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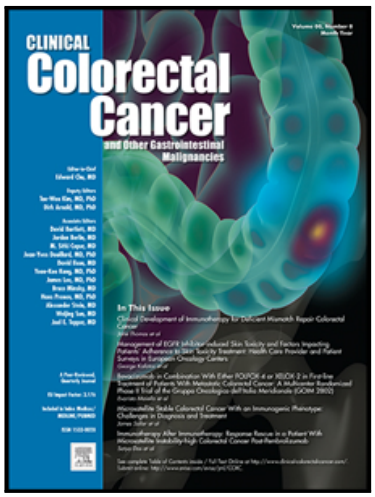

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Retrospective study of regorafenib versus TAS-102 efficacy and safety in chemorefractory metastatic colorectal cancer (mCRC) patients: a multi institution real life clinical data.

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Keywords: regorafenib, TAS-102, chemorefractory, mCRC

Abstract

Introduction: There have been significant developments in CRC research over the last few years, with the introduction of new agents that have been prolonged median overall survival of mCRC. These therapies have improved patient outcomes; however, despite significant progress in strategies for cancer treatment, their use is limited by development of resistant mechanism. Almost 30% of patients with refractory mCRC will remain good candidates for further treatment. Regorafenib and TAS-102 are novel antitumor agents for patients with refractory mCRC. However, it is unclear which patients may derive a survival benefit from these drugs in real-life clinical practice.

Methods: We performed a retrospective analysis evaluating safety and efficacy of TAS-102 and regorafenib in a cohort of refractory mCRC patients, in three different centers between January 1th 2018 and May 31 2020, with the aim of assessing the optimal sequence treatment for these two drugs.

Results: 140 mCRC patients were included in the analysis. Of these patients, 64 received regorafenib and 76 received TAS-102 as first treatment. After progression, in the regorafenib 24 (37%) patients switched to secondary treatment with TAS-102, instead, in the TAS-102 group, among 76 patients, 29 (45%) patients switched to secondary treatment with regorafenib. Disease control was achieved in 8 (12,5%) out of 64 patients in the regorafenib group and 17 (22,4%) out of 76 patients in the TAS-102 group. In terms of efficacy, the PFS and OS were similar in both treatment groups for primary and secondary treatments. AEs reported in this analysis were mostly consistent with the known safety profiles of regorafenib and TAS-102 in previous clinical trials.

Conclusions: The present study is the first one to compare the activity of the two agents in a large cohort of chemo-refractory mCRC patients providing more details about the best sequence, to be incorporated in clinical practice.

Introduction

Colorectal cancer (CRC) is considered the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.8 million new cases in 2018 (1). In the same year, CRC was responsible for 862000 deaths, making it the third leading cause of cancer-related death in men and women (1). Although the advances in screening and medical treatments have led a trend in reduction of both incidence and mortality, almost 20% of patients present metastases at the time of diagnosis, and approximately 35% of patients will subsequently develop a metastatic disease (2). The prognosis of patients with metastatic colorectal cancer (mCRC) has improved over the last 20 years, thanks to the introduction of active chemotherapy drugs, such as fluoropyrimidines, oxaliplatin, irinotecan, and of targeted drugs, such as bevacizumab, cetuximab, panitumumab, aflibercept, and ramucirumab that led to an increase in median overall survival (OS) from 6 months, with the only best supportive care (BSC), to approximately 30 months (2,3).

In addition, almost 30% of patients with mCRC refractory to standard chemotherapy regimens will remain good candidates for further treatment (4). Recent studies have demonstrated clinical benefit from regorafenib and TAS-102 treatments in this setting of patients (5-7).

Regorafenib is an oral multikinase inhibitor that selectively targets three key pathologic processes implicated in oncogenesis (by inhibition of *KIT*, *RET*, *RAF-1* and *BRAF* activity), angiogenesis (by targeting VEGFR1–3 and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), and regulation of tumor microenvironment (8,9) by blocking stromal kinases such as platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) (8-10). The phase III study showed that regorafenib provided a significant improvement in OS and in progression free survival (PFS) in patients with mCRC who failed previous therapies. (5) Thus, Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved regorafenib as the first oral multikinase inhibitor for the treatment of mCRC patients.

TAS-102 is an oral combination of an antineoplastic thymidine-based nucleoside analog (FTD, trifluridine) and tipiracil hydrochloride, a potent inhibitor of thymidine phosphorylase, an enzyme that degrades trifluridine (11,12). Based on results of the RECOURSE study, a randomized phase III trial demonstrating a significant improvement in OS, PFS, with a favorable safety profile (6), TAS-102 has been approved for the treatment of mCRC refractory to standard treatments.

TAS-102 and the multitargeted tyrosine kinase inhibitor regorafenib represent the last approved drugs for the overgrowing population of patients with chemo refractory mCRC that still maintain a

good clinical condition after failure of the two initial lines of treatment. Unfortunately, we are currently lacking predictive biomarkers for efficacy for both drugs, and we do not know which is the best choice between the two therapeutic options or the best sequential treatment in this patient setting.

To address this question, we conducted a retrospective analysis evaluating safety and efficacy of TAS-102 and regorafenib in a cohort of mCRC patients refractory to standard therapies with the aim of assessing the optimal sequence treatment for these two drugs.

Material and Methods

Patients selection: This retrospective analysis included patients with histologically confirmed, unresectable, mCRC, who had previously treated with, or are not candidate for available therapies including fluoropyrimidine based chemotherapies, an anti-VEGF therapy and an anti-EGFR therapy (RAS wild-type tumors). 140 mCRC patient's refractory to the standard drugs (oxaliplatin, 5-Fluoruracil, irinotecan) have been selected and treated with regorafenib or TAS-102 treatment in three different centers (Precision Medicine Department, Medical Oncology, University of Campania, "L. Vanvitelli", Naples, Italy; Department of Medical Oncology, INCLIVA Biomedical Research institute, University of Valencia, Valencia, Spain; Department of Oncology, University of Turin, Candiolo Cancer Institute - FPO- IRCSS, Candiolo, Italy) between January 1th 2018 and May 31 2020.

The eligibility criteria were as follows: i) histologically confirmed adenocarcinoma of the colon or rectum, and presence of unresectable metastatic disease; ii) history of treatments with fluoropyrimidine, irinotecan, oxaliplatin, and anti-VEGF antibody (bevacizumab), or anti-epidermal growth factor receptor (EGFR) antibody (cetuximab or panitumumab) for patients who had *RAS* wild-type tumor; iii) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; and iv) adequate bone-marrow, liver, and renal function at the start of the treatment. Patients were excluded if they had previously received regorafenib or TAS-102, or had uncontrolled medical disorders.

The Institutional Review Board for Clinical Research approved all procedures for this retrospective observational study (no. 54 of 29/01/2020), which was conducted in accordance with the Declaration of Helsinki.

Treatments: Regorafenib was administered at 160 mg once daily on days 1-21 of every 28-day cycle. TAS-102 was administered at 35 mg/m2 orally, twice daily, on days 1-5 and 8-12 of every

28-day cycle. Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest**.**

Assessments: All patients underwent computed tomography every 8 weeks to assess tumor responses to therapy in terms of change from baseline during treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patient characteristics, adverse events (AEs), treatment compliance, treatment response, and PFS and OS were analyzed retrospectively.

The tumor response rate was defined as the proportion of patients with complete (CR) or partial (PR) responses, and the disease control rate (DCR) was defined as the proportion of patients with a best response of CR or PR or stable disease (SD).

The primary endpoint was the PFS (progression free survival). Secondary endpoint included overall survival (OS), and evaluation of the toxicity.

PFS1 has been defined as the interval from the first administration of the first treatment to the first radiologic or clinical observation of disease progression or death from any cause, whichever came first (Figure 1).

PFS2 has been defined as the interval from the initiation of the secondary treatment to the second progression, for those who had undertaken crossover between treatments after a first progression (Figure 1). OS1 has been defined as the time between the administration date of the primary treatment and the date of death from any cause, and OS2 as the time between the administration date of the secondary treatment, if applicable, and the date of death (Figure 1). The median PFS1, PFS2, OS1 and OS2 were estimated using the Kaplan-Meier method.

Statistical analysis: Descriptive statistical analysis was performed for the overall data and the most interesting stratification factors. Differences between categorical data were calculated with Fisher's exact test. Survival curves were plotted using the Kaplan-Meier method and compared using the Log-rank test at a significance level of 5%. Cox regression models were used to generate Hazard Ratios (HR) and corresponding 95% Confidence Intervals (CI). All statistical analyses were performed using the SPSS package (v.18) and Graph Pad Prism 9.

Results

Patient characteristics

Between 1th January 2018 and May 2020, in three different institutions, 140 mCRC patients who were treated with regorafenib or TAS-102 were included in the analysis. All patients had received prior chemotherapy regimens containing fluoropyrimidines, oxaliplatin, and irinotecan. Of these patients, 64 received regorafenib and 76 received TAS-102 as first treatment. Table 1 shows the patients' baseline characteristics. In according to demographics tables (Table 1), the baseline characteristics were similar and well balanced between two arms of treatment. All patients had previously received an anti-VEGF monoclonal antibody. More patients in the TAS-102 group had received previous anti-EGFR treatment than those in the regorafenib group (50% versus 32%, p-value=0.89). Baseline characteristics in patients with extended RAS mutational status were pretty similar in both groups (62 % in the regorafenib group and 48 % in the TAS-102 group) (p=0.09). Moreover, more patients in the TAS-102 group showed BRAFV600E mutation than in the regorafenib group. (9,5 % versus 4,9%, p-value=0.51). At the time of the analysis among 64 patients in the regorafenib group, 4 (6%) are still ongoing whereas 60 patients showed disease progression. After progression, 24 (37%) patients switched to secondary treatment with TAS-102, 7 (11%) patients switched to other treatments and 29 (45%) patients switched to best supportive care. Instead, in the TAS-102 group, among 76 patients, 6 (8%) are still ongoing, 29 (45%) patients switched to secondary treatment with regorafenib, 7 (9%) patients switched to other treatments, 29 (38%) switched to best supportive care.

Efficacy

Table 2 shows the tumor responses. No patient in either group had a CR or PR. Disease control was achieved in 8 (12,5%) out of 64 patients in the regorafenib group and 17 (22,4 %) out of 76 patients in the TAS-102 group. The median PFS1 was 2.5 months [CI 95% confidence interval (CI)= 2.05-3.07 months] in the regorafenib group and 3.0 months (CI 95% =2.3-3.6 months) in the TAS-102 group with the p-value: 0.25 (Table 2, Figure 2). The median OS1 was 6.8 months (CI 95% =5.1-8.5 months) in the regorafenib group and 7.6 months (CI 95% =5.5-9.6 months) in TAS-102 group with p-value: 0.41 (Table 2, Figure 2). Moreover, we provide also data on analysis of PFS2 and OS2 for patients that switched to a secondary treatment with TAS-102 or regorafenib respectively. In particular, PFS2 was 2.6 months (CI 95%=2.1-3.1 months) in who received crossover treatment with regorafenib to TAS-102 and 2.0 months (CI 95% =1.2-2.6 months) in who received crossover treatment with TAS-102 to regorafenib with a p-value: 0.11 (Table 2, Figure 2). The median OS2

was 5.1 (CI 95%=1.8-8.4 months) in TAS-102 group and 4.5 months (CI 95% =3.3-5.6 months) in regorafenib group respectively, with a no statistically significant p-value of 0.08 (Table 2, Figure 2). Additionally, we performed a subgroup analysis according to baseline characteristic, in order to better define differences between two groups. No statistical differences have been reported between two groups in PFS and OS for all parameters analyzed (Figure 3, Supplementary Table 1-4).

In particular, regarding RAS mutational status, the PFS1 for RAS wild type was 3.4 months CI 95% (2.4-4.2) in TAS-102 group and 3.0 months Ci 95% (1.6-4.5) in regorafenib group respectively, with no statistical difference. The PFS1 for RAS mutant was 1.9 months CI 95% (1.6-2.2) in TAS-102 group and 2.7 months CI 95% (1.9-3.4) in regorafenib. Regarding OS1, the OS1 for RAS wild type was 8.8 months CI 95% (6.2-11.4) in TAS-102 group, 8.0 months Ci 95% (5.6-10.5) in regorafenib group. Moreover, we performed the same sub-group analysis according to RAS status, for the patients that switched to second treatment as well. The PFS2 for RAS wild type was 2.7 months with CI 95% (2.0-3.4) in TAS-102 group and 1.8 months CI 95% (1.0-2.5) in regorafenib group. The PFS2 for RAS mutant was 2.6 months CI 95% (1.7-3.5) in TAS-102 group and 2.4 months CI 95% (1.6-3.2) in regorafenib group. The OS2 for RAS wild type was 4.3 CI 95% (3.3-5.5) in TAS-102 group 4.6 months CI 95% (3.1-6.0) in regorafenib group. The OS2 for RAS mutant was 6.1 months CI 95% (0.4-11.4) in TAS-102 group and 4.5 CI 95% (3.0-6.0) in regorafenib group. No statistical differences have been observed for any of parameter analyzed.

Safety and Adverse Events

Patients received a median daily dose of regorafenib of 160 mg. The median daily dose of TAS-102 was 110 mg. For that concern the toxicity there was no evidence of any unexpected toxicity, generally both drugs were well tolerated. Dose modifications were required in 78 out of 93 patients (83.9% of total number of patients) receiving regorafenib and 73 out of 100 patients (73% of total number of patients) receiving TAS-102 (Table 3). Adverse Events (AEs) were the most common reason for dose modification, although no one led to treatment discontinuation. In both groups, the reason for treatment discontinuation was radiological disease progression. No patient in either group had a treatment-related death.

The most common AEs with regorafenib were fatigue, followed by hand foot syndrome rash (HFS), diarrhea, hyperbilirubinemia and hypertransaminasemia. Grade 3 or more drug-related AEs occurred in 53 out of 93 patients receiving regorafenib treatment (57%) (Table 4A).

One dose reduction (120mg) has been observed in 26 out of 93 patients (28%) in regorafenib group, two dose reduction level (80 mg) in 41 out of 93 patients (44 %) and three dose level reduction was necessary in 11 out of 93 patients (12%) of regorafenib treated patients (Table 3).

Similarly, for the TAS-102 (Table 4B) no unexpected toxicity where observed. The most frequent AE was neutropenia. Grade 3 or more drug-related AEs occurred in 37 out of 100 patients receiving TAS.102 treatment (37%) (Table 4B). Other toxicity reported were: diarrhea, fatigue and anemia. One dose reduction has been observed in 41 out of 100 patients (41%), two dose reduction has been observed in 32 out of 100 patients (32%), whereas no one experienced a three-dose reduction (Table 3).

Discussion

Colorectal cancer (CRC) is considered the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.8 million new cases in 2018 (1). Approximately 25% of patients with CRC present with metastases, and 50% of patients presenting with locoregional disease eventually develop metastatic disease (2). For patients with surgically unresectable/metastatic colorectal cancer (mCRC), the expected 5-year survival is less than 15%. Despite significant advances in treatment of mCRC with currently available regimens, response rates for those that progress after first-line treatment are only 4–17% (2,3). Therefore, novel therapies are needed to improve survival outcomes for patients with this widely prevalent malignancy. Recently, there has been interest in clinical research for the treatment of chemotherapy-resistant mCRC to further improve outcomes in this specific setting. Thus, the need for efficacious and less toxic treatment options has been recognized. Recently, survival benefits have been demonstrated with the introduction of two new agents, TAS-102 and regorafenib, that have been approved after the failure of standard chemotherapies in patients with mCRC (5,6). However, criteria for the appropriate selection of regorafenib or TAS-102 have not yet been established. Moreover, which subpopulations of patients may derive the greatest benefit from salvage-line treatment with these drugs compare to best supportive care, need to be addressed. Thus, we evaluated retrospectively the efficacy and toxicity of both drugs in a head to head comparation study in patients with mCRC who were intolerant to standard chemotherapies. The present study is the first one to compare the activity of the two agents in a large cohort of chemo-refractory mCRC patients providing more details about the best sequence, to be incorporated in clinical practice. The evaluation of efficacy and safety in patients treated with regorafenib or TAS-102 in the real-life setting is important for physicians, because patient characteristics in real-life, such as ECOG PS, mutational status, number of prior regimen lines, may differ from those in clinical trials.

Previously, Tanaka et al have performed a retrospective study on a single cohort of Asian population (13). In particular, a relatively small number of forty-four patients treated with regorafenib or TAS-102 were included in their analysis; among them, only 17 received crossover treatment. The authors conclude that the two drugs were equivalent in terms of DCR: 75.0 % regorafenib and 70.8% for TAS-102 in primary salvage treatment, and 60.0 and 57.1%, respectively, in secondary use (13). Crossover administration was achieved in 7 out of 20 (35.0%) patients treated with regorafenib first, and in 10 out of 24 (41.7%) patients treated with TAS-102 first, but this does not imply inferiority (13).

Moreover, a recent meta-analysis has observed similar results for TAS-102 and regorafenib, at a starting dose of 160 mg/day, with no statistically significant difference in OS between the two drug regimens (14). These findings can be explained by the different toxicity profile of the 2 drugs. Although both drugs are associated with increased incidence of treatment-emergent grade 3–4 AEs, the two drugs have very distinct type of adverse event profiles (14). Regorafenib is frequently associated with AEs commonly reported for tyrosine kinase inhibitors, such as diarrhea, hand–foot skin reaction, or hypertension, while TAS-102 is more frequently associated with hematological abnormalities. In their meta-analysis authors concluded that Regorafenib was associated with higher toxicity than TAS-102 overall (14).

Here, in our retrospective study, we reported data collected in three different institutions, of 140 mCRC patients treated with regorafenib or TAS-102. The tumor response in this analysis was similar between the two treatment groups. No patient had a CR or PR in either group. The DCR was 12.5% in the regorafenib group and 22.4% in the TAS-102 group. The DCR found in this analysis was less in both groups than that in found in previous clinical trials. In terms of efficacy, the PFS and OS were similar in both treatment groups and these data were consistent with that of previous clinical trials. These results indicate that regorafenib or TAS-102 confer similar improvements in survival among patients with mCRC who are refractory to standard treatments.

Concerning the toxicity profile, AEs reported in this analysis were mostly consistent with the known safety profiles of regorafenib and TAS-102 in previous clinical trials. AEs associated with both drugs were mainly reversible and not life-threatening. In particular, AEs of grade 3 or more were more frequent in the regorafenib group than in the TAS-102 group. The mostly frequents reported grade 3 or more AEs in patients receiving regorafenib were neutropenia, hand–foot syndrome, and liver dysfunction. These adverse events can cause significant suffering and require dose adjustment and treatment discontinuation. Grade 3 or more drug-related AEs occurred in 57% patients receiving regorafenib treatment compared to 37% patients receiving TAS-102 treatment. Additionally, three dose level reduction was necessary in 12% of regorafenib treated patients,

whereas no one experienced a three-dose reduction in TAS-102 treated patients. Because of worsen regorafenib-related events, it is possible that regorafenib-related adverse events affected disease progression during treatment and prompted treatment discontinuation. Therefore, it is highly important to consider toxicity-driven dosing in order to determine treatment choice (15).

Finally, the decision of which drug to choose for an individual patient should consider several factors including tumor shrinkage, patient comorbidities, and the toxicity profile. Overall, the optimal sequence of these drugs remains unknown.

Conclusions

In conclusion, in the absence of direct head-to-head comparison studies, the present retrospective study evaluated and compared the efficacy and safety of regorafenib and TAS-102 in a large cohort of mCRC patient's refractory to standard therapies with the aim of assessing the optimal sequence treatment for these two drugs.

These observations have potential relevance and could be useful to design future clinical trials.

Limitations of this study include that the cohort of patients, in our retrospective analysis is small therefore, one cannot make wider inferences based on this data.

In the future, the detection of potential predictive or prognostic biomarkers, or the evaluation of combination therapy with other cytotoxic and biological drugs is warranted to address further tailoring treatments for mCRC refractory to standard therapies.

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Figure Legend

Figure 1: Study design. Flow diagram of salvage-line therapy. Each agent was administered at the discretion of the attending physician. TAS-102, trifluridine and tipiracil; OT, other treatments; BSC, best supportive care; OS, overall survival; PFS, progression-free survival.

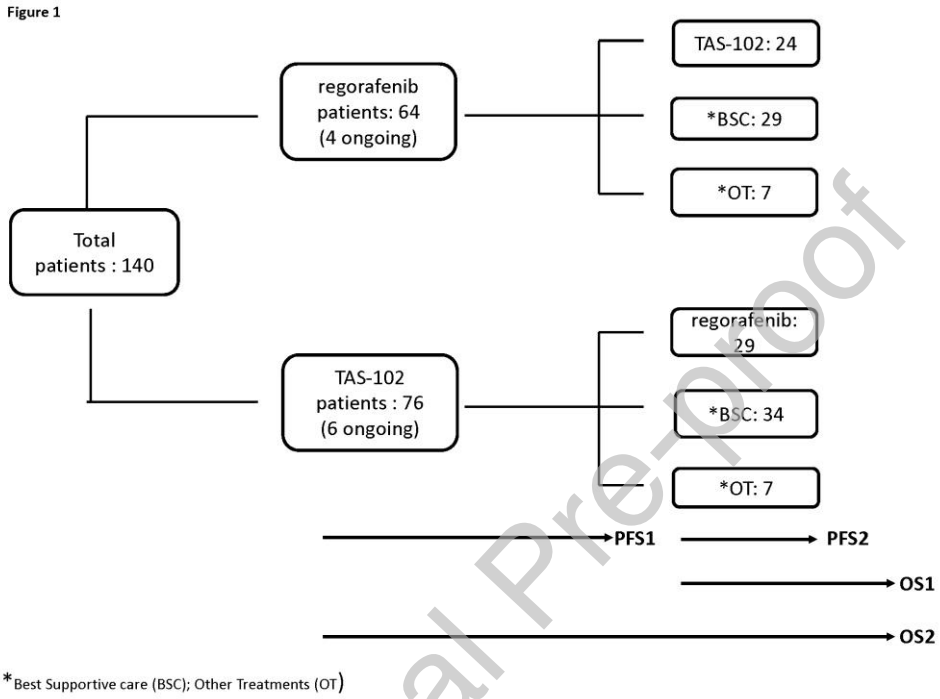

Figure 2: Efficacy of regorafenib versus TAS-102 in chemorefractory mCRC patients. Kaplan-Meier analysis of progression-free survival and overall survival. HRs are from stratified log-rank tests. HR=hazard ratio. CI, confidence interval.

Figure 2

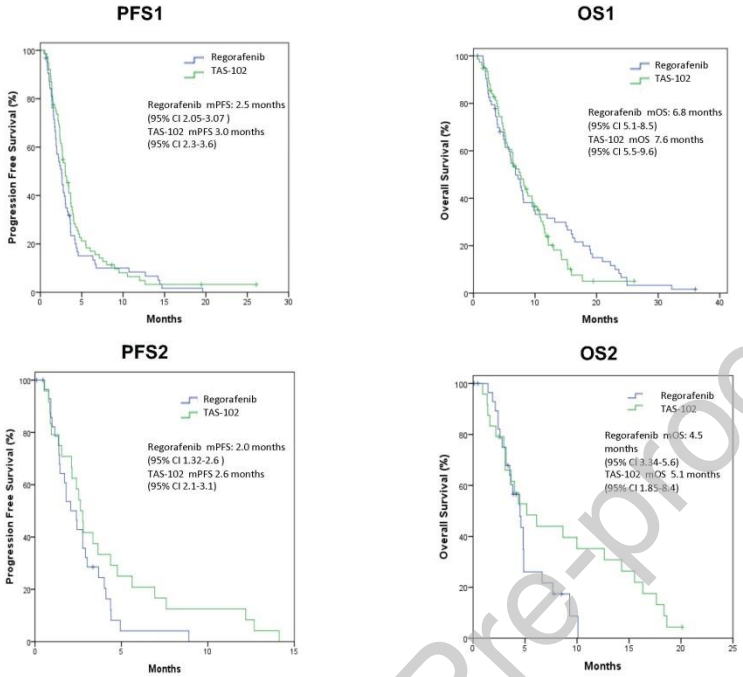

Figure 3: Efficacy in subgroups. Subgroup analysis of progression-free survival and overall survival in the regorafenib group versus TAS-102 group. ECOG, Eastern Cooperative Oncology Group.

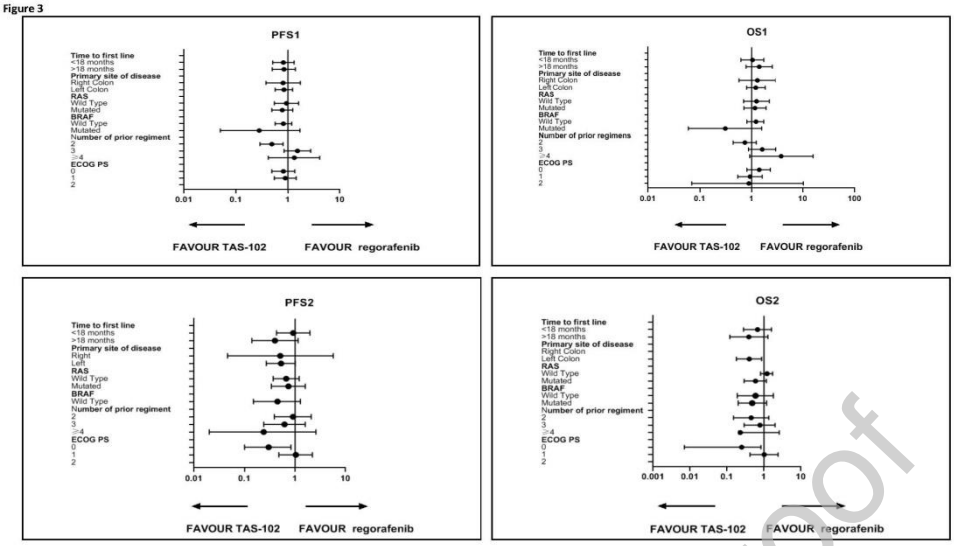

Table 1: Patients demographics and baseline characteristics. Data are n (%). ECOG, Eastern Cooperative Oncology Group. EGFR, epidermal growth factor receptor. VEGF, vascular endothelial growth factor. BSC, best supportive care.

Table 2: Tumor Response. Response evaluation criteria in solid tumors (RECIST) version 1.1; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; OS, overall survival; PFS, progression-free survival.

Table 3: Dose reductions. Data are n (%). The table lists dose reductions events that occurred in both treatment groups.

Table 4 Drug related adverse event. **A**: Regorafenib related adverse events. **B.** TAS-102 related adverse events. Data are n (%). The table lists any grade events that occurred in regorafenib treatment group. HFS, hand and foot syndrome reaction.

Table 1: Patients demographics and baseline characteristics

Characteristics	*regorafenib*	*TAS-102*	*p-value*
ECOG PS			
0	29(45%)	38(50%)	0.50
1	32(50%)	37(49%)	
2	3(5%)	1(1%)	
Primary site of disease			
Right Colon	14(22%)	16(21%)	1.00
Left Colon	50(78%)	60(79%)	
RAS			
Wild type	24(37%)	39 (52%)	0.09
Mutated	40(62%)	36(48%)	
BRAF			
Wild type	58(95%)	67(90%)	0.51
Mutated	3(5%)	7(9%)	
Number of prior regimens			
2	32 (50%)	42(55%)	0.74
3	25(39%)	28(37%)	
>4	7(11%)	6(8%)	
Metastatic Sites			
Liver	45(70%)	52(68%)	0,96
Lung	37(58%)	40(52%)	
Peritoneum	20(31%)	21(27%)	
Lymph Node	27(42%)	25(32%)	
Others	17(26%)	21(27%)	
Time to first line			
<18 months	35 (55%)	38 (50%)	0.61
>18 months	29 (45%)	38 (50%)	
Systemic chemotherapy			
Fluoropyrimidine	64 (100%)	76 (100%)	0.89
Irinotecan	63 (98%)	74 (97%)	
Oxaliplatin	59 (92%)	72 (95%)	
Anti-VEGF	64 (100%)	76 (100%)	
Anti-EGFR	21 (32%)	34 (50%)	
Patient switched to TAS-102 or regorafenib	24(37%)	29(38%)	0.97
Patient switched to other treatments	7(11%)	7(9%)	
Patients switched to BSC	29(45%)	34(45%)	
Patient ongoing to first treatments	4(6%)	6(8%)	

Table 2: Tumor Response

Characteristics	*regorafenib*	*TAS-102*	*p-value*
FIRST TREATMENT RESPONSE			
RR (CR+PR), n(%)	0(0%)	0(0%)	
DCR (CR+PR+SD), n(%)	8(12%)	17(22%)	
CR, n(%)	0(0%)	0(0%)	0,18
PR, n(%)	0(0%)	0(0 %)	
SD, n(%)	8(12%)	17(22%)	
PD, n(%)	56(87%)	59(78%)	
SECONDARY TREATMENT RESPONSE			
RR (CR+PR), n(%)	0(0%)	0(0%)	
DCR (CR+PR+SD), n(%)	3(10%)	4(17%)	
CR, n(%)	0(0%)	0(0%)	0,68
PR, n(%)	0(0%)	0(0%)	
SD, n(%)	3(10%)	4(17%)	
PD, n(%)	27(90%)	20(83%)	
Median PFS1 (months)	2.5 (95%CI 2.05-3.07)	3.0 (95%CI 2.3-3.6)	0.25
Median OS1 (months)	6.8 (95%CI 5.1-8.5)	7.6 (95%CI 5.5-9.6)	0.41
Median PFS2 (months)	2.0 (95%CI 1.32-2.6)	2,6 (95%CI 2.1-3.1)	0.11
Median OS2 (months)	4,5 (95%CI 3.34-5.6)	5,1 (95%CI 1.85-8.4)	0.08

Table 3: Dose reductions.

Number of the patients with dose reductions	***regorafenib 93 (100%)***	***TAS-102 100 (100%)***
One level dose reductions	26(28%)	41(41%)
Two level dose reductions	41(44%)	32(32%)
Three level dose reductions	11 (12%)	0(0%)
Total dose reductions	78(84%)	73(73%)

Table 4A: Regorafenib related adverse events.

Patients' number (93)	***Any grade***	***Grade ≥ 3***
Drug's allergy	1(1%)	0(0%)
Fatigue	46(49%)	15(16%)
Anorexia	5(5%)	0(0%)
Diarrhea	11(12%)	2(2%)
Dyspnea	2(2%)	0(0%)
Pain	1(1%)	1(1%)
Hemorrhage	2(2%)	0(0%)
HFS	34(36%)	25(27%)
Hyperbilirubinemia	4(4%)	1(1%)
Hypertension	6(6%)	1(1%)
Hypertransaminasemia	8(9%)	0(0%)
Proteinuria	3(3%)	0(0%)
Rash	10(11%)	2(2%)
Mucositis	5(5%)	3(3%)
Nausea	3(3%)	0(0%)
Neutropenia	3(3%)	2(2%)
Dysphonia	3(3%)	1(1%)
Anemia	2(2%)	0(0%)
Total	149	53

Table 4B: TAS-102 related adverse events.

Patients' number (100)	*Any grade*	*Grade ≥ 3*
Anemia	10 (10%)	6 (6%)
Neutropenia	49 (49%)	16 (16%)
Febrile Neutropenia	0 (0%)	5 (5%)
Constipation	2 (2%)	0 (0%)
Diarrhea	8 (8%)	1 (1%)
Thrombocytopenia	4 (4%)	2 (2%)
Nausea	5 (5%)	1 (1%)
Fatigue	41(41%)	6 (6%)
Total	119	37

Clinical Practice Points

- Regorafenib and TAS-102 are novel antitumor agents for patients with refractory mCRC. However, it is unclear which patients may derive a survival benefit from these drugs in real-life clinical practice.

- In the absence of direct head-to-head comparison studies, the present retrospective study evaluated and compared the efficacy and safety of regorafenib and TAS-102 in a large cohort of mCRC patient's refractory to standard therapies with the aim of assessing the optimal sequence treatment for these two drugs.

- The evaluation of efficacy and safety in patients treated with regorafenib or TAS-102 in the real-life setting is important for physicians, because patient characteristics in real-life, such as ECOG PS, mutational status, number of prior regimen lines, may differ from those in clinical trials.

MicroAbstract

Regorafenib and TAS-102 are novel antitumor agents for patients with refractory mCRC. We performed a retrospective analysis evaluating safety and efficacy of TAS-102 and regorafenib in 140 refractory mCRC patients, in three different centers, with the aim of assessing the optimal sequence treatment for these two drugs. PFS, OS were similar in both treatment groups for primary and secondary treatments.