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**Age does not influence efficacy of ramucirumab in advanced gastric cancer:
subgroup analyses of REGARD and RAINBOW**

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Abstract

Background and Aim: REGARD and RAINBOW were global, phase 3, randomized, double-blind trials of second-line ramucirumab for metastatic gastric or gastroesophageal junction adenocarcinoma. We describe exploratory subgroup analyses to assess the efficacy and safety of ramucirumab in REGARD and

RAINBOW in young (≤ 45 and < 65 years) and elderly (≥ 65 , ≥ 70 and ≥ 75 years) patients.

Methods: Patients were randomized 2:1 to receive ramucirumab plus best supportive care or placebo plus best supportive care (REGARD) or 1:1 to ramucirumab plus paclitaxel or placebo plus paclitaxel (RAINBOW). Subpopulation Treatment Effect Pattern Plots assessed efficacy and adverse events by age groups for ramucirumab versus placebo.

Results: The hazard ratios (HRs) for overall survival favored treatment with ramucirumab: REGARD ≤ 45 years (HR: 0.59, 95% confidence interval [CI]: 0.27–1.26), < 65 years (0.80, 0.59–1.10), ≥ 65 years (0.72, 0.48–1.08), ≥ 70 years (0.73, 0.44–1.23), ≥ 75 years (0.59, 0.25–1.37); and RAINBOW ≤ 45 years (0.56, 0.33–0.93), < 65 years (0.78, 0.63–0.97), ≥ 65 years (0.88, 0.66–1.18), ≥ 70 years (0.88, 0.60–1.28). The exception was elderly patients aged ≥ 75 years in RAINBOW (0.97, 0.47–2.01); however, patient numbers were low in this subgroup ($n=36$). Similar findings were observed for progression-free survival, for which HRs numerically favored ramucirumab-treated patients. Adverse events (including grade ≥ 3) were not associated with age.

Conclusions: In comparison to placebo, ramucirumab conferred improvements in efficacy across age groups with a tolerable safety profile. Despite some limitations,

these exploratory analyses support the use of ramucirumab in advanced gastric cancer, irrespective of age.

Key words

Elderly, Gastroesophageal neoplasms, Ramucirumab, Vascular endothelial growth factor receptor-2, Young patients

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Introduction

Gastric cancer is the fifth most common malignancy and the third most common cause of cancer-related deaths worldwide.¹ Most patients with gastric cancer present with advanced unresectable disease.² The burden of gastric cancer morbidity and mortality falls largely on the elderly. More than 60% of gastric cancer cases are diagnosed in patients who are 65 years of age or older and more than one-third of patients are 75 years of age or older.²

Elderly patients with gastric cancer often receive less aggressive diagnostic evaluation, surgery, and chemotherapy in comparison to their younger counterparts.³ Patient age is not associated with advanced gastric cancer prognosis,^{3,4} yet many oncologists hesitate recommending systemic chemotherapy to elderly patients.³ This may be due to a higher likelihood of comorbidities or age-related changes in pharmacokinetics and pharmacodynamics, which may lead to higher toxicity amongst elderly patients.³ Current guidelines lack clarity for the management of gastric cancer in elderly patients, which may play a role in undertreatment of this cohort.³

The frequency of gastric cancer in young patients is relatively low, with approximately 6% of cases being diagnosed in patients 44 years of age or less.² However, a US national study revealed that the annual rate of gastric cancer

diagnoses among younger patients is increasing.⁵ In comparison to elderly patients, young patients with gastric cancer are more likely to be female,^{6,7} carry genetic abnormalities, and present with aggressive clinicopathological features, including poorly differentiated diffuse adenocarcinoma and higher rates of nodal and distant metastases.^{6,8-11} Controversy remains as to whether young age derives a poor prognosis, with some studies concluding that young age is an unfavorable prognostic factor.^{11,12} Other reports conclude that young patients do equally as well, and possibly better, than their elderly counterparts if patients undergo curative resection.¹³⁻¹⁶ These contradictory findings may be due to inclusion of study subjects from single referral centers, inhomogeneity of patient cohorts among studies, and/or lack of adjustment for potential confounding factors.

Ramucirumab is a human immunoglobulin G1 monoclonal antibody targeting vascular endothelial growth factor (VEGF) receptor-2,¹⁷ a key mediator of VEGF-induced angiogenesis.¹⁸ The efficacy and safety of ramucirumab treatment for advanced gastric or gastroesophageal (GEJ) adenocarcinoma was demonstrated in two pivotal phase 3 trials, REGARD and RAINBOW.^{19,20} Both studies demonstrated statistically significant improvements in overall survival (OS) and progression-free survival (PFS).^{19,20} Based on the outcomes of these trials, ramucirumab was approved for the treatment of advanced gastric and GEJ adenocarcinoma, as either monotherapy or in combination with paclitaxel, in

patients with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy.^{21,22}

REGARD and RAINBOW did not evaluate ramucirumab in specific age groups. Neither trial had an upper age limit, but unfit patients were excluded based on assessment of performance status (PS) and organ preservation.^{19,20} The median patient age in the REGARD and RAINBOW studies was 60 years (range: 51-71) and 61 years (range: 24-84), respectively. The objective of these exploratory analyses was to assess the effect of age on the efficacy, safety, and feasibility of ramucirumab treatment in gastric cancer and GEJ adenocarcinoma in both young and elderly populations from REGARD and RAINBOW.

Methods

Study design and patients

The study designs for REGARD and RAINBOW were previously published.^{19,20} Eligible patients had metastatic or unresectable, locally advanced gastric or GEJ adenocarcinoma. Patients had either documented objective radiological or clinical disease progression during or within 4 months of the last dose of either first-line platinum- or fluoropyrimidine-containing chemotherapy or first-line platinum and fluoropyrimidine doublet therapy with or without anthracycline, or within 6 months

of the last dose of platinum-containing or flouoropyrimidine-containing adjuvant treatment. Patients had an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1.

Each center's institutional review board or independent ethics committee approved the study. The trials followed the guiding principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provided written informed consent.

Randomization and procedures

Randomization and procedures have been published previously.^{19,20} In REGARD, patients were randomly assigned 2:1 to receive best supportive care (BSC) plus either ramucirumab 8 mg/kg or placebo intravenously once every 2 weeks.¹⁹ In RAINBOW, patients were randomly assigned 1:1 to receive either ramucirumab 8 mg/kg or placebo intravenously on days 1 and 15, plus paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of a 28-day cycle.²⁰ Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. All patients received supportive care.

Statistical analyses

Detailed statistical methods were published previously.^{19,20} The primary endpoint for both studies was OS. These outcome analyses were mainly based on the intention-to-treat population with predefined age groups (<65 years, ≥65 years). In order to explore the impact of age on ramucirumab outcomes, we included additional age cut-offs: ≤45 years, ≥70 years, and ≥75 years (≥75 years is a subgroup of ≥70 years).

The endpoints evaluated for each age group were OS, PFS, and safety. For OS and PFS, survival curves were generated by the Kaplan-Meier method. The hazard ratio (HR) was estimated with a 95% confidence interval (CI) using a Cox proportional hazards model.

Patient outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life (QoL) questionnaire (EORTC QLQ-C30) with responses collated by age. The EORTC QLQ-C30 assesses global health status, symptoms, and overall functioning scales and is specific for cancer patients.²³ Patient-reported outcomes were evaluated at baseline and every 6 weeks following the first dose of study therapy.

The influence of age on OS and PFS and selected adverse events (AEs) was evaluated using Subpopulation Treatment Effect Pattern Plot (STEPP) analysis, a non-parametric graphical approach that constructs overlapping patient

subpopulations with varying values of a characteristic,²⁴ such as age. In these analyses, each group was designed to contain at least 200 patients and to overlap with the previous group by at most 50 patients. The odds ratio of AEs was determined within each group, and the results were plotted graphically to illustrate how risk changes across various age groups.

These trials are registered with ClinicalTrials.gov, REGARD (NCT00917384) and RAINBOW (NCT01170663).

Results

Patients

In REGARD, the ≤ 45 , < 65 , ≥ 65 , ≥ 70 , and ≥ 75 age groups had 40, 227, 128, 79, and 34 patients, respectively. In RAINBOW, the ≤ 45 , < 65 , ≥ 65 , ≥ 70 , and ≥ 75 age groups had 74, 416, 249, 136, and 36 patients, respectively. Baseline patient and tumor characteristics by age from REGARD and RAINBOW are summarized in Tables 1 and 2. The demographics and tumor characteristics were mostly balanced between treatment arms across the age groups. In REGARD, the younger age groups (≤ 45 and < 65 years) tended to have more female patients and more patients of Asian ethnicity. In RAINBOW, there were more elderly patients (≥ 65 , ≥ 70 , and ≥ 75 years) with intestinal-type tumors.

Survival and response

In REGARD, there were improvements in OS for elderly patients receiving ramucirumab compared to placebo: median 5.2 versus 3.8 months in ≥ 65 years (HR: 0.72, 95% CI: 0.48–1.08), median 5.9 versus 3.8 months in ≥ 70 years (HR: 0.73, 95% CI: 0.44–1.23), and median 9.3 versus 5.1 months in ≥ 75 years (HR: 0.59, 95% CI: 0.25–1.37) (Fig. 1). Similarly, in RAINBOW, OS benefits were seen for ramucirumab and paclitaxel versus placebo in elderly patients aged ≥ 65 years (median 10.7 versus 8.7 months; HR: 0.88, 95% CI: 0.66–1.18) and ≥ 70 years (median 10.8 versus 8.6 months; HR: 0.88, 95% CI: 0.60–1.28), but not in elderly patients aged ≥ 75 years (median 11.0 months for both treatment arms; HR: 0.97, 95% CI: 0.47–2.01) (Fig. 1).

In REGARD, median PFS was 2.8 versus 1.4 months (HR: 0.48, 95% CI: 0.32–0.72) in elderly patients ≥ 65 years, 2.1 versus 1.4 months in patients ≥ 70 years (HR: 0.56, 95% CI: 0.34–0.92), and 2.8 versus 1.4 months in those ≥ 75 years (HR: 0.42, 95% CI: 0.19–0.95) (Fig. 2). A similar benefit in median PFS was observed in RAINBOW in elderly patients ≥ 65 years (4.6 versus 2.9 months; HR: 0.72, 95% CI: 0.55–0.94), ≥ 70 years (4.7 versus 2.9 months; HR: 0.68, 95% CI: 0.47–0.97), and ≥ 75 years (4.2 versus 2.8 months; HR: 0.70, 95% CI: 0.33–1.47) (Fig. 2).

In the young patient cohorts of REGARD, treatment with ramucirumab was associated with longer OS in comparison to placebo: median 5.8 versus 2.9 months in patients ≤ 45 years (HR: 0.59, 95% CI: 0.27–1.26) and median 5.3 versus 4.1 months in those < 65 years (HR: 0.80, 95% CI: 0.59–1.10) (Fig. 1). Benefits in OS were also observed in younger patients in RAINBOW treated with ramucirumab plus paclitaxel compared to those receiving placebo plus paclitaxel: median 9.0 versus 4.2 months in patients ≤ 45 years (HR: 0.56, 95% CI: 0.33–0.93) and median 9.3 versus 7.1 months in those < 65 years (HR: 0.78, 95% CI: 0.63–0.97) (Fig. 1).

Median PFS in young patients from REGARD was 1.9 versus 1.4 in patients ≤ 45 years (HR: 0.58, 95% CI: 0.27–1.26) and 1.9 versus 1.3 months in those < 65 years (HR: 0.52, 95% CI: 0.38–0.70) (Fig. 2). In RAINBOW, median PFS was 3.9 versus 2.8 months in young patients ≤ 45 years (HR: 0.50, 95% CI: 0.30–0.83) and 4.3 versus 2.8 months in those < 65 years (HR: 0.59, 95% CI: 0.48–0.73) (Fig. 2).

The objective response in ramucirumab- and placebo-treated patients from REGARD was 0 versus 8.3% in patients aged ≤ 45 years, 3.8% versus 2.8% in patients aged < 65 years, 2.4% versus 2.2% in patients aged ≥ 65 years, and 2.3% versus 2.9% in patients aged ≥ 70 years, respectively (central review not performed). In RAINBOW, the objective response in ramucirumab- and placebo-

treated patients was 18.9% versus 10.8% in patients aged ≤ 45 years, 28.4% versus 14.2% in patients aged < 65 years, 27.0% versus 19.5% in patients aged ≥ 65 years, and 29.4% versus 17.6% in patients aged ≥ 70 years, respectively. STEPP analysis revealed no differential risk regarding OS and PFS in both REGARD and RAINBOW in terms of age (Fig. 3).

Safety

Defining by age ≥ 65 years allowed for sufficient patient numbers to be included in the elderly safety groups. In REGARD, which may reflect common AEs of ramucirumab, the majority of grade ≥ 3 treatment-emergent AEs were comparable between treatment arms for both the < 65 -year age group ($n=227$) and ≥ 65 -year age group ($n=128$).²⁵ The most frequently reported grade ≥ 3 AEs in $\geq 5\%$ of ramucirumab patients included hypertension and fatigue.²⁵ No specific grade ≥ 3 AE was observed in $>10\%$ of patients.²⁵ Similarly, toxicity profiles were comparable between younger (< 65 years, $n=416$) and older (≥ 65 years, $n=249$) patients in RAINBOW, although relatively higher incidences of grade ≥ 3 neutropenia and leukopenia were noted in patients aged ≥ 65 years, regardless of treatment arm.²⁶ STEPP analysis of patient subsets revealed no substantial variance in AEs across the various age groups (total and grade ≥ 3 AEs; Fig. 4). We were unable to apply STEPP analyses for gastrointestinal perforation, wound healing, and

thromboembolic complications due to the small number of patients reporting these AEs.

Quality of life

Time to deterioration in ECOG PS ≥ 2 was generally comparable among patients of all age groups in both REGARD and RAINBOW (Fig. 5). The analysis of QLQ-C30 data in REGARD showed that a greater percentage of ramucirumab-treated patients reported improved or stable QoL in terms of global health status, physical and role functioning, pain, appetite loss, and fatigue (Supplementary Fig. 1).

Analysis of QLQ-C30 data in RAINBOW revealed mostly comparable improved/stable status scores between placebo- and ramucirumab-treated patients across the age groups. Appetite loss, physical functioning, and fatigue were the exception, with more elderly patients reporting an improved/stable status, albeit in placebo-treated patients (Supplementary Fig. 2).

Discussion

REGARD and RAINBOW showed that second-line ramucirumab, as monotherapy or in combination with paclitaxel, extended survival of patients with advanced gastric or GEJ cancer.^{19,20} These analyses by age from the REGARD and

RAINBOW studies indicate that the beneficial effects of ramucirumab are maintained in both young and elderly age groups, with similar rates of toxicity.

In both studies, ramucirumab-treated patients aged ≥ 65 years experienced longer OS and PFS compared to placebo-treated patients. The interaction test did not show any significant difference in terms of survival ($p=0.48$ in RAINBOW; $p=0.62$ in REGARD). We also performed additional exploratory analyses using ≥ 70 years and ≥ 75 years as cut-off points within the REGARD and RAINBOW studies. The comparable differentiation in the survival curves between the two treatment arms conferred similar trends towards improved OS and PFS across almost all age categories except patients aged ≥ 75 years in RAINBOW where the PFS change (HR: 0.70) appeared to be consistent with that in patients aged ≥ 65 or ≥ 70 years. There were no differences in OS between ramucirumab- or placebo-treated patients aged ≥ 75 years in RAINBOW (HR: 0.97, 95% CI: 0.47–2.01). However, this older subgroup had few patients (36 of 665) and the small population size yielded more variable (less reliable) results. Furthermore, some patient characteristics were imbalanced in this subset, including ethnicity, the presence of a primary tumor, and ECOG PS, with such imbalances tending to favor the placebo arm. Another possible explanation for the lack of difference in OS between treatment arms in the ≥ 75 age group is that this analysis used OS as an outcome measure, rather than cancer-specific survival.

Young people comprise a small minority of patients with gastric cancer. There is currently no consensus on the definition of young patients in gastric cancer, with age ranging from less than 30 to less than 45 years.²⁹⁻³² We chose to analyze data in patients aged ≤ 45 years as representative of a young gastric cancer cohort. In accordance with previous reports, the proportion of female patients in REGARD and patients with diffuse-type cancers in RAINBOW was higher in the younger patients.^{6,11} Differentiation in the survival curves between the two treatment arms conferred similar trends towards improved OS and PFS in the younger age cohort, supporting the use of ramucirumab in this age group.

Ramucirumab had a generally acceptable tolerability profile in the phase 3 trials, with no differences in discontinuation rates due to AEs between treatment arms.^{19,20} Hypertension was the most common grade ≥ 3 non-hematologic AE with ramucirumab treatment (either alone or with paclitaxel).^{19,20} The prevalence of hypertension and cardiovascular events have been shown to increase with age,^{33,34} however the present retrospective analyses found comparable incidences of hypertension and bleeding regardless of age, indicating advanced age is not necessarily a predisposing factor for development of these cardiovascular AEs during exposure to ramucirumab. Older cancer patients, due to age-related renal structural changes and limited nephron reserve, may be at increased risk of antiangiogenic-induced proteinuria, however, our findings suggest that the

occurrence of proteinuria (all-grade and grade ≥ 3) is not associated with age. It is anticipated that fit, elderly patients should have similar rates of antiangiogenic-related AEs when undergoing treatment with ramucriumab as long as they are accurately screened, carefully monitored, and appropriately managed.

Age is a clinically important factor when determining treatment for oncology patients,³⁵ particularly with the elderly population increasing worldwide. Elderly cancer patients also often suffer from comorbidities and/or poor physical conditions,²⁷ which affect treatment decisions. However chronological age is not the only factor deciding the pharmacotherapy requirements of each patient. Future analyses should consider factors such as lifestyle, genetics, and overall health during the development of multi-dimensional tools to evaluate geriatric fitness for intensive treatment.^{36,37}

There were limitations to these subgroup analyses. These age analyses are mainly limited by their retrospective nature. Elderly patients, aged ≥ 65 years, accounted for 36% and 37% of ITT populations in REGARD and RAINBOW, respectively. Although substantial percentages, these numbers are still less than those encountered in clinical practice where more than 60% of gastric cancer cases develop in patients over 65 years.² Furthermore, these trials selected healthy, non-frail, elderly patients whereas clinicians are often confronted with frail, elderly

patients suffering from comorbidities. Some baseline characteristics were unbalanced between arms in the different age groups, thus results could be affected by inevitable confounding. Furthermore, limited patient numbers in some age groups (≤ 45 years and ≥ 75 years) restricted informative analysis. There are also limitations employing STEPP analysis. For example, the results may vary with different specifications of each subgroup size and the overlapping size. A further limitation of STEPP is that the incidence rate of some AEs would be too low for informative analysis in some age groups.

Despite these limitations, our exploratory analyses continue to support the use of ramucirumab for the treatment of advanced gastric cancer, irrespective of patient age. Careful selection of patients and vigilant monitoring of potential treatment-related side effects are recommended due to the heterogeneity in overall health status and comorbid conditions of elderly patients. Clinicians will need to assess the results of both studies to determine which regimen (monotherapy or in combination with paclitaxel) is most appropriate. Future clinical trials should aim to increase the accrual rate of elderly cancer patients to obtain a better understanding of appropriate therapies for this patient population, which may have an impact on cancer-related morbidity and mortality.

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Figure 1 Overall survival in gastric cancer patients by age. Kaplan-Meier estimates of overall survival by age in REGARD (—, ramucirumab plus best supportive care; ---, placebo plus best supportive care) and RAINBOW (—, ramucirumab plus paclitaxel; ---, placebo plus paclitaxel); ≤45 yrs (a and b), <65 yrs (c and d), ≥65 yrs (e and f), ≥70 yrs (g and h), and ≥75 yrs (i and j). BSC=best supportive care; CI=confidence interval; HR=hazard ratio; n=number of patients; PAC=paclitaxel; PBO=placebo; RAM=ramucirumab; yrs=years.

Figure 2 Progression-free survival in gastric cancer patients by age. Kaplan-Meier estimates of progression-free survival by age in REGARD (—, ramucirumab plus best supportive care; ---, placebo plus best supportive care) and RAINBOW (—, ramucirumab plus paclitaxel ---, placebo plus paclitaxel); ≤45 yrs (a and b), <65 yrs (c and d), ≥65 yrs (e and f), ≥70 yrs (g and h), and ≥75 yrs (i and j). BSC=best supportive care; CI=confidence interval; HR=hazard ratio; n=number of patients; PAC=paclitaxel; PBO=placebo; RAM=ramucirumab; yrs=years.

Figure 3 STEPP analysis of overall survival (a and b) and progression-free survival (c and d) in REGARD and RAINBOW using deduced medians. Subgroup 200/overlap 150.

Figure 4 STEPP analysis for selected adverse events using deduced medians.

STEPP analysis of any-grade (—) and grade ≥ 3 (—) selected adverse events in

REGARD and RAINBOW including hypertension (a and b), bleeding (c and d), and neutropenia (e and f). Subgroup 200/overlap 150.

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REGARD

RAINBOW

Figure 5 Time to deterioration in ECOG performance status ≥ 2 in REGARD and RAINBOW. Forest plots for age analysis of time to deterioration in ECOG performance status in REGARD and RAINBOW. Data are stratified by HR (95% CI). Horizontal lines represent 95% CI. The size of the squares is proportional to

the size of the subgroup. CI=confidence interval; ECOG=Eastern Cooperative
Oncology Group; HR=hazard ratio; n=number of patients.

Supplementary Figure 1 Percentage of patients reporting improved/stable QoL by age in REGARD. Quality of life as assessed by EORTC QLQ-C30 by age in

REGARD at weeks 6 ( ) and 12 ( ). An improvement is defined as an increase of 10 or more points from the baseline assessment and stable is defined as a less than 10 point change. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life questionnaire. PBO=placebo; RAM=ramucirumab; Wk=week.

Supplementary Figure 2 Percentage of patients reporting improved/stable QoL by age in RAINBOW. Quality of life as assessed by EORTC QLQ-C30 by age in RAINBOW at weeks 6 (■) and 12 (■). An improvement is defined as an increase of 10 or more points from the baseline assessment and stable is defined as a less than 10 point change. EORTC QLQ-C30=European Organisation for Research and

Treatment of Cancer Quality of Life questionnaire. PBO=placebo;

RAM=ramucirumab; Wk=week.

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Table 1: Baseline patient and disease characteristics by age in REGARD

	≤45 years		<65 years		≥65 years		≥70 years		≥75 years	
	RAM + BSC (n=28)	Placebo + BSC (n=12)	RAM + BSC (n=156)	Placebo + BSC (n=71)	RAM + BSC (n=82)	Placebo + BSC (n=46)	RAM + BSC (n=44)	Placebo + BSC (n=35)	RAM + BSC (n=21)	Placebo + BSC (n=13)
Age (years), mean (SD)	41.4 (4.0)	38.3 (7.0)	53.4 (7.4)	51.9 (8.3)	71.4 (5.1)	72.5 (4.8)	75.3 (3.8)	74.3 (3.8)	78.5 (2.8)	78.3 (3.2)
Male, n (%)	17 (60.7)	3 (25.0)	109 (69.9)	45 (63.4)	60 (73.2)	34 (73.9)	30 (68.2)	25 (71.4)	14 (66.7)	9 (69.2)
Primary tumor present, n (%)	21 (75.0)	10 (83.3)	113 (72.4)	53 (74.6)	61 (74.4)	33 (71.7)	31 (70.5)	26 (74.3)	14 (66.7)	10 (76.9)
Measurable disease, n (%)	26 (92.9)	12 (100.0)	145 (92.9)	66 (93.0)	73 (89.0)	40 (87.0)	40 (90.9)	31 (88.6)	21 (100.0)	12 (92.3)
Race, n (%)										
Caucasian	18 (64.3)	5 (41.7)	115 (73.7)	48 (67.6)	66 (80.5)	43 (93.5)	33 (75.0)	33 (94.3)	17 (81.0)	12 (92.3)
Asian	8 (28.6)	4 (33.3)	27 (17.3)	14 (19.7)	12 (14.6)	3 (6.5)	8 (18.2)	2 (5.7)	3 (14.3)	1 (7.7)
Black	1 (3.6)	1 (8.3)	2 (1.3)	2 (2.8)	2 (2.4)	0	1 (2.3)	0	0	0
Other	1 (3.6)	2 (16.7)	12 (7.7)	7 (9.9)	2 (2.4)	0	2 (4.5)	0	1 (4.8)	0
ECOG PS, n (%)										
0	12 (42.9)	2 (16.7)	45 (28.8)	20 (28.2)	22 (26.8)	11 (23.9)	10 (22.7)	7 (20.0)	3 (14.3)	1 (7.7)
1	16 (57.1)	10 (83.3)	111 (71.2)	50 (70.4)	60 (73.2)	35 (76.1)	34 (77.3)	28 (80.0)	18 (85.7)	12 (92.3)
Type of cancer, n (%)										
Metastatic gastric	24 (85.7)	10 (83.3)	117 (75.0)	53 (74.6)	62 (75.6)	32 (69.6)	39 (88.6)	27 (77.1)	17 (81.0)	11 (84.6)
Gastroesophageal junction	4 (14.3)	2 (16.7)	39 (25.0)	18 (25.4)	20 (24.4)	14 (30.4)	5 (11.4)	8 (22.9)	4 (19.0)	2 (15.4)
Histological subtype, n (%)										
Intestinal	3 (10.7)	3 (25.0)	27 (17.3)	21 (29.6)	25 (30.5)	14 (30.4)	12 (27.3)	11 (31.4)	6 (28.6)	6 (46.2)
Diffuse	16 (57.1)	3 (25.0)	71 (45.5)	27 (38.0)	25 (30.5)	17 (37.0)	15 (34.1)	12 (34.3)	6 (28.6)	5 (38.5)
Unknown	9 (32.1)	6 (50.0)	58 (37.2)	23 (32.4)	32 (39.0)	15 (32.6)	17 (38.6)	12 (34.3)	9 (42.9)	2 (15.4)

Abbreviations: BSC=best supportive care; ECOG PS=Eastern Cooperative Oncology Group performance status; n=number of patients; RAM=ramucirumab; SD=standard deviation

Table 2: Baseline patient and disease characteristics by age in RAINBOW

	≤45 years		<65 years		≥65 years		≥70 years		≥75 years	
	RAM + PAC (n=37)	Placebo + PAC (n=37)	RAM + PAC (n=204)	Placebo + PAC (n=212)	RAM + PAC (n=126)	Placebo + PAC (n=123)	RAM + PAC (n=68)	Placebo + PAC (n=68)	RAM + PAC (n=20)	Placebo + PAC (n=16)
Age (years), mean (SD)	38.0 (5.1)	38.4 (5.8)	53.6 (8.8)	53.2 (8.8)	70.5 (4.1)	70.6 (3.8)	73.5 (2.9)	73.3 (2.9)	77.3 (2.1)	77.1 (2.8)
Male, n (%)	22 (59.5)	22 (59.5)	141 (69.1)	144 (67.9)	88 (69.8)	99 (80.5)	47 (69.1)	51 (75.0)	12 (60.0)	12 (75.0)
Primary tumor present, n (%)	23 (62.2)	25 (67.6)	133 (65.2)	128 (60.4)	76 (60.3)	81 (65.9)	39 (57.4)	43 (63.2)	14 (70.0)	8 (50.0)
Measurable disease, n (%)	26 (70.3)	28 (75.7)	153 (75.0)	162 (76.4)	103 (81.7)	103 (83.7)	55 (80.9)	55 (80.9)	16 (80.0)	15 (93.8)
Race, n (%)										
Caucasian	27 (73.0)	23 (62.2)	127 (62.3)	127 (59.9)	81 (64.3)	72 (58.5)	41 (60.3)	38 (55.9)	16 (80.0)	9 (56.3)
Asian	7 (18.9)	11 (29.7)	68 (33.3)	73 (34.4)	42 (33.3)	48 (39.0)	26 (38.2)	28 (41.2)	4 (20.0)	5 (31.3)
Black	1 (2.7)	0	4 (2.0)	4 (1.9)	2 (1.6)	2 (1.6)	1 (1.5)	1 (1.5)	0	1 (6.3)
Other	2 (5.4)	3 (8.1)	5 (2.5)	8 (3.8)	1 (0.8)	1 (0.8)	0	1 (1.5)	0	1 (6.3)
ECOG PS, n (%)										
0	13 (35.1)	20 (54.1)	73 (35.8)	95 (44.8)	44 (34.9)	49 (39.8)	25 (36.8)	29 (42.6)	7 (35.0)	9 (56.3)
1	24 (64.9)	17 (45.9)	131 (64.2)	117 (55.2)	82 (65.1)	74 (60.2)	43 (63.2)	39 (57.4)	13 (65.0)	7 (43.8)
Type of cancer, n (%)										
Gastric	26 (70.3)	31 (83.8)	157 (77.0)	168 (79.2)	107 (84.9)	96 (78.0)	55 (80.9)	56 (82.4)	16 (80.0)	11 (68.8)
Gastroesophageal junction	11 (29.7)	6 (16.2)	47 (23.0)	44 (20.8)	19 (15.1)	27 (22.0)	13 (19.1)	12 (17.6)	4 (20.0)	5 (31.3)
Histological subtype, n (%)										
Intestinal	13 (35.1)	11 (29.7)	80 (39.2)	77 (36.3)	65 (51.6)	58 (47.2)	36 (52.9)	32 (47.1)	12 (60.0)	8 (50.0)
Diffuse	16 (43.2)	22 (59.5)	80 (39.2)	89 (42.0)	35 (27.8)	44 (35.8)	20 (29.4)	26 (38.2)	5 (25.0)	7 (43.8)
Mixed	1 (2.7)	1 (2.7)	11 (5.4)	10 (4.7)	10 (7.9)	4 (3.3)	4 (5.9)	2 (2.9)	0	0
Unknown/Missing	7 (18.9)	3 (8.1)	33 (16.2)	36 (17.0)	16 (12.7)	17 (13.8)	8 (11.8)	8 (11.8)	3 (15.0)	1 (6.3)

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; n=number of patients; PAC=paclitaxel; RAM=ramucirumab; SD=standard deviation

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