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Tumor response and symptom palliation from RAINBOW, a phase 3 trial of ramucirumab plus paclitaxel in previously treated advanced gastric cancer

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Abstract

Background: In the intent-to-treat (ITT) population of the RAINBOW study, objective response rate (ORR) was 28% and 16% in the ramucirumab and control arms, respectively. To further characterize tumor response, we present details on timing and extent of tumor shrinkage, as well as associations with symptom palliation. Clinicaltrials.gov NCT01170663

Materials and Methods: Tumor response was assessed with RECIST v1.1, and quality of life (QoL) was assessed with the EORTC QLQ-C30 v3.0. Pre-specified and post hoc analyses were conducted in the ITT population, patients with measurable disease, or responders, and included best overall response (BOR), ORR, disease control rate (DCR), duration of response, time to response (TtR), change in tumor size, and associations of QoL with tumor shrinkage and BOR.

Results: In both treatment arms, median TtR was 1.5 months. Responses were more durable in the ramucirumab versus control arm (median 4.4 vs 2.8 months). In patients with measurable disease (78% of ITT), ORR was 36% versus 20%; DCR was 81% versus 61% in the ramucirumab versus control arms. Waterfall plots demonstrated more tumor shrinkage in the ramucirumab versus control arm. Regardless of treatment, tumor response and stable disease were associated with improved/stable QoL, with more tumor shrinkage associated with greater symptom palliation.

Conclusions: Treatment with ramucirumab plus paclitaxel yielded the highest ORR reported to date for patients with previously treated advanced gastric/gastroesophageal junction adenocarcinoma. Additional details demonstrate robustness of tumor response results. The extent of tumor shrinkage is directly associated with symptom palliation and should be considered when evaluating patient needs and treatment selection.

Implications for Practice:

Ramucirumab plus paclitaxel is a recognized standard of care as it improves survival for patients with advanced gastric or gastroesophageal junction adenocarcinoma who have been previously treated with recommended first-line therapy. These additional data on tumor response demonstrate a positive association between tumor shrinkage and symptom palliation in a patient population that is often symptomatic. These observations included patients with non-measurable disease, a group of patients often underrepresented in clinical trials. This knowledge can inform treatment decisions, which align individual patient characteristics and needs with demonstrated benefits.

Introduction

Gastric cancer is the fifth most common cancer worldwide with an annual incidence of more than 1,000,000. With an estimated 783,000 deaths in 2018, it is the third most common cause of cancer-related death [1]. In the first-line setting, chemotherapy and/or chemoradiation may extend survival and improve quality of life (QoL) of patients with locally advanced, metastatic, and/or unresectable gastric/gastroesophageal junction (GEJ) adenocarcinoma, but durable responses are rare [2]. Even with the advances in chemotherapy in the last twenty years and the introduction of anti-HER2 therapy for patients with HER2+ disease, patients with locally advanced or metastatic gastric/GEJ cancer have a median survival of less than 2 years [2].

With initial therapy for advanced disease, extending survival is generally the primary goal. However, as disease progresses, symptom palliation and preservation of QoL gain prominence as additional goals of treatment. Control of tumor progression is likely key in symptom control. A recent study of QoL data from two large phase 3 studies in patients previously treated for gastric/GEJ cancer confirmed that disease control is important for maintaining or improving QoL [3]. Chau et al observed that fatigue, pain, and appetite loss were the most prominent patient-reported baseline symptoms. For patients who achieved an objective response, scores improved for global QoL, emotional functioning, pain, appetite loss, and nausea/vomiting. Patients achieving stable disease maintained their QoL with treatment. Disease progression resulted in worsening QoL across all functional domains and most symptoms [3]. The negative QoL impact of disease progression has been reported for other tumor types [4], but reports on QoL and symptom palliation with tumor response are more limited.

Although tumor response criteria are generally standardized across clinical trials, differences in eligibility criteria and analysis populations may impact applicability of some results

to the clinical practice setting. Advanced gastric cancer is often accompanied by peritoneal metastases or ascites, which are considered non-measurable by the Response Evaluation Criteria in Solid Tumors (RECIST) standards [5]. In clinical studies where response is the primary endpoint, patients with only non-measurable disease are excluded, and all eligible patients are expected to be included in the response calculation [5]. When response is a secondary endpoint and non-measurable only disease is not an exclusion criterion, the protocol must prespecify the analysis population for calculating response rates [5]. Thus, depending on the study, patients with only non-measurable disease may be excluded from secondary response analyses despite being included in the intent-to-treat (ITT) population [5, 6]. Consequently, it would be unclear if patients with only non-measurable disease who were excluded from the response analyses derive any of the benefits of disease control from the tested interventions. Reports of response calculated in this manner may limit the applicability to the real world clinical population.

Patients with advanced gastric cancer whose disease progresses on or after first-line therapy typically have low response rates to subsequent lines of treatments. In the second-line setting, response rates from 0% to 21% have been reported for chemotherapy regimens without targeted agents recommended by current guidelines for advanced or metastatic disease [7-12]. Among these studies, one study excluded patients without measurable disease [8], and 3 calculated response based on a subset of patients [7, 10, 11].

In the global phase 3 RAINBOW trial, ramucirumab plus paclitaxel improved overall survival (OS) and progression-free survival (PFS) in patients with advanced, fluoropyrimidine- and platinum-resistant gastric/GEJ adenocarcinoma versus placebo plus paclitaxel [13]. As a tumor-based outcome, the hazard ratio for PFS was 0.635 (95% confidence interval: 0.536-0.752), with early separation of the Kaplan-Meier curves and 6-week PFS rates of 88% in the ramucirumab arm and 75% in the placebo arm. Ramucirumab plus paclitaxel demonstrated the highest objective response rate (ORR) reported in the second-line setting for an unselected

patient population with an ORR of 28% versus 16% in the ramucirumab plus placebo arm (p=0.0001) [13]. This is noteworthy as the trial enrolled patients with RECIST v1.1 evaluable disease, regardless of whether it was measurable or non-measurable only (approximately 20% of those enrolled in each arm for the latter), and ORR was estimated in the ITT population [13]. RAINBOW also demonstrated that the addition of ramucirumab to paclitaxel maintained patient-reported QoL while delaying symptom worsening and functional status deterioration [14]. Ramucirumab is approved worldwide in combination with paclitaxel and as monotherapy for previously treated gastric/GEJ adenocarcinoma.

To further characterize the relationship between tumor response and symptoms from the RAINBOW study, we present details on timing and extent of tumor shrinkage, and the association of response with symptom palliation. Published data examining the benefits of disease control and tumor reduction in relation to QoL and symptom control in advanced gastric/GEJ cancer are limited. Results from this study will provide additional context when considering second-line options for patients with advanced gastric/GEJ cancer.

Materials and Methods

Study Design

Details for the RAINBOW trial have been published elsewhere [13]. Eligibility included patients 18 years of age and older with unresectable or metastatic disease that progressed on or within four months of last dose of first-line therapy and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients were randomized 1:1 to receive paclitaxel intravenously on days 1, 8, and 15 in combination with either ramucirumab (8 mg/kg) or placebo administered intravenously on days 1 and 15 of a 28-day cycle. Randomization was stratified by geographic region (region 1, Europe, Australia, and the USA; region 2, rest of world including South America; and region 3, East Asia), time to progression after first dose of first-line therapy

(<6 months vs ≥6 months), and disease measurability (measurable vs non-measurable only). The primary outcome was OS in the ITT population. Secondary outcomes included ORR and QoL. The ITT population consisted of 330 and 335 patients treated in the ramucirumab and control arms, respectively (**Supplemental Figure 1** and **Supplementary Table S1**).

Assessments

Images of the chest, abdomen, and pelvic areas were obtained (computed tomography scan or magnetic resonance imaging) on all patients at baseline and every 6 weeks for the first 6 months and every 9 weeks thereafter. Tumor response was assessed according to the RECIST version 1.1 [5]. Quality of life was assessed using the EORTC QLQ-C30 (version 3.0), which patients completed at baseline, every 6 weeks, and at end of therapy.

Pre-specified Analyses

Objective response rate (ORR) in the ITT population was defined as the proportion of patients who achieved a BOR of complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the proportion of patients in the ITT population who achieved a BOR of CR, PR, or stable disease (SD). Additional analyses for those with measurable disease included ORR and DCR estimations.

Duration of response (DOR) was measured in the ITT population and defined as the time from CR or PR until progressive disease (PD) or death. DOR was compared between arms with an unstratified log-rank test and median DOR was estimated using the Kaplan-Meier method.

For each patient in the ITT population, changes from baseline in QLQ-C30 scores were calculated for each post-baseline assessment. Changes of ≥10 points (on 100-point scale) were considered meaningful [15]. Changes were classified as improved if ≥10 points favorable,

worsened if ≥10 points deteriorated, or stable if <10 points. Best change from baseline was also calculated and classified. Proportions of patients with improved or stable scores were compared between arms using Fisher's exact test.

Post hoc Analyses

Baseline patient and disease characteristics were reported by BOR and by disease measurability. Waterfall plots were constructed to display the best percent change in tumor size for each patient by treatment arm. Because a waterfall plot utilizes a calculation of change from baseline the analysis is limited to patients with measurable disease who had both a baseline and at least one post-baseline assessment. Fatigue, pain, and appetite loss were previously identified as the three most prominent patient-reported baseline symptoms for previously treated patients with advanced gastric/GEJ cancer [3]. Thus, the association of best change from baseline for these 3 symptoms with best percent change in tumor size was explored by plotting symptom improvement for patients included in the waterfall plot.

Descriptive statistics were used to estimate the median time to response, defined as time from randomization to first response estimated for patients with a BOR of CR or PR. A swimmer's plot was constructed to describe the following outcomes for each individual patient with BOR of CR or PR: time to objective response (estimated from randomization date to first assessment of CR or PR), duration of response, and time on study.

Best change in QoL scores of fatigue, pain, and appetite loss, and global QoL were plotted by BOR for the ITT population. Within each BOR group, proportions of patients with improved or stable scores were compared between arms.

Results

Baseline Characteristics and Tumor Response

As previously reported in the RAINBOW ITT population, the ramucirumab arm had an ORR of 28%; two (<1%) patients had a CR and 90 (27%) patients had a PR. Additionally, 172 (52%) patients achieved a BOR of SD resulting in a DCR of 80%. The control arm had an ORR of 16%, 1 (<1%) patient had a CR and 53 (16%) patients had a PR; 159 (47%) patients had a BOR of SD with a DCR of 64% [13]. **Tables 1 and 2** show baseline characteristics for patients by BOR. In the BOR groups of CR/PR or SD, a higher proportion of patients were Asians or from East Asia compared with the PD group (independent of treatment). Relative to those in the SD and PD groups, patients in the CR/PR group all had measurable disease; they also had a higher proportion of liver metastasis and a lower proportion of ascites and peritoneal disease, regardless of treatment arm. Examination of those achieving BOR of CR/PR in each treatment group revealed patient and tumor characteristics were generally equally distributed although there were higher percentages of patients with ECOG PS 1 and ascites in the ramucirumab arm. In patients with a BOR of SD, 67% had measurable disease in each treatment arm. For those with a BOR of PD, 72% in the ramucirumab arm had measurable disease versus 87% in the control arm.

Additional Outcomes in Patients With Tumor Response

For those achieving an objective response, the median time to first response was 1.5 months (interquartile range 1.4 to 2.8 months) for both treatment arms. The median duration of response was 4.4 months in the ramucirumab arm versus 2.8 months in the control arm (**Figure 1**).

For patients with an objective response, regardless of treatment arm, more than half of patients achieved a tumor response at 6 weeks (53/92 [58%] in the ramucirumab arm and 33/54 [61%] in the control arm) (**Figure 2**). Among those who responded within 6 weeks, those treated with ramucirumab maintained a more durable response than those treated in the control arm.

Sustained response at six months was 36% (19/53) in the ramucirumab arm and 18% (6/33) in the control arm. This trend continued at 12 months with rates of 11% and 6% in the ramucirumab and control arms, respectively.

Similar trends were observed when considering all patients that had responded by 12 weeks. In the ramucirumab arm, 79/92 (86%) demonstrated response by 12 weeks similar to 47/54 (87%) in the control arm. After six months, 48% (38/79) versus 23% (11/47) had sustained response in the ramucirumab and control arms, respectively. This trend persisted at 12 months, with rates of 13% versus 6% in the ramucirumab and control arms, respectively.

Outcomes in Patients With Measurable Disease

From the ITT population, the proportion of patients with measurable disease was similar in the ramucirumab and control arms (78% [256/330] vs 79% [265/335] respectively). When dichotomized by disease measurability, patient and disease baseline characteristics were similar between treatment arms; however, a higher proportion of patients with non-measurable only disease were female, Asian, and had ascites, whereas a lower proportion had GEJ disease (**Supplemental Table 2**).

Tumor Response and Disease Control Rates

In the subgroup of patients with measurable disease, both ORR and DCR were higher in the ramucirumab arm. The ORR was 36% (92/256) in the ramucirumab arm versus 20% (54/265) in the control arm. The DCR was 81% (207/256) in the ramucirumab arm and 61% (161/265) in the control arm.

Waterfall Plot of Best Percent Change in Tumor Size

Figure 3 demonstrates the best percent change from baseline in the sum of tumor diameters from the subgroup of patients with measurable disease that also had both baseline and post-

baseline assessments. Thus, 238/330 (72%) patients from the ramucirumab arm and 236/335 (70%) patients from the control arm are included in the waterfall plot. Of the patients represented in the plot, a larger proportion in the ramucirumab arm experienced any tumor shrinkage compared with the control arm (185/238 [78%] vs 141/236 [60%], respectively) (**Figure 3**).

Association of Tumor Response and Quality of Life

Fatigue, pain, and appetite loss were previously identified as the three most prominent patient-reported baseline symptoms for previously treated patients with advanced gastric/GEJ cancer [3]. **Figure 4** presents the association between best percent change in tumor size and best improvement in these selected symptoms, using the same patient population as in **Figure 3**. Baseline symptom levels were similar between arms (**Supplemental Table 3**). The number of non-evaluable patients (those without both baseline and post-baseline QoL) was low (18/330 [5%] in the ramucirumab arm, 30/335 [9%] in the control arm), and more common among patients with increased tumor size from the control arm. For pain and appetite loss, approximately two-thirds of patients were symptomatic at baseline. Regarding fatigue, the vast majority (>90%) of the patients were symptomatic at baseline, indicating the potential for improvement.

Improvement in these 3 symptoms was more common among patients with tumor shrinkage and in the ramucirumab arm. For each symptom, approximately 40% of patients in the ramucirumab arm reported improvement and nearly 85% of these patients experienced tumor shrinkage. Approximately 30% patients in the control arm reported symptom improvement and nearly 70% of these patients experienced tumor shrinkage. Of note, among those patients with a BOR of SD who were symptomatic at baseline, were evaluable for symptom change, and experienced tumor shrinkage, at least 60% reported improved pain and appetite loss, and more than 50% reported improved fatigue, regardless of treatment arm.

Figure 5 presents best change in global QoL and selected symptoms by BOR for each treatment arm. In both arms, for global QoL, nearly half of patients reported stable and nearly 25% reported improved scores. Those who improved most commonly had a BOR of CR/PR or SD. For each of the symptoms, improvement was reported in approximately 35-40% of patients in the ramucirumab arm and 24-31% of patients in the control arm, with almost all of these patients having a BOR of CR/PR or SD. For fatigue, approximately 25% of patients in each arm reported stable scores; regardless of treatment arm, approximately twice as many patients with a BOR of CR/PR reported improved versus stable fatigue scores. For pain, approximately 40% of patients in each arm reported stable scores; within each treatment arm, the numbers of patients with a BOR of CR/PR or of SD were similar between the improved and stable score groups. For appetite loss, more patients in each arm reported stable scores compared to improved scores; within the ramucirumab arm, the number of patients with a BOR of CR/PR or of SD was similar between the improved and stable score groups, but within the control arm, the number of patients with a BOR of CR/PR with stable scores was nearly twice that of those with CR/PR with improved scores. Fewer than 20% of patients reported deterioration as best change for global QoL, pain, and appetite loss. Among those whose symptoms worsened, very few had a BOR of CR/PR. Patients classified as non-evaluable most commonly had a BOR of PD or non-evaluable for each of these scales. Within each of the BOR groups, the largest numerical difference observed in proportions of patients with improved or stable scores was for pain in the CR/PR group (92% for ramucirumab vs 80% for placebo, p=0.0353).

Discussion

To the best of our knowledge, the phase 3 RAINBOW study demonstrated the highest second-line response rate to date in patients with advanced gastric/GEJ carcinoma. This response rate was seen in a trial that included patients with either measurable or non-measurable only disease, which is more representative of a real-world clinical patient population [13]. In the

RAINBOW study subpopulation of patients with measurable disease, more than one-third of patients in the ramucirumab arm achieved a tumor response, compared to one-fifth in the control arm. The data in the analyses presented here provide additional context when evaluating other studies that entirely exclude patients with non-measurable only disease from the study or from tumor response analyses [7-11, 16, 17].

In pre-specified and post hoc analyses of patients with objective responses in the RAINBOW study, just over half of the responses occurred within the first 6 weeks of the study treatment. By 12 weeks, just over 80% of patients in both arms had responded, with ongoing responses still observed at 6 and 12 months. The durability of responses was longer in the ramucirumab arm than with paclitaxel alone. The demonstrated improvements to OS and response rates were unlikely to be driven by the under-performance of the control arm in RAINBOW, as the observed results were in line with previous reports for paclitaxel [9-11, 13, 16].

Waterfall plots are a useful tool to visualize tumor shrinkage in a study, but there are limitations that need to be considered when interpreting data between treatment arms or across different clinical trials. Waterfall plots do not always represent the ITT population; both baseline factors and treatment outcomes will determine which patients are included in the waterfall plot population. They exclude patients who have only non-measurable disease at baseline and patients who discontinue the study early due to rapid disease progression or toxicity and thus may have no post-baseline tumor assessment. Further, if patients are not stratified by disease measurability, or if there are differential rates of early discontinuation, the patients who are excluded may be disproportionate between the treatment arms. These factors may introduce a bias to the visual presentation of tumor shrinkage for a given treatment, potentially presenting a more favorable picture of a treatment by excluding those patients with worse outcomes [18]. In order to interpret data from clinical trials, one must consider the number of patients excluded

and the associated reasons for exclusion. The majority of the patients excluded from the RAINBOW study waterfall plots presented here had non-measurable only disease at baseline, and only a small percentage lacked a post-baseline assessment; furthermore, these exclusions were mostly balanced between treatment arms. The majority of patients included in the waterfall plots experienced at least some degree of tumor shrinkage, regardless of treatment arm, even when defined as stable disease by RECIST.

The additional waterfall plots in this report suggest an association of tumor shrinkage with palliation of fatigue and pain, symptoms commonly observed in patients with advanced gastric/GEJ cancer. Not unexpectedly, greater symptom improvement was observed in patients achieving a complete or partial response, although this report demonstrates that symptom control, and even improvement, is achievable when the best response is only that of stable disease. Notably, more patients in the ramucirumab arm experienced tumor shrinkage, greater symptom control, and maintained QoL. These data are in alignment with previous reports demonstrating improved OS and PFS, acceptable toxicity, and delayed functional status deterioration from the addition of ramucirumab to paclitaxel [13, 14]. In addition, for time-to-deterioration analyses in QLQ-C30 scores, hazard ratios for fatigue, pain, and appetite loss were among the most favorable for ramucirumab plus paclitaxel (<0.85; however, 95% confidence intervals included 1) [14].

Taken as a whole, these analyses show consistent findings of greater symptom palliation associated with tumor shrinkage. However, palliation was also observed in some patients who did not experience tumor shrinkage. Potential explanations include supportive care interventions and variable symptom manifestations of tumor burden, which could not be addressed in these analyses. While tumor response may not necessarily correlate with improved survival, the benefits of tumor shrinkage include reduction in symptoms and maintenance or improvement in QoL [19]. A similar relationship between symptom palliation and

tumor response has been observed in metastatic breast cancer patients receiving chemotherapy [20].

Conclusion

Ramucirumab plus paclitaxel is a recognized standard of care for patients with advanced gastric or GEJ adenocarcinoma who have been previously treated with recommended first-line therapy for advanced disease. In addition to the survival benefit with acceptable toxicity, these supplemental data demonstrate that patients with tumor response as well as those with stable disease experience improved or stable fatigue, pain, appetite loss, and global QoL with ramucirumab treatment, and tumor response was associated with more improvement. This information can inform treatment decisions, which align individual patient characteristics and needs with demonstrated benefits.

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Figure Legends

Figure 1. Duration of response for patients with objective tumor response

Kaplan-Meier analysis of the duration of response for patients from the RAINBOW study who had a complete or partial response in the ramucirumab (red line) versus the control (blue line) arms.

CI, confidence interval; HR, hazard ratio; N, number of patients; PAC, paclitaxel; PBO, placebo; RAM, ramucirumab.

Figure 2. Time to and duration of tumor responses for patients with an objective response

The swimmer's plot characterizes the time to and duration of response (weeks) to ramucirumab plus paclitaxel (n=92) (left panel) or to placebo plus paclitaxel (n=54) (right panel) for each patient who achieved a complete or partial response in the RAINBOW trial.

Figure 3. Best percent change in tumor size from baseline.

The waterfall plot shows the best percent change in the sum of tumor diameters measured at baseline and reassessed at least once post-baseline. Blue bars denote a sum of tumor diameters that decreased less than 30% from baseline. Red bars denote a sum of tumor diameters that decreased ≥30% from baseline, which is categorized as a complete or a partial response per RECIST v1.1. N = 238 in the ramucirumab plus paclitaxel arm, and N = 236 in the placebo plus paclitaxel arm.

Note: From the ramucirumab arm and the control arm in the ITT population, 92/330 (28%) and 99/335 (30%) patients were not included in this figure. The most frequent reason for exclusion was non-measurable disease in 74/330 (22%) patients in the ramucirumab arm and 69/335 (21%) in the control arm. The second most common reason for exclusion was no post-baseline

tumor assessment in 17/330 (5%) ramucirumab patients and 28/335 (8%) control patients. Less than 1% of patients in each treatment arm had no baseline tumor assessment.

CR, complete response; ITT, intent-to-treat; n, number of patients; PAC, paclitaxel; PBO, placebo; PR, partial response; RAM, ramucirumab.

Figure 4. Association of best percent change in tumor size with best improvement in selected symptoms

Patient population is the same as that shown in the waterfall plots in Figure 3. Red bars are improved symptom scores, grey bars are stable or worsened symptom scores, white bars indicate patients who were not symptomatic at baseline, and black bars are patients who were not evaluable (without both a baseline and post-baseline assessment).

PAC, paclitaxel; PBO, placebo; RAM, ramucirumab.

Figure 5. Best improvement of global QoL and selected symptoms by best overall tumor response

All patients from the ITT population with best change in global QoL or symptoms (fatigue, pain, appetite loss) classified as improved, stable, deteriorated, or not evaluable are shown by their best overall tumor response. Best overall tumor response is denoted with blue bars for a complete response (CR) or partial response (PR), orange bars for stable disease (SD), grey bars for progressive disease (PD), and yellow indicates not-evaluable (NE) or not available. 'Not evaluable' indicates that baseline and/or post-baseline assessment was not available.

ITT, intent-to-treat; PAC, paclitaxel; PBO, placebo; QoL, quality of life; RAM, ramucirumab.

Table 1. Patient and Disease Characteristics by Best Overall Response

Characteristics		CR/PR		SD		PD		NE/Other	
		RAM+PAC (N=92)	PBO+PAC (N=54)	RAM+PAC (N=172)	PBO+PAC (N=159)	RAM+PAC (N=43)	PBO+PAC (N=83)	RAM+PAC (N=23)	PBO+PAC (N=39)
Sex, n (%)	Male	73 (79)	45 (83)	110 (64)	108 (70)	25 (58)	61 (74)	21 (91)	29 (74)
Age (years)	Median (Range)	61 (30-77)	63 (28-78)	60 (25-81)	63 (30-84)	61 (35-78)	59 (26-77)	60 (43-83)	58 (24-81)
Race, n (%)	White	55 (60)	27 (50)	104 (61)	89 (56)	32 (74)	55 (66)	17 (74)	28 (72)
	Asian	37 (40)	25 (46)	60 (40)	64 (40)	8 (19)	25 (30)	5 (22)	7 (18)
	Other	0	2 (4)	8 (5)	6 (4)	3 (7)	3 (4)	1 (4)	4 (10)
Geographic Region, n (%)	Eur/N Am/Aus	53 (58)	26 (48)	99 (58)	87 (55)	32 (74)	57 (69)	14 (61)	30 (77)
	Rest of world including S Am	2 (2)	5 (9)	13 (8)	10 (6)	4 (9)	3 (4)	4 (17)	3 (8)
	East Asia	37 (40)	23 (43)	60 (35)	62 (39)	7 (16)	23 (28)	5 (22)	6 (15)
ECOG PS, n (%)	0	34 (37)	29 (54)	67 (39)	76 (48)	15 (35)	26 (31)	1 (4)	13 (33)
	1	58 (63)	25 (46)	105 (61)	83 (52)	28 (65)	57 (69)	22 (96)	26 (67)
Primary Tumor Location, n (%)	Gastric	70 (76)	43 (80)	141 (82)	133 (84)	34 (79)	57 (69)	19 (83)	31 (80)
	GEJ	22 (24)	11 (20)	31 (18)	26 (16)	9 (21)	26 (31)	4 (17)	8 (21)
Disease Measurability[a], n (%)	Measurable	92 (100)	54 (100)	115 (67)	107 (67)	31 (72)	72 (87)	18 (78)	32 (82)
	Non-measurable Only	0	0	57 (33)	52 (33)	12 (28)	11 (13)	5 (22)	6 (15)
Time to PD on 1L, n (%)	< 6 months	50 (54)	34 (63)	111 (65)	96 (60)	31 (72)	45 (54)	16 (70)	25 (64)
Weight Loss Over Prior 3	≥10%	17 (19)	7 (13)	15 (9)	20 (13)	11 (26)	14 (17)	10 (44)	6 (15)

Months, n (%)								
Ascites Present n (%)	26 (28)	8 (15)	74 (43)	63 (40)	20 (47)	21 (25)	10 (44)	15 (39)

[a]As reported in case report forms.

1L, first-line; Aus, Australia; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; Eur, Europe; GEJ, gastroesophageal junction; N Am, North America; NE, not evaluable (missing baseline and/or post baseline tumor assessment); ORR, objective response rate; PAC, paclitaxel; PBO, placebo; PD, progressive disease; PR, partial response; RAM, ramucirumab; S Am, South America; SD, stable disease.

Table 2: Additional Tumor Characteristics by Best Overall Response

Characteristics		CR/PR		SD		PD		NE/Other	
		RAM+PAC (N=92)	PBO+PAC (N=54)	RAM+PAC (N=172)	PBO+PAC (N=159)	RAM+PAC (N=43)	PBO+PAC (N=83)	RAM+PAC (N=23)	PBO+PAC (N=39)
Histological/ Pathological Type, n (%)	Intestinal	43 (47)	20 (37)	73 (42)	59 (37)	22 (51)	42 (51)	7 (30)	14 (36)
	Diffuse	24 (26)	21 (39)	66 (38)	72 (45)	15 (35)	25 (30)	10 (43)	15 (38)
	Mixed	12 (13)	5 (9)	7 (4)	5 (3)	1 (2)	2 (2)	1 (4)	2 (5)
	Unknown	13 (14)	8 (15)	26 (15)	23 (14)	5 (12)	14 (17)	5 (22)	8 (21)
Grade, n (%)	Well differentiated	6 (7)	2 (4)	19 (11)	9 (6)	3 (7)	9 (11)	0	2 (5)
	Moderately differentiated	29 (32)	22 (41)	47 (27)	45 (28)	11 (26)	29 (35)	9 (39)	10 (26)
	Poorly differentiated	52 (57)	26 (48)	96 (56)	98 (62)	27 (63)	39 (47)	11 (48)	23 (59)
Number of Metastatic Sites, n (%)	0	0	1 (2)	0	5 (3)	1 (2)	0	0	1 (3)
	1	22 (24)	16 (30)	50 (29)	46 (29)	9 (21)	23 (28)	4 (17)	6 (15)
	2	35 (38)	19 (35)	68 (40)	65 (41)	15 (35)	32 (39)	5 (22)	18 (46)
	≥3	35 (38)	18 (33)	54 (31)	43 (27)	18 (42)	28 (34)	14 (61)	14 (36)
Sites of Metastases, n (%)	Lung	19 (21)	17 (31)	34 (20)	28 (18)	14 (33)	17 (20)	10 (43)	8 (21)
	Liver	57 (62)	33 (61)	62 (36)	44 (28)	16 (37)	45 (54)	15 (65)	16 (41)
	Bone	7 (8)	2 (4)	10 (6)	11 (7)	3 (7)	9 (11)	5 (22)	6 (15)
	Lymph nodes	70 (76)	38 (70)	108 (63)	90 (57)	24 (56)	53 (64)	13 (57)	24 (62)
	Pleural	9 (10)	3 (6)	15 (9)	17 (11)	4 (9)	9 (11)	4 (17)	5 (13)
	Peritoneal	33 (36)	16 (30)	93 (54)	90 (57)	26 (60)	29 (35)	11 (48)	17 (44)
	Other	18 (20)	4 (7)	43 (25)	36 (23)	13 (30)	20 (24)	6 (26)	16 (41)

CR, complete response; NE, not evaluable (missing baseline and/or post baseline tumor assessment); ORR, objective response rate; PAC, paclitaxel; PBO, placebo; PD, progressive disease; PR, partial response; RAM, ramucirumab; SD, stable disease.

Figure 1. Duration of response

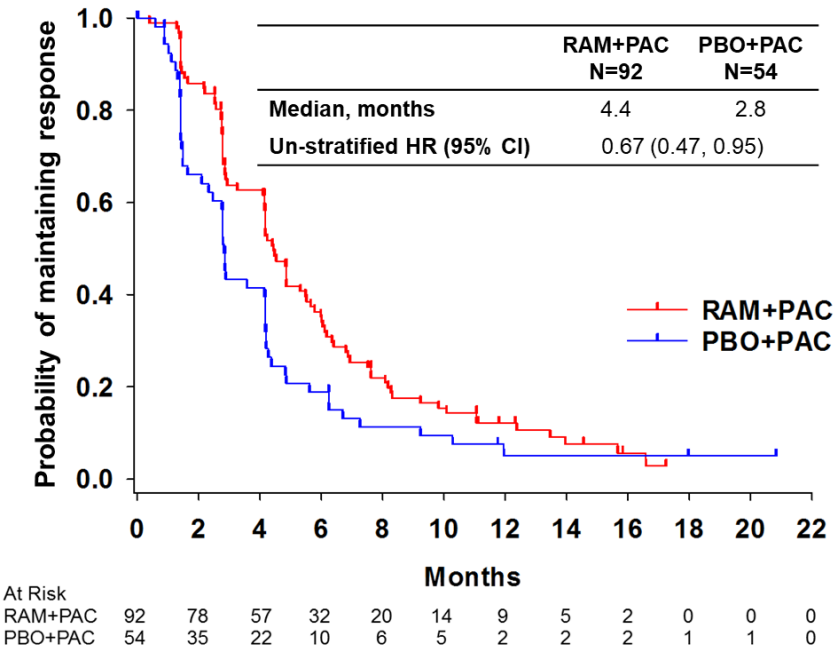


Figure 2. Time to and duration of tumor responses

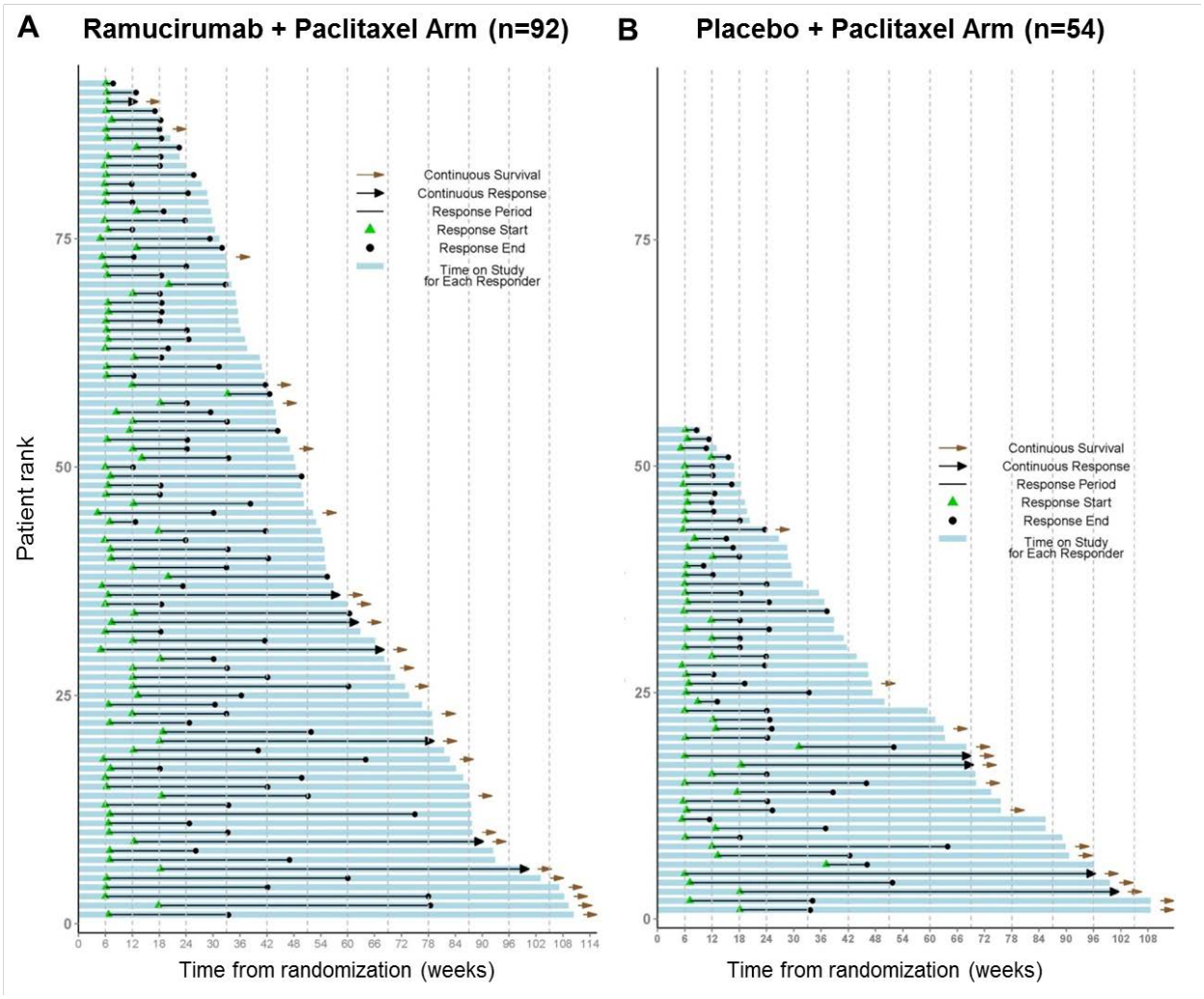


Figure 3. Best percent change in tumor size from baseline

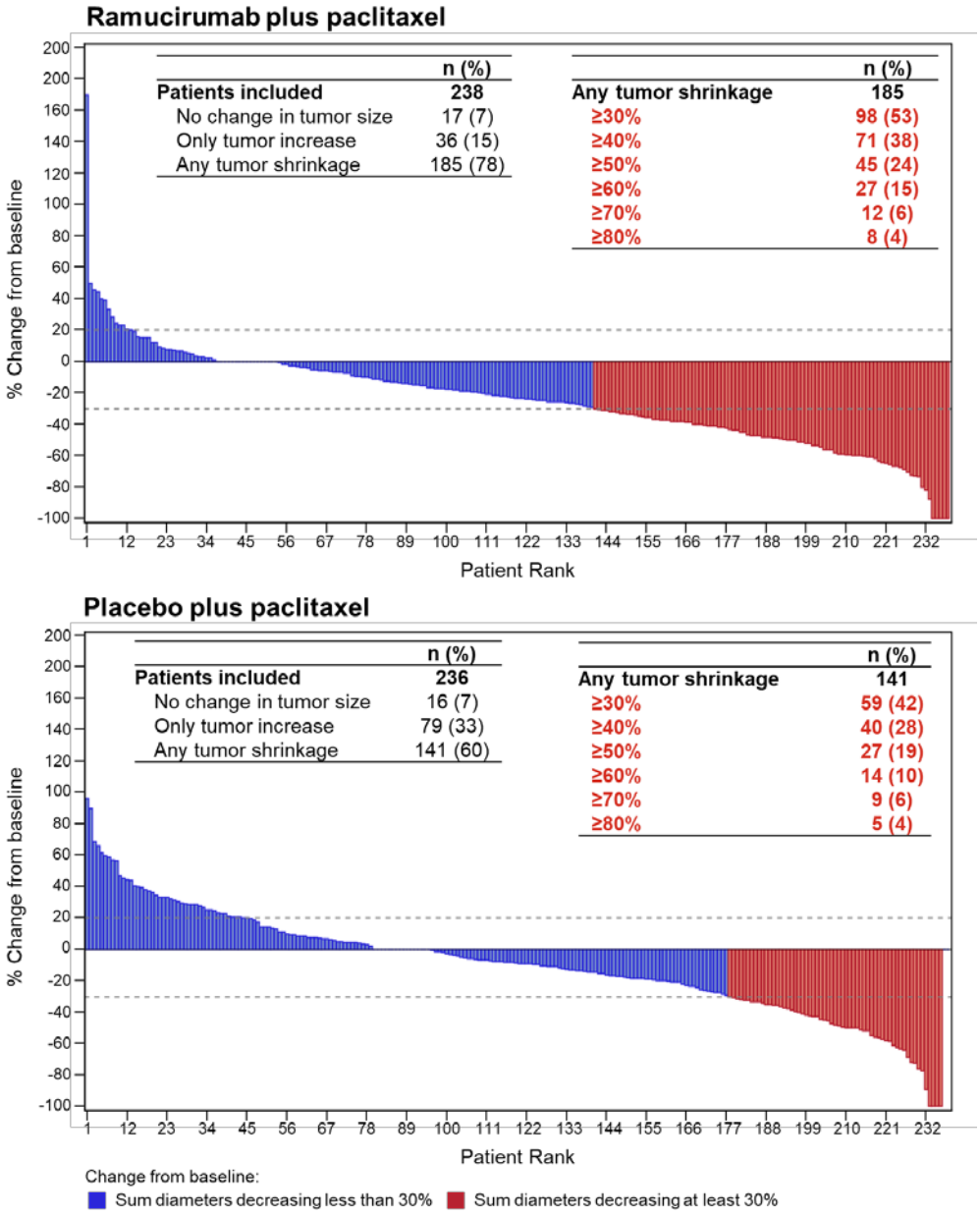


Figure 4. Association of best percent change in tumor size with best improvement in selected symptoms

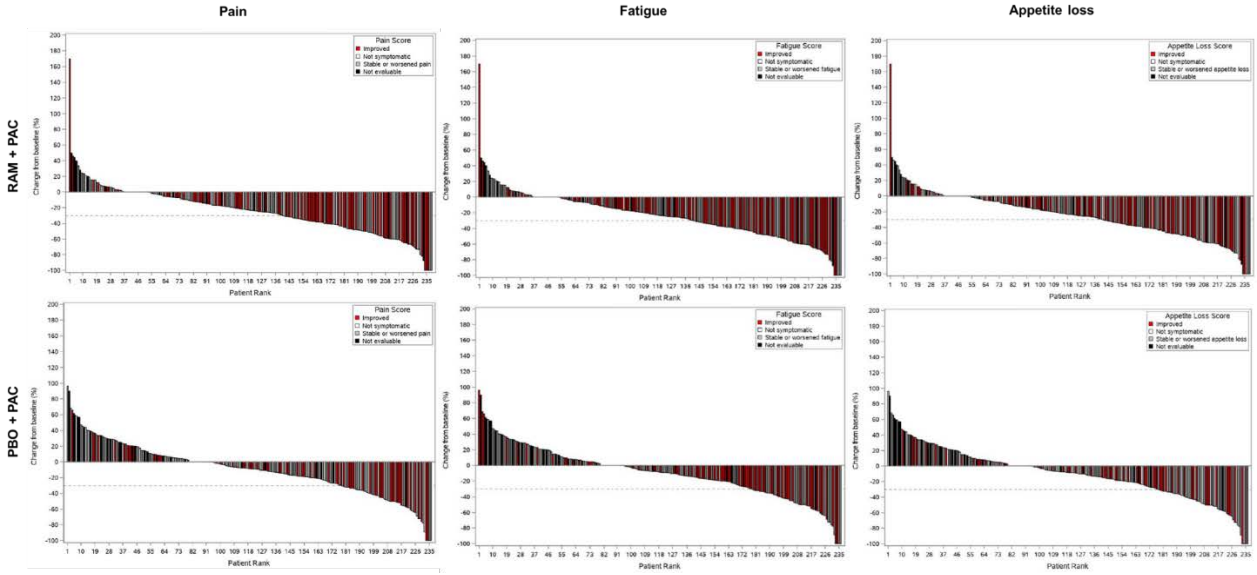
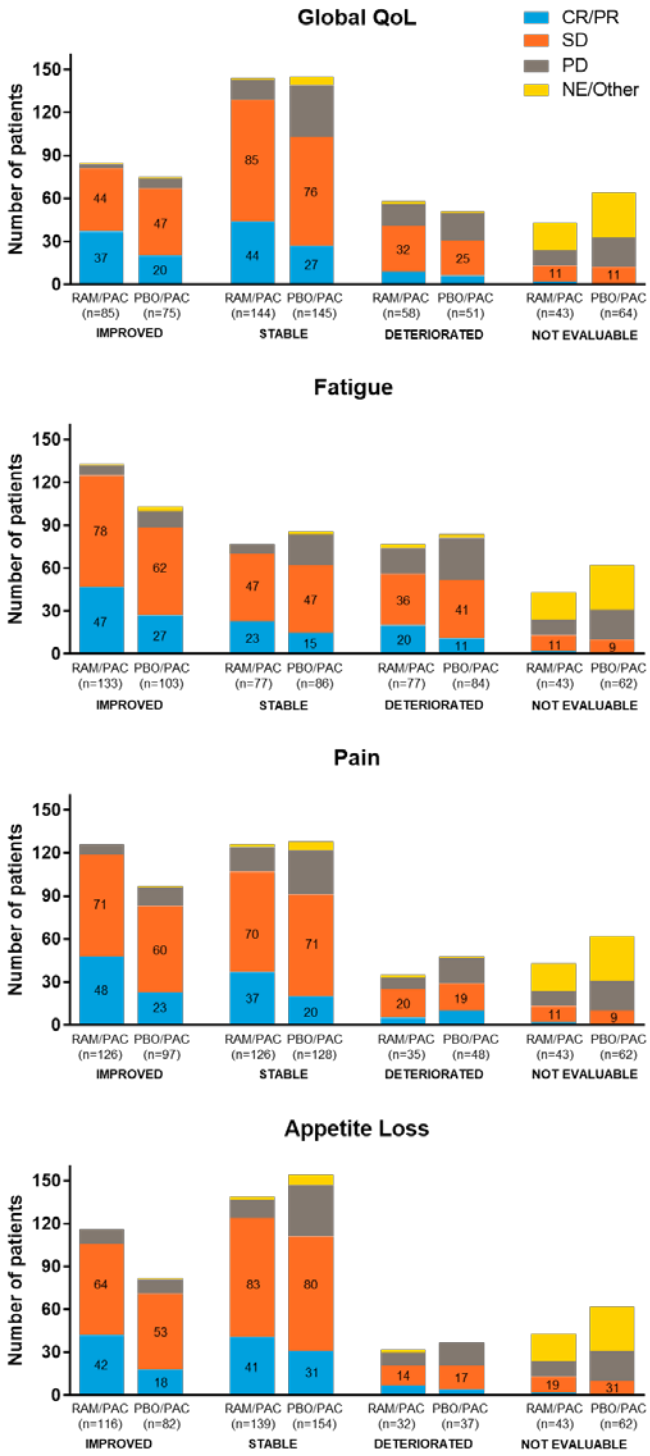


Figure 5. Association of best quality of life improvement with best overall tumor response



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