Regorafenib Is Associated With Increased Skeletal Muscle Loss Compared to TAS-102 in Metastatic Colorectal Cancer

Florian Huemer,[1] Verena Schlintl,[1] Stefan Hecht,[2] Hubert Hackl,[3] Thomas Melchardt,[1] Gabriel Rinnerthaler,[1] Richard Greil,[1] Lukas Weiss[1]

Abstract

Regorafenib and TAS-102 therapy sequencing in metastatic colorectal cancer (mCRC) is still under debate. In a study of 32 mCRC patients, treatment with regorafenib was associated with a statistically significant skeletal muscle loss, which was not the case with TAS-102. Regorafenib should be used with caution in mCRC patients with preexisting sarcopenia or a history of recent weight loss.

Background: Current guidelines of the National Comprehensive Cancer Network and the European Society of Medical Oncology recommend regorafenib or trifluridine/tipiracil (TAS-102) for third-line therapy of metastatic colorectal cancer (mCRC). We evaluated the impact of regorafenib and TAS-102 treatment on skeletal muscle dynamics and sarcopenia. **Patients and Methods:** This retrospective analysis was based on unselected, consecutive mCRC patients treated with regorafenib and/or TAS-102 during third or later line of therapy at our tertiary-care cancer center in Salzburg, Austria. The skeletal muscle index (SMI, cm^2/m^2) and sarcopenia were evaluated from cross-sectional computed tomographic images at the level of the third lumbar vertebra. **Results:** Between January 2013 and April 2018, a total of 45 patients had received regorafenib and/or TAS-102. At initial mCRC diagnosis and at initiation of third-line therapy, 24% and 54% of patients presented with sarcopenia. A statistically significant skeletal muscle loss was observed during regorafenib treatment (median SMI change: -2.75 cm^2/m^2 [-6.3%]; $P < .0001$), which was not the case during TAS-102 therapy (-1.5 cm^2/m^2 [-3.5%]; $P = .575$). Furthermore, subclassification of patients into 3 groups—normal muscle mass, stable sarcopenia, and new-onset sarcopenia—at initiation of third-line therapy permitted discrimination of overall survival, with 1-year overall survival rates of 61%, 29%, and 16%, respectively ($P = .04$). **Conclusion:** The frequency of sarcopenia increases during the course of mCRC and negatively affects survival. In contrast to TAS-102, regorafenib is associated with increased skeletal muscle loss during mCRC treatment and should therefore be used with caution in mCRC patients with preexisting sarcopenia or a history of recent weight loss.

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Introduction

Colorectal cancer is the second leading cause of cancer-related death in Europe and worldwide.[1,2] While the combination of systemic therapy, surgery, or ablative techniques may yield long-term survival in a subset of colorectal cancer patients with liver- and/or lung-limited metastases, the treatment approach for the majority of metastatic colorectal cancer (mCRC) patients is palliative.[3] By considering the localization of the primary tumor and the molecular

R.G. and L.W. contributed equally to this article, and both should be considered senior author.

[1]Department of Internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology, and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute, Laboratory for Immunological and Molecular Cancer Research (SCRI-LIMCR)
[2]Department of Radiology, Paracelsus Medical University Salzburg, Salzburg, Austria
[3]Division of Bioinformatics, Biocenter, Medical University of Innsbruck, Innsbruck, Austria

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Address for correspondence: Lukas Weiss, MD, PhD, Department of Internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology, and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute, Laboratory for Immunological and Molecular Cancer Research (SCRI-LIMCR), Paracelsus Medical University, Cancer Cluster Salzburg, Muellner Hauptstrasse 48, 5020 Salzburg, Austria
E-mail contact: lu.weiss@salk.at

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pathology in terms of a personalized treatment approach, a median overall survival (OS) of about 30 months can be achieved in mCRC.[4]

The oral tyrosine kinase inhibitor regorafenib and the oral cytotoxic drug combination trifluridine/tipiracil (TAS-102) have been approved for the treatment of mCRC after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and of anti-VEGF and/or anti-EGFR (in case of *RAS* wild-type status) targeted therapy. Approval is based on phase 3 trial data: the CORRECT trial, including 760 mCRC patients, reported a median OS benefit of 1.4 months (hazard ratio, 0.77) for regorafenib compared to placebo.[5] TAS-102 demonstrated an improvement in median OS of 1.8 months (hazard ratio, 0.68) against placebo in the RECOURSE trial, which included 800 mCRC patients.[6] As a result of the different mode of action, the tolerability and adverse effects of both drugs differ considerably: while reversible hematoxicity is frequently reported with the use of TAS-102,[6] fatigue and hand, foot, and skin reactions are commonly observed with regorafenib.[5] The current recommendations of the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) do not favor one drug over the other for third-line therapy of mCRC.[4,7]

The frequently observed weight loss during treatment with regorafenib compared to TAS-102 in daily clinical practice inspired us to investigate the impact of both drugs on patients' body composition. Sarcopenia, which is defined by skeletal muscle depletion, is a major issue during the course of mCRC, especially in advanced therapy lines.[8,9] Despite their prognostic utility, dynamics of the body weight and body mass index (BMI) are susceptible to common influences in mCRC, such as peripheral edema and ascites, and they are poorly correlated with skeletal muscle area or adipose tissue.[10,11] 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.[12] Skeletal muscle area predicts clinical outcome independent of body weight, and objective assessment is feasible.[13] Estimation of skeletal muscle area from cross-sectional computed tomographic (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.[14-18]

Here we report the results of the impact of regorafenib and TAS-102 on skeletal muscle dynamics in 32 mCRC patients treated at our tertiary-care cancer center in Salzburg, Austria.

Patients and Methods

This retrospective analysis was based on unselected consecutive mCRC patients treated with regorafenib and/or TAS-102. Prior disease progression while receiving therapy with fluorouracil, oxaliplatin, or irinotecan, or with anti-VEGF and/or anti-EGFR (in case of *RAS* wild-type status) targeted therapy, was a prerequisite before the initiation of regorafenib and/or TAS-102 therapy. Extended *RAS* mutational status summarizes mutations in *KRAS* (exons 2-4) and *NRAS* (exons 2-4); for *BRAF* mutational status, only mutations in exon 9 were considered. Early access to regorafenib and/or TAS-102 within a named patient program was available for patients who had received regorafenib and/or TAS-102 before their respective approval by the European Medicines Agency (EMA).

TAS-102 was provided orally twice a day at a dose of 35 mg/m^2 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period, and repeated every 4 weeks.[6] Regorafenib was either prescribed at an oral daily dose of 160 mg for the first 3 weeks of each 4-week cycle[5] or at a starting dose of 80 mg per day with weekly dose escalation to a target dose of 160 mg.[19] Radiologic reassessment by CT scans was performed every 3 months or as clinically indicated.

Skeletal muscle dynamics were assessed by the skeletal muscle area (cm^2). Adjustment of the skeletal muscle area for body surface area yielded the skeletal muscle index (SMI; cm^2/m^2). Measurement was based on cross-sectional CT images using ImageJ 1.51 software (Image Processing and Analysis in Java; US National Institutes of Health, Bethesda, MD, USA; https://imagej.nih.gov/ij/), as previously described.[17]

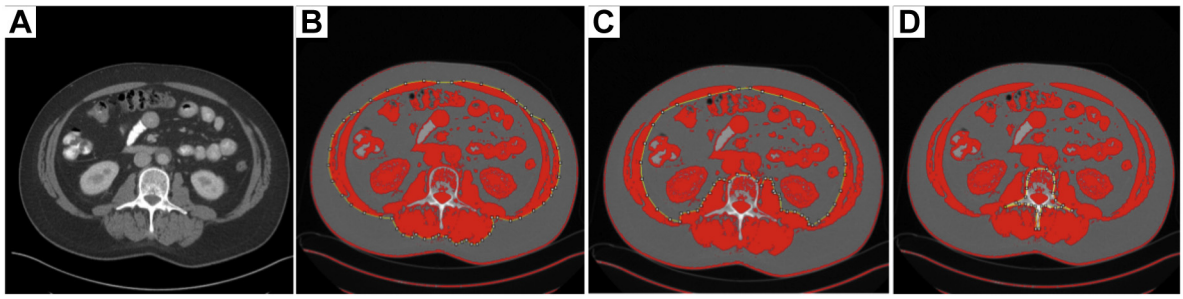
Cross-sectional CT images at the level of the third lumbar vertebra were analyzed in the DICOM format using the manual method by 2 independent trained researchers (F.H. and S.H.). The abdominal perimeter for waist circumference was measured within an attenuation range of −250 to 1000 Hounsfield units (HU), and the outer and inner musculature perimeter and the lumbar vertebra within a range of −29 to 150 HU (Figure 1). The skeletal muscle area was calculated by subtracting the inner musculature perimeter and the lumbar vertebra from the outer musculature perimeter. The SMI dynamics was calculated from CT images before regorafenib or TAS-102 introduction and from the first radiologic reassessment. Interrater variabilities were assessed for the SMI dynamics (delta), the absolute SMI before and after therapy (regorafenib or TAS-102) (baseline and restaging), and at initial mCRC diagnosis. For that purpose, we analyzed Bland-Altman diagrams; SMI differences are plotted against the average SMI between the 2 raters, whereby the deviation from 0 of the mean SMI difference indicates a systemic bias. The intraclass correlation coefficient (ICC) including a 95% confidence interval was calculated using the R package "irr" with a 2-way random model, absolute agreement, and single rater/measurement settings (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/), and the standard error of measurements was calculated as the square root of residual mean squares from a 1-way ANOVA model with subjects referred as groups.

Sarcopenia was defined by sex-specific cutoffs for SMI (men, < 52.4 cm^2/m^2; women, < 38.5 cm^2/m^2).[11] OS was calculated from the start of third-line treatment until the date of death or date of last known follow-up. Differences in patient baseline characteristics between the regorafenib and TAS-102 group were tested by the Pearson chi-square test. For continuous data, the difference between the two groups was calculated with the 2-sided Wilcoxon rank-sum test. Survival curves were estimated by the Kaplan-Meier method. The log-rank test was used to compare survival distributions between patient groups.

Results

Between January 2013 and April 2018, a total of 45 mCRC patients received systemic therapy with regorafenib and/or TAS-102. CT images were available for 41 patients at the time of initial diagnosis of mCRC as well as at the time of initiation of third-line therapy with regorafenib or TAS-102. The median SMI

Figure 1 Skeletal Muscle Area Calculation From Cross-Sectional CT Images. Skeletal Muscle Area Calculation Based on Cross-Sectional CT Images Using ImageJ Software. Cross-Sectional CT Image at Third Lumbar Vertebra (A). Assessment of Outer Muscle Perimeter (B) and Inner Muscle Perimeter for Skeletal Muscle Area (C) as Well as of Third Lumbar Vertebra (D) by Manual Method



Abbreviation: CT = computed tomography.

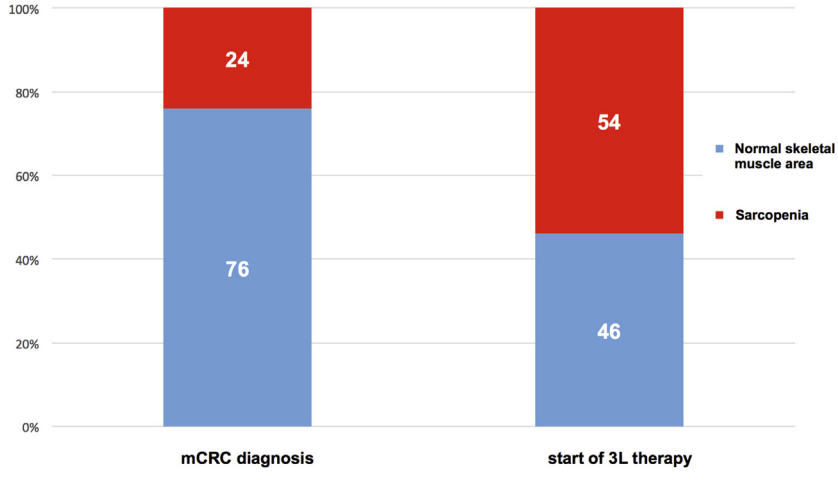
was 49.5 cm^2/m^2, and 24% (10/41) of patients presented with sarcopenia at the establishment of the mCRC diagnosis. At the time of initiation of third-line therapy, the number of patients with sarcopenia had increased to 54% (22/41; Figure 2) with a corresponding median SMI loss of -5.4 cm^2/m^2 (-9.3%).

Sarcopenia was found irrespective of body mass index (BMI): at first diagnosis of metastatic disease, sarcopenia was observed in 30.0% (3/10) of patients with underweight or normal weight, and in 18% (3/14) of overweight and obese patients. At the time of initiation of third-line therapy, sarcopenia increased to 62% (8/13) in the underweight/normal-weight group and to 31% (5/16) in the overweight/obese group. SMI showed a strong positive correlation with body weight ($n = 87$; $r = 0.590$; $P < .001$, Pearson 2-sided test).

Baseline Characteristics of Third-Line mCRC Cohort

Sequential CT scans for SMI measurements during regorafenib and/or TAS-102 treatment were available for 32 patients. Among these 32 patients, 22 (69%) and 10 (31%) received regorafenib and TAS-102 as third-line therapy, respectively. The baseline characteristics were well balanced between the groups and are depicted in Table 1. However, there was a trend for better a performance status (Eastern Cooperative Oncology Group performance status 0-1, 96% vs. 70%) and younger age (median age, 59 vs. 72 years) in patients treated with regorafenib in third-line therapy compared to TAS-102, although this did not reach statistical significance. The time from establishment of mCRC diagnosis to the initiation third-line therapy (26.2 vs. 25.8 months) and the median time on third-

Figure 2 Sarcopenia at mCRC Diagnosis and at Initiation of 3L Therapy. Sarcopenia Was Defined by Sex-specific SMI (cm^2/m^2) Cutoff Values (Men: SMI < 52.4 cm^2/m^2; Women: SMI < 38.5 cm^2/m^2) at Time Point of mCRC Diagnosis and at Time Point of Initiation of 3L Therapy With Either Regorafenib or TAS-102



Abbreviations: mCRC = metastatic colorectal cancer; SMI = skeletal muscle index; 3L = third line.

Table 1 Baseline Characteristics of 3L Cohort

Characteristic	All	Regorafenib	TAS-102	
N (%)	**32 (100%)**	**22 (100%)**	**10 (100%)**	***P***
Age at 3L start (years), median (range)	65 (42-81)	59 (42-74)	72 (54-81)	.166[a]
Sex				.599
Male	17 (53)	11 (50)	6 (60)	
Female	15 (47)	11 (50)	4 (40)	
ECOG PS at 3L Start				.127
0	9 (28)	7 (32)	2 (20)	
1	19 (59)	14 (64)	5 (50)	
2	4 (13)	1 (4)	3 (30)	
Detection of Metastases				.811
Synchronous	17 (53)	12 (55)	5 (50)	
Metachronous	15 (47)	10 (45)	5 (50)	
Primary Tumor Resected				.101
No	5 (16)	5 (23)	0	
Yes	27 (84)	17 (77)	10 (100)	
Primary Tumor Location				.186
Left sided	24 (75)	15 (68)	9 (90)	
Right sided	8 (25)	7 (32)	1 (10)	
Ascites present at 3L start	2 (6)	1 (4)	1 (10)	.555
***RAS* Status**				.961
Wild type	19 (59)	13 (59)	6 (60)	
Mutant	13 (41)	9 (41)	4 (40)	
***BRAF* Status**				.137
Wild type	24 (96)	17 (100)	7 (88)	
Mutant	1 (4)	0	1 (12)	
Missing	7	5	2	
Microsatellite Status				.469
MSS	20 (95)	13 (93)	7 (100)	
MSI	1 (5)	1 (7)	0	
Missing	11	8	3	
Subsequent Systemic Therapy				.186
No	8 (25)	4 (18)	4 (40)	
Yes	24 (75)	18 (82)	6 (60)	
Time from mCRC diagnosis to 3L start (months), median (range)	26.2 (8.9-88.5)	26.2 (11.4-88.5)	25.8 (8.9-74.7)	.703[a]
Time Receiving 3L Therapy	3.0 (1.2-26.4)	3.1 (1.2-26.4)	3.0 (1.8-4.2)	.703[a]

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; mCRC = metastatic colorectal cancer; MSI = microsatellite instability; MSS = microsatellite stability; 3L = third line.
[a]Two-sided Wilcoxon rank-sum test; chi-square test in all other cases.

line therapy (3.1 vs. 3.0 months) were comparable between the regorafenib and TAS-102 groups. After a median follow-up of 12.3 months, the median OS was 11.4 months for both regorafenib and TAS-102 ($P = .562$; Supplemental Figure 1 in the online version).

Skeletal Muscle Loss and Sarcopenia: Regorafenib Versus TAS-102

Third-line mCRC Cohort. A statistically significant decrease in SMI was observed during third-line therapy with regorafenib (median SMI change: -2.75 cm^2/m^2 [-6.3%]; $P < .0001$), and the frequency of sarcopenia increased from 41% to 59%. In contrast, SMI was not affected by TAS-102 therapy (median SMI change: -1.5 cm^2/m^2 [-3.5%]; $P = .575$), and the number of patients with sarcopenia decreased from 60% to 50% (Figure 3). SMI dynamics showed a significant positive correlation with body weight dynamics ($r = 0.572$; $P = .002$, Pearson 2-sided test) and with BMI dynamics ($r = 0.565$; $P = .003$, Pearson 2-sided test).

Entire mCRC Cohort. Thirteen (41%) of 32 patients sequentially received both agents, regorafenib and TAS-102 (or vice versa), and

as a consequence, 45 skeletal muscle dynamics were available for comparison. Irrespective of the therapy line, significant skeletal muscle loss was apparent in patients treated with regorafenib (median SMI change: -2.7 cm^2/m^2 [-6.2%]; $P < .0001$), whereas the SMI remained stable during TAS-102 therapy (median SMI change: $+0.3$ cm^2/m^2 [$+0.6$ %]; $P = .795$; Figure 4). SMI dynamics showed a significant positive correlation with body weight dynamics ($r = 0.685$; $P < .001$, Pearson 2-sided test) as well as with BMI dynamics ($r = 0.595$; $P = .001$, Pearson 2-sided test).

Sarcopenia During Sequential Systemic Therapy

Twelve patients received TAS-102 as fourth-line therapy after regorafenib in third-line therapy. Of these, 92% (11/12) experienced a loss in SMI (mean SMI change: -3.3 cm^2/m^2, range -0.2 to -6.9 cm^2/m^2) during regorafenib treatment, whereas 75% (9/12) could gain SMI (mean SMI change: $+1.9$ cm^2/m^2, range $+0.2$ to $+6.5$ cm^2/m^2) during subsequent TAS-102 treatment.

Association of Sarcopenia (Dynamics) and OS

In order to evaluate the impact of skeletal muscle dynamics on OS at initiation of third-line therapy, patients were subclassified into the one of the following categories: normal muscle area, stable sarcopenia, and new-onset sarcopenia. Sarcopenia dynamics before the initiation of third-line therapy were statistically significantly associated with clinical outcome, with a median 1-year OS rate of 61%, 29% and 16%, respectively ($P = .04$; Figure 5).

Impact of Skeletal Muscle Dynamics During Third-Line Therapy on OS

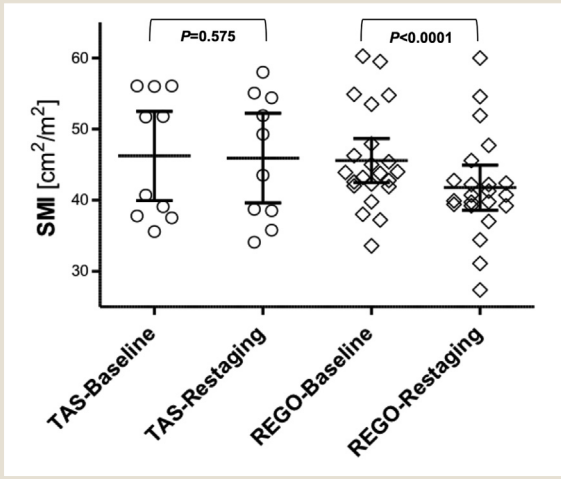
Relative muscle change was categorized into quartiles of muscle change: quartile 1, highest muscle loss below 2%; quartile 2, muscle loss of 2% to 5%; quartile 3, muscle loss of 5% to 8%; and quartile 4, muscle loss exceeding 8%. The extent of skeletal muscle loss during third-line therapy was not associated with OS for the entire third-line cohort ($P = .18$; Supplemental Figure 2A in the online version), or for the regorafenib ($P = .08$; Supplemental Figure 2B in the online version) or TAS-102 ($P = .33$; Supplemental Figure 2C in the online version) cohorts.

SMI was consistently assessed between the 2 raters. The assessment of SMI dynamics showed good to excellent interrater reliability (ICC for agreement of 0.85; 95% confidence interval, 0.74-0.91) with minimal systemic bias (mean SMI difference $= -0.26$ cm^2/m^2) and standard error of measurements of 1.56 (Supplemental Table 1 and Supplemental Figure 3 in the online version). For absolute SMI measurements, the ICC was even higher (> 0.9); however, the interrater variability performance tended to be rather moderate according to the lower limit of the ICC confidence interval, increased bias between raters (less than -2 cm^2/m^2), and higher standard error of measurements (> 2). In summary, this indicates that raters performed consistently in SMI measurements within individual patients under different conditions.

Discussion

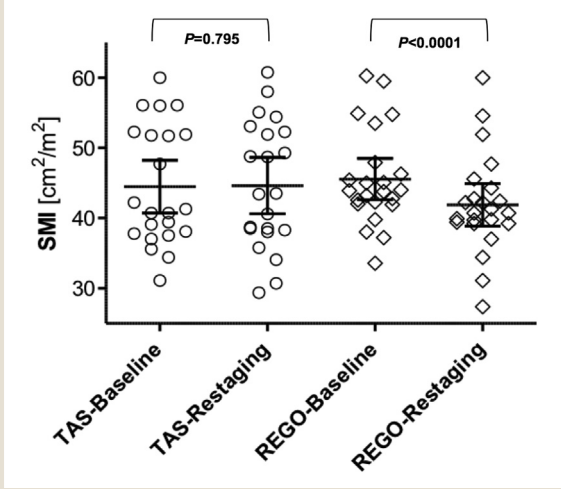
As a result of a significant but modest OS advantage of 1.4 and 1.8 months against placebo in two phase 3 trials, regorafenib and TAS-102 have been approved for third-line therapy of mCRC by the US Food and Drug Administration and the EMA.[5,6] The survival benefit with regorafenib has been confirmed in Asian mCRC patients in the CONCUR trial.[20] The NCCN and ESMO guidelines support the use of both drugs with a category IB recommendation for third-line therapy of mCRC.[4,7] Despite an

Figure 3 Skeletal Muscle Dynamics During Regorafenib and TAS-102 Treatment for 3L Cohort. Comparison of SMI (cm^2/m^2) Between Initiation of 3L Therapy and First Radiologic Reassessment During Regorafenib and TAS-102 Treatment. Bars Represent Mean; Whiskers, 95% Confidence Interval



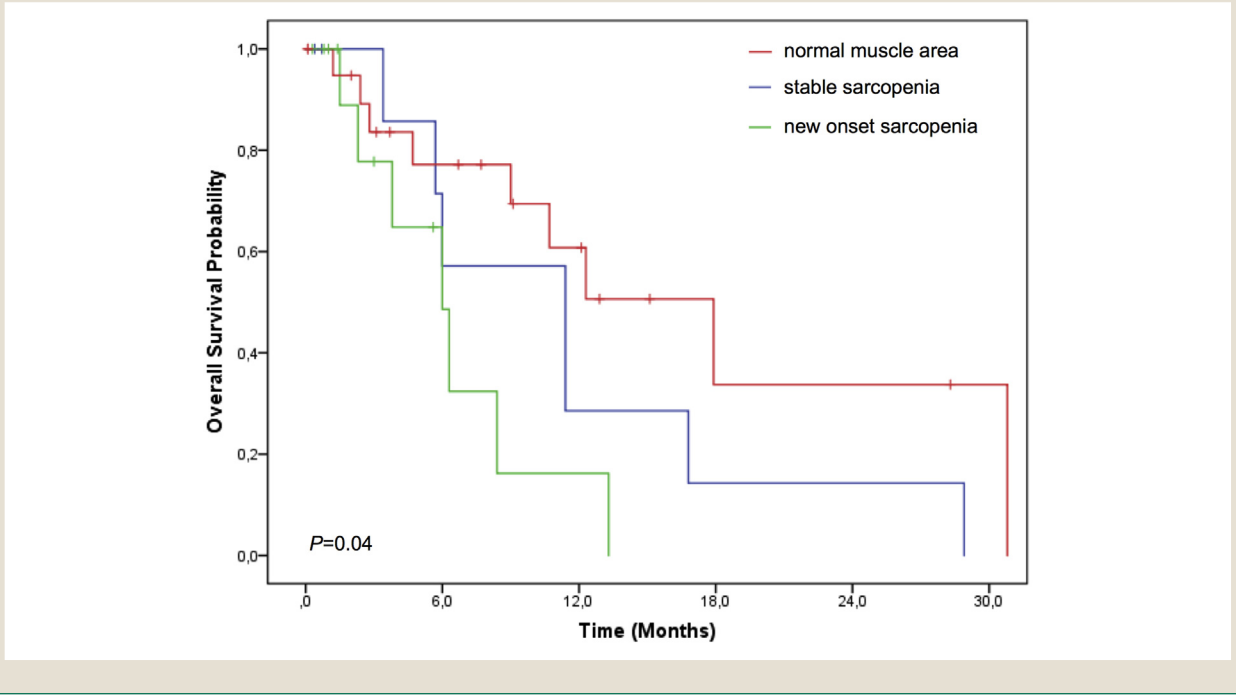
Abbreviations: SMI = skeletal muscle index; 3L = third line.

Figure 4 Skeletal Muscle Dynamics During Regorafenib and TAS-102 Treatment for Entire Cohort. Comparison of SMI (cm^2/m^2) Between Initiation of Regorafenib or TAS-102 Treatment and First Radiologic Reassessment, Irrespective of Therapy Line. Bars Represent Mean; Whiskers, 95% Confidence Interval



Abbreviations: SMI = skeletal muscle index; 3L = third line.

Figure 5 Overall Survival According to Skeletal Muscle Dynamics Preceding 3L Therapy. Kaplan-Meier Curves for Overall Survival According to Classification of mCRC Patients Into Risk Groups: Normal Muscle Area at Initiation of 3L Therapy (A), Stable Sarcopenia at Initiation of 3L Therapy (B), and New Onset Sarcopenia at Initiation of 3L Therapy (C). Tick Marks on Curves Represent Censored Patients



Abbreviations: mCRC = colorectal cancer; 3L = third line.

ESMO statement regarding toxicity concerns with the use of regorafenib in frail patients, neither drug is favored over the other.[4]

In this retrospective analysis, we found a statistically significant and clinically relevant loss of SMI during third-line therapy with regorafenib (Figure 3), resulting in an increased frequency of sarcopenia. The same observation was made when regorafenib was investigated beyond third-line therapy (Figure 4). These results contrast with the stabilization of SMI during TAS-102 treatment in third-line therapy (Figure 3) and in third and later therapy lines (Figure 4), even after previous regorafenib treatment.

In the CORRECT trial, weight loss ranging from 5% to 20% from baseline was documented in 14% of patients in the regorafenib group (vs. 2% in the placebo arm), highlighting the negative impact of tyrosine kinase inhibitor therapy on patients' nutritional status.[5] In an attempt to alleviate therapy-related adverse events and to enhance therapy adherence, regorafenib was investigated with a starting dose of 80 mg with weekly dose escalation to a target dose of 160 mg in the ReDOS study. Significantly more patients tolerated initiation of treatment cycle 3 with the dose-escalation strategy, with a trend to improved OS in the experimental arm.[19] Data on the impact on body weight dynamics with this ramp-up regimen have not yet been reported.

In recent decades, the mean BMI of the general population in Western Europe and North America has been continuously increasing. In 2008, the mean BMI in North America exceeded 28 kg/m^2, highlighting the major public health concern of increasing obesity.[21] Solely considering body weight as a surrogate marker for patients' nutritional condition may overlook skeletal muscle depletion. In advanced colorectal cancer, body weight can be influenced by several factors such as ascites or peripheral edema, and can therefore be subject to high variability during the disease course. Sarcopenic obesity is prevalent in about 1 in every 10 cancer patients (cutoff for obesity: BMI $>$ 25 kg/m^2) and even in 1 in every 4 patients if a BMI cutoff of $>$ 30 kg/m^2 is chosen.[22] The worse clinical outcome associated with sarcopenic obesity corroborates the necessity for SMI assessment during the course of disease.[11,23,24] SMI dynamics showed a significant positive correlation with BMI as well as with body weight dynamics in our cohort. However, obesity and other factors such as ascites may abrogate the information gained through assessment of body weight and/or BMI but not of SMI, which is expected to become more evident in a larger cohort including overweight and obese patients. Therefore, we believe that SMI may represent a more reliable marker of muscle mass than body weight and/or BMI. Because of the strong correlation between patients' whole-body skeletal area and estimations from cross-sectional imaging studies and the availability of repeat imaging studies during systemic therapy, the calculation of SMI is feasible in clinical practice.[16] Furthermore, SMI evaluation at the level of the third lumbar vertebra is better at detecting sarcopenia compared to several other modalities, such as psoas muscle assessment or anthropometric measurements.[18,25] The feasibility of this approach in clinical practice is corroborated by the good to excellent interrater reliability when comparing SMI measurements between the 2 observers in our analysis (Supplemental Table 1 in the online version).

Several mechanisms are involved in the development of skeletal muscle loss in cancer patients. Metabolic dysregulation such as activation of the ubiquitin—proteasome pathway is linked to enhanced muscle protein degradation.[26] Resting energy expenditure is higher among cancer patients as a result of alterations in the mitochondrial respiratory chain.[27] Furthermore, elevated levels of proinflammatory cytokines including interleukin-1β, interleukin-6, and tumor necrosis factor alpha are found in tumor tissue, whereas tumor necrosis factor alpha drives insulin resistance and plays a major role in proteolysis and inhibition of protein synthesis.[28-30] Sarcopenia is evident in up to 39% of patients at the initial mCRC diagnosis.[8,11] Patients presenting with sarcopenia at the time of initial mCRC diagnosis are at risk for shorter OS[8,31] and increased chemotherapy toxicity.[32] Given a positive selection bias by including only mCRC patients undergoing third-line therapy, we observed a lower percentage of sarcopenia at first diagnosis of metastatic disease (24%), which further increased to 54% at the time of initiation of third-line therapy after a median time interval of 26.2 months. Furthermore, the extent of skeletal muscle loss during palliative systemic therapy is an independent predictive factor for poorer survival.[9,33,34] Skeletal muscle depletion exceeding 5% to 9% during palliative systemic therapy negatively affects OS in mCRC.[9,34] Data on the influence of skeletal muscle dynamics before the initiation of third-line therapy with either regorafenib or TAS-102 on clinical outcome have not been reported so far.

Our classification of patients into groups (normal muscle area at initiation of third-line therapy, stable sarcopenia at initiation of third-line therapy, and new-onset sarcopenia at initiation of third-line therapy) could adequately discriminate OS between the 3 groups (Figure 5). Patients who developed new sarcopenia during their disease course displayed the worst clinical outcome, with a 1-year OS rate of 16% from initiation of third-line therapy. Despite a significant impact of skeletal muscle dynamics before initiation of treatment with regorafenib or TAS-102, the extent of further skeletal muscle depletion did not predict OS in the entire third-line cohort (Supplemental Figure 2A in the online version). It is noteworthy that the statistically significant SMI loss during third-line therapy with regorafenib did not translate into inferior OS (Supplemental Figure 2B in the online version). Several circumstances may explain this observation. First, the number of patients receiving regorafenib during third-line was small, at 22 subjects. Second, the inclusion of only mCRC patients who had undergone radiologic reassessment during third-line therapy might have biased the results. Third, cancer-driven skeletal muscle loss and therapy-induced skeletal muscle loss might have a different impact on survival in mCRC.

RAS mutational status did not affect skeletal muscle dynamics (data not shown). Only one patient harbored a *BRAF* mutation, and therefore no conclusions of the influence on skeletal muscle dynamics could be drawn.

The retrospective character of the study and the small number of included patients are potential limitations of this analysis. Therefore, it would be highly desirable to confirm these findings in a larger cohort in the future.

Conclusion

The results of our analyses have several practical implications. The majority of patients developed sarcopenia during their disease course, before initiation of third-line therapy. Therefore, prophylactic nutritional support, exercise training, and rigorous skeletal muscle area reassessment is mandatory. Furthermore, skeletal muscle loss dynamics before third-line therapy was prognostic of OS, with an exceptionally worse outcome evident in patients with new-onset sarcopenia. As a consequence, comparison of SMI between the time of initial mCRC diagnosis and the time of initiation of third-line therapy could be of prognostic value. In consideration of the significant and clinically meaningful skeletal muscle loss during treatment with regorafenib but not TAS-102, our results may help to guide the choice of third-line therapy in mCRC patients with preexisting sarcopenia and/or a history of recent weight loss. Validation of our findings in larger mCRC patient cohorts such as in the CORRECT or RECOURSE study are desirable.

Clinical Practice Points

- Current guidelines of the National Comprehensive Cancer Network and the European Society of Medical Oncology recommend regorafenib or TAS-102 for third-line therapy of mCRC and do not favor one drug over the other. Practical tools for the choice of third-line therapy in mCRC are needed.
- This article highlights the concern of skeletal muscle loss during the course of mCRC and the inferior OS of patients with new onset of sarcopenia before initiation of third-line therapy.
- The clinically meaningful skeletal muscle loss during regorafenib treatment contrasts with skeletal muscle stabilization during TAS-102 therapy during third-line therapy of mCRC.
- Our results may guide the choice of third-line therapy in mCRC patients with preexisting sarcopenia and/or a history of recent weight loss.

Disclosure

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Supplemental Data

A supplemental table and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.04.003.

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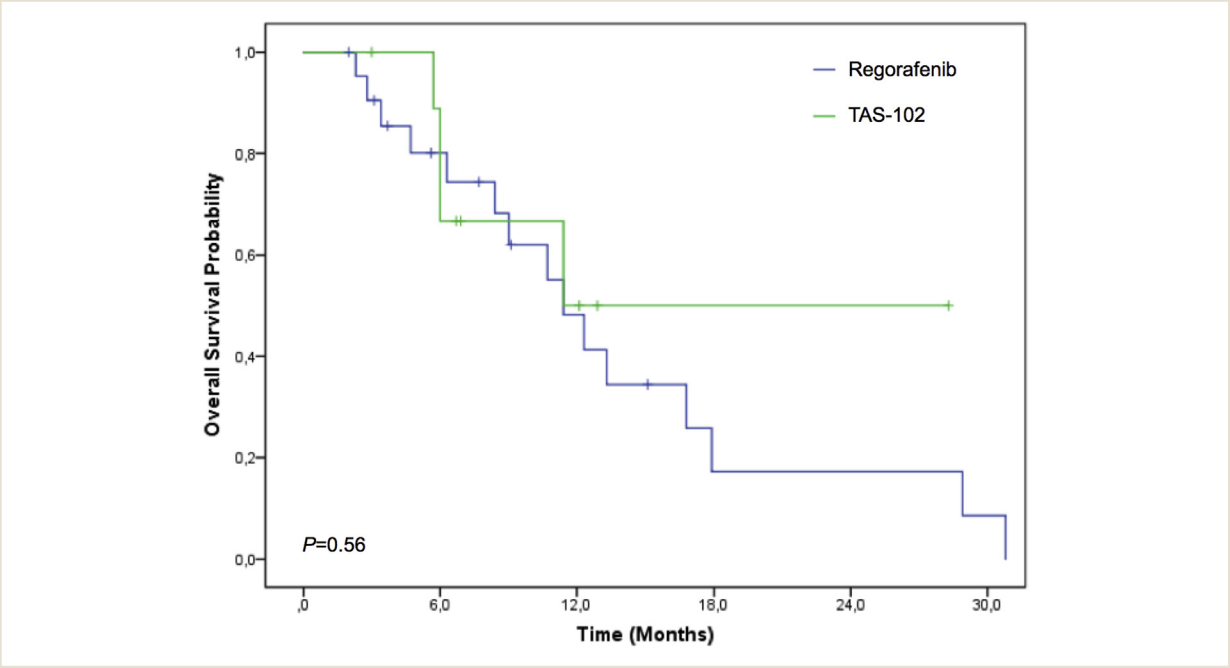
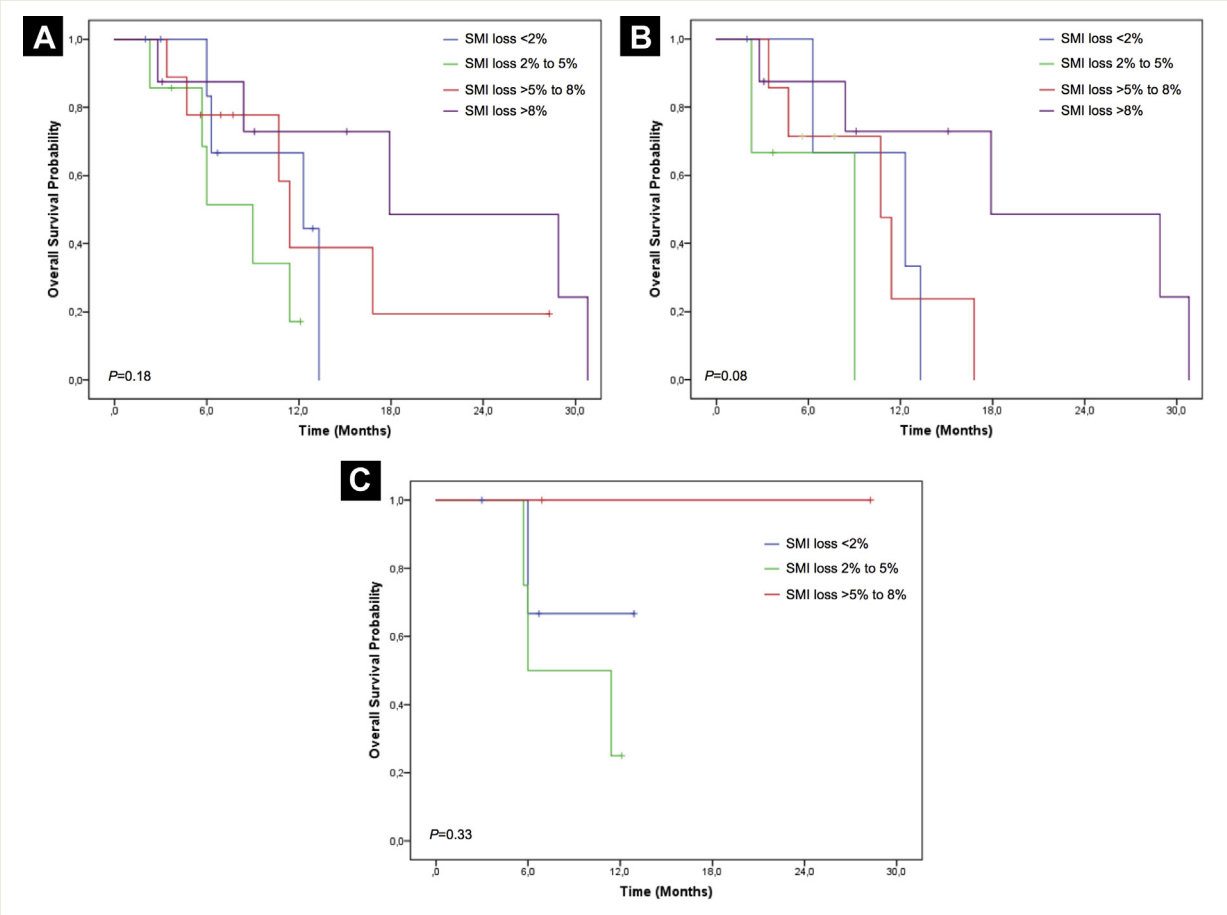
Supplemental Data

Supplemental Figure 1 Overall Survival From 3L Therapy With Regorafenib and TAS-102. Kaplan-Meier Curves for Overall Survival From 3L Therapy With Regorafenib and TAS-102. Tick Marks on Curves Represent Censored Patients



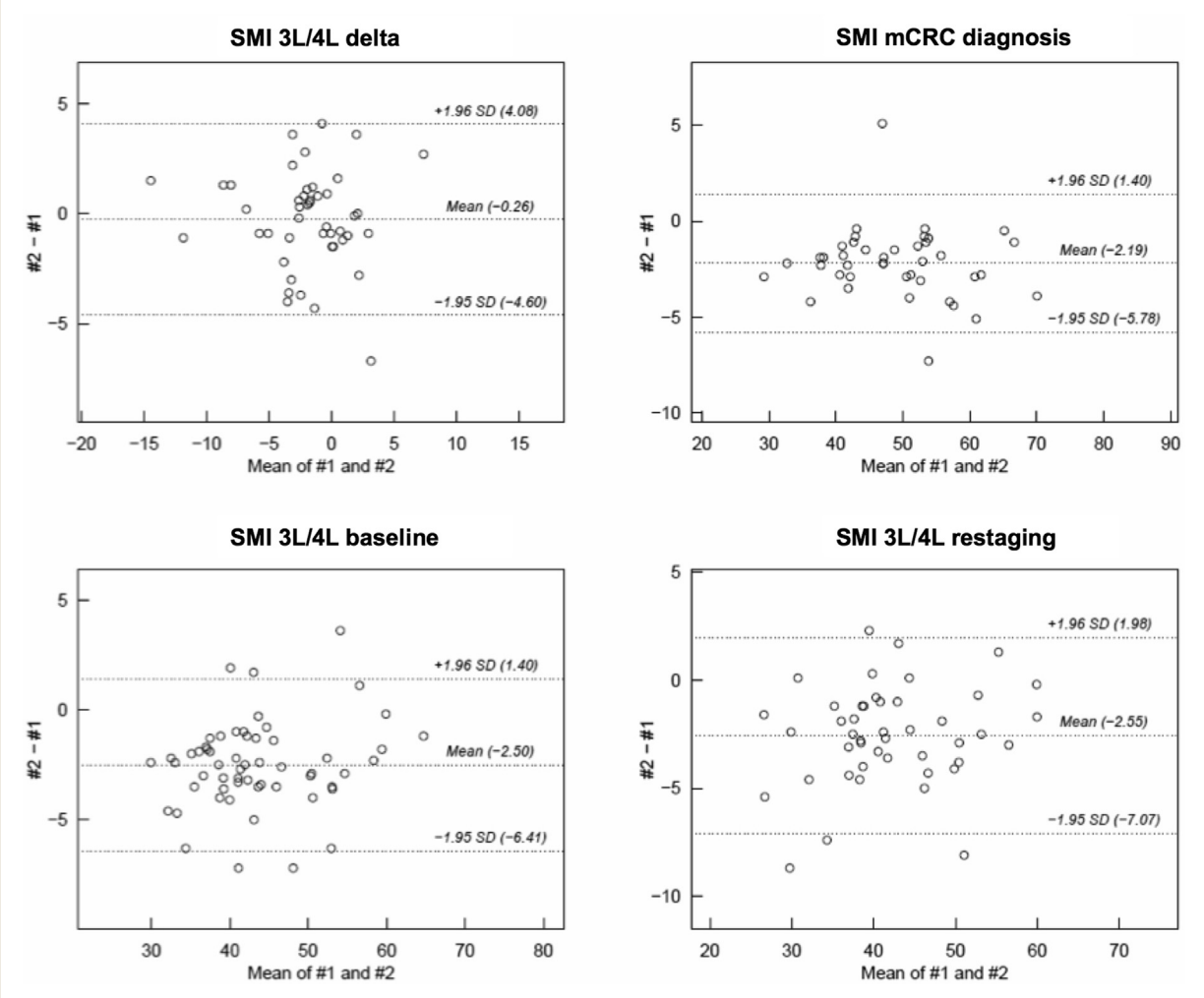
Abbreviation: 3L = third line.

Supplemental Figure 2 **Overall Survival According to Skeletal Muscle Loss During 3L Therapy. Kaplan-Meier Curves for Overall Survival From 3L Therapy According to Quartiles of Skeletal Muscle Change for Entire 3L Cohort (A), for Regorafenib Cohort (B), and for TAS-102 Cohort (C). Tick Marks on Curves Represent Censored Patients**



Abbreviation: 3L = third line.

Supplemental Figure 3 Bland-Altman Diagrams Indicating Interrater Variability. SMI Differences Are Plotted Against Average SMI Between 2 Raters (Rater 1 and 2) for SMI Dynamics (Delta), Absolute SMI Before and After Therapy (Regorafenib or TAS-102) (Baseline and Restaging), Respectively, as well as at Initial mCRC Diagnosis (All Values in cm^2/m^2). SMI Dynamics (SMI 3L/4L Delta) Shows Minimal Systemic Bias (Mean = -0.26 cm^2/m^2) Between Raters, for Absolute Measurements Bias Was More Pronounced (Mean = -2 cm^2/m^2). Few Samples Were Beyond Respective Limits of Agreement (± 1.96 SD)



Abbreviations: 4L = fourth line; mCRC = metastatic colorectal cancer; SMI = skeletal muscle index; 3L = third line.

Supplemental Table 1 Interrater Variability

Characteristic	No. Subjects	No. Raters	ICC[a]	95% CI[a]	Mean	SD	SEM
SMI 3L/4L delta	45	2	0.85	0.74-0.91	−0.26	2.22	1.56
SMI mCRC diagnosis	41	2	0.96	0.54-0.99	−2.19	1.83	2.01
SMI 3L/4L baseline	57	2	0.92	0.33-0.98	−2.50	1.99	2.25
SMI 3L/4L restaging	45	2	0.92	0.44-0.97	−2.55	2.31	2.42

SMI 3L/4L delta calculated according to SMI patient differences (SMI 3L restaging minus SMI 3L baseline).
Abbreviations: 4L = fourth line; ICC = intraclass correlation coefficient; mCRC = metastatic colorectal cancer; SD = standard deviation of SMI differences (#1 − #2); SEM = standard error of measurements; SMI = skeletal muscle index; 3L = third line.
[a]Calculated by R package "irr" (2-way random model, absolute agreement, single measurement) with ICC < 0.5 poor, 0.5 ≤ ICC < 0.75 moderate, 0.75 ≤ ICC < 0.9 good, and ICC ≥ 0.90 excellent reliability.