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ORIGINAL ARTICLE

Exposure–response relationship of ramucirumab in East Asian patients from RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer

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Abstract

Background Ramucirumab is a recombinant human IgG1 neutralizing monoclonal antibody specific for vascular endothelial growth factor receptor-2. Second-line ramucirumab, in conjunction with paclitaxel (ramucirumab 8 mg/kg or placebo in combination with 80 mg/m^2 paclitaxel), has been shown to be effective and safe in patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma in RAINBOW, a global phase III randomized clinical trial. We conducted an exploratory exposure–response analysis of efficacy and safety of ramucirumab in East Asian patients from the RAINBOW trial.

Methods Using sparse pharmacokinetic samples collected in the RAINBOW trial, a population pharmacokinetic analysis was conducted to predict ramucirumab minimum trough concentration at steady state ($C_{min,ss}$) using a nonlinear mixed-effect modeling approach. Kaplan–Meier and Cox proportional hazards analyses were conducted to evaluate ramucirumab exposure ($C_{min,ss}$) and efficacy relationship by overall survival and progression-free survival. Exposure-safety relationships were assessed descriptively.

Results Two hundred and twenty-two East Asian patients were included in this exposure–response analysis. Higher ramucirumab $C_{min,ss}$ was associated with longer overall survival ($p = 0.0115$) and progression-free survival ($p = 0.0179$) in this patient cohort. Patients with higher ramucirumab $C_{min,ss}$ ($\geq$56.87 ng/ml median) had higher incidences of grade $\geq$3 leukopenia and neutropenia, but not febrile neutropenia or hypertension.

Conclusions This exploratory analysis suggests a positive relationship between efficacy and ramucirumab exposure with manageable toxicities in East Asian patients from RAINBOW, consistent with the overall exposure–response analysis from this trial. A regimen with a higher dosage of ramucirumab warrants further consideration for East Asian patients with gastric/GEJ cancer.

Keywords East Asian patients · Exposure response · Gastric cancer · Ramucirumab · Vascular endothelial growth factor receptor-2

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Introduction

Ramucirumab (Cyramza; Eli Lilly) is a recombinant human IgG1 monoclonal antibody (mAb) specific for vascular endothelial growth factor receptor-2 (VEGFR-2) [1]. The safety and efficacy of ramucirumab in patients with previously treated advanced gastric or gastroesophageal junction (GEJ) cancer were evaluated in two global, randomized, double-blind phase III trials (REGARD and RAINBOW) [2, 3]. In both the REGARD

trial (ramucirumab 8 mg/kg versus placebo) and the RAINBOW trial (ramucirumab 8 mg/kg or placebo in combination with 80 mg/m^2 paclitaxel), overall survival (OS) and progression-free survival (PFS) were significantly improved in the ramucirumab arm [2, 3]. The most common grade ≥3 adverse events (AEs) in ramucirumab-treated patients were neutropenia, leukopenia, hypertension, fatigue, abdominal pain, and anemia [2, 3]. Based on the outcomes of the REGARD and RAINBOW trials, ramucirumab has been approved worldwide for use as monotherapy, or in combination with paclitaxel, for the treatment of patients with previously treated advanced gastric/GEJ cancer [4, 5].

Approximately one-third of patients from the RAINBOW trial (231 of 665 patients) were enrolled in East Asia. Among these East Asian patients, response rate and survival times favored treatment with ramucirumab plus paclitaxel over placebo plus paclitaxel [6], despite a higher use of post-discontinuation treatment in East Asian patients, which may have affected the OS hazard ratio (HR) [6]. Consistent with the safety results of the entire study population and non-East Asian counterparts, neutropenia was the most frequently reported high-grade toxicity among East Asian patients [3, 6]. Bleeding, proteinuria, and hypertension appeared to be the most common AEs possibly attributed to VEGFR-2 inhibition; however, the majority of these EVENTS were grade 1 or 2 [6].

Exposure–response analyses are vital to determine the efficacy and safety of cancer treatments. Such analyses optimize the benefits for patients by establishing a relationship between efficacy or AEs and exposure for an optimal drug dosage [7]. Exploratory analyses examining ramucirumab exposure and response relationships have been performed separately for the REGARD and RAINBOW trials [8]. These analyses suggested a positive association between ramucirumab exposure and efficacy as well as increased incidences of selected toxicities [8]. Specifically, in the RAINBOW trial, it was noted that Asian patients may have an increased risk of both neutropenia and leukopenia in comparison to non-East Asian patients in both the ramucirumab and placebo arms [6]. A higher rate of grade ≥3 neutropenia (60% versus 28%) and leukopenia (34% versus 13%) was observed in the ramucirumab arm in comparison to the placebo arm in East Asian patients [6]. Additionally, geographic region was one of the covariates significantly associated with OS in the RAINBOW study [3].

This article reports the outcomes of an exploratory exposure–response analysis in East Asian patients from the RAINBOW trial. We aim to evaluate the relationship between predicted ramucirumab exposure and OS and PFS, as well as commonly reported AEs, in previously treated patients with advanced gastric cancer. Findings from this analysis may facilitate the optimization of ramucirumab dosage for the treatment of gastric cancer in East Asian patients.

Methods

Study design and patients

The study design for the RAINBOW trial has been previously described [3]. Briefly, patients with advanced gastric/GEJ cancer who had progressed on or within 4 months of first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline) were randomized (1:1) to receive ramucirumab 8 mg/kg or placebo on days 1 and 15, plus paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. The primary endpoint was OS. Key secondary endpoints included PFS and safety [3]. Each center's institutional review board or independent ethics committee approved the study. The trial followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent.

Population pharmacokinetics

Population pharmacokinetics (PK) analyses were conducted as previously described [9]. Samples for PK analysis were collected before and 1 h after infusions 1, 4, and 7 and at the end of the trial. The population PK-predicted exposure value of minimum trough concentration at steady-state ($C_{min,ss}$) for ramucirumab-treated patients was calculated using a nonlinear mixed-effect modeling approach (NONMEM VI; ICON, Ellicott City, MD, USA). Analyses were conducted in accordance with the U.S. Food and Drug Administration (FDA) Guidance for Industry on Population Pharmacokinetics [10].

Exposure-efficacy analyses

All statistical analyses were undertaken using SAS version 9.2 (SAS Institute, Cary, NC, USA). Univariate and stepwise multivariable Cox regression analyses were performed to evaluate if there was a significant relationship between ramucirumab exposure ($C_{min,ss}$) and efficacy (OS and PFS). East Asian patients with nonmissing ramucirumab concentration data were included in the exposure populations. For the multivariable analyses, HRs were adjusted for significant baseline covariates. A stepwise Cox regression model was used to select baseline covariates at an entry p value of 0.05 and an exit p value of 0.1. The list of factors evaluated for potential prognostic significance

were gender, age, Eastern Cooperative Oncology Group performance status (ECOG PS), weight and weight loss in the 3 months before randomization, primary tumor location, tumor grade and histological subtype, tumor metastases, presence of ascites, disease progression, and prior gastrectomy.

To evaluate the exposure-efficacy relationship compared with the control group, East Asian patients in the exposure population were stratified into two exposure groups by the median $C_{min,ss}$ of 56.87 ng/ml. The median was used to ensure both high and low exposure groups had sufficient, and equal, numbers of patients to allow for meaningful statistical analyses. The Kaplan–Meier method was used to evaluate OS and PFS for each of the individual exposure groups versus the control group. The HR for each exposure group versus the control arm was estimated using a Cox proportional hazards model. All HRs for the multivariable analyses were adjusted for significant baseline covariates.

Exposure-safety analyses

The three most common grade ≥3 treatment-emergent AEs (TEAEs) occurring in ≥10% of patients in the RAINBOW intent-to-treat (ITT) population and at a higher rate in the ramucirumab plus paclitaxel arm were selected as the safety endpoints for all exposure-safety analyses. These TEAEs were neutropenia (including febrile neutropenia), leukopenia, and hypertension, and all were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02 (3). The relationship between TEAE incidence and ramucirumab $C_{min,ss}$ was assessed descriptively.

Results

Patients

The East Asian population consisted of 223 randomly assigned patients: 114 in the placebo plus paclitaxel arm and 109 in the ramucirumab plus paclitaxel arm. One patient in the ramucirumab plus paclitaxel arm did not receive treatment; hence 108 ramucirumab-treated patients were included in this analysis (54 patients each with $C_{min,ss}$ <median of 56.87 ng/ml and $C_{min,ss}$ ≥median of 56.87 ng/ml). The baseline patient and tumor characteristics are summarized in Table 1.

Exposure efficacy

Exploratory univariate analysis evaluating ramucirumab exposure as a continuous variable identified a significant association between ramucirumab $C_{min,ss}$ and OS ($p = 0.0115$) as well as PFS ($p = 0.0179$) (Table 2). As log_2 transformation was applied before fitting the model, the HR should be interpreted as the change in hazard when the $C_{min,ss}$ doubles in value. Stepwise Cox regression analysis identified prognostic factors significantly associated with OS including prior gastrectomy, number of metastatic sites, ECOG PS, weight loss, presence of ascites, and tumor differentiation. After accounting for these factors in a multivariate analysis, the association between OS and $C_{min,ss}$ remained statistically significant ($p = 0.0275$). PFS was significantly associated with liver metastasis, weight loss, gender, and number of metastatic sites in stepwise Cox regression analysis. After adjusting for these factors, the association between PFS and $C_{min,ss}$ also remained statistically significant ($p = 0.0046$) (Table 3).

Ramucirumab exposure was also evaluated as a categorical variable by median to facilitate comparisons with the control group. The Kaplan–Meier curves for OS and PFS depict a distinct separation between the two $C_{min,ss}$ median exposure groups (Fig. 1). Median OS was 10.5 months in the placebo plus paclitaxel arm. For patients receiving ramucirumab plus paclitaxel, median OS for $C_{min,ss}$ <median was 9.2 months (HR 1.225) and for $C_{min,ss}$ ≥median was 12.6 months (HR 0.801) (Table 4). Median PFS was 2.8 months for placebo plus paclitaxel patients, 4.2 months for ramucirumab plus paclitaxel patients with $C_{min,ss}$ <median (HR 0.775), and 6.8 months for ramucirumab plus paclitaxel patients with $C_{min,ss}$ ≥median (HR 0.496) (Table 4). In summary, patients with higher ramucirumab exposure had better clinical outcomes, including longer survival and smaller HRs.

Exposure safety

Analysis by $C_{min,ss}$ was undertaken for safety outcomes. The observed incidence of safety endpoints by $C_{min,ss}$ is shown in Table 5. The rate of hypertension was 0.9% in the placebo plus paclitaxel arm and 11.1% and 5.6% in the ramucirumab plus paclitaxel arm for $C_{min,ss}$ <median and $C_{min,ss}$ ≥median, respectively. The rate of leukopenia was 13.2% in the placebo plus paclitaxel arm and 29.6% and 38.9% in the ramucirumab plus paclitaxel arm for $C_{min,ss}$ <median and $C_{min,ss}$ ≥median, respectively. Similarly, the rate of neutropenia was associated with ramucirumab exposure: 28.1% in the placebo plus paclitaxel arm and 50.0% and 72.2% in the ramucirumab plus paclitaxel arm for $C_{min,ss}$ <median and $C_{min,ss}$ ≥median, respectively. The rate of febrile neutropenia, however, did not appear to be associated with ramucirumab exposure: 4.4% in the placebo plus paclitaxel arm and 5.6% and 1.9% in the ramucirumab plus paclitaxel arm for $C_{min,ss}$ <median and $C_{min,ss}$ ≥median, respectively (Table 5).

Table 1 East Asian RAINBOW population baseline characteristics

	Placebo + paclitaxel, *n* (%)	Ramucirumab + paclitaxel, *n* (%)	
		<Median[a]	≥Median[a]
Number of patients	114	54	54
Age <65 years	68 (59.6)	34 (63.0)	33 (61.1)
Gender, male	81 (71.1)	39 (72.2)	33 (61.1)
ECOG performance status			
0	60 (52.6)	17 (31.5)	27 (50.0)
1	54 (47.4)	37 (68.5)	27 (50.0)
Baseline body weight (kg), mean (SD)	55.3 (9.8)	54.0 (9.6)	55.6 (9.2)
Weight loss over prior 3 months			
<10%	100 (87.7)	45 (83.3)	49 (90.7)
≥10%	14 (12.3)	9 (16.7)	5 (9.3)
Primary tumor present	70 (61.4)	35 (64.8)	30 (55.6)
Primary tumor location			
Gastric	107 (93.9)	54 (100.0)	51 (94.4)
GEJ	7 (6.1)	0	3 (5.6)
Histological subtype			
Diffuse	53 (46.5)	27 (50.0)	17 (31.5)
Intestinal	39 (34.2)	15 (27.8)	26 (48.1)
Mixed	22 (19.3)	12 (22.2)	11 (20.4)
Metastatic disease	113 (91.1)	54 (100.0)	54 (100.0)
Number of metastatic sites			
0	1 (0.9)	0	0
1	44 (38.6)	19 (35.2)	17 (31.5)
2	43 (37.7)	22 (40.7)	23 (42.6)
≥3	26 (22.8)	13 (24.1)	14 (25.9)
Most common site of metastasis			
Liver	38 (33.3)	14 (25.9)	27 (50.0)
Lung	12 (10.5)	4 (7.4)	8 (14.8)
Lymph nodes	69 (60.5)	35 (64.8)	33 (61.1)
Peritoneal	60 (52.6)	38 (70.4)	26 (48.1)
Tumor grade			
Well differentiated	9 (7.9)	6 (11.1)	5 (9.3)
Moderately differentiated	31 (27.2)	16 (29.6)	18 (33.3)
Poorly differentiated	68 (59.6)	30 (55.6)	30 (55.6)
Unknown	6 (5.3)	2 (3.7)	1 (1.9)
Disease progression			
During first-line therapy	93 (81.6)	47 (87.0)	44 (81.5)
Less than 4 months after first-line therapy	20 (17.5)	7 (13.0)	10 (18.5)
Missing	1 (0.9)	0	0
Presence of ascites	46 (40.4)	32 (59.3)	22 (40.7)
Prior gastrectomy			
No	71 (62.3)	31 (57.4)	24 (44.4)
Partial gastrectomy	22 (19.3)	12 (22.2)	21 (38.9)
Total gastrectomy	21 (18.4)	11 (20.4)	9 (16.7)

ECOG Eastern Cooperative Oncology Group, *GEJ* gastroesophageal junction, *n* number of patients, *SD* standard deviation

[a] Median, 56.87 ng/ml

Table 2 OS and PFS in East Asian RAINBOW patients by $C_{min,ss}$

Efficacy parameter	*n*/events	Hazard ratio[a,b] (95% CI)	*p* value[a]
OS	108/84	0.598 (0.401, 0.891)	0.0115
PFS	108/92	0.636 (0.437, 0.925)	0.0179

CI confidence interval, *n* number of patients, $C_{min,ss}$ minimum concentration at steady-state, *OS* overall survival; *PFS* progression-free survival

[a] Hazard ratio and *p* value were obtained from an unstratified univariate Cox model

[b] Log_2 transformation was applied before fitting the model; hence, the HR should be interpreted as the change in hazard when $C_{min,ss}$ doubles in value

Discussion

To our knowledge, this exploratory analysis is the first report regarding the exposure–response relationship of ramucirumab in East Asian patients. Approximately half of the world total gastric cancer cases occur in East Asian countries, where the highest estimated mortality rates are also reported [11]. The disparity in incidence and mortality between East Asian and non-East Asian countries, despite being speculative, may be attributable to genetic susceptibility [12, 13], dietary patterns [14], and *Helicobacter pylori* infection [15]. On the other hand, genetic differences in pharmacokinetics or pharmacodynamics may potentially lead to variability in drug response or dosing [16]. Considered together, these geographic or ethnic differences warranted the analysis of exposure–response outcomes among this population from the RAINBOW trial.

This analysis supports the approved ramucirumab dosages for East Asian patients while providing a guide on developing strategies for dose optimization by further improving efficacy in East Asian patients through modifications to the ramucirumab dosing regimen. Our findings are consistent with those of the RAINBOW exposure–response analysis [8], although the number of East Asian ramucirumab-treated patients was too small to be stratified by quartiles.

We observed a positive association between ramucirumab exposure and survival in East Asian patients with advanced gastric/GEJ cancer. A clear separation was observed between the exposure groups in the OS and PFS curves, indicating that higher ramucirumab exposure was associated with longer survival. After accounting for prognostic factors, the higher ramucirumab exposure remained associated with smaller HRs for both OS and PFS. Our findings indicate that OS for C_{min} <median patients was similar to that of placebo patients, although there were improvements in PFS in this patient cohort. Improvements in both OS and PFS were observed for C_{min} ≥median patients in comparison to placebo. Compared to the ramucirumab-treated patients reported in the initial East Asian subgroup analysis of RAINBOW, we observed a further increase in efficacy in the East Asian C_{min} ≥median patients in terms of median months and HRs for OS [12.6 versus 12.1 months; HR 0.801 (95% CI 0.549, 1.169) versus 0.986 (95% CI 0.727, 1.337)] and PFS [6.8 versus 5.5 months; HR 0.496 (95% CI 0.348, 0.706) versus 0.628 (95% CI 0.473, 0.834)] [6]. Our findings suggest that further improvements in efficacy may be possible for East Asian patients by employing additional modifications to the ramucirumab dosing regimen.

In a previous analysis of the RAINBOW population, Asian patients were found to have an increased risk of both grade ≥3 neutropenia and leukopenia and any grade hypertension [6]. With regard to the exposure–response analysis for safety, the incidence of grade ≥3 hypertension was not correlated with predicted ramucirumab concentration. This discrepancy may be the result of the relatively small number of East Asian patients, and, in particular, the low number of high-grade hypertension events in our East Asian cohort. Concomitant medications and lifestyle factors may also have contributed to this finding. Higher ramucirumab exposure likely led to an increased incidence of grade 3 or higher neutropenia and leukopenia. However, ramucirumab exposure was not associated with a higher likelihood of developing grade ≥3 febrile neutropenia, a known clinically meaningful toxicity.

Collectively, the findings of this exposure–response analysis for efficacy and safety for RAINBOW East Asian patients suggest an opportunity to further improve efficacy outcomes. Further exploratory exposure–response analyses using the data from RAINBOW have been undertaken by the FDA. In this study, the relationship between $C_{min,1}$ (minimum concentration after first dose) and OS based on exposure subgroups and matched placebo controls was assessed by Kaplan–Meier analyses [17]. This study concluded that patients with higher ramucirumab exposure may derive more benefit from the addition of ramucirumab to paclitaxel after an incremental increase in OS was observed with increasing exposure of ramucirumab [17]. Furthermore, a clinical trial examining the efficacy and safety of higher ramucirumab doses was recommended [17]. Additional trials are currently underway. A phase II trial examining the pharmacokinetics and safety of 4 ramucirumab dosing regimens in second-line gastric/GEJ cancer is currently underway (NCT02443883). Another phase II trial in gastric/GEJ cancer will evaluate second-line ramucirumab (8 versus 12 mg/kg plus paclitaxel) (NCT02514551).

A limitation of this subgroup analysis is the relatively small number of East Asian patients. We could only generate two patient subgroups of ramucirumab exposure

Table 3 Exposure-efficacy outcomes in East Asian RAINBOW patients by $C_{min,ss}$ after adjusting for confounding factors

	Number of patients	Hazard ratio[a] (95% CI)	p value[a] (Wald's)
OS			
$C_{min,ss}$		0.612 (0.396, 0.947)	0.0275
Prior gastrectomy			
Yes versus no	55	0.490 (0.309, 0.779)	0.0025
Number of metastatic sites			
0–2 versus ≥3	27	0.463 (0.269, 0.798)	0.0055
ECOG PS			
1 versus 0	44	1.330 (0.831, 2.127)	0.2342
Weight loss over prior 3 months			
≥10 versus <10%	94	1.416 (0.716, 2.803)	0.3175
Tumor differentiation			
Moderately versus poorly	60	0.902 (0.557, 1.461)	0.6749
Unknown versus poorly	60	0.180 (0.023, 1.427)	0.1045
Well versus poorly	60	0.492 (0.207, 1.168)	0.1079
Presence of ascites			
Yes versus no	54	1.100 (0.658, 1.836)	0.7167
PFS			
$C_{min,ss}$		0.560 (0.375, 0.837)	0.0046
Weight loss over prior 3 months			
≥10 versus <10%	94	1.559 (0.812, 2.992)	0.1822
Liver metastasis			
Yes versus no	67	1.480 (0.932, 2.349)	0.0964
Gender			
Male versus female	36	0.774 (0.481, 1.247)	0.2927
Number of metastatic sites			
0–2 versus ≥3	27	0.840 (0.520, 1.357)	0.4760

CI confidence interval, $C_{min,ss}$ minimum concentration at steady-state, *ECOG PS* Eastern Cooperative Oncology performance status, *OS* overall survival, *PFS* progression-free survival

The covariates ECOG performance status, weight loss, number of metastatic sites, presence of ascites, tumor differentiation, and prior gastrectomy that were found to be significantly associated with OS were included in this multivariate analysis. The covariates gender, weight loss, number of metastatic sites, and liver metastasis that were found to be significantly associated with PFS were included in this multivariate analysis

[a] HR and p value were obtained from an unstratified multivariate Cox model

dichotomized by median $C_{min,ss}$. However, the 95% CIs for OS and PFS were still very wide, with overlapping evident for the two exposure groups. Another limitation is that the applied multivariate model identified potential prognostic factors based on the RAINBOW ITT population, which may not account for risk factors that are specific to the East Asian subgroup. Of note, East Asian patients in this analysis were defined based on geographic region, which was a

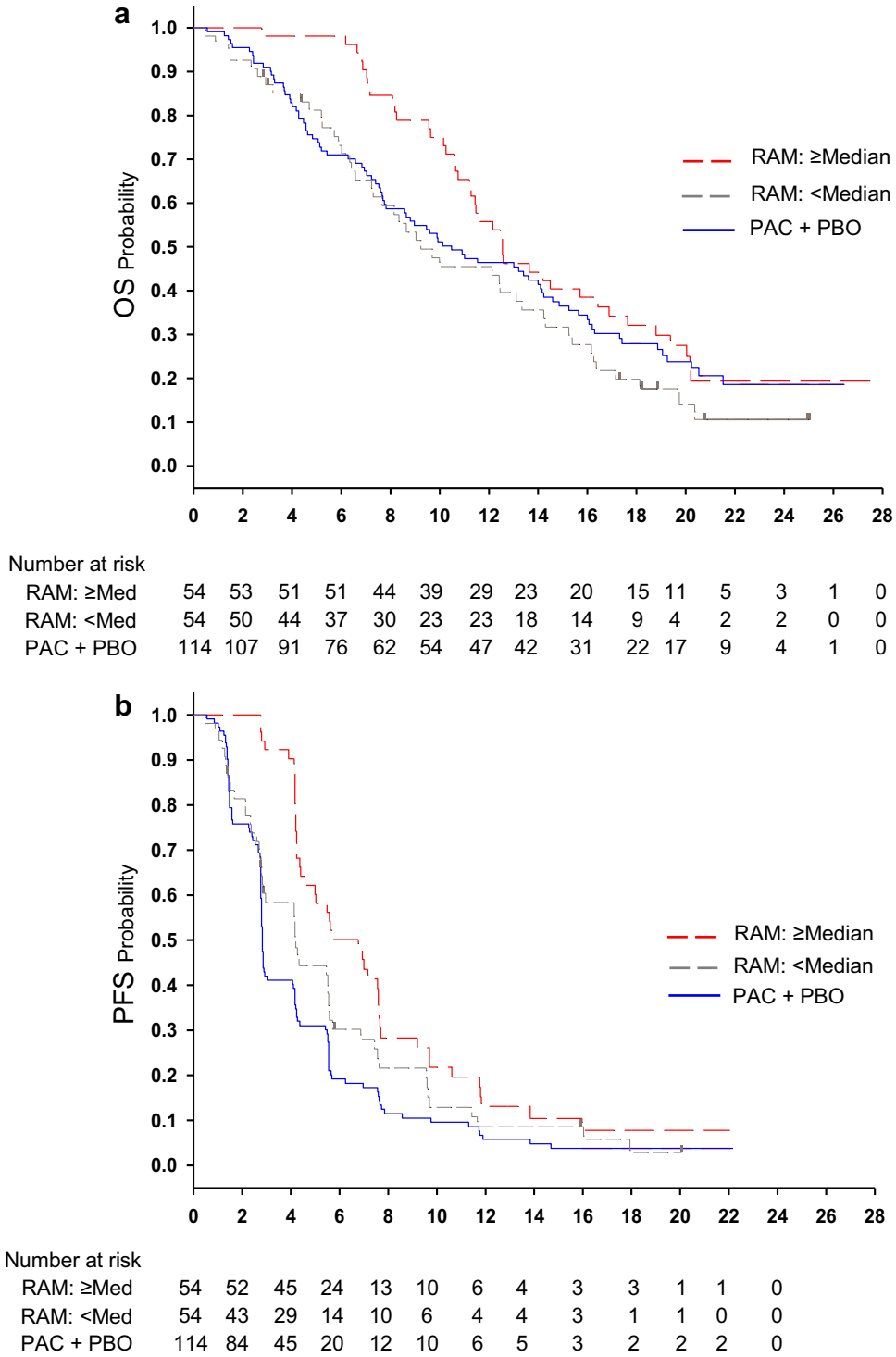

Fig. 1 Kaplan–Meier analysis of RAINBOW East Asian efficacy outcomes in exposure–response populations by RAM $C_{min,ss}$. RAINBOW overall survival (**a**) and progression-free survival (**b**) are stratified by $C_{min,ss}$ median and compared with paclitaxel plus placebo patients. *Med* median 56.87 ng/ml, *OS* overall survival, *PAC* paclitaxel, *PBO* placebo, *PFS* progression-free survival, *RAM* ramucirumab

stratification factor in the RAINBOW study [3]. In addition, we did not conduct an analysis across different ethnicities. Therefore, we cannot conclude any ethnic difference existing in the exposure–response relationship.

In conclusion, this exposure–response analysis suggests a positive relationship between efficacy and ramucirumab exposure in East Asian patients. Coinciding with the RAINBOW PK study [8], this analysis demonstrated that ramucirumab 8 mg/kg given every 2 weeks is an effective and safe dose that offers a favorable benefit–risk profile when administered in combination with paclitaxel in this patient cohort.

Table 4 Exposure-efficacy outcomes in East Asian RAINBOW patients by $C_{min,ss}$ median

Efficacy parameter	*n*/events	Months (median)	Hazard ratio[a] (95% CI)	*p* value
OS				
PBO + PAC	114/82	10.5		
RAM + PAC <median[a]	54/44	9.2	1.225 (0.849, 1.769)	0.2776
RAM + PAC ≥median[a]	54/40	12.6	0.801 (0.549, 1.169)	0.2501
PFS				
PBO + PAC	114/105	2.8		
RAM + PAC <median[b]	54/48	4.2	0.775 (0.550, 1.092)	0.1447
RAM + PAC ≥median[b]	54/44	6.8	0.496 (0.348. 0.706)	0.0001

CI confidence interval, $C_{min,ss}$ minimum concentration at steady-state, *n* number of patients, *OS* overall survival, *PAC* paclitaxel, *PBO* placebo, *PFS* progression-free survival, *RAM* ramucirumab

Factors evaluated for potential prognostic significance include geographic region, disease measurability, time to progression from first-line chemotherapy, gender, age, race, Eastern Cooperative Oncology Group Performance Status, weight loss, primary tumor location, prior first-line chemotherapy, histological subtype, number of metastatic sites, peritoneal/liver metastasis, presence of ascites, tumor differentiation, number of previous treatment lines, and prior gastrectomy

[a] Median = 56.87 ng/ml

[b] Relative to placebo

Table 5 Incidence of adverse events (grade ≥3) by median $C_{min,ss}$ in East Asian RAINBOW patients

	Placebo + paclitaxel	Ramucirumab + paclitaxel		
		Overall	<Median[a]	≥Median[a]
Number of patients	114	108	54	54
Ramucirumab concentration range (μg/ml)	–	22.7–121	22.7 to <56.9	≥56.9 to 121
Hypertension (%)	0.9	8.3	11.1	5.6
Neutropenia (%)	28.1	61.1	50.0	72.2
Febrile neutropenia (%)	4.4	3.7	5.6	1.9
Leukopenia (%)	13.2	34.3	29.6	38.9

$C_{min,ss}$ minimum concentration at steady state

[a] Median = 56.87 ng/ml

Although these results suggest that higher ramucirumab exposure may be associated with increased AEs, the toxicities were manageable. A regimen with a higher dosage of ramucirumab warrants further investigation in East Asian patients with gastric/GEJ cancer.

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Compliance with ethical standards

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Conflict of interest Salah-Eddin Al-Batran has an advisory role at Merck Serono, Roche, Celgene, Eli Lilly and Company, and Nordic Pharma. He also reports research grants from Merck Serono, Roche, Celgene, Vifor Pharma, Medac Pharma, Hospira, and Eli Lilly and Company, and is a speaker for Roche, Celgene, Eli Lilly and Company, and Nordic Pharma. Rebecca Cheng, Mauro Orlando, Ling Gao, Yanzhi Hsu, and David Ferry are employees of Eli Lilly and Company and own stock in Eli Lilly and Company. Atsushi Ohtsu, Tae You Kim, and Chia-Jui Yen declare no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients included in the study.

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