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Early weight loss is an independent risk factor for shorter survival and increased side effects in patients with metastatic colorectal cancer undergoing first-line treatment within the randomized Phase III trial FIRE-3 (AIO KRK-0306)

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Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; CTCAE, the Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ESPEN, European Society for Clinical Nutrition and Metabolism; EWL, early weight loss; GI, gastrointestinal; HR, hazard ratio; mCRC, metastatic colorectal cancer; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; *RAS*-WT, *RAS* wild-type; WC, weight change.

Lian Liu and Nicole Tonya Erickson contributed equally.

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Abstract

Body weight loss is frequently regarded as negatively related to outcomes in patients with malignancies. This retrospective analysis of the FIRE-3 study evaluated the evolution of body weight in patients with metastatic colorectal cancer (mCRC). FIRE-3 evaluated first-line FOLFIRI (folinic acid, fluorouracil and irinotecan) plus cetuximab or bevacizumab in mCRC patients with *RAS*-WT tumors (ie, wild-type in *KRAS* and *NRAS* exons 2-4). The prognostic and predictive relevance of early weight loss (EWL) regarding patient outcomes and treatment side effects were evaluated. Retrospective data on body weight during first 6 months of treatment were evaluated (N = 326). To correlate with efficacy endpoints and treatment side effects, patients were grouped according to clinically significant EWL ≥5% and <5% at Month 3. Age constituted the only significant predictor of EWL following a linear relationship with the corresponding log odds ratio ($P = .016$). EWL was significantly associated with the incident frequencies of diarrhea, edema, fatigue, nausea and vomiting. Further, a multivariate analysis revealed EWL to be an independent negative prognostic factor for overall survival (32.4 vs 21.1 months; hazard ratio [HR]: 1.64; 95% confidence interval [CI] = 1.13-2.38; $P = .0098$) and progression-free survival (11.8 vs 9.0 months; HR: 1.72; 95% CI = 1.18-2.5; $P = .0048$). In conclusion, EWL during systemic treatment against mCRC is significantly associated with patient age. Patients exhibiting EWL had worse survival and higher frequencies of adverse events. Early preventative measures targeted at weight maintenance should be evaluated, especially in elderly patients being at highest risk of EWL.

KEYWORDS
biomarker, metastatic colorectal cancer, *RAS* wild-type, weight loss

What's new

When patients with metastatic colorectal cancer (mCRC) rapidly lose weight early in the course of treatment, that often forebodes a negative outcome. Here, the authors examined changes in body weight in the first 3 months of treatment. Older patients had the highest risk of extreme early weight loss (greater than 5%). This weight loss was correlated with adverse events such as nausea, vomiting, and diarrhoea, and also with an 11-month reduction in overall survival. These results should increase oncologists' awareness of patients' body weight change early in treatment and encourage intervention from dietitians to help prevent weight loss.

1 | BACKGROUND

With over 1.8 million newly diagnosed cases in 2018, colorectal cancer (CRC) is the second most common malignancy for females and third most common malignancy for males worldwide.[1] The 5-year survival rate for the metastatic colorectal cancer (mCRC) is estimated at less than 12.5%.[2] With the introduction of modern targeted therapy, median overall survival (OS) times exceeding 30 months have been reached in mCRC.[3-5] However, side effects occur in almost all patients and do compromise quality of life and impair physical performance.[6-8] Literature shows that patients exhibiting loss of body weight during antineoplastic treatment have been identified being at higher risk for treatment side effects.[9-11] The frequency of weight loss prior to chemotherapy reported in the literature ranges from 31% for

TABLE 1 Baseline characteristics

Baseline characteristics	Weight loss <5% (N = 279)	Weight loss ≥5% (N = 47)	*P* value
Treatment			.75
Cetuximab	133 (47.7%)	21 (44.7%)	
Bevacizumab	146 (52.3%)	26 (55.3%)	
Sex			1
Male	202 (72.4%)	34 (72.3%)	
Female	77 (27.6%)	13 (27.7%)	
Age (y)			**.011**
<65	147 (52.7%)	15 (31.9%)	
≥65	132 (47.3%)	32 (68.1%)	
ECOG performance status			.43
0	157 (56.3%)	23 (48.9%)	
1 and 2	122 (43.7%)	24 (51.1%)	
Number of metastatic sites			.057
1	125 (45%)	14 (29.8%)	
≥2	153 (55%)	33 (70.2%)	
Missing	1 (0.4%)	0 (0%)	
BMI (kg/m^2)			.16
<30	231 (83.1%)	35 (74.5%)	
≥30	47 (16.9%)	12 (25.5%)	
Missing	1 (0.4%)	0 (0%)	
Primary sidedness			1
Left	217 (78.6%)	36 (78.3%)	
Right	59 (21.4%)	10 (21.7%)	
Missing	3 (1.1%)	1 (2.1%)	
Alkaline phosphatase (IU/L)			.46
<300	241 (88.9%)	39 (84.8%)	
≥300	30 (11.1%)	7 (15.2%)	
Missing	8 (2.9%)	1 (2.1%)	
Leucocyte (/L)			.87
$<8 \times 10^9$	160 (58.2%)	28 (60.9%)	
$\geq 8 \times 10^9$	115 (41.8%)	18 (39.1%)	
Missing	4 (1.4%)	1 (2.1%)	
Site of primary tumor			.27
Colon	178 (63.8%)	24 (51.1%)	
Rectum	90 (32.3%)	22 (46.8%)	
Colon and rectum	10 (3.6%)	1 (2.1%)	
Unknown	1 (0.4%)	0 (0%)	
Metastasis in liver			**.014**
Yes	243 (87.1%)	34 (72.3%)	
No	36 (12.9%)	13 (27.7%)	
Metastasis in lung			.87
Yes	102 (36.6%)	18 (38.3%)	
No	177 (63.4%)	29 (61.7%)	
Metastasis in lymph nodes			.32
Yes	96 (34.4%)	20 (42.6%)	
No	183 (65.6%)	27 (57.4%)	

TABLE 1 (Continued)

Baseline characteristics	Weight loss <5% (N = 279)	Weight loss ≥5% (N = 47)	*P* value
Metastasis in peritoneum			.077
Yes	19 (6.8%)	7 (14.9%)	
No	260 (93.2%)	40 (85.1%)	

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.
Note: Bold values indicate $P < .05$.

non-Hodgkin's lymphoma patients to 87% for gastric cancer patients and nearly 100% of patients with pancreatic cancer.[12,13] The frequency of weight loss ≥5% postdiagnosis is 19.7% for Stage I-III CRC patients.[14] Postdiagnosis weight loss before and during chemotherapy is known to impair physical performance and can subsequently result in a continuous deterioration of the patient's overall state and well-being.[8] Additionally, unintentional weight loss before treatment initiation has been shown to be an independent prognostic factor for OS among patients with gastrointestinal (GI) or lung tumors.[12,15-18] Last, weight loss was associated with an inferior OS in a variety of tumor entities.[19-23] A multicenter, Phase II study of 41 patients with locally advanced rectal cancer undergoing chemoradiotherapy suggested that body weight loss ≥5% (defined as malnutrition) is commonly observed and is associated with adverse events.[24] What is more, body weight losses 5% to <10%, 10% to <20% and ≥20% are defined according to the Common Terminology Criteria for Adverse Events (CTCAE) as Grade 1, Grade 2 and Grade 3, respectively. Severe CTCAE grading of body weight loss is usually rare and malnutrition is underestimated in clinical trials. In clinic, the nutritional assessment contains more aspects, including anthropometric assessment, biochemical analysis, clinical evaluation and dietary behavior, as well as quality of life assessment. Our study defined a body weight loss different from CTCAE evaluation. We defined early weight loss (EWL) as body weight loss of ≥5% after 3 months of treatment.

Therefore, we aimed to evaluate the evolution of body weight and the consequence of EWL ≥5% after 3 months of treatment on survival and side effects of patients with *RAS* wild-type (*RAS*-WT) mCRC treated in the large Phase III FIRE-3 trial. We performed this study to raise the awareness of oncologists and dietitians on patients' body weight change (WC) at an earlier time and encouraged researchers to investigate patients' characteristics and interventions specific to these patients intensely. Methods to prevent further weight loss such as nutrition interventions should be incorporated into the cancer care.

2 | PATIENTS AND METHODS

2.1 | Study design

FIRE-3 was a prospective, multicenter, open-label Phase III study (NCT00433927).[25] Briefly, FIRE-3 compared FOLFIRI (irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 intravenously followed by a continuous infusion of 2400 mg/m^2) combined with either cetuximab (initial dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2) or bevacizumab (5 mg/kg) as first-line treatment of patients with unresectable mCRC with an intent-to-treat population of 593 patients with *KRAS*-WT tumors. As the benefit of bevacizumab was limited to *RAS*-WT patients, a post hoc analysis was performed among the 400 patients with extended *RAS*-WT tumors.[3] Among these 400 patients, 326 patients with body weight data at both baseline and Month 3 are available for this study. Patients' inclusion and exclusion criteria are presented in Figure S1. Regarding the design, conduct of the trial, the full study population, treatment schedules, concordance with the Declaration of Helsinki and approval of ethics committees were reported previously.[25]

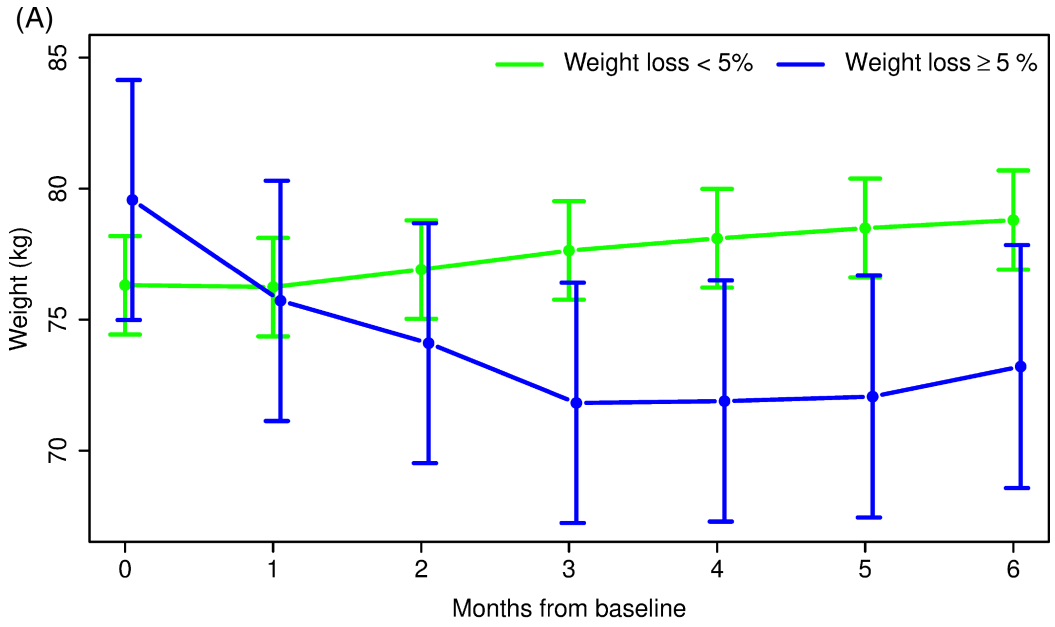
2.2 | Patients

In light of the adoption of RAS analyses as an improved biomarker of response to cetuximab therapy and its evaluation in FIRE-3, we decided to perform the present analyses in the *RAS*-WT population with unresectable mCRC as previously described.[3] Patients with available baseline and follow-up body weight data were included. The percentage of WC from baseline to Month 3 ≥5% is denoted EWL thereafter. WC is defined as:

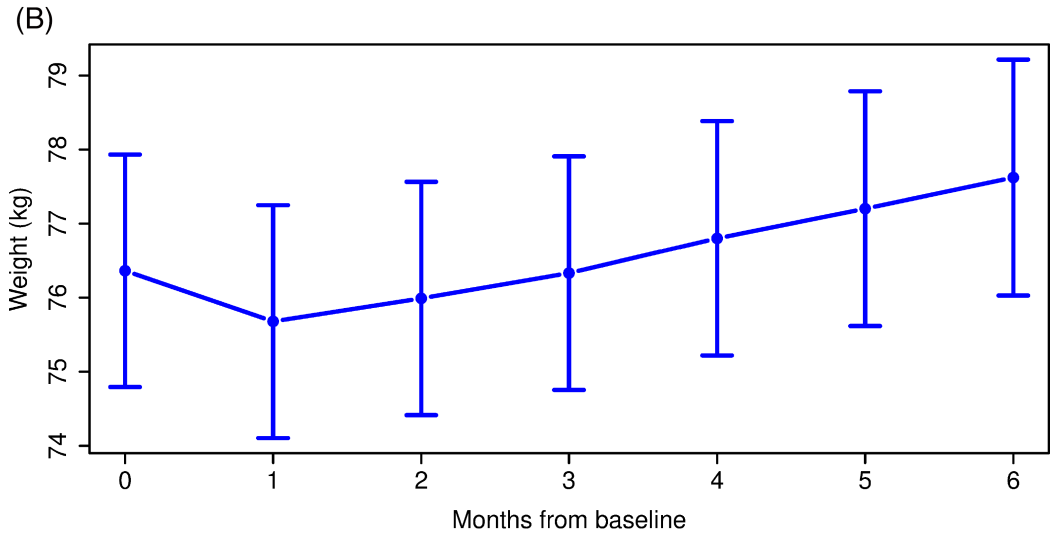
$$\frac{\text{Body weight}_{\text{Month 3}} - \text{Body weight}_{\text{baseline}}}{\text{Body weight}_{\text{baseline}}} \times 100\%$$

2.3 | Statistics

Statistical analyses were performed using R (version 3.6.1) and more particularly the packages survival (version 2.44-1.1), mgcv (version 1.8-28), withr (version 2.1.2) and forestplot (version 1.9). In this exploratory analysis, patients were grouped into two cohorts weight loss ≥5% and weight loss <5% after 3 months of treatment. The cutoff point of 5% is widely accepted in the literature as well as in international and national guidelines as a malnutrition indicator.[8,9,26-30] Baseline characteristics between the two weight loss groups and between cohorts with available body weight data after 3 months of treatment and the rest of *RAS*-WT population were compared with Fisher's exact tests. Univariate and multivariate logistic regression analyses were used to explore the possible predictors for weight loss. A penalized



Month 0 (N = 400)	Month 1 (N = 374)	Month 2 (N = 352)	Month 3 (N = 352)	Month 4 (N = 283)	Month 5 (N = 248)	Month 6 (N = 208)
76.4 (74.8-77.9)	75.7 (74.1-77.2)	76 (74.4-77.6)	76.3 (74.8-77.9)	76.8 (75.2-78.4)	77.2 (75.6-78.8)	77.6 (76-79.2)



	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Weight loss < 5%	N = 279 76.3 (74.4-78.2)	N = 279 76.2 (74.4-78.1)	N = 279 76.9 (75-78.8)	N = 279 77.6 (75.8-79.5)	N = 246 78.1 (76.2-80)	N = 218 78.5 (76.6-80.4)	N = 184 78.8 (76.9-80.7)
Weight loss ≥ 5%	N = 47 79.6 (75-84.2)	N = 47 75.7 (71.1-80.3)	N = 47 74.1 (69.5-78.7)	N = 47 71.8 (67.2-76.4)	N = 37 71.9 (67.3-76.5)	N = 30 72.1 (67.5-76.7)	N = 24 73.2 (68.6-77.9)

FIGURE 1 Representation of the mean evolution of weight with 95% CI over time (from baseline to Month 6). A, Main evolution. B, Evolution according to weight group at Month 3. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

logistic regression spline was fitted to explore the functional relationship between weight loss and age.

Adverse events were monitored throughout the treatment period and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Fisher's exact tests were used to compare the number of patients experiencing at least one adverse event in each cohort.

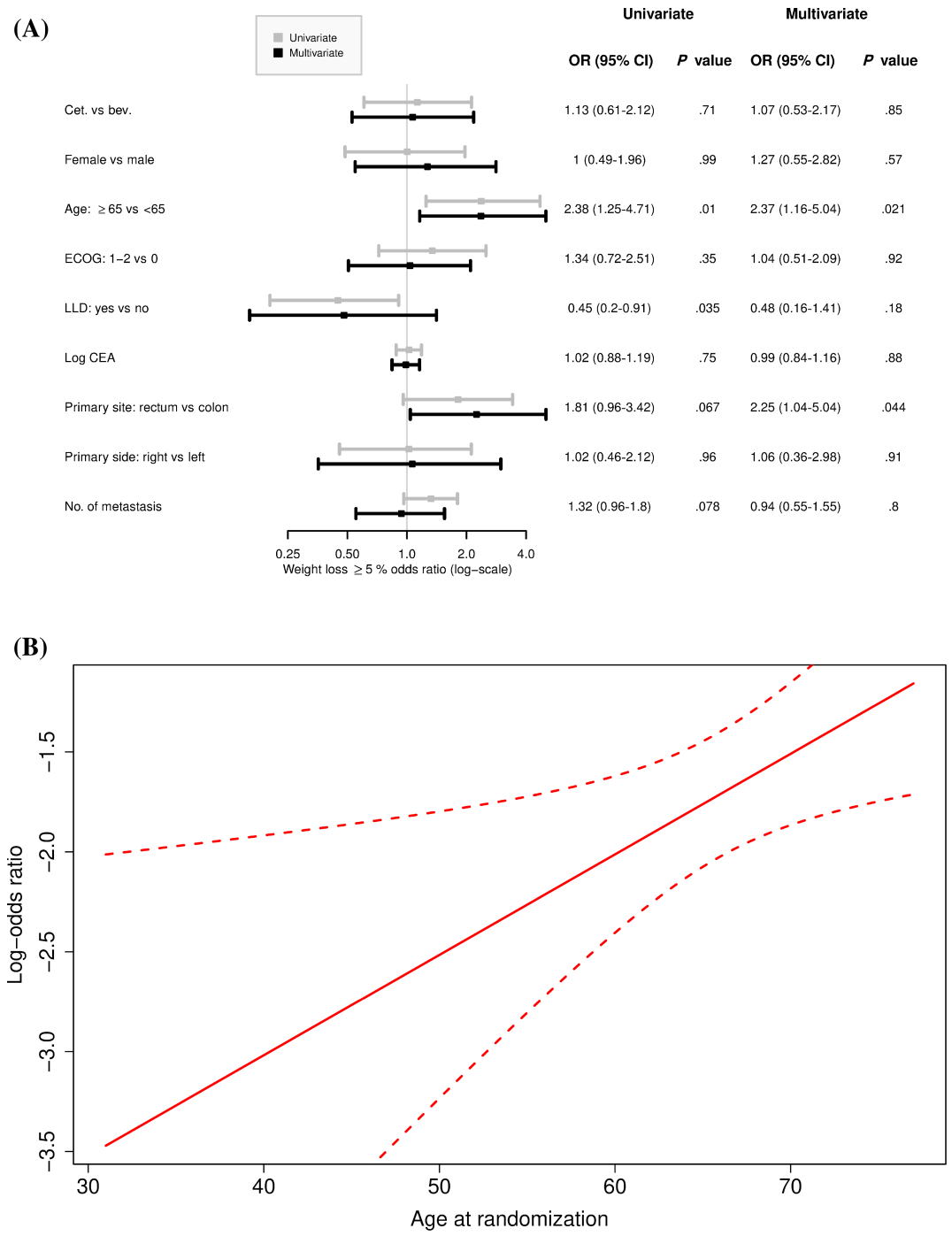


FIGURE 2 A, Univariate and multivariate logistic regression analysis of weight loss prediction. B, Impact of age on weight loss [Color figure can be viewed at wileyonlinelibrary.com]

Progression-free survival (PFS) and OS were displayed as Kaplan-Meier estimation curves and compared using log-rank tests. PFS and OS were calculated from Month 3 on to control for potential guarantee-time bias. Median survival times and corresponding 95% confidence intervals (CIs) were computed. Univariate Cox proportional hazards models were used to calculate the hazard ratios (HRs) and corresponding 95% CIs of all influencing parameters for survival. Multivariate Cox proportional hazards regression models were fitted to adjust the effect of weight loss during treatment for potentially prognostic covariates: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, liver limited disease, baseline carcinoembryonic antigen (CEA), primary tumor side, number of metastatic sites and treatment. Linear mixed effect models were fitted to explore the mean evolution of weight over time. The significance level was set to .05 for all analyses.

3 | RESULTS

3.1 | Patients' characteristics

Of 400 patients with *RAS*-WT tumors in the FIRE-3 study, baseline weight data were available for 400 patients (100%). Weight data after 3 months of systemic treatment were available for 326 patients (81.5%). Patients were divided into subgroups of EWL <5% (N = 279, 85.6%) and ≥5% (N = 47, 14.4%) after 3 months of systemic treatment. Within each subgroup, baseline patient and tumor characteristics were analyzed (Table 1). Here, EWL ≥5% was significantly associated with patients age ≥ 65 years ($P = .011$). Further, patients exhibiting EWL ≥5% appeared to have less hepatic metastasis at baseline ($P = .014$) (Table 1). Additionally, baseline characteristics of patients with available body weight data after 3 months of treatment were compared with whole *RAS*-WT population of FIRE-3 (Table S1). No significant differences were detected.

3.2 | Evolution of body weight and body weight change over time

During the first month of treatment, patients lost an average of 0.7 kg of initial body weight (Figure 1A). From Month 1 to Month 6, the evolution of weight seems to be linear with an average gain of 0.38 kg/mo.

Patients with an EWL ≥5% of treatment experienced a greater average weight loss from baseline to Month 1 than patients with EWL < 5% (weight loss: 3.9 vs 0.1 kg, difference: 3.8; 95% CI = 2.8-4.8, $P < .001$). From baseline to Month 3, patients with EWL < 5% gained an average of 1.3 kg of initial body weight, while patients with EWL ≥5% lost an average of 7.8 kg (95% CI = 6.8-8.7, $P < .001$). The difference between the two groups was 9.1 kg from baseline to Month 3 (95% CI = 8-10.1, $P < .001$) (Figure 1B).

3.3 | Prediction of EWL

Univariate and multivariate logistic regressions were used to evaluate predictive factors for EWL. Here, only patient age ≥ 65 independently predicted the occurrence of EWL (odds ratio [OR]: 2.37; 95% CI = 1.16-5.04; $P = .021$) (Figure 2A). Of note, patient age exhibited a linear effect on log-odds ratio regarding the occurrence of EWL ($P = .016$) (Figure 2B).

3.4 | Adverse events

Among all patients with available body weight data, the number of patients receiving full 3 months of treatment was 307 (93.9%). Only these patients were evaluated to allow for comparison of adverse event rates.

A significant relationship between EWL and side effects after 3 months of treatment was observed as follows: diarrhea, edema, fatigue, nausea and vomiting (Table 2). Of note, comparable results were observed for side effects after 1 month of treatment (Table S2). From baseline to Month 1, EWL was associated with a higher risk of diarrhea, edema and fatigue (Table S2).

3.5 | The prognostic relevance of weight loss

To control for guarantee-time bias, only patients who had completed at least 3 months of treatment were considered. In Kaplan-Meier

TABLE 2 Treatment related adverse events in two weight groups at Month 3

	Weight loss <5% (N = 265)		Weight loss ≥5% (N = 42)		
	Any grade	Grade 3-4	Any grade	Grade 3-4	*P* value
Diarrhea	123 (46.4)	13 (4.9)	32 (76.2)	6 (14.3)	**.00039**
Edema (eg, peripheral)	16 (6)	0 (0)	7 (16.7)	0 (0)	**.025**
Fatigue (asthenia, lethargy)	113 (42.6)	0 (0)	25 (59.5)	1 (2.4)	**.046**
Hematotoxicity	238 (89.8)	36 (13.6)	38 (90.5)	14 (33.3)	1
Hypertension	63 (23.8)	15 (5.7)	7 (16.7)	0 (0)	.43
Infection	78 (29.4)	7 (2.6)	18 (42.9)	2 (4.8)	.11
Liver toxicity	150 (56.6)	10 (3.8)	29 (69)	3 (7.1)	.18
Mucositis/stomatitis	85 (32.1)	7 (2.6)	18 (42.9)	3 (7.1)	.22
Nausea	121 (45.7)	5 (1.9)	27 (64.3)	3 (7.1)	**.03**
Neurotoxicity	59 (22.3)	0 (0)	14 (33.3)	1 (2.4)	.12
Obstipation	58 (21.9)	1 (0.4)	9 (21.4)	0 (0)	1
Pain	101 (38.1)	4 (1.5)	19 (45.2)	3 (7.1)	.4
Vomiting	39 (14.7)	4 (1.5)	14 (33.3)	0 (0)	**.0069**

Note: Bold values indicate $P < .05$.

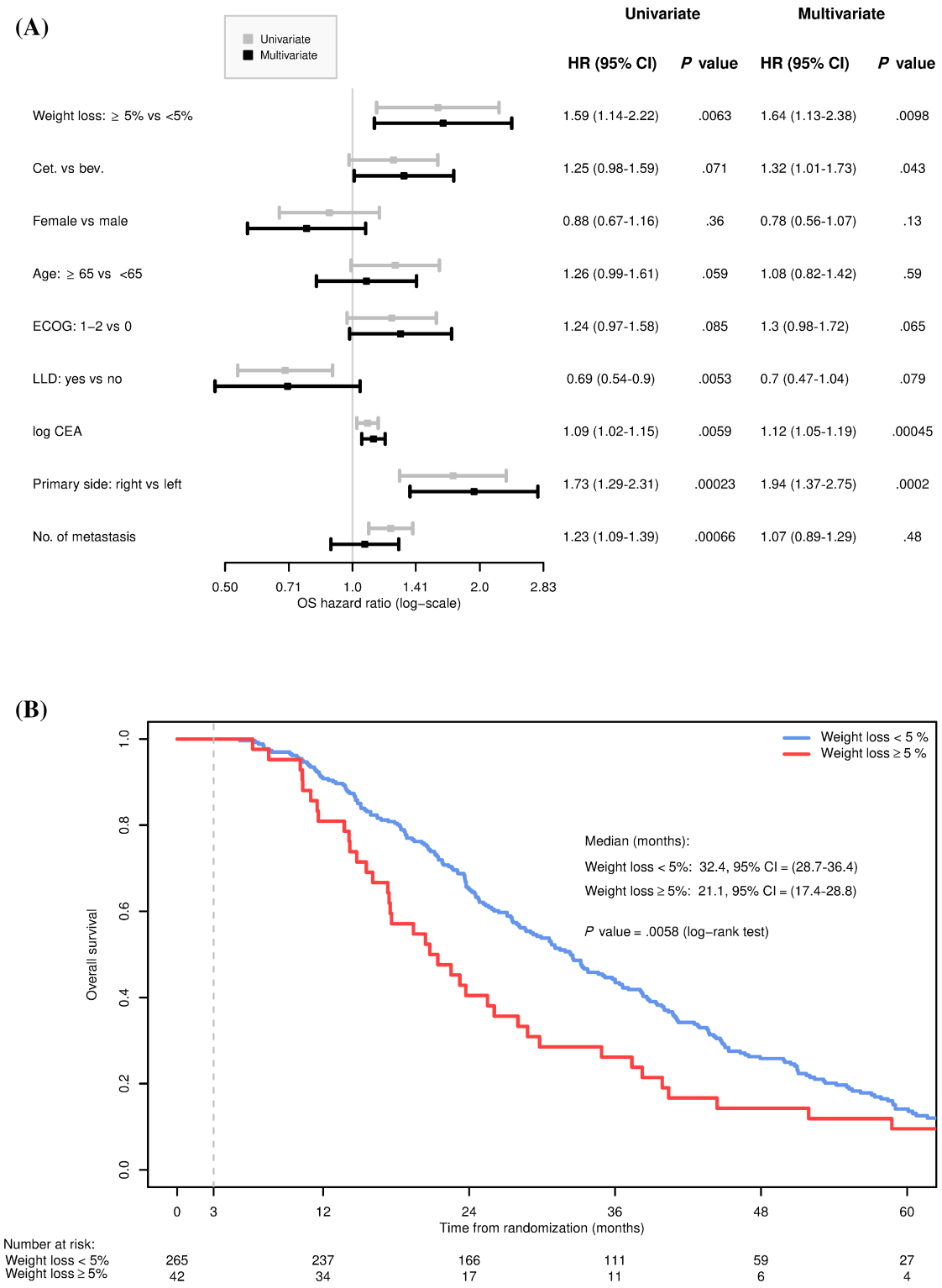


FIGURE 3 Impact of weight loss on OS after 3 months. A, Evaluation of independent prognostic factors for OS after 3 months using Cox regression analysis. B, Kaplan-Meier plot. OS, overall survival [Color figure can be viewed at wileyonlinelibrary.com]

analyses, a prognostic relevance of EWL on OS and PFS was observed. Patients with EWL ≥5% exhibited an inferior OS and PFS compared to patients with EWL < 5% (OS: 21.1 vs 32.4 months, $P = .00084$, Figure 3B; PFS: 9.0 vs 11.8 months, $P = .0022$, Figure 4). Here, EWL independently predicted OS and PFS in patients with *RAS*-WT mCRC (HR for OS: 1.64, 95% CI = 1.13-2.38, $P = .0098$, Figure 3A; HR for PFS: 1.72, 95% CI = 1.18-2.5, $P = .0048$, Figure S2). Univariate and multivariate logistic regression analysis

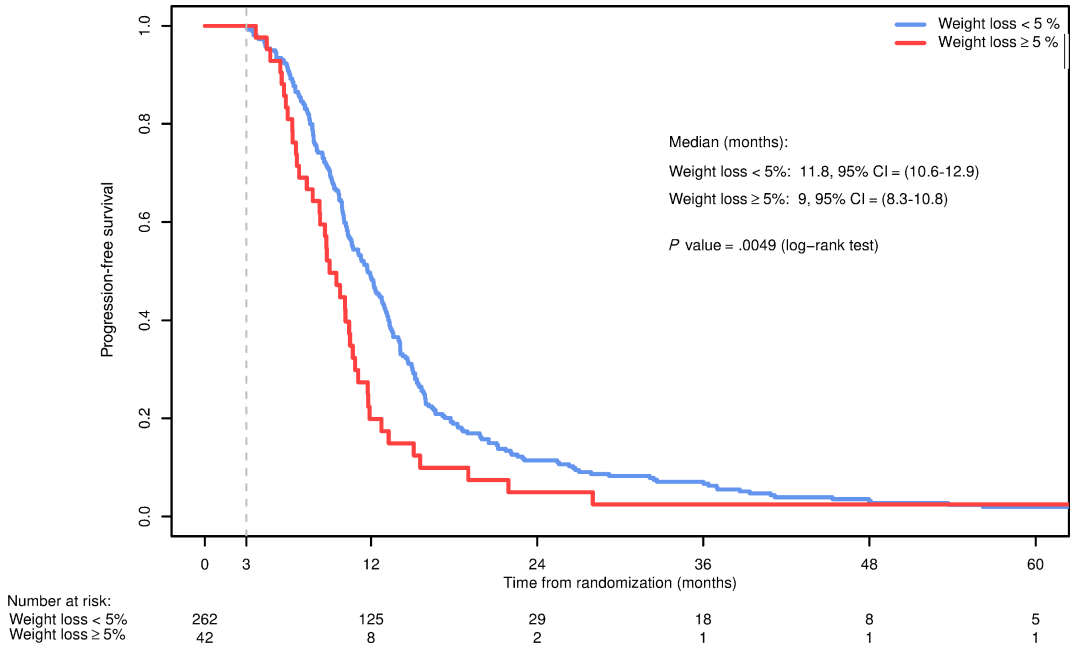


FIGURE 4 Kaplan-Meier plot of PFS after 3 months. PFS, progression-free survival [Color figure can be viewed at wileyonlinelibrary.com]

showed that EWL was not significantly associated with overall response rate (ORR) (HR 0.5, 95% CI = 0.21-1.24, $P = .12$, Figure S3), most probably reflecting the disadvantages of this parameter in the assessment of targeted first-line treatment in mCRC patients.

3.6 | The predictive relevance of weight loss

To evaluate the relevance of EWL to predict a treatment benefit of FOLFIRI plus either bevacizumab or cetuximab, we compared EWL subgroups within each treatment arm. Here, no formal interaction of treatment arm with EWL was detected ($P = .65$) (Figure S4).

4 | DISCUSSION

We investigated the evolution of body weight during standard first-line treatment for mCRC and evaluated the prognostic and predictive relevance of EWL, that is, weight loss evaluated after 3 months. To this end, we used data from the large Phase III trial FIRE-3 comparing FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab in *RAS*-WT mCRC patients.[3,25] An important finding of FIRE-3 was prolonged OS favoring FOLFIRI/cetuximab in the absence of significant differences in PFS and ORR.

Body weight loss according to CTCAE assessment is different from nutritional assessment in the clinic, which contains more evaluations regarding the overall nutritional status with consideration of quality of life. In our cohort, all patients were categorized as Grade 1 (body weight loss 5% to <10%) or Grade 2 (body weight loss 10% to <20%) according to CTCAE. No patients were categorized as Grade 3 (body weight loss ≥20%). We first examined the evolution of body weight during the first 6 months of treatment within FIRE-3. Here, we found that patients lost most weight during the first month of treatment (an average of 0.7 kg), whereas patients slowly recovered hereafter with a weight gain of average 0.38 kg/mo (Figure 1A). To evaluate the impact of weight loss on treatment side effects and patient outcome, we divided patients according to early and clinically relevant weight loss ≥5% or <5% after 3 months of treatment (EWL).[15,19,31,32] Patients with EWL ≥5% showed an average maximum weight loss of 1.1 kg/mo during first 6 month of treatment (Figure 1B). Of note, patients' age at randomization (>65 years) was the only baseline parameter that seemed to predict occurrence of EWL ≥5% with an OR of 2.37. This relationship between OR and patient age looks linear indicating elderly patients being at highest risk for the development of EWL. Here, it is well known that elderly patients lose more weight in general due to changes of the metabolic state and taste as well as fatigue on chewing or difficulty with food preparation.[33]

Next, we examined potential consequences of EWL. We analyzed the impact of EWL on adverse event rates during the first 3 months of treatment. We found that patients exhibiting EWL ≥5% were at higher risk for the development of the following adverse events: fatigue, diarrhea, nausea/vomiting and edema. Here, our results are in accordance with a previous publication, which indicates that especially GI symptoms, such as nausea and vomiting, significantly correlated with weight loss.[34] Thus, GI symptoms besides fatigue and edema should be included in early nutritional evaluations.

We then evaluated the association of EWL ≥5% with patient outcome. Here, we found a significant difference in median OS between the two subgroups of 11.3 months favoring patients with

EWL < 5% (32.4 vs 21.1 months). Further, EWL affected PFS with a median difference of 2.8 months between the two subgroups (11.8 vs 9.0 months). Both results remained significant in multivariate analysis after adjusting for treatment and further prognostic parameters, such as primary tumor sidedness, baseline CEA and ECOG (all $P < .05$). Of note, no significant association of EWL and ORR was observed, most probably reflecting the early time point of ORR within the treatment of mCRC and therefore less dependence on nutritional status than long-term parameters such as survival.[25,35,36]

Finally, we analyzed whether EWL ≥5% might predict treatment benefit comparing FOLFIRI/cetuximab with FOLFIRI/bevacizumab. Here, no significant interaction between treatment arm and EWL was observed ($P = .65$).

To the best of our knowledge, our study is the detailed analysis of the evolution of body weight during modern targeted first-line treatment among patients with mCRC and *RAS*-WT tumor. Here, we identified elderly mCRC patients being at highest risk of weight loss. In line with previous publications in the field of mCRC and various other tumor entities, weight loss was identified as risk factor for frequent adverse events during first-line treatment, especially GI symptoms as well as fatigue and edema. Further, EWL ≥5% was associated with inferior patient survival.

These results indicate that weight maintenance during treatment should become a standard part of clinical oncologists' assessment. Methods to prevent further weight loss such as nutrition interventions should be incorporated into cancer care. All mCRC patients should have access to nutritional counseling during treatment provided by clinical dietitians.[8,37] Dietitians are qualified to discuss strategies to prevent weight loss, reinforce the importance of maintaining a normal body weight throughout life. Additionally, clinicians should stress the importance of weight management in patients with mCRC. These results are in line with current European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, which recommend that patients maintain a normal weight.[8,38]

Our study is certainly limited by its retrospective nature. The patient number in our cohort gradually decreased due to discontinuation of treatment. Patients' dietary behaviors, situations or environments that could promote WC were not recorded. Furthermore, baseline and follow-up data regarding body weight were evaluable among 81.5% of the patients (326 out of 400). In consideration of the guarantee-time-bias, we did a landmark analysis to rule out that EWL merely indicated treatment duration. Here, we decided to focus our investigation on impact of weight loss at Month 3 on survival since this is the most recognized time point.[20,39] In addition, we admitted that dose intensity could be the confounding factor associated with prognosis. Further prospective study with consideration of dose intensity is needed to validate our results.[40]

In conclusion, EWL ≥5% from baseline to Month 3 is an independent prognostic biomarker for patient survival and adverse events in *RAS*-WT mCRC patients receiving first-line targeted therapy. Of note, age correlates significantly with the occurrence of weight loss. Awareness about early detection of weight loss needs to be raised and interventions are needed for weight maintenance for all mCRC patients during treatment. Hence, early preventative measures targeting weight maintenance should be evaluated, especially in elderly patients who are at highest risk.

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CONFLICT OF INTEREST

Nicole Tonya Erickson has received honoraria for participating in symposia for CSL Behring, Fresenius, Baxter, Havas Lynx Group, Nutricia and GHD. Ingrid Ricard received personal fees from Roche. Thomas Decker received advisory board honoraria from Novarits and Roche. Florian Kaiser plays a consulting role from Elsevier. Markus Moehler reports potential conflict of interest from Merck Germany, MSD, BMS, Servier, Pierre-Fabre Pharma, Lilly Deutschland, Dragonfly. Marlies Michl received honoraria for talks from Sirtex, Roche, and MSD and travel expenses from Sirtex, Amgen and Merck. Dominik P. Modest received honoraria from Merck, Amgen, Roche, Servier, Pierre-Fabre, MSD, BMS, Incyte, Lilly, Sanofi and Onkowissen. Sebastian Stintzing received honoraria for talks and advisory board role from Amgen, Bayer, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Takeda, Servier, Taiho. He received research funding from Servier, Pierre-Fabre, Roche and Merck KGaA. Volker Heinemann has received honoraria from Merck, Roche, Celgene, Amgen, Sanofi, Lilly, Sirtex, Boehringer-Ingelheim, Taiho, Servier. He plays a consulting or advisory role from Merck, Roche, Amgen, Sanofi, Sirtex, Servier, Celgene, Boehringer-Ingelheim, Halozyme, MSD, BMS. He has also received research funding from Merck, Roche, Amgen, Sirtex, Servier, Celgene, Boehringer-Ingelheim, Shire. He has received travel accommodation expenses from Merck, Roche, Amgen, Sirtex, Servier, Shire, MSD and BMS. Julian W. Holch is a member of the advisory board for Roche. He has also received honoraria from Roche and travel support from Novartis. All remaining authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data that are minimally required to replicate the outcomes of the study will be made available upon reasonable request.

ETHICS STATEMENT

This study was a retrospective analysis within the randomized Phase III trial FIRE-3 (AIO KRK-0306), which was approved by Ethics Committee of the Medical Faculty Munich with Project No. 370-06. All patients provided written informed consent before entry of the FIRE-3 study.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and

mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;64:252-271.
3. Stintzing S, Modest DP, Rossius L, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol*. 2016;17:1426-1434.
4. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023-1034.
5. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371:1609-1618.
6. Iwamoto S, Ooki A, Morita S, et al. A prospective Phase II study to examine the relationship between quality of life and adverse events of first-line chemotherapy plus cetuximab in patients with KRAS wild-type unresectable metastatic colorectal cancer: QUACK trial. *Cancer Med*. 2018;7:4217-4227.
7. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol*. 2013;31:2699-2707.
8. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11-48.
9. Fukahori M, Shibata M, Hamauchi S, Kasamatsu E, Machii K. A retrospective cohort study to investigate the incidence of cancer-related weight loss during chemotherapy in gastric cancer patients. *Support Care Cancer*. 2020;29(1):341-348.
10. Bernadach M, Lapeyre M, Dillies AF, et al. Toxicity of docetaxel, platine, 5-fluorouracil-based induction chemotherapy for locally advanced head and neck cancer: the importance of nutritional status. *Cancer Radiother*. 2019;23:273-280.
11. da Rocha IMG, Marcadenti A, de Medeiros GOC, et al. Is cachexia associated with chemotherapy toxicities in gastrointestinal cancer patients? A prospective study. *J Cachexia Sarcopenia Muscle*. 2019;10:445-454.
12. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med*. 1980;69:491-497.
13. Kritchevsky SB, Wilcosky TC, Morris DL, Truong KN, Tyroler HA. Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. *Cancer Res*. 1991;51:3198-3203.
14. Meyerhardt JA, Kroenke CH, Prado CM, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. *Cancer Epidemiol Biomarkers Prev*. 2017;26:30-37.
15. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer*. 1998;34:503-509.
16. Ross PJ, Ashley S, Norton A, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer*. 2004;90:1905-1911.
17. Aapro M, Arends J, Bozzetti F, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. *Ann Oncol*. 2014;25:1492-1499.
18. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. 2015;33:90-99.
19. Vergidis J, Gresham G, Lim HJ, et al. Impact of weight changes after the diagnosis of stage III colon cancer on survival outcomes. *Clin Colorectal Cancer*. 2016;15:16-23.
20. McKay RR, Vu P, Albiges LK, et al. The effect of weight change during treatment with targeted therapy in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2019;17(6):443-450.
21. Yoon SL, Kim JA, Kelly DL, Lyon D, George TJ Jr. Predicting unintentional weight loss in patients with gastrointestinal cancer. *J Cachexia Sarcopenia Muscle*. 2019;10:526-535.
22. Takayoshi K, Uchino K, Nakano M, Ikejiri K, Baba E. Weight loss during initial chemotherapy predicts survival in patients with advanced gastric cancer. *Nutr Cancer*. 2017;69:408-415.
23. Lu Z, Yang L, Yu J, et al. Change of body weight and macrophage inhibitory cytokine-1 during chemotherapy in advanced gastric cancer: what is their clinical significance? *PLoS One*. 2014;9:e88553.
24. Yamano T, Tomita N, Sato T, et al. Influence of chemoradiotherapy on nutritional status in locally advanced rectal cancer: prospective multicenter study. *Nutrition*. 2020;77:110807.
25. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:1065-1075.
26. Liu N, Birstler J, Venkatesh M, Hanrahan LP, Chen G, Funk LM. Weight loss for patients with obesity: an analysis of long-term electronic health record data. *Med Care*. 2020;58:265-272.
27. Patel JD, Pereira JR, Chen J, et al. Relationship between efficacy outcomes and weight gain during treatment of advanced, non-squamous, non-small-cell lung cancer patients. *Ann Oncol*. 2016;27:1612-1619.
28. Troeschel AN, Hartman TJ, Jacobs EJ, et al. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. *J Clin Oncol*. 2020;38(18):2018-2027.
29. Cespedes Feliciano EM, Kroenke CH, Bradshaw PT, et al. Postdiagnosis weight change and survival following a diagnosis of early-stage breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2017;26:44-50.
30. Cederholm T, Jensen GL, Correia M, et al. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38:1-9.
31. Tisdale MJ. Cachexia in cancer patients. *Nat Rev Cancer*. 2002;2:862-871.
32. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. *J Clin Oncol*. 2008;26:4109-4115.
33. Cichero JAY. Age-related changes to eating and swallowing impact frailty: aspiration, choking risk, modified food texture and autonomy of choice. *Geriatrics*. 2018;3(4):69.
34. Sanchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D. Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. *Br J Nutr*. 2013;109:894-897.
35. Heinemann V, Stintzing S, Modest DP, Giessen-Jung C, Michl M, Mansmann UR. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). *Eur J Cancer*. 2015;51:1927-1936.
36. Grothey A, Hedrick EE, Mass RD, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. *J Clin Oncol*. 2008;26:183-189.
37. de Man F, Barazonni R, Garel P, et al. Towards optimal nutritional care for all: a multi-disciplinary patient centred approach to a complex challenge. *Clin Nutr*. 2020;39:1309-1314.
38. Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr*. 2017;36:1187-1196.
39. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA*. 2014;312:923-933.

40. Liu L, Erickson NT, Holch JW, et al. Effect of weight loss in patients with metastatic colorectal cancer treated within the randomized phase III FIRE-3 trial (AIO KRK 0306). *J Clin Oncol*. 2020;38(4 suppl):87.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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