOI: 10.1136/esmoopen-2017-000261

[50] Nukatsuka M, Nakagawa F, Takechi T. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, with oxaliplatin on human colorectal and gastric cancer xenografts. Anticancer Research. 2015;**35**:4605-4615

[51] Nukatsuka M, Nakagawa F, Saito H, Sakata M, Uchida J, Takechi T. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, with irinotecan hydrochloride on human colorectal and gastric cancer xenografts. Anticancer Research. 2015;**35**:1437-1445

[52] Tsukihara H, Nakagawa F, Sakamoto K, Ishida K, Tanaka N, Okabe H, et al. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. Oncology Reports. 2015;**33**:2135-2142. DOI: 10.3892/or.2015.3876

[53] Suzuki N, Nakagawa F, Matsuoka K, Takechi T. Effect of a novel oral chemotherapeutic agent containing a combination of trifluridine, tipiracil and the novel triple angiokinase inhibitor nintedanib, on human colorectal cancer xenografts. Oncology Reports. 2016;**36**:3123-3130. DOI: 10.3892/or.2016.5208

[54] Kuboki Y, Nishina T, Shinozaki E, Yamazaki K, Shitara K, Okamoto W, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): An investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. The Lancet Oncology. 2017;**18**:1172-1181. DOI: 10.1016/S1470-2045(17)30425-4

[55] Yoshino T, Oki E, Nozawa H, Eguchi-Nakajima T, Taniguchi H, Morita S, et al. Open rationale and design of the TRUSTY study: A randomised, multicentre, open-label phase II/III study of trifluridine/tipiracil plus bevacizumab versus irinotecan, fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer progressive during or following first-line oxaliplatin-based chemotherapy. ESMO Open. 2018;**3**:e000411. DOI: 10.1136/esmoopen-2018-000411

[56] Abrahao ABK, Ko YJ, Berry S, Chan KKW. A comparison of regorafenib and TAS-102 for metastatic colorectal cancer: A systematic review and network meta-analysis. Clinical Colorectal Cancer. 2018;**17**:113-120. DOI: 10.1016/j.clcc.2017.10.016

[57] Sueda T, Sakai D, Kudo T, Sugiura T, Takahashi H, Haraguchi N, et al. Efficacy and safety of regorafenib or TAS-102 in patients with metastatic colorectal cancer refractory to standard therapies. Anticancer Research. 2016;**36**:4299-4306

[58] Masuishi T, Taniguchi H, Hamauchi S, Komori A, Kito Y, Narita Y, et al. Regorafenib versus trifluridine/tipiracil for refractory metastatic colorectal cancer: A retrospective comparison. Clinical Colorectal Cancer. 2017;**16**:e15-e22. DOI: 10.1016/j.clcc.2016.07.019

[59] Tsuchihashi K, Ito M, Moriwaki T, Fukuoka S, Taniguchi H, Takashima A, et al. Role of predictive value of the modified Glasgow prognostic score for later-line chemotherapy in patients with metastatic colorectal cancer. Clinical Colorectal Cancer. 2018;**17**:e687-e697. DOI: 10.1016/j.clcc.2018.07.004

[60] Moriwaki T, Fukuoka S, Taniguchi H, Takashima A, Kumekawa Y, Kajiwara T, et al. Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): A Japanese society for cancer of the colon and rectum multicenter observational study. The Oncologist. 2018;**23**:7-15. DOI: 10.1634/theoncologist.2017-0275

[61] Kotani D, Shitara K, Kawazoe A, Fukuoka S, Kuboki Y, Bando H, et al. Safety and efficacy of trifluridine/tipiracil monotherapy in clinical practice for patients with metastatic

colorectal cancer: Experience at a single institution. Clinical Colorectal Cancer. 2016;**15**:e109-e115. DOI: 10.1016/j.clcc.2015.11.005

[62] Unseld M, Drimmel M, Siebenhuner A, Gleiss A, Bianconi D, Kieler M, et al. Optimizing treatment sequence for late-line metastatic colorectal cancer patients using trifluridine/tipiracil and regorafenib. Clinical Colorectal Cancer. 2018;**17**:274-279. DOI: 10.1016/j.clcc.2018.05.012

[63] Chambers AE, Frick J, Tanner N, Gerkin R, Kundranda M, Dragovich T. Chemotherapy re-challenge response rate in metastatic colorectal cancer. Journal of Gastrointestinal Oncology. 2018;**9**:679-686. DOI: 10.21037/jgo.2018.04.08

[64] Vogel A, Hofheinz RD, Kubicka S, Arnold D. Treatment decisions in metastatic colorectal cancer—Beyond first and second line combination therapies. Cancer Treatment Reviews. 2017;**59**:54-60. DOI: 10.1016/j.ctrv.2017.04.007

[65] Takeuchi N, Koike K, Yoshida S, Kudo A, Sekiguchi N, Nakayama A, et al. Treatment of metastatic refractory colorectal cancer following regorafenib failure. Molecular and Clinical Oncology. 2017;**7**:308-312. DOI: 10.3892/mco.2017.1307

[66] Bertocchi P, Aroldi F, Prochilo T, Meriggi F, Beretta GD, Zaniboni A. Chemotherapy rechallenge after regorafenib treatment in metastatic colorectal cancer: Still hope after the last hope? Journal of Chemotherapy. 2017;**29**:102-105. DOI: 10.1080/1120009X.2016.1247205

[67] Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Induction of thymidine phosphorylase activity and enhancement of capcitabine efficacy by taxol/taxotere in human cancer xenografts. Clinical Cancer Research. 1998;**4**:1013-1019

[68] Vdorljak E, Omrcen T, Boban M, Hrepic D. Capecitabine and mitomycin-C in the therapy of pretreated patients with metastatic colorectal cancer: Single center retrospective study with 36 patients. Journal of BUON. 2008;**13**:513-518

[69] Chong G, Dickson JLB, Cunningham D, Norman AR, Rao S, Hill ME, et al. Capecitabine and mitomycin C as third-line therapy for patients with metastatic colorectal cancer resistant to fluorouracil and irinotecan. British Journal of Cancer. 2005;**93**:510-514

[70] Rimassal L, Gullo G, Carnaghi C, Abbadessa G, Zuradelli M, Tronconi MC, et al. Chemotherapy with mitomycin C and capecitabine in patients with advanced colorectal cancer pretreated with irinotecan and oxaliplatin. Tumori. 2006;**92**:285-289

[71] Scartozzi M, Falcone A, Fucci F, Braconi C, Pierantoni C, Cavanna L, et al. Capecitabine and mitomycin C may be an effective treatment option for third-line chemotherapy in advanced colorectal cancer. Tumori. 2006;**92**:384-388

[72] Saif MW, Kaley K, Brennan M, Garcon MC, Rodriguez G. Mitomycin-C and capecitabine (MIXE) as salvage treatment in patients with refractory, metastatic colorectal cancer: A retrospective study. Anticancer Research. 2013;**33**:2743-2746

[73] Ferrarotto R, Machado K, Mak MP, Shah N, Takahashi TK, Costa FP, et al. Multicenter, multinational analysis of mitomycin C in refractory metastatic colorectal cancer. European Journal of Cancer. 2012;**48**:820-826

[74] Zygulska AL, Krzemieniecki K. Salvage chemotherapy in metastatic colorectal cancer with the combination of capeitabine and mitomycin C. Neoplasma. 2015;**62**:793-797