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ORIGINAL ARTICLE

# Comparison of skeletal muscle mass loss in patients with metastatic colorectal cancer treated with regorafenib or TAS-102

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## Summary

***Purpose:*** *To assess whether regorafenib and TAS-102 treatments are associated with a change in Skeletal Muscle Area (SMA) as well as to compare Skeletal Muscle Mass (SMM) loss levels between regorafenib and TAS-102 treatments and prognostic significance in the patients with metastatic colorectal cancer (mCRC).*

***Methods:*** *A total of 36 mCRC patients, who received regorafenib or TAS-102 in the third-line and subsequent settings were assessed in the analysis. SMM changes were assessed with CT scans findings, and they were categorized into two groups as SMM-loss (SMM decrease ≥2%) and SMM-stable (SMM change <2%).*

***Results:*** *The SMM change after regorafenib therapy was significantly worse compared with TAS-102 therapy (p=0.001). The median overall survival (OS) was longer in SMM-stable group than in SMM-loss group (12.8 months; 95%CI:9.8-15.7) vs. 6.4 months; 95%CI:5.2-7.7, respectively;p=0.04). Cox regression analysis showed that SMM loss was independent prognostic indicator for OS (HR, 2.87; 95%CI: 1.07-7.42, p=0.03).*

***Conclusion:*** *Although patients who received regorafenib had more SMM loss than those who received TAS-102, there was no difference in OS between drugs.*

***Key words:*** *metastatic colorectal cancer, regorafenib, TAS-102, sarcopenia, skeletal muscle mass*

## Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and one of the leading cause of cancer-related deaths in Europe and the United States [1]. Approximately 25% of newly diagnosed CRC patients are *de novo* metastatic. Approximately 25-30% of patients with stages 2 and 3 disease become metastatic within 5 years [2,3].

Regorafenib, a new oral multi-kinase inhibitor, has shown antitumor activity in previously treated metastatic colorectal cancer (mCRC) patients previously treated with fluoropyrimidine plus oxaliplatin or fluoropyrimidine and irinotecan-based chemotherapy±anti-vascular endothelial growth factor (anti-VEGF) treatment or anti-epidermal growth factor receptor (anti-EGFR) treatment [4]. The efficacy of regorafenib has been shown in two randomized placebo-controlled phase III trials, CORRECT and CONCUR, that were conducted in patients with mCRC progressing on standard treatments [5-7].

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Trifluridine and tipiracil hydrochloride (TAS-102) is a combination of the thymidine-based nucleoside analog trifluridine and the thymidine phosphorylase inhibitor tipiracil. Efficacy and safety of TAS-102 in patients with mCRC refractory or intolerant to standard therapies were evaluated in the phase 3 RECOURSE trial. Results of RECOURSE demonstrated significant improvement in overall survival (OS) and progression-free survival (PFS) with TAS-102 versus placebo [hazard ratio (HR) = 0.68 and 0.48 for OS and PFS, respectively; both p<0.001] [8].

Muscle mass loss in cancer patients, including mCRC, is common and not exclusive to underweight patients [9]. Muscle mass loss and low muscle mass (sarcopenia) are associated with poor treatment outcomes [10]. Skeletal muscle area predicts clinical outcome independent of body weight, and objective assessment is feasible [11-15]. Despite their prognostic utility, dynamics of the body weight and body mass index (BMI) are susceptible to common conditions in mCRC, such as peripheral edema and ascites, and they are poorly correlated with skeletal muscle area or adipose tissue. In contrast to visceral adipose tissue, skeletal muscle dynamics differ considerably between regional muscle compartments, whereas the upper extremities are most susceptible to skeletal muscle loss. Estimation of skeletal muscle area from cross-sectional computed tomography (CT) scans at the level of the third lumbar vertebra is considered to be a reference method in clinical practice and was our modality of choice because of the availability of CT scans performed during the routine care of cancer patients [16,17].

Sarcopenia diagnosed with skeletal muscle area (SMA) at the level of L3 vertebra can be a negative predictor of survival outcomes for mCRC and non-metastatic CRC patients [18,19].

In this study, we aimed to investigate whether regorafenib and TAS-102 treatments are associated with a change in SMA as well as to compare skeletal muscle mass loss levels between regorafenib and TAS-102 treatments and prognostic significance in the patients with mCRC.

## Methods

*Study design*

The medical records of mCRC patients admitted to oncology outpatient clinics, who were treated with regorafenib monotherapy or TAS-102 for refractory mCRC as third-line and subsequent treatment settings, in 2015 through 2019, were retrospectively analyzed. Finally, 36 mCRC patients histologically confirmed, who received regorafenib or TAS-102 in the third-line and subsequent settings, who were previously treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy±anti-VEGF therapy (e.g. bevacizumab, ziv-aflibercept) or anti-EGFR [20] (e.g. panitumumab, cetuximab) when appropriate were included in the analysis.

The baseline data of all patients were derived from file data, including disease characteristics, patient demographics, the Eastern Cooperative Oncology Group Performance Status (ECOG PS), treatments and response to treatments. After the failure of standard treatments, regorafenib started as monotherapy at a dose of 160 mg/day for 21 days with a 28-day administration. At the discretion of the treating physicians, a lower initial dose was allowed depending on the clinical condition of the patient and thereafter the dose was increased 40 mg/week up to a maximum dose of 160 mg, based on the patient's tolerability. TAS-102 started as 35 mg/m$^2$ for 5 days a week, with 2-day rest, for 2 weeks, followed by a 14-day rest period, thus completing one treatment cycle. The regimen was repeated every 4 weeks. The protocol allowed for a maximum of three reductions in dose in decrements of 5 mg/m$^2$. OS was calculated as the time from the date of regorafenib and TAS-102 initiation to the date of death due to any reason or lost follow-up.

*Ethical approval*

This study was conducted after obtaining ethical approval from the Local Research Ethics Committee, with decision number 2019/484. All procedures and stages in this multicenter retrospective study were carried out in line with the World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects", amended in October 2013.

*Skeletal muscle parameters*

Baseline and follow-up CT studies of the patients were performed (Aquillon, 64- detector, Toshiba Medical Systems, Tokyo, Japan) and the CT parameters were as follows: gantry rotation time, 0.5 s; section collimation, 0.5 mm; helical pitch 53; 125 mAs; and 120 kVp. CT images which were performed at the diagnosis and follow-up during the treatment period were used for analysis. To measure the cross-sectional areas of SMA, L3 was set as a landmark [21], and muscles were identified based on their anatomic features, and the structure of those specific muscles was quantified based on pre-established thresholds of skeletal muscle tissue [22]. Cross-sectional areas (cm$^2$) of muscle tissues were computed from each image. The total lumbar-skeletal muscle cross-sectional area is linearly correlated to the whole-body muscle [9].

Skeletal muscle volume (SMV) (L) = 0.1 66 L/cm$^2$ × skeletal muscle area in cm$^2$ + 2.1 42 L;

Skeletal muscle mass (SMM) (kg) = Skeletal muscle volume in L × 1.06 g/cm$^3$.

Absolute and percentage of SMM changes were calculated for any two available consecutive CT scans. A measurement error of 2% was adopted based on previously reported accuracy of CT for skeletal muscle analysis as in the available literature [9]. SMM changes were categorized into two groups: SMM loss (SMM decrease ≥2%) and not loss (SMM change <2%). Moreover, the

images were evaluated by two radiologists who had abdominal imaging experience and were blind about treatment groups.

*Statistics*

Data were presented as median and 25th-75th interquartile range (IQR). Categorical variables were reported as frequencies and group percentages. Changes from baseline SMA, SMV and SMM were summarized by median (25-75th IQR). Change from baseline was tested by signed rank test. OS values were estimated using the Kaplan-Meier method. Univariate and multivariate analysis to determine independent risk factors on skeletal muscle loss were analyzed by the binary logistic regression method which was adjusted for age, gender and treatment choice. Cox regression method adjusted for age, presence of skeletal muscle loss and treatment choice was used to determine predictors of survival. A p value less than 0.05 was considered as statistically significant.

**Table 1.** Demographic and clinical characteristics

| *Characteristics* | *All (n=36)* *n (%)* | *Regorafenib (n=21)* *n (%)* | *TAS-102 (n=15)* *n (%)* | *p value* |
|---|---|---|---|---|
| Age, years | | | | <0.001 |
| Median | 62 | 67 | 53 | |
| Interquartile range | 52-69 | 62-72 | 48-69 | |
| Gender | | | | 0.73 |
| Female | 18 (50.0) | 11 (52.4) | 7 (46.7) | |
| Male | 18 (50.0) | 10 (47.6) | 8 (53.3) | |
| Primary tumor site | | | | 0.84 |
| Right | 9 (25.0) | 5 (23.8) | 4 (26.7) | |
| Left | 27 (75.0) | 16 (76.2) | 11 (73.3) | |
| RAS status | | | | 0.46 |
| Wild | 17 (47.2) | 11 (52.4) | 6 (40.0) | |
| Mutant | 19 (52.8) | 10 (47.6) | 9 (60.0) | |
| Primary tumor resection | 26 (72.2) | 13 (61.9) | 13 (86.7) | 0.10 |
| Metastasis status | | | | 0.32 |
| Synchronous | 27 (75.0) | 4 (19.0) | 5 (33.3) | |
| Metachronous | 9 (25.0) | 17 (81.0) | 10 (66.7) | |
| Metastasis site | | | | |
| Liver | 24 (68.6) | 13 (65.0) | 11 (73.3) | 0.59 |
| Lung | 7 (20.6) | 3 (15.8) | 4 (26.7) | 0.43 |
| Peritoneal | 5 (14.7) | 5 (26.3) | 0 (0) | 0.05 |
| Metastasectomy | 13 (36.1) | 5 (23.8) | 8 (53.3) | 0.09 |
| First-line backbone | | | | 0.66 |
| FOLFOX/CapeOx | 25 (69.4) | 14 (66.7) | 11 (73.3) | |
| FOLFIRI | 11 (30.6) | 7 (33.3) | 4 (26.7) | |
| First-line targeted option | | | | 0.82 |
| Anti-VEGF | 20 (55.6) | 12 (57.1) | 8 (53.3) | |
| Anti-EGFR | 7 (19.4) | 4 (19.0) | 3 (20.0) | |
| Second-line backbone | | | | |
| FOLFOX/CapeOx | 13 (36.1) | 7 (33.2) | 6 (40.0) | 0.68 |
| FOLFIRI | 23 (63.9) | 14 (66.7) | 9 (60.0) | |
| Second-line targeted option | | | | |
| Anti-VEGF | 18 (50.0) | 10 (47.6) | 8 (53.3) | 0.73 |
| Anti-EGFR | 7 (19.4) | 4 (19.0) | 3 (20.0) | 0.94 |
| Treatment-line | | | | 0.47 |
| 3rd line | 23 (63.9) | 15 (71.4) | 8 (53.3) | |
| 4th line | 10 (27.8) | 5 (23.8) | 5 (33.3) | |
| 5th line | 3 (8.3) | 1 (4.8) | 2 (13.3) | |

FOLFOX/CapeOX: 5-Fluorouracil-oxaliplatin-folinic acid/capecitabine-oxaliplatin, FOLFIRI: 5-Fluorouracil-irinotecan-folinic acid, Anti-VEGF: anti-vascular endothelial growth factor, Anti-EGFR: anti-epidermal growth factor receptor

## Results

A total of 36 patients (21 patients in regorafenib and 15 patients in TAS-102) were treated at the third-, fourth- and fifth-line settings. Median age was 62 years (IQR, 52-69) and patients receiving TAS-102 were younger comparing with those with regorafenib group (53, IQR, 48-69) vs. 67 (IQR, 62-72) years p<0.001, respectively). Table 1 demonstrates the demographic and clinical characteristics of the study subjects. Treatment regimens at the first- and second-line were similar between groups. Subsequently, 15 (71.4%) were treated with regorafenib at the third-line, 5 (23.8%) at the fourth-line, and 1 (4.8%) at the fifth-line. For TAS-102, 8 patients (53.3%) were treated at the third-line, 5 (33.3%) at the fourth-line and 2 (13.3%) at the fifth-line.

Median duration of treatment was comparable between groups; it was 13.2 (IQR,11.2-21.0) weeks in the regorafenib and 8.3 (IQR,7.3-23.0) weeks in the TAS-102 group (p=0.35). Table 2 shows the skeletal muscle measurements of the study subjects. Although baseline CT image analysis of SMA, SMV and SMM were similar between groups, these parameters at progression CT analysis showed that in the sorafenib group there was a trend towards reduced skeletal muscle parameters compared with the TAS-102 therapy (p=0.06). Accordingly, skeletal muscle mass change after regorafenib therapy was significantly worse than TAS-102 therapy (p=0.001). Predictors of the skeletal muscle loss are shown in Table 3. Whereas age, gender, tumor site, RAS mutation, treatment line, liver and peritoneal metastasis were not significant predictors of skeletal muscle loss, only regorafenib therapy was an independent predictor of the skeletal muscle loss (HR 10.0, 95%CI 1.46-68.5, p=0.01).

Median OS was 6.9 months (95%CI 4.7-9.2); it was similar in the regorafenib group (median 6.5; 95%CI 3.7-9.2 months) compared with the TAS-102 group (median 7.8; 95%CI 6.2-9.4 months) (p=0.96). On the other hand, there was a significant association between OS in the skeletal muscle groups; it

**Table 2.** Skeletal muscle measurements of the study subjects

| | *All* | *Regorafenib* | *TAS-102* | *p value* |
|---|---|---|---|---|
| Baseline | | | | 0.34 |
| SMA | 112.8 (97.3-124.4) | 108.1 (94.3-122.5) | 117.1 (106.1-135.2) | |
| SMV | 18.7 (16.1-20.6) | 17.9 (15.6-20.3) | 19.4 (17.6-22.4) | |
| SMM | 19.8 (17.1-21.9) | 19.0 (16.6-21.5) | 20.6 (18.7-23.8) | |
| Time at progression | | | | 0.06 |
| SMA | 101.4 (85.5-118.3) | 95.7 (80.5-113.7) | 113.7 (102.8-134.2) | |
| SMV | 17.8 (14.2-20.1) | 15.9 (13.4-18.9) | 18.9 (16.9-134.2) | |
| SMM | 18.8 (15.1-21.4) | 16.8 (14.2-20.0) | 20.0 (17.8-24.4) | |
| Change | | | | 0.001 |
| SMM | -5.3 (-9.1 - -1.9) | -7.8 (-13.9 - -4.8) | -2.1 (-5.1 - -0.6) | |
| P value | <0.001 | <0.001 | 0.02 | |

SMA: skeletal muscle area, SMV: skeletal muscle volume, SMM: skeletal muscle mass

**Table 3.** Uni- and multivariate analysis of predictors of the skeletal muscle loss

| *Variables* | *Univariate analysis* | | | *Multivariate analysis* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95%CI* | *p value* | *HR* | *95%CI* | *p value* |
| Age, >60 y | 4.37 | 0.88-21.61 | 0.07 | 2.30 | 0.24-21.50 | 0.46 |
| Gender, male | 0.19 | 0.03-1.13 | 0.06 | 0.15 | 0.02-1.10 | 0.06 |
| Right side | 0.28 | 0.05-1.45 | 0.13 | N/A | N/A | N/A |
| Regorafenib | 8.31 | 1.40-49.1 | 0.02 | 10.0 | 1.46-68.5 | 0.01 |
| RAS mutant | 1.56 | 0.34-7.13 | 0.56 | N/A | N/A | N/A |
| Liver metastasis | 1.12 | 0.22-5.66 | 0.88 | N/A | N/A | N/A |
| Peritoneal metastasis | 1.52 | 0.14-15.78 | 0.72 | N/A | N/A | N/A |
| Treatment line (>3) | 2.40 | 0.41-13.8 | 0.32 | N/A | N/A | N/A |

N/A: no assessment

**Table 4.** Cox regression analysis of OS in study subjects

| *Variables* | *HR* | *95% Confidential interval* | | *p value* |
|---|---|---|---|---|
| | | *Lower* | *Upper* | |
| Skeletal muscle loss | 2.82 | 1.07 | 7.42 | 0.03 |
| Age (> 60 years) | 0.58 | 0.22 | 1.55 | 0.28 |
| Regorafenib | 0.80 | 0.30 | 2.17 | 0.67 |

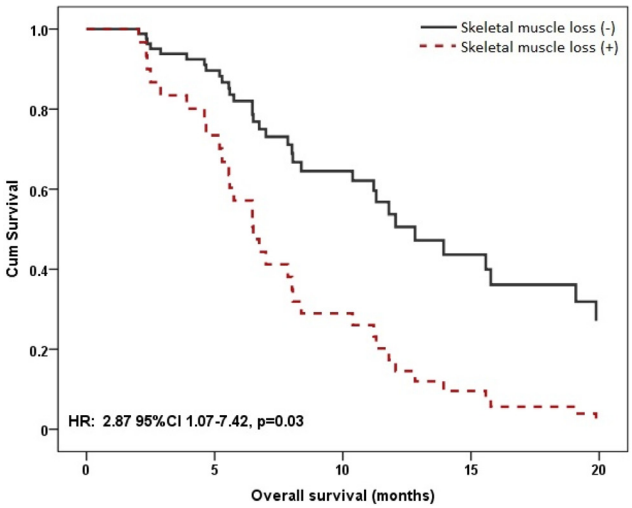


**Figure 1.** Overall survival of the patients according to skeletal muscle loss.

was longer (median 12.8; 95%CI 9.8-15.7 months) in the skeletal muscles stable group than those in skeletal muscle loss group (median 6.4; 95%CI 5.2-7.7 months) (p=0.04;Figure 1). Cox regression analysis showed that skeletal muscle loss was a significant prognostic indicator of OS (HR 2.87; 95%CI 1.07-7.42, p=0.03) (Table 4;Figure 1).

## Discussion

There is no standard chemotherapy for refractory mCRC patients [23]. In the phase III trials (CORRECT and RESOURCE) regorafenib and TAS-102 have been shown to be superior to placebo as new treatment option [5,8]. The ESMO and NCCN guidelines recommend these two agents as an additional line of therapy for mCRC refractory to chemotherapy. Regorafenib or TAS-102 can be before or after each other [24,25]. There is not any head to head study, comparing regorafenib to TAS-102 therapy. On the other hand, recent studies have shown that muscle loss is associated with prognosis in patients with CRC. In our study, the clinical efficacy of regorafenib and TAS-102 was similar. In addition, patients who received regorafenib therapy had more muscle mass loss than TAS-102 therapy, and also muscle loss predicted mortality regardless of treatment options.

Sarcopenia has been described by Rosenberg as a systemic and progressive loss of skeletal muscle associated with age and atrophy [26]. Generally, the surface area of the muscle measured by CT at the level of L3 vertebra can be identified by SMA [27]. Sarcopenia is associated with poor prognosis in various types of cancer [28-30]. Sarcopenia accompanied by cancer-associated cachexia is responsible for 20% of cancer-related deaths [31]. This condition has also been shown to be associated with poor prognosis in patients with CRC [18]. In addition, sarcopenia has been reported to adversely affect treatment response rates, OS and PFS, independent of disease progression [32,33]. In our study, it has been shown that the OS of patients with muscle loss was worse. In the light of this information, changes in skeletal muscle mass during and after treatment may indicate prognostic significance and may be an important marker for the tumor biology.

Regorafenib inhibits tyrosine kinases involved in tumor angio- and oncogenesis and further stabilizes the microenvironment that is effective in tumor growth. These effects consist of multiple kinase inhibition (VEGF receptors 1-3, KIT, PDGFR-alpha, PDGFR-beta, RET, FGFR1 and 2, TIE2, DDR2, TrkA, Eph2A, RAF-1. BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl). Recently, in an animal study, Huot et al reported that regorafenib has been shown to cause skeletal muscle loss by a possible mechanism including increasing levels of autophagy-dependent protein markers and abnormal mitochondrial homeostasis via ERK1/2 and GSK3β pathway [34]. TAS-102 is a novel oral anticancer agent consisting of trifluorothymidine as a thymidine analog which is incorporated into DNA in order to interfere with DNA synthesis and inhibit proliferation, and tipiracil hydrochloride, which prevents the degradation by inhibition of thymidine phosphorylase [8]. The effect of TAS-102 on skeletal muscle loss is not well known. In a recent study, regorafenib has been shown to cause more skeletal loss than TAS-102 [35]. In our study, skeletal muscle loss was seen in both TAS-102 and regorafenib patients, however in patients who received regorafenib, the skeletal muscle loss was significantly higher than in patients who received TAS-102. In the sex and age

adjusted multivariate analysis, regorafenib caused more muscle loss than TAS-102.

Regorafenib and TAS-102 are the treatment options in the third or the fourth lines of patients with mCRC. Median OS with regorafenib in the CORRECT trial was 6.4 months [5] and in the CONCUR trial median OS was 8.8 months with regorafenib treatment [6]. In the RESOURCE, a prospective randomized trial of TAS-102, the median OS was 7.1 months [8]. A retrospective comparative study of real-life data showed that median OS was 6.7 months with regorafenib and 6.5 months with TAS-102. According to this study, although there was no difference in efficacy between the two drugs, different toxicity profiles were reported [36]. In our study, median OS was 7.8 months in patients who received TAS-102 and 6.5 months in patients who received regorafenib (p=0.96). Similarly, no difference was observed between the efficacy of the two drugs, and skeletal muscle loss was significantly higher in the regorafenib arm. However, this difference does not present a drug-related OS difference in patients with skeletal muscle loss.

There are some major limitations of our study. Its retrospective nature caused some disadvantages in the assessment of treatment-associated symptoms and toxicities. In addition, the study was made on a small number of patients. Also, SMM measurements were evaluated twice: at baseline and under treatment. Moreover, there was not any data on the change in quality of life (QoL) scores and detailed toxicity profiles at the baseline and under treatment. Despite these limitations, it has been an outstanding strength of the study to conclude that regorafenib therapy resulted significantly in higher loss of SMM compared to TAS-102 therapy. We suggest that the results of this study give an opinion to treat more fragile mCRC patients to prevent muscle loss during the third- and subsequent lines.

In conclusion, both drugs had similar efficacy, however OS was shorter in patients with muscle loss. Although patients who received regorafenib had more muscle loss than those who received TAS-102, there was no difference in OS between the two groups.

## Conflict of interests

The authors declare no conflict of interests.

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