The Oncologist®

Gastrointestinal Cancer

Early Weight Loss as a Prognostic Factor in Patients with Advanced Gastric Cancer: Analyses from REGARD, RAINBOW, and RAINFALL Phase III Studies

Wasat Mansoor,[a] Eric J. Roeland,[b] Aafia Chaudhry,[c] Astra M. Liepa,[c] Ran Wei,[c] Holly Knoderer,[c] Paolo Abada,[c] Anindya Chatterjee,[c] Samuel J. Klempner[b]

[a]The Christie NHS Foundation Trust, Manchester, United Kingdom; [b]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; [c]Eli Lilly and Company, Indianapolis, Indiana, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gastric cancer • Gastroesophageal junction adenocarcinoma (G/GEA) • Ramucirumab • Weight loss • Nutrition

Abstract

Background. Weight loss is common in advanced gastric and gastroesophageal junction adenocarcinoma (G/GEA); however, the prognostic implications of weight loss during the first cycle (C1) of chemotherapy remain poorly characterized. In this study, we investigated the impact of early weight loss during systemic treatment as a potential prognostic factor for overall survival (OS) in patients with advanced G/GEA.

Materials and Methods. We performed a post hoc analysis of three phase III studies of ramucirumab. Patients were categorized into two groups: weight loss of ≥3% and <3% based on weight change during C1 (3–4 weeks) of treatment. OS by weight groups was assessed for each study and as a pooled meta-analysis. The effect of C1 weight change on patient survival was evaluated using univariate and multivariate Cox models.

Results. A total of 1,464 patients with weight data at the end of C1 were analyzed: REGARD ($n = 311$), RAINBOW ($n = 591$), and RAINFALL ($n = 562$). For all three studies, there were fewer patients in the weight loss ≥3% than <3% group. OS was numerically shorter for patients with weight loss of ≥3% than for patients with weight loss of <3% during C1 irrespective of treatment arm. Similar treatment independent effects of early weight loss on OS were observed in the meta-analysis. Overall, early weight loss ≥3% was associated with shorter survival in patients receiving active drug as well as placebo/best supportive care.

Conclusion. This large post hoc analysis demonstrated that weight loss of ≥3% during C1 was a negative prognostic factor for OS in patients with advanced G/GEA. ***The Oncologist*** 2021;26:e1538–e1547

Implications for Practice: This comprehensive analysis examining early weight loss during systemic treatment as a predictor of survival outcomes in patients with advanced gastric and gastroesophageal junction adenocarcinoma (G/GEA) includes a large sample size, reliable on-treatment data reported in well-conducted phase III clinical trials, and global representation of cancer patients with advanced G/GEA. Understanding the impact of on-treatment weight loss is clinically relevant and may represent an opportunity for targeted interventions.

Introduction

Gastric cancer is the fifth most common cancer type and the third leading cause of cancer-related deaths worldwide [1]. Despite considerable improvements in treatment options for advanced gastric and gastroesophageal junction adenocarcinoma (G/GEA), the overall prognosis remains poor [2–4]. Because of the asymptomatic nature of G/GEA in early stages, patients often present with advanced (i.e., locally advanced or metastatic) disease at diagnosis [4, 5]. Continued efforts to identify prognostic factors for survival outcomes are crucial to optimize treatment

Correspondence: Wasat Mansoor, Ph.D., Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX, United Kingdom. Telephone: 0161446-3209; e-mail: was.mansoor@nhs.net Received March 8, 2021; accepted for publication May 13, 2021; published Online First on June 9, 2021. http://dx.doi.org/10.1002/onco.13836

strategies, identify opportunities to change the disease's course, and prioritize additional clinical resources for patients and their caregivers. In addition, because advanced G/GEA remains an incurable condition, individualized treatment strategies must aim to preserve patients' quality of life (QoL) while prolonging overall survival (OS) [6, 7].

Various factors correlate with shorter survival in late-stage G/GEA, including poor performance status (PS), primary tumor site (gastroesophageal junction adenocarcinoma or midgastric location), high lymph node burden, peritoneal metastases, and poor/unknown tumor differentiation [8–10]. Previous investigators have assessed the relationship between survival outcomes and several nutrition-based indices in patients with G/GEA, including body mass index (BMI), serum albumin, and preoperative weight loss [11, 12].

Weight loss is common in advanced G/GEA, and maintaining weight and adequate nutrition during systemic treatment remains a challenge [5, 11, 12]. Weight loss before diagnosis is often a result of inadequate caloric intake caused by tumor-related obstruction of the upper digestive tract, malabsorption, anorexia, and hypermetabolism [11]. Symptoms such as dysphagia, anorexia, early satiety, nausea, vomiting, and pain further contribute to cancer-related malnutrition and weight loss [11, 12]. Pre- and/or postoperative weight loss as a prognostic factor for survival outcomes in patients with G/GEA has been evaluated in several studies [13–17]. In particular, Fuchs et al. reported the results of a pooled analysis of two global, randomized clinical trials (RCTs) of ramucirumab as second-line therapy for advanced G/GEA (RAINBOW and REGARD). This analysis showed that ≥10% weight loss within 3 months before baseline evaluation was associated with a worse OS versus <10% weight loss [13]. However, studies investigating the clinical applications of early weight loss (i.e., during the first cycle of chemotherapy [C1]) are limited, particularly as a prognostic factor on survival in patients with advanced G/GEA [18, 19]. Understanding the impact of on-treatment weight loss is clinically relevant and may represent an opportunity for targeted interventions. Weight-correcting interventions are more likely to work if the weight loss is recognized early in a patient's treatment.

In this study, we present post hoc analyses investigating the impact of weight loss within the first 3 to 4 weeks of systemic treatment and define a cutoff weight loss of ≥3% as a potential prognostic indicator of OS in patients with advanced G/GEA using data from both first- and second-line phase III RCTs of ramucirumab.

Materials and Methods

Patient Selection

Patient data were obtained from three large, global phase III RCTs of ramucirumab, a human immunoglobulin G1 monoclonal antibody against the vascular endothelial growth factor receptor-2 (Cyramza; Eli Lilly and Co, Indianapolis, IN), as second-line (REGARD and RAINBOW) or first-line (RAINFALL) treatment in patients with locally advanced or metastatic G/GEA [20–23]. In REGARD (NCT00917384), 355 patients were randomized to receive either ramucirumab (8 mg/kg; $n = 238$) or placebo ($n = 117$) once every 2 weeks plus best supportive care. In RAINBOW (NCT01170663), 665 patients were randomized to receive either ramucirumab (8 mg/kg; $n = 330$) or placebo ($n = 335$) on days 1 and 15 plus paclitaxel (80 mg/m^2) on days 1, 8, and 15 of a 28-day treatment cycle. RAINFALL (NCT02314117) enrolled 645 patients with metastatic, HER2-negative G/GEA, randomized to receive either ramucirumab (8 mg/kg; $n = 326$) or placebo ($n = 319$) on days 1 and 8 of a 21-day treatment cycle [22]. Treatment was administered in combination with cisplatin (80 mg/m^2, day 1) plus capecitabine (1,000 mg/m^2 twice daily on days 1–14) of the treatment cycle. Patients with a contraindication to capecitabine received 5-fluorouracil (800 mg/m^2 daily on days 1–5).

Study designs and results of each trial were previously published [20–22]. Of note, weight was assessed prior to the start of each cycle, and concomitant medications were documented throughout study treatment. QoL was assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire, version 3 (EORTC QLQ-C30), at baseline and during treatment [24]. Each study had similar eligibility criteria except for the number of previous therapies. For all trials, eligible patients had measurable or evaluable disease per RECIST and an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1 [25, 26].

Studies were conducted in accordance with the guiding principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and all applicable laws and regulations. The institutional review board at each participating center approved the study, and all patients provided written informed consent before undergoing any study procedure.

Study Design

In this post hoc analysis of ramucirumab as second-line (REGARD and RAINBOW) or first-line (RAINFALL) treatment in patients with locally advanced or metastatic G/GEA, we analyzed the relationship between weight loss during the first treatment cycle and OS [20–22]. For the meta-analysis, the individual data from REGARD, RAINBOW, and RAINFALL were pooled.

Statistical Analysis

Weight loss of more than 3% after 1 month of chemotherapy has previously been shown to be associated with negative survival outcomes; thus, 3% was chosen as the cutoff in this study (18). Patients were categorized into two groups: weight loss of ≥3% and <3% based on body weight change from the start to the end of C1 (3–4 weeks). For purposes of these analyses, and consistent with the respective trial designs, a cycle was defined as 21 days (3 weeks) for RAINFALL and 28 days (4 weeks) for REGARD and RAINBOW. Patients in the intent-to-treat (ITT) population from the three studies were included in the analysis with available weight measurements at baseline and at the end of C1. Baseline characteristics and QoL scores were summarized descriptively, as were selected concomitant medications.

The efficacy endpoint was OS, defined as the time from randomization to death from any cause.

For each study, the Kaplan-Meier method was used to estimate the median survival time within subgroups. Also, the following Cox proportional-hazard (Cox PH) models were performed to evaluate the effects of C1 body weight loss on OS, regardless of treatment arm and within each treatment arm: univariate Cox PH model with C1 weight loss change group (≥3% vs. <3%) as the only covariate and multivariate Cox PH model with C1 weight loss change (≥3% vs. <3%) in the model, adjusted by prognostic baseline disease factors identified for OS in each study [20–22]. Specifically, REGARD was adjusted by ECOG PS, peritoneal metastasis, and location of the primary tumor; RAINBOW was adjusted by geographic region, ECOG PS, weight loss prior to enrollment, number of metastatic sites, ascites, tumor differentiation, and prior gastrectomy; and RAINFALL was adjusted by geographic region, ECOG PS, weight loss prior to enrollment, and peritoneal metastasis. In the meta-analysis, patient-level data were combined from the three studies, and a univariate Cox PH model was performed stratified by study with C1 weight loss group as the only covariate. A similar analysis was performed within each treatment arm in the pooled data.

Results

This post hoc analysis included a total of 1,464 patients with body weight data during C1 (3–4 weeks) of systemic treatment: 311 patients (87.6%) from REGARD received ramucirumab + best supportive care ($n = 212$) or placebo + best supportive care ($n = 99$), 591 patients (88.9%) from RAINBOW received ramucirumab + paclitaxel ($n = 306$) or placebo + paclitaxel ($n = 285$), and 562 (87.1%) from RAINFALL received ramucirumab + cisplatin/capecitabine ($n = 279$) or placebo + cisplatin/capecitabine ($n = 283$).

Patient Characteristics

The number and general characteristics of patients with weight loss of ≥3% and <3% from each trial are shown in Table 1. The proportion of patients with weight loss of ≥3% was similar for the second-line REGARD and RAINBOW trials (14.5% and 15.6%, respectively) but was higher in the first-line RAINFALL trial (28.6%). Sex and age were relatively similar between the three studies and within weight change groups (≥3% vs. <3%). Patients with ECOG PS of 1 at baseline were more likely to experience weight loss of ≥3% after C1 of treatment.

For the RAINBOW and REGARD trials, patients who progressed more rapidly (i.e., <6 months on first-line therapy) were more likely to be in the ≥3% weight loss group than the <3% weight loss group.

A larger proportion of patients presented with ascites in the second-line RAINBOW trial (34.7%) than the first-line RAINFALL trial (27.6%). In both trials, those with ascites were more likely to experience weight loss of ≥3%. Prior gastrectomy was more common in patients in RAINBOW (40.4%) than RAINFALL (11.9%). In RAINBOW, patients with gastrectomy more frequently demonstrated <3% weight loss. Data on baseline ascites and prior gastrectomy were not collected for REGARD. The proportion of patients with weight loss of ≥10% within 3 months prior to baseline evaluation was similar for the second-line REGARD and RAINBOW trials (13.5% and 13.9%, respectively) but was higher in the first-line RAINFALL trial (30.8%). In REGARD and RAINFALL, those who experienced ≥10% weight loss in the 3 months prior to diagnosis were more likely to lose ≥3% weight loss in C1. This was not observed in the RAINBOW trial.

Across all studies, patients with ≥3% weight loss in C1 generally experienced worse baseline QoL scores than patients with <3% weight loss (Figs. 1, 2). These numerical differences were more prominent for symptoms than functional scales. The symptoms with the greatest differences were fatigue, nausea/vomiting, pain, and appetite loss.

In general, the proportion of patients receiving supportive care medications was generally greater for those patients with weight loss of ≥3% (supplemental online Table 1). Not considering use as premedications, antiemetic use was 20% versus 23% for REGARD, 34% versus 24% for RAINBOW, and 69% versus 61% for RAINFALL for those with weight loss of ≥3% versus <3%, respectively. Less than 15% of patients were documented as receiving appetite stimulants.

Survival Outcomes Analysis

For patients in the pooled treatment arm in each study, early ≥3% weight loss was a strong negative prognostic factor for OS, in both univariate and multivariate analyses (Figs. 3, 4; Table 2). In each trial evaluated, patients with <3% C1 weight loss in the pooled treatment arm were associated with longer median OS and reduced hazard of death than those with ≥3% weight loss (Fig. 3; Table 2; supplemental online Fig. 1). In the meta-analysis combining the three studies, the univariate Cox PH model stratified by study showed a similar effect of early weight loss on OS regardless of treatment arm (unadjusted hazard ratio [HR], 0.632; 95% confidence interval [CI], 0.546–0.732; Fig. 3; supplemental online Fig. 1).

Within each treatment arm across the three studies, univariate and multivariate Cox PH models showed consistent negative effects on OS with ≥3% weight loss during C1. Patients with <3% weight loss had longer OS than those with ≥3% C1 weight loss, regardless of the treatment arms (Fig. 4; Table 3; supplemental online Fig. 2). The percentage weight change from baseline to C1 is summarized in supplemental online Table 2, indicating a higher degree (median change, min–max range) of weight loss in patients with ≥3% as compared with <3% weight loss in each study. In the meta-analysis that combined the three studies, the univariate Cox PH model stratified by study showed a similar effect of early weight loss on OS in each treatment arm. The unadjusted HRs were 0.689 (95% CI, 0.563–0.843) and 0.565 (0.457–0.698) for the ramucirumab and placebo treatment arms, respectively (Fig. 4).

Discussion

Weight loss and malnutrition are prevalent among patients with advanced G/GEA (5, 11, 12). The relationship between

Table 1. Summary of baseline characteristics by weight change groups

Characteristic	REGARD ($n = 311$)		RAINBOW ($n = 591$)		RAINFALL ($n = 562$)	
	Weight loss ≥3%, $n = 45$ (14.5)	Weight loss <3%, $n = 266$, (85.5)	Weight loss ≥3%, $n = 92$, (15.6)	Weight loss <3%, $n = 499$, (84.4)	Weight loss ≥3%, $n = 161$, (28.6)	Weight loss <3%, $n = 401$, (71.4)
Sex						
Male	32 (71.1)	182 (68.4)	58 (63.0)	355 (71.1)	103 (64.0)	271 (67.6)
Age group						
<65 yr	30 (66.7)	167 (62.8)	55 (59.8)	306 (61.3)	100 (62.1)	264 (65.8)
Geographical region						
Asia[a]	4 (8.9)	20 (7.5)	29 (31.5)	177 (35.5)	9 (5.6)	47 (11.7)
Rest of world[b]	41 (91.1)	246 (92.5)	63 (68.5)	322 (64.5)	152 (94.4)	354 (88.3)
ECOG PS						
0	7 (15.6)	87 (32.7)	28 (30.4)	216 (43.3)	63 (39.1)	188 (46.9)
1	38 (84.4)	179 (67.3)	64 (69.6)	283 (56.7)	98 (60.9)	213 (53.1)
Time to PD on first-line therapy						
<6 mo	31 (68.9)	147 (55.3)	60 (65.2)	299 (59.9)	NA	NA
≥6 mo	8 (17.8)	77 (28.9)	32 (34.8)	200 (40.1)	NA	NA
Missing	6 (13.3)	42 (15.8)	NA	NA	NA	NA
Number of metastatic sites						
≤2	29 (64.4)	177 (66.5)	66 (71.7)	329 (65.9)	110 (68.3)	315 (78.6)
≥3	16 (35.6)	89 (33.5)	26 (28.3)	170 (34.1)	51 (31.7)	85 (21.2)
Weight loss within 3 mo prior to enrollment						
<10%	34 (75.6)	235 (88.3)	80 (87.0)	427 (85.6)	101 (62.7)	284 (70.8)
≥10%	11 (24.4)	31 (11.7)	12 (13.0)	70 (14.0)	56 (34.8)	115 (28.7)
Missing	NA	NA	0	2 (0.4)	4 (2.5)	2 (0.5)
Presence of ascites at baseline						
Yes			56 (60.9)	149 (29.9)	64 (39.8)	91 (22.7)
No			36 (39.1)	350 (70.1)	97 (60.2)	310 (77.3)
Prior gastrectomy						
Yes			23 (25.0)	216 (43.3)	15 (9.3)	52 (13.0)
No			69 (75.0)	283 (56.7)	146 (90.7)	349 (87.0)

Data are reported as *n* (%).
[a]RAINFALL patients in Asian countries were only from Japan.
[b]REGARD includes patients from North America and Latin America; RAINBOW includes patients from North America and South America, Europe, and Australia; RAINFALL includes patients from North America, Europe, and others.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; PD, progressive disease.

cancer survival and weight loss has been demonstrated in numerous cancer types [12, 18, 27]. However, limited investigations exist describing the clinical impact of early minimal weight loss (≥3% weight loss as opposed to ≥10% weight loss) during the first cycle of systemic treatment as a prognostic factor in advanced G/GEA. In the present study, we demonstrate that early minimal weight loss during systemic treatment in patients with advanced G/GEA is a negative prognostic factor for OS. To the best of our knowledge, this is the most comprehensive analysis examining early weight loss during systemic treatment as a predictor of survival outcomes in patients with advanced G/GEA.

Weight loss can be described both in severity and in timing. Preoperative weight loss and nutritional deficiency are well-established prognostic factors in patients with G/GEA [12, 28]. Weight loss of ≥10% before diagnosis has been shown to be a significant negative prognostic factor for OS in patients with advanced G/GEA undergoing second-line chemotherapy [29]. Consistently, pooled analysis of REGARD and RAINBOW showed that ≥10% weight loss within 3 months prior to baseline evaluation had a negative prognostic value for OS compared with patients with <10% weight loss [13].

Fewer data exist on whether weight loss during treatment is also prognostic. Previously, we demonstrated that early weight loss during the first 3–4 weeks of second-line systemic therapy was a negative prognostic factor for OS in patients with advanced G/GEA from the RAINBOW study [30]. In this report, we demonstrate consistent findings with two additional phase III G/GEA trials, including one in the first-line setting. Similar to the findings of the current analysis, Ock et al. reported that patients with advanced G/GEA

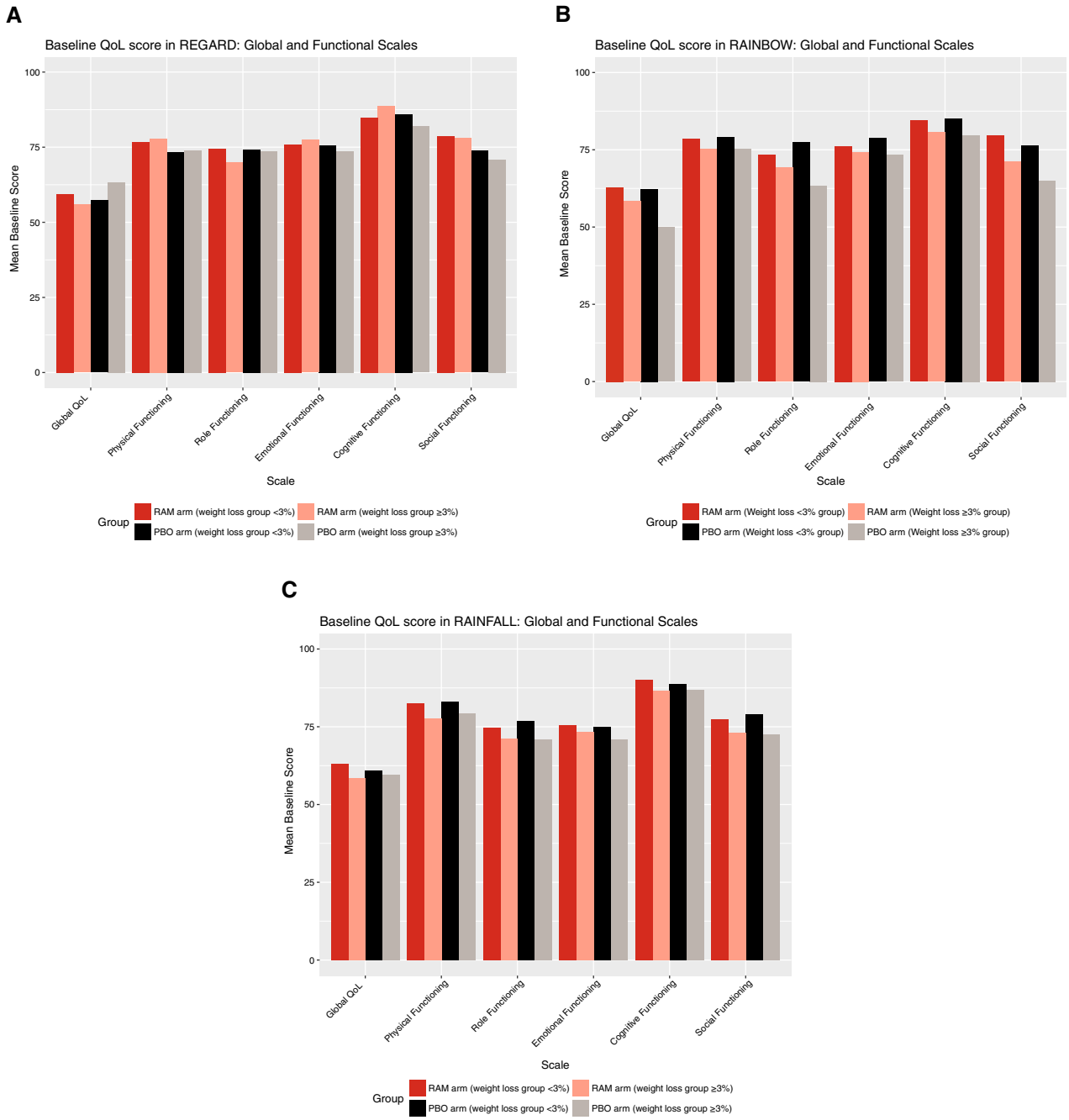

Figure 1. European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire, version 3 mean baseline scores: global and functional scales. Scores range from 0 to 100. High scores represent better QoL for functional scales and global QoL.
Abbreviations: PBO, placebo; QoL, quality of life; RAM, ramucirumab.

and ≥3% weight loss after 1 month of palliative chemotherapy had shorter median OS than those with <3% weight loss (OS; 9.7 vs. 16.3 months; $p < .001$) [18]. Yet, in contrast to our current analysis, Ock et al. performed a retrospective analysis of medical records from a single hospital and only included patients who received first-line chemotherapy. Another report also demonstrated that weight loss during chemotherapy is a negative prognostic indicator of OS in patients with advanced G/GEA. Only the rate of weight loss during chemotherapy was evaluated because the study was performed in patients receiving various chemotherapy regimens, and the sample size analyzed ($n = 53$) was much smaller than our current analysis [19].

Here, we investigated the impact of minimal weight loss (≥3%) within the first 3–4 weeks of systemic treatment on survival outcomes for patients with advanced G/GEA. The analyses included patients from three large multinational trials of ramucirumab therapy, administered as monotherapy in the second-line (REGARD), in combination with single chemotherapy in the second-line

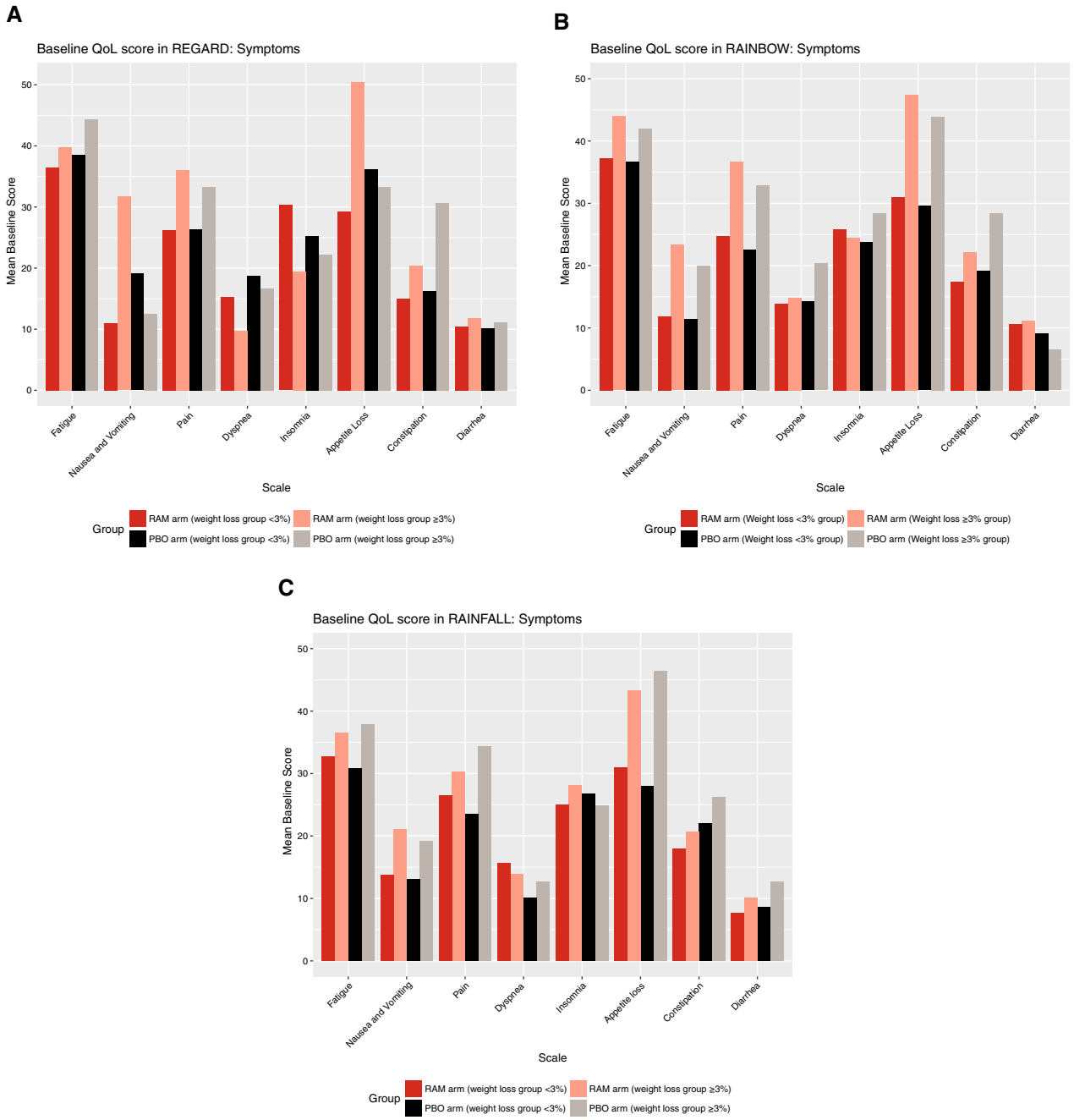

Figure 2. European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire, version 3 mean baseline scores: symptoms. Scores range from 0 to 100. Low scores represent less burden for symptom scales.
Abbreviations: PBO, placebo; QoL, quality of life; RAM, ramucirumab.

(RAINBOW), or dual chemotherapy in the first-line (RAINFALL) [20–22]. Findings from all three studies demonstrated consistent prognostic effects of weight loss on OS in patients with advanced G/GEA.

The proportion of patients with ≥3% weight loss was higher in the first-line RAINFALL trial (28.6%) than the second-line REGARD and RAINBOW trials (14.5% and 15.6%, respectively). There are several possible explanations for the increased proportion of patients who experienced ≥3% weight loss in first-line versus second-line trials. First, patients often present with weight loss at initial cancer diagnosis but less so at relapse or progression (second-line+) [11]. Consistent with this clinical finding, the proportion of patients with ≥10% weight loss within 3 months prior to baseline evaluation was higher in the first-line RAINFALL trial (30.8%) than the second-line REGARD and RAINBOW trials (13.5% and 13.9%, respectively). Second, weight stabilization may signal better disease control with amelioration of cancer-induced cachexia and would be most evident in first-line therapy when the disease burden is presumably higher. Third, weight loss happens because of the cancer and from the initial period of adjustment to chemotherapy. Patients often experience increased nausea and anorexia in early first-line cycles compared with later cycles when supportive care management has been

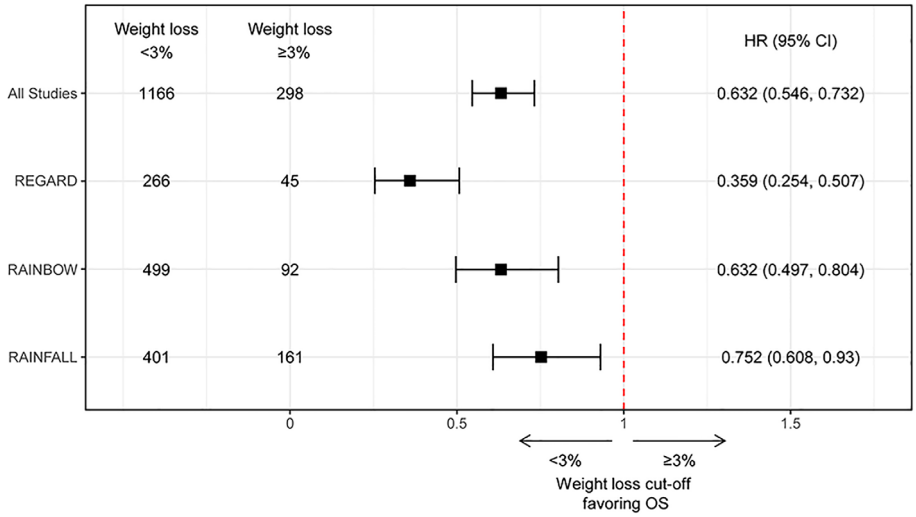

Figure 3. Weight loss <3% in cycle 1 is associated with better survival (pooled analysis). Hazard ratios are shown for overall survival for the pooled analysis and each individual study in the <3% weight loss arm, compared with the ≥3% weight loss arm. Horizontal bars represent 95% confidence limits.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

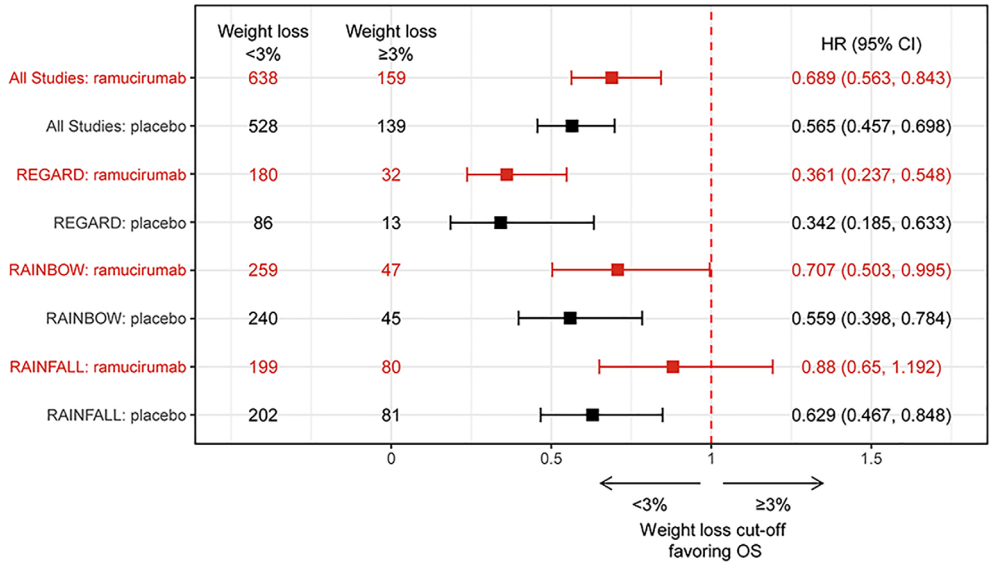

Figure 4. Weight loss <3% in cycle 1 is associated with better survival regardless of treatment arm. Hazard ratios are shown for overall survival for the pooled analysis and each individual study by treatment arm in the <3% weight loss arm compared with the ≥3% weight loss arm. Horizontal bars represent 95% confidence limits.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Table 2. Overall survival by weight loss from baseline to end of C1

Study Name	**REGARD**		**RAINBOW**		**RAINFALL**	
Weight loss in C1, *n* (%)	**45 (≥3)**	**266 (<3)**	**92 (≥3)**	**499 (<3)**	**161 (≥3)**	**401 (<3)**
Median OS, mo	2.6	5.8	7.3	9.8	9.7	11.7
Unadjusted HR (95% CI)	0.359 (0.254–0.507)		0.632 (0.497–0.804)		0.752 (0.608–0.930)	
Adjusted[a] HR (95% CI)	0.406 (0.284–0.579)		0.899 (0.689–1.174)		0.792 (0.638–0.983)	

[a]REGARD-adjusted by ECOG PS, peritoneal metastasis, location of the primary tumor; RAINBOW-adjusted by region, ECOG PS, weight loss prior to enrollment, number of meta sites, ascites, tumor differentiation, and prior gastrectomy; RAINFALL-adjusted by region, ECOG PS, weight loss prior to enrollment, and peritoneal metastasis.
Abbreviations: C1, cycle 1; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival.

Table 3. Overall survival by weight loss in patients by treatment arm

Study Name	REGARD			RAINBOW			RAINFALL		
	RAM + BSC ($n = 212$)	PBO + BSC ($n = 99$)		RAM + PAC ($n = 306$)	PBO + PAC ($n = 285$)		RAM + CC ($n = 279$)	PBO + CC ($n = 283$)	
Weight loss in C1, *n* (%)	32 (≥3)	180 (<3)	13 (≥3)	86 (<3)	47 (≥3)	259 (<3)	45 (≥3)	240 (<3)	80 (≥3)	199 (<3)	81 (≥3)	202 (<3)
Median OS, mo	2.6	6.3	2.5	4.8	8.0	10.8	5.4	9.0	10.6	11.7	9.3	11.9
Unadjusted HR (95% CI)	0.361 (0.237–0.548)		0.342 (0.185–0.633)		0.707 (0.503–0.995)		0.559 (0.398–0.784)		0.880 (0.650–1.192)		0.629 (0.467–0.848)	
Adjusted HR[a] (95% CI)	0.414 (0.268–0.639)		0.341 (0.180–0.645)		1.069 (0.726–1.574)		0.763 (0.523–1.114)		0.903 (0.664–1.229)		0.690 (0.507–0.938)	

[a]REGARD-adjusted by ECOG PS, peritoneal metastasis, location of primary tumor; RAINBOW-adjusted by region, ECOG PS, weight loss prior to enrollment, number of meta sites, ascites, tumor differentiation, and prior gastrectomy; RAINFALL-adjusted by region, ECOG PS, weight loss prior to enrollment, and peritoneal metastasis.

Abbreviations: BSC, best supportive care; C1, cycle 1; CC, cisplatin + capecitabine; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PAC, paclitaxel; PBO, placebo; RAM, ramucirumab; OS, overall survival.

tailored to individual symptoms [11, 12]. There is also a significant psychosocial component early in cancer, whereas, in subsequent cycles and later therapies, patients and caregivers are more experienced and better equipped to manage symptoms. Last, given that patients with very aggressive disease experience the most weight loss and often do not advance beyond first line, it is important to consider a selection bias for patients who receive second-line therapy.

In the reported analyses, weight loss group (≥3% vs. <3%) differences were observed for several baseline characteristics previously identified as negative prognostic factors for OS in patients with advanced G/GEA. We observed that a larger proportion of patients with ≥3% weight loss had poorer PS and reduced time to progressive disease on first-line therapy compared with those with <3% weight loss. This observation is consistent with previous studies demonstrating that preoperative weight loss was associated with increased tumor size, higher TNM stage, and poorer PS [12]. Similarly, BMI has previously been shown to inversely correlate with tumor size and depth, lymph node metastasis, and tumor stage [31].

In addition, we found that the proportion of patients presenting with ascites at baseline was greater for patients with ≥3% weight loss compared with those with <3% weight loss in RAINBOW and RAINFALL. In line with these findings, several symptoms of ascites (e.g., abdominal pain, dyspnea, nausea, vomiting, and anorexia) are known to contribute to weight loss, and malignant ascites is associated with worse prognosis in patients with G/GEA [13, 32, 33].

For the RAINBOW trial, a smaller percentage of patients with ≥3% weight loss had undergone gastrectomy compared with those with <3% weight loss, whereas no differences in the number of patients who had undergone gastrectomy were observed between weight groups for RAINFALL. However, the current analysis did not differentiate between partial and total gastrectomy, and the extent of gastric resection has previously been identified as a risk factor for weight loss [34–36]. Thus, additional analyses are warranted to further evaluate the relationship between prior gastrectomy and early weight loss during first-line or second-line therapy. Further studies investigating the impact of other previously identified risk factors for weight loss in patients with advanced G/GEA are also warranted, such as serum albumin levels, BMI, and tumor size/location. Nonetheless, in the current study, multivariate analyses adjusted by OS prognostic baseline disease factors identified in each study showed that, irrespective of those factors, weight loss had significant negative prognostic value.

The present findings further highlight the clinical importance of identifying early minimal weight loss in patients with advanced G/GEA. Early weight changes may serve as an important prognostic indicator of overall patient survival and may provide key insights in identifying patients at higher risk of experiencing treatment-related toxicity as well as those who might benefit from early interdisciplinary supportive care interventions. In fact, a recent phase III trial in 1L advanced esophagogastric cancers suggests an OS improvement with early interdisciplinary supportive care (ESC), including nutritional support, as compared with

standard oncology care [37]. Although similar to results of the ITT populations, numerical OS benefit was observed in the ramucirumab treatment arms of REGARD and RAINBOW, irrespective of weight loss group (Fig. 4; Table 3). This improved OS, regardless of early weight loss during treatment, shows the benefit from ramucirumab in the second-line setting either as monotherapy or combined with chemotherapy.

The reported analyses have several strengths, including the large sample size, the reliability of the data reported in well-conducted phase III clinical trials, and the global representation of patients with advanced G/GEA. However, some limitations should be considered in the interpretation of our results. Given the exploratory nature of the analyses, which retrospectively evaluated the impact of weight loss on survival, it lacks the statistical requirement of randomization and robust type I error control to make definitive conclusions on causality. The observed association between C1 weight loss and baseline disease characteristics limits the interpretation of the OS-weight loss relationship given the confounding effects of other prognostic factors on OS, such as ECOG PS and the presence of ascites. Furthermore, the study included only limited information regarding supportive care without any information on specific symptom management or dietary interventions. Information on body composition and prognostic biomarkers were also not included in the current analysis. Certain baseline patient characteristics were also not available for all three studies. For example, the presence of ascites was not recorded for the REGARD trial and therefore was not included in the current study. Similarly, it would be of interest to annotate weight loss groups to The Cancer Genome Atlas– and Asian Cancer Research Group–defined molecular subsets to further explore biologic relationships. These data are not available for this data set, nor are they available from any phase III trials in G/GEA. Small patient numbers preclude additional weight cutoffs and analysis of weight changes in subsequent cycles. Nevertheless, these findings provide valuable data regarding the impact of early minimal weight loss during systemic therapy on survival outcomes. Prospectively, it would be interesting to observe what happens to the prognostic impact of early minimal weight loss during treatment when it is reversed. It would be useful to grade the interventions used to reverse the weight loss ranging from simple verbal advice, nutritional supplementation, and use of pharmacological agents to use of enteral or parenteral feeding.

Recent studies have shown that cancer exacerbates muscle loss (sarcopenia) and that patients continually lose muscle mass while on treatment, thereby contributing to impaired physical function, increased chemotherapy toxicity, impaired QoL, and reduced survival [27]. It would be important to further characterize the effect of sarcopenia on survival in these clinical trials and in future prospective trials. As discussed earlier in this section, Lu et al. provided clinical evidence demonstrating prolonged OS in patients receiving early ESC as compared with standard oncology care (HR, 0.68; $p = .021$). These findings highlight the profound impact of early nutritional and psychological intervention (ESC) when provided by a team of gastrointestinal oncology specialists, oncology nurse specialists, dietitians, and psychologists [37]. Future prospective studies evaluating the impact of nutritional interventions and muscle preservation on OS in patients with advanced G/GEA could offer additional insights, especially conducting analyses to determine the interaction between interventions and ≥ 3% weight loss during C1. As with early weight loss, in a prospective study, it would also be interesting to see whether the detrimental effects of muscle loss continue to have their effect if the muscle loss is reversed either by introducing prehabilitation muscle building protocols for patients commencing therapy or by introducing pharmacological agents which encourage muscle growth.

Conclusion

This post hoc analysis demonstrated that early ≥3% weight loss within the first 3–4 weeks of systemic treatment was associated with higher risk of death in patients with advanced G/GEA. The results support the need for future trials to investigate whether mitigating early weight loss can improve outcomes for patients with advanced G/GEA and highlight the importance of considering the prognostic value of weight loss in clinical decision-making. Future prospective studies are needed to further optimize treatment strategies and identify opportunities to change the course of disease for patients with advanced G/GEA, including baseline comprehensive nutritional assessments and early interventions to preserve weight.

Acknowledgments

The authors thank the patients and their caregivers for their participation, the study investigators and their staff, and the institutions involved in these studies. Hannah M. Messersmith of Eli Lilly and Company provided writing supporting for this manuscript.

Funding for this research was provided by Eli Lilly and Company.

Author Contributions

Conception/design: Wasat Mansoor, Aafia Chaudhry, Astra M. Liepa, Paolo Abada, Anindya Chatterjee, Samuel J. Klempner

Data analysis and interpretation: Wasat Mansoor, Eric J. Roeland, Aafia Chaudhry, Astra M. Liepa, Ran Wei, Holly Knoderer, Paolo Abada, Anindya Chatterjee, Samuel J. Klempner

Manuscript writing: Wasat Mansoor, Eric J. Roeland, Aafia Chaudhry, Astra M. Liepa, Ran Wei, Holly Knoderer, Paolo Abada, Anindya Chatterjee, Samuel J. Klempner

Final approval of manuscript: Wasat Mansoor, Eric J. Roeland, Aafia Chaudhry, Astra M. Liepa, Ran Wei, Holly Knoderer, Paolo Abada, Anindya Chatterjee, Samuel J. Klempner

Disclosures

Wasat Mansoor: Bristol Myers Squibb, Servier (C/A, H), Eli Lilly and Company (Other-Speakers' Bureau), Ipsen, Servier (Other-Travel, Accommodations, Expenses); **Eric J. Roeland:** AIM Specialty Health, Asahi Kasei, BASF, Helsinn Healthcare, Heron Therapeutics, Immuneering, Napo Pharmaceuticals, Oragenics, Pfizer/EMD Serono, Vector Oncology (C/A); **Aafia Chaudhry:** Eli Lilly and Company (E); **Astra M. Liepa:** Eli Lilly and Company (E, OI); **Ran Wei:** Eli Lilly and Company (E, OI); **Holly Knoderer:** Eli Lilly and Company (E, OI); **Paolo B. Abada:** Eli Lilly and Company (E, OI); **Anindya Chatterjee:** Eli Lilly and Company

(E, OI); **Samuel J. Klempner:** Eli Lilly and Company, Bristol Myers Squibb, Foundation Medicine, Daiichi-Sankyo, Astellas, Merck, Natera Inc, Pieris Pharmaceuticals (C/A), Turning Point Therapeutics (OI).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Bray F, Ferlay J, Soerjomataram I et al. 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. Song Z, Wu Y, Yang J et al. Progress in the treatment of advanced gastric cancer. Tumour Biol 2017;39:1010428317714626.

3. Bonelli P, Borrelli A, Tuccillo FM et al. Precision medicine in gastric cancer. World J Gastrointest Oncol 2019;11:804–829.

4. Takahashi T, Saikawa Y, Kitagawa Y. Gastric cancer: Current status of diagnosis and treatment. Cancers (Basel) 2013;5:48–63.

5. Layke JC, Lopez PP. Gastric cancer: Diagnosis and treatment options. Am Fam Physician 2004; 69:1133–1140.

6. Al-Batran SE, Van Cutsem E, Oh SC et al. Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma. Ann Oncol 2016;27:673–679.

7. Munene G, Francis W, Garland SN et al. The quality of life trajectory of resected gastric cancer. J Surg Oncol 2012;105:337–341.

8. Han J, Tu J, Tang C et al. Clinicopathological characteristics and prognosis of cT1N0M1 gastric cancer: A population-based study. Dis Markers 2019;2019:5902091.

9. Dixon M, Mahar AL, Helyer LK et al. Prognostic factors in metastatic gastric cancer: Results of a population-based, retrospective cohort study in Ontario. Gastric Cancer 2016;19:150–159.

10. Park JM, Ryu WS, Kim JH et al. Prognostic factors for advanced gastric cancer: Stage-stratified analysis of patients who underwent curative resection. Cancer Res Treat 2006;38: 13–18.

11. Rosania R, Chiapponi C, Malfertheiner P et al. Nutrition in patients with gastric cancer: An update. Gastrointest Tumors 2016;2:178–187.

12. Liu X, Qiu H, Kong P et al. Gastric cancer, nutritional status, and outcome. Onco Targets Ther 2017;10:2107–2114.

13. Fuchs CS, Muro K, Tomasek J et al. Prognostic factor analysis of overall survival in gastric cancer from two phase III studies of second-line ramucirumab (REGARD and RAINBOW) using pooled patient data. J Gastric Cancer. 2017;17: 132–144.

14. Kubo H, Komatsu S, Ichikawa D et al. Impact of body weight loss on recurrence after curative gastrectomy for gastric cancer. Anticancer Res 2016;36:807–813.

15. Aoyama T, Sato T, Maezawa Y et al. Postoperative weight loss leads to poor survival through poor S-1 efficacy in patients with stage II/III gastric cancer. Int J Clin Oncol 2017;22:476–483.

16. Lee SE, Lee JH, Ryu KW et al. Changing pattern of postoperative body weight and its association with recurrence and survival after curative resection for gastric cancer. Hepatogastroenterology 2012;59:430–435.

17. Park YS, Park DJ, Lee Y et al. Prognostic roles of perioperative body mass index and weight loss in the long-term survival of gastric cancer patients. Cancer Epidemiol Biomarkers Prev 2018;27:955–962.

18. Ock CY, Oh DY, Lee J et al. Weight loss at the first month of palliative chemotherapy predicts survival outcomes in patients with advanced gastric cancer. Gastric Cancer 2016;19: 597–606.

19. Takayoshi K, Uchino K, Nakano M et al. Weight loss during initial chemotherapy predicts survival in patients with advanced gastric cancer. Nutr Cancer 2017;69:408–415.

20. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31–39.

21. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 2014;15: 1224–1235.

22. Fuchs CS, Shitara K, Di Bartolomeo M et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:420–435.

23. Spratlin JL, Cohen RB, Eadens M et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28:780–787.

24. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–376.

25. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.

26. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.

27. Ryan AM, Prado CM, Sullivan ES et al. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. Nutrition 2019;67–68:110539.

28. Fujiwara Y, Fukuda S, Tsujie M et al. Outcome predictors for patients with stage II/III gastric cancer who undergo gastrectomy and S-1 adjuvant chemotherapy. Oncol Lett 2017;14: 1621–1627.

29. Kanagavel D, Pokataev IA, Fedyanin MY et al. A prognostic model in patients treated for metastatic gastric cancer with second-line chemotherapy. Ann Oncol 2010;21:1779–1785.

30. Mansoor W, Roeland E, Abraham M et al. Analysis of weight loss as a prognostic factor in patients with advanced gastric cancer from the phase 3 RAINBOW study. Ann Oncol. 2019;30 (suppl 4):PD-005a.

31. Feng F, Zheng G, Guo X et al. Impact of body mass index on surgical outcomes of gastric cancer. BMC Cancer. 2018;18:151.

32. Zheng LN, Wen F, Xu P et al. Prognostic significance of malignant ascites in gastric cancer patients with peritoneal metastasis: A systemic review and meta-analysis. World J Clin Cases 2019;7:3247–3258.

33. Sangisetty SL, Miner TJ. Malignant ascites: A review of prognostic factors, pathophysiology and therapeutic measures. World J Gastrointest Surg 2012;4:87–95.

34. Davis JL, Selby LV, Chou JF et al. Patterns and predictors of weight loss after gastrectomy for cancer. Ann Surg Oncol 2016;23:1639–1645.

35. Climent M, Munarriz M, Blazeby JM et al. Weight loss and quality of life in patients surviving 2 years after gastric cancer resection. Eur J Surg Oncol 2017;43:1337–1343.

36. Segami K, Aoyama T, Kano K et al. Risk factors for severe weight loss at 1 month after gastrectomy for gastric cancer. Asian J Surg 2018;41: 349–355.

37. Lu Z, Fang Y, Liu C et al. Early interdisciplinary supportive care in patients with previously untreated metastatic esophagogastric cancer: A PHASE III randomized controlled trial. J Clin Oncol 2021;39:748–756.

See http://www.TheOncologist.com for supplemental material available online.