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Journal

Journal of Gastric Cancer, 23(2)

ISSN

2093-582X

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Publication Date

2023

DOI

10.5230/jgc.2023.23.e15

Peer reviewed

J Gastric Cancer. 2023 Apr;23(2):289-302
https://doi.org/10.5230/jgc.2023.23.e15
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Original Article

Exploratory Analysis of Patients With Gastric/Gastroesophageal Junction Adenocarcinoma With or Without Liver Metastasis From the Phase 3 RAINBOW Study

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Received: Jun 27, 2022
Revised: Dec 19, 2022
Accepted: Dec 25, 2022
Published online: Mar 9, 2023

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Trial Registration
ClinicalTrials.gov Identifier: NCT01170663

Funding
This study was funded by Eli Lilly and Company (grant numbers not applicable).

Conflict of Interest
Takatsugu Ogata has nothing to disclose. Yukiya Narita reports grants and personal fees from Ono Pharma and Bristol-Mayers Squibb (C/A, RF), Eli Lilly and Company, Yakult Honsha, Daiichi-Sankyo, and Taiho (C/A). Zev Wainberg Eli Lilly and Company, BMS, Bayer, Merck, Genentech Daiichi, EMD

ABSTRACT

Purpose: Liver metastasis (LM) is reported in approximately 40% of patients with advanced/metastatic gastric/gastroesophageal junction adenocarcinoma (metastatic esophagogastric adenocarcinoma; mGEA) and is associated with a worse prognosis. This post-hoc analysis from the RAINBOW trial reported the efficacy, safety, and biomarker outcomes of ramucirumab and paclitaxel combination treatment (RAM+PAC) in patients with (LM+) and without (LM−) LM at baseline.

Materials and Methods: Patients (n=665) were randomly assigned on a 1:1 basis to receive either RAM+PAC (LM+: 150, LM−: 180) or placebo and paclitaxel (PL+PAC) (LM+: 138, LM−: 197). The overall survival (OS) and progression-free survival (PFS) were evaluated using stratified Kaplan–Meier and Cox regression models. The correlation of dichotomized biomarkers (VEGF-C, D; VEGFR-1,2) with efficacy in the LM+ versus LM− subgroups was analyzed using the Cox regression model with reported interaction P-values.

Results: The presence of LM was associated with earlier progression than those without LM, particularly in patients receiving PL+PAC (hazard ratio [HR], 1.68). RAM+PAC treatment improved OS and PFS irrespective of LM status but showed greater improvement in LM+ than that in LM− (OS HR, 0.71 [LM+] vs. 0.88 [LM−]; PFS HR, 0.47 [LM+] vs. 0.76 [LM−]). Treatment-emergent adverse events were similar between patients with and without LM. No predictive relationship was observed between biomarker levels (VEGF-C, D; VEGFR-1,2) and efficacy outcome (OS, PFS) (all interaction P-values >0.05).

Conclusions: RAM provided a significant benefit, irrespective of LM status; however, its effect was numerically stronger in patients with LM. Therefore, RAM+PAC is a clinically meaningful therapeutic option for patients with mGEA and LM.

Trial Registration: ClinicalTrials.gov Identifier: NCT01170663

Keywords: Ramucirumab; Stomach neoplasms; Vascular endothelial growth factors

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Serono, Amgen, and Astra Zeneca (C/A).Eric Van Cutsem Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, and Servier (C/A, RF), Amgen (C/A), AbbVie, Array, Astellas, AstraZeneca, BeiGene, Biocartis, Daiichi-Sankyo, GlaxoSmithKline, Halozyme, Helsinn, Incyte, Janssen Research, Mirati, Pierre Fabre, Seattle Genetics, Sirtex, Terumo, Taiho, TRIGR, and Zymeworks (RF). Kensei Yamaguchi Taiho Pharmaceutical, Ono Pharm, and Elli Lilly and Company (C/A, RF); Chugai Pharm, Bristol-Myers Squibb Japan, Merck Biopharm, and Takeda (C/A); Yakult Honsha and Sanofi (RF). Yongzhe Piao, Yumin Zhao, Patrick M. Peterson, Sameera R. Wijayawardana, Paolo Abada, and Anindya Chatterjee Eli Lilly and Company (E, OI). Kei Muro Solasia Pharma, Merck Serono, Daiichi-Sankyo, Parexel International, Pfizer, and MSD (RF); Amgen, ONO Pharmaceutical Co. Ltd., Sanofi, and Taiho (C/A, RF); and AstraZeneca, Eli Lilly and Company, Takeda, Chugai, Bristol-Myers Squibb, and Bayer (C/A).

Author Contributions

Conceptualization: O.T., N.Y., Y.K., P.Y., Z.Y., W.S.R., A.P., C.A., M.K.; Data curation: W.Z.A., V.C.E., P.Y., Z.Y., P.P.M., W.S.R., A.P., C.A., M.K.; Formal analysis: O.T., W.Z.A., V.C.E., Y.K., P.Y., Z.Y., P.P.M., W.S.R., A.P., C.A., M.K.; Investigation: O.T., W.Z.A., V.C.E., Y.K., P.Y., Z.Y., P.P.M., W.S.R., A.P., C.A., M.K.; Writing - original draft: O.T., N.Y., W.Z.A., V.C.E., Y.K., P.Y., Z.Y., P.P.M., W.S.R., A.P., C.A., M.K.; Writing - review & editing: O.T., N.Y., W.Z.A., V.C.E., Y.K., P.Y., Z.Y., P.P.M., W.S.R., A.P., C.A., M.K.

INTRODUCTION

Globally, gastric cancer is the fifth most common malignancy and is responsible for an estimated 769,000 deaths, which equates to 1 in every 13 deaths globally [1]. Eastern Asia (Japan and Mongolia) has the highest incidence of gastric cancer among men and women. The prognosis of patients with advanced/metastatic gastric/gastroesophageal junction adenocarcinoma (metastatic esophagogastric adenocarcinoma; mGEA) remains poor, with liver metastasis (LM) reported in approximately 40% of patients [2,3]. Patients with LM often have multiple metastatic tumors in the liver, and their development is associated with high mortality (6-month survival rates of 20%–50%) [4]. The metastatic pattern of gastric cancers is complex owing to the heterogeneous histological types observed with the disease; however, intestinal-type carcinoma is associated with an increased risk of LM [3,5,6]. In addition, several LM risk factors have been identified, including advanced age, tumor site, and pathology grade [7]. Interestingly, the patient's treatment may positively or negatively increase the risk of LM and long-term survival [3]. In addition, several studies have identified vascular endothelial growth factor (VEGF) expression as an important risk factor for LM [8-10].

Ramucirumab (RAM), a human IgG1 monoclonal antibody VEGFR-2 antagonist, prevents ligand-binding and receptor-mediated pathway activation in endothelial cells [11,12]. The phase 3 RAINBOW study (NCT01170663) showed improved overall survival (OS) for patients treated with a combination of RAM+ paclitaxel (PAC) versus placebo (PL) and PAC [12] and is regarded as the standard second-line treatment for patients with mGEA [13,14].

A retrospective analysis of patients with mGEA and LM who received treatment at the Aichi Cancer Center Hospital from 2005 to 2019 showed significant improvements in OS ($P<0.001$) after approval of ramucirumab and nivolumab (from 2015 to 2019) [15]. An improved benefit was also observed within the phase 3 RAINBOW-Asia LM subgroup analysis, as patients with LM tended to receive more benefit from RAM+PAC treatment than those without LM [16].

This post-hoc analysis from the RAINBOW trial reported the efficacy, safety, and biomarker outcomes of RAM+PAC treatment in patients with (+) and without (−) LM at baseline.

MATERIALS AND METHODS

Study design, biomarker sample collection, and analysis

The randomized, placebo-controlled, double-blind, phase 3 RAINBOW trial was conducted at 170 centers in 27 countries in North and South America, Europe, Asia, and Australia. Patients (n=665) were randomly assigned on a 1:1 basis to receive RAM+PAC (LM+: 150, LM−: 180) or PL+PAC (LM+: 138, LM−: 197) (**Supplementary Figs. 1** and **2**). The detailed eligibility criteria have been described previously [12]. Briefly, patients had locally advanced mGEA, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline, and measurable or non-measurable evaluable disease defined by the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1. Patient demographics and baseline clinical characteristics were generally well-balanced across the treatment arms, as previously described [12].

https://doi.org/10.5230/jgc.2023.23.e15

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Plasma was collected from all patients before RAM+PAC treatment, prior to cycle 2, day 15 (4th RAM/PL infusion), prior to cycle 4, day 1 (7th RAM/PL infusion), and 30 days after discontinuation of treatment. At the study onset, available samples were assayed for circulating protein factors using electrochemiluminescent assays performed by Alta Intertek Pharmaceutical Services (San Diego, CA, USA). Later, Eli Lilly and Company developed assays that became available, which targeted key VEGF-family markers. These assays were also quantitative sandwich electrochemiluminescent assays used exclusively for baseline plasma samples. VEGF-A was not assessed in either assay platform because plasma samples were collected in heparin tubes, and heparin has been found to interfere with the VEGF-A assay.

Statistical analysis

Efficacy (objective response rate [ORR], disease control rate [DCR], OS, and progression-free survival [PFS]) analyses were based on predefined subgroups (LM+ vs. LM−) within the intent-to-treat (ITT) population, which comprised all randomly assigned patients irrespective of whether the patient received study medication. Kaplan–Meier (KM) and Cox regression models stratified by geographic region, time to progression on first-line therapy, and disease measurability were used for OS and PFS. The frequency and percentage of ORR and DCR in each group are reported.

The safety analyses included all patients who received at least one dose of any study drug and were based on predefined subgroups (LM+ vs. LM−). The frequency and percentage of treatment-emergent adverse events (TEAEs) and special interest TEAEs were reported.

For the prognosis analyses, exploratory post-hoc analyses were performed using the Cox univariate model of LM stratified by randomization factors (disease measurability, time to progression on first-line therapy, and geographical regions) within each treatment arm (RAM+PAC or PL+PAC) and with the ITT population stratified by treatment arm. The hazard ratio (HR), its 2-sided 95% confidence limits, and P-value were reported accordingly, with a significance level of 0.05 for testing prognosis factors.

To assess the correlation of biomarkers detected in plasma (VEGF-C, D; VEGFR-1,2) with efficacy in the LM+ versus LM− subgroups, the biomarkers were dichotomized at the observed median concentration. Data were separated into high and low groups and treated as binary variables. The Intertek population consisted of all patients in the ITT population with ≥1 Intertek biomarker value across all visits [17]. The predictive effect of each biomarker on OS/PFS was determined using the Cox univariate model of LM stratified by randomization factors (geographic region, disease measurability, and time to disease progression after beginning first-line treatment). The effect of treatment on OS and PFS was analyzed using Cox regression in patients with or without LM. The HR, its 2-sided 95% confidence limits, and P-value of testing the interaction of treatment and biomarkers were reported accordingly.

As the analyses were exploratory and post hoc, P-values were descriptive and not inferential.

RESULTS

A total of 665 randomized patients (LM+: 288, LM−: 377) from the phase 3 RAINBOW study were included in the analysis. The patient demographics and baseline characteristics are presented in **Table 1**. Irrespective of the treatment arm, patients with LM were more

https://doi.org/10.5230/jgc.2023.23.e15

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commonly male and had measurable disease, intestinal subtype, and ≥3 metastatic sites (**Table 1**). Conversely, patients without LM had a higher incidence of ascites, non-measurable disease, diffuse subtype, and 0–2 metastatic sites.

The presence of LM was not a prognostic factor for OS (HR, 1.13; 95% confidence interval [CI], 0.95–1.35; P=0.1575), as shown in **Table 2**. However, the presence of LM for PFS was determined to be prognostically negative as the HR value was significantly greater than 1 (HR, 1.36; 95% CI, 1.15–1.61; P=0.0003) at a nominal level of 5% in the ITT population. This was mainly driven by patients receiving PL+PAC (HR, 1.68; 95% CI, 1.30–2.17; P=0.0001).

Table 1. Patient baseline demographics and disease characteristics

Characteristic	LM+		LM−	
	RAM+PAC (n=150)	PL+PAC (n=138)	RAM+PAC (n=180)	PL+PAC (n=197)
Mean age (yr)	62	61	59	59
Male	121 (80.7)	109 (79.0)	108 (60.0)	134 (68.0)
ECOG PS				
0	56 (37.3)	53 (38.4)	61 (33.9)	91 (46.2)
1	94 (62.7)	85 (61.6)	119 (66.1)	106 (53.8)
Weight loss in the previous 3 months				
≥10%	27 (18.0)	20 (14.5)	26 (14.4)	27 (13.7)
<10%	123 (82.0)	118 (85.5)	154 (85.6)	168 (85.3)
Race				
Asian	41 (27.3)	41 (29.7)	69 (38.3)	80 (40.6)
White	105 (70.0)	93 (67.4)	103 (57.2)	106 (53.8)
Other*	4 (2.6)	4 (2.8)	8 (4.4)	11 (5.5)
Primary tumor location				
Gastric	113 (75.3)	100 (72.5)	151 (83.9)	164 (83.2)
Presence of ascites	39 (26.0)	21 (15.2)	91 (50.6)	86 (43.7)
Extent of disease				
Locally advanced	0 (0.0)	0 (0.0)	6 (3.3)	10 (5.1)
Metastatic	150 (100.0)	138 (100.0)	174 (96.7)	186 (94.4)
Measurability				
Measurable	144 (96.0)	136 (98.6)	112 (62.2)	129 (65.5)
Non-measurable	6 (4.0)	2 (1.4)	68 (37.8)	67 (34.0)
Histological subtype				
Intestinal	81 (54.0)	74 (53.6)	64 (35.6)	61 (31.0)
Diffuse	28 (18.7)	37 (26.8)	87 (48.3)	96 (48.7)
Mixed	12 (8.0)	6 (4.3)	9 (5.0)	8 (4.1)
Unknown	29 (19.3)	21 (15.2)	20 (11.1)	32 (16.2)
Primary tumor present	89 (59.3)	90 (65.2)	120 (66.7)	119 (60.4)
Number of metastatic sites				
0–2	76 (50.7)	72 (52.2)	133 (73.9)	160 (81.2)
≥3	74 (49.3)	66 (47.8)	47 (26.1)	37 (18.8)
Prior treatment lines				
First-line	150 (100.0)	138 (100.0)	179 (99.4)	197 (100.0)
Second-line	3 (2.0)	1 (0.7)	2 (1.1)	1 (0.5)
Adjuvant	16 (10.7)	9 (6.5)	15 (8.3)	23 (11.7)
Neoadjuvant	8 (5.3)	5 (3.6)	16 (8.9)	10 (5.1)
Any prior anti-cancer therapy				
chemotherapy	150 (100.0)	138 (100.0)	180 (100.0)	197 (100.0)
targeted antibody	17 (11.3)	15 (10.9)	13 (7.2)	10 (5.1)
Prior surgery				
Yes	61 (40.7)	49 (35.5)	72 (40.0)	77 (39.1)
No	89 (59.3)	89 (64.5)	108 (60.0)	120 (60.9)

Values are presented as number of participants (%).
ECOG PS = Eastern Cooperative Oncology Group Performance Score; LM+/− = with/without liver metastasis; PAC = paclitaxel; PL = placebo; RAM = ramucirumab.
*Other include Black, American Indian, Alaska Native, and others.

https://doi.org/10.5230/jgc.2023.23.e15

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Table 2. Cox univariate model of LM (yes vs. no) stratified by randomization factors or treatment arm (RAM+PAC or PL+PAC and total column)

Variables	LM (yes vs. no)		Total (n=665)
	RAM+PAC (n=288)	PL+PAC (n=377)	
OS			
HR (95% CI)	1.17 (0.88–1.54)	1.15 (0.88–1.49)	1.13 (0.95–1.35)
P-value	0.2771	0.3135	0.1575
PFS			
HR (95% CI)	1.16 (0.89–1.51)	1.68 (1.30–2.17)	1.36 (1.15–1.61)
P-value	0.2583	0.0001	0.0003

The model includes randomization stratification factors, and results by treatment arm and total column. Total refers to the intent-to-treat population (n=665).
LM = liver metastasis; RAM = ramucirumab; PAC = paclitaxel; PL = placebo; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.

A survival benefit favoring RAM+PAC was observed, irrespective of LM status (**Fig. 1**). The median OS (mOS) among patients treated with RAM+PAC was 9.6 months regardless of the presence of LM, but a greater treatment benefit was observed in patients with LM (HR, 0.71; 95% CI, 0.54–0.93) than in those without LM (HR, 0.88; 95% CI, 0.69–1.11). Similarly, patients treated with RAM+PAC experienced improved median PFS (mPFS) irrespective of LM status, with more treatment benefits observed in patients with LM (HR, 0.47; 95% CI, 0.36–0.60) than in those without (HR, 0.76; 95% CI, 0.61–0.96). The interaction P-value obtained for OS was not significant (P=0.3622), whereas a significant interaction P-value (P=0.0061) was obtained for PFS. Better ORR was observed in patients with LM treated with RAM+PAC than those without LM (38% vs. 19%); however, similar disease control rates were obtained (79% vs. 81%), as shown in **Table 3**.

Regarding safety, the occurrence of adverse events was well-balanced between the patients with and without LM. However, patients with LM experienced lower incidences of proteinuria of any grade than those without LM, irrespective of treatment arm (RAM+PAC: 11% vs. 22%; PL+PAC: 3% vs. 8%) (**Table 4**). Patients with LM treated with RAM+PAC experienced a lower incidence of vomiting than those without LM (22% vs. 31%) (**Table 5**). Regarding liver injury and failure, the incidence of adverse events reported among patients with (any grade: 16%; grade ≥3:4%) and without LM (any grade: 17%; grade ≥3:5%) was similar in the RAM+PAC treatment arm (**Supplementary Table 1**). A similar trend was observed in the PL+PAC treatment arms with (any grade: 16%; grade ≥3:5%) and without LM (any grade: 10%; grade ≥3:3%).

The mean and median biomarker levels in patients with and without LM are shown in **Supplementary Table 2**. The median levels were used as cut-off points for Cox regression analyses. Similar mOS in months was obtained for patients with and without LM treated with RAM+PAC for high levels of VEGF-C (9.7 vs. 10.0; **Supplementary Table 3**), VEGF-D (11.4 vs. 11.4; **Supplementary Table 4**), and VEGFR-1 (9.2 vs. 9.6; **Supplementary Table 5**). The mPFS was similar among patients with and without LM across all biomarkers, as shown in **Supplementary Tables 3-6**.

Baseline Intertek assay results were analyzed for a predictive relationship between biomarker levels (VEGF-C, D; VEGFR-1,2) and efficacy outcome (OS, PFS) using interaction models in the LM+ versus LM− subgroups. The OS and PFS HR values obtained for patients with LM were similar to or lower than those without LM across all biomarkers and expression levels, as shown in **Table 6**. However, no significant interaction indicative of a predictive relationship was found (all P-values >0.05).

https://doi.org/10.5230/jgc.2023.23.e15

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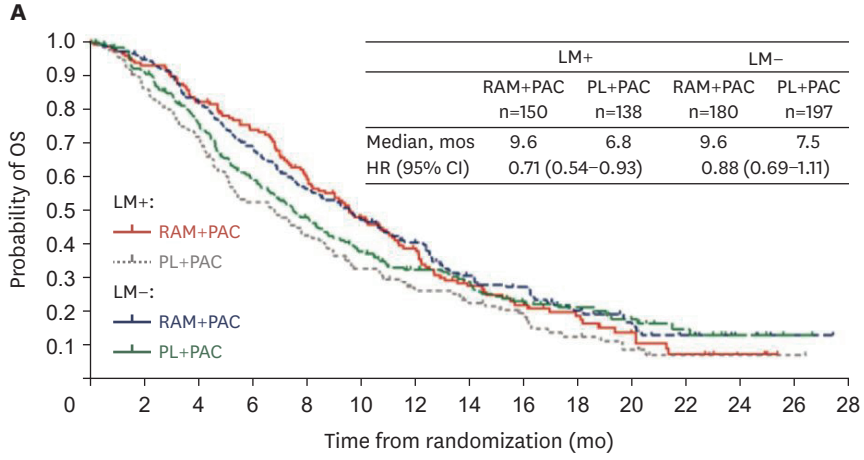
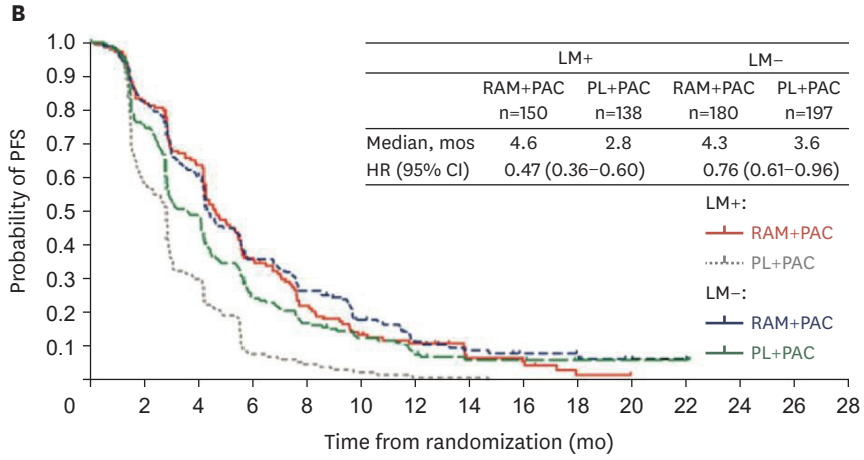


	LM+		LM−	
	RAM+PAC n=150	PL+PAC n=138	RAM+PAC n=180	PL+PAC n=197
Median, mos	9.6	6.8	9.6	7.5
HR (95% CI)	0.71 (0.54–0.93)		0.88 (0.69–1.11)	

At risk															
LM+: RAM+PAC	150	138	122	107	86	66	50	33	23	17	10	5	3	0	0
PL+PAC	138	117	98	70	57	42	30	24	17	11	7	4	2	1	0
LM−: RAM+PAC	180	170	145	121	99	82	66	45	37	24	14	8	3	1	0
PL+PAC	197	177	143	110	86	67	51	40	28	19	15	9	3	1	0

OS treatment-by-subgroup interaction by P-value*	0.3622



	LM+		LM−	
	RAM+PAC n=150	PL+PAC n=138	RAM+PAC n=180	PL+PAC n=197
Median, mos	4.6	2.8	4.3	3.6
HR (95% CI)	0.47 (0.36–0.60)		0.76 (0.61–0.96)	

At risk														
LM+: RAM+PAC	150	117	88	47	28	17	13	6	5	1	1	0	0	
PL+PAC	138	77	39	10	6	3	1	1	0	0	0	0	0	
LM−: RAM+PAC	180	142	100	57	42	26	15	9	6	6	2	1	0	
PL+PAC	197	137	85	40	28	18	11	7	5	3	3	3	0	

PFS treatment-by-subgroup interaction by P-value*	0.0061

Fig. 1. KM plots of (A) OS and (B) PFS by LM status for RAM+PAC vs. PL+PAC.
KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival; LM = liver metastasis; RAM = ramucirumab; PAC = paclitaxel; PL = placebo; LM+/− = with/without liver metastasis; HR = hazard ratio; CI = confidence interval.
*Wald test of treatment-by-subgroup interaction from stratified Cox model, stratified by study randomization factors: geographic region, time to progression on first-line therapy, and disease measurability.

DISCUSSION

RAM+PAC is the standard of care in second-line settings worldwide; however, the second-line transition rate for patients with mGEA remains very low in most countries, except Japan.

https://doi.org/10.5230/jgc.2023.23.e15

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Table 3. Tumor response of patients with and without LM treated with RAM+PAC versus PL+PAC*

Variables	LM+		LM−	
	RAM+PAC (n=150)	PL+PAC (n=138)	RAM+PAC (n=180)	PL+PAC (n=197)
CR	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.5)
PR	56 (37.3)	33 (23.9)	34 (18.9)	20 (10.2)
SD	62 (41.3)	44 (31.9)	110 (61.1)	115 (58.4)
PD	16 (10.7)	45 (32.6)	27 (15.0)	38 (19.3)
Non-evaluable	15 (10.0)	16 (11.6)	8 (4.4)	23 (11.7)
ORR (CR/PR)	57 (38.0)	33 (23.9)	35 (19.4)	21 (10.7)
DCR (CR/PR/SD)	119 (79.3)	77 (55.8)	145 (80.6)	136 (69.0)

Values are presented as number of participants (%). Total refers to the intent-to-treat population (n=665).
LM = liver metastasis; RAM = ramucirumab; PAC = paclitaxel; PL = placebo; LM+/− = with/without liver metastasis; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = overall response rate; DCR = disease control rate.

Table 4. Occurrence of adverse events of special interest by the presence of LM

AE of special interest	LM+				LM−			
	RAM+PAC (n=147)		PL+PAC (n=136)		RAM+PAC (n=180)		PL+PAC (n=193)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Bleeding/hemorrhage events	66 (44.9)	10 (6.8)	17 (12.5)	3 (2.2)	71 (39.4)	4 (2.2)	42 (21.8)	5 (2.6)
Hypertension	39 (26.5)	27 (18.4)	8 (5.9)	3 (2.2)	43 (23.9)	21 (11.7)	11 (5.7)	6 (3.1)
Liver injury/failure	23 (15.6)	6 (4.1)	22 (16.2)	7 (5.1)	31 (17.2)	9 (5.0)	19 (9.8)	6 (3.1)
GI hemorrhage events	19 (12.9)	8 (5.4)	4 (2.9)	3 (2.2)	14 (7.8)	4 (2.2)	16 (8.3)	2 (1.0)
Arterial thromboembolic events	3 (2.0)	2 (1.4)	2 (1.5)	2 (1.5)	3 (1.7)	1 (0.6)	3 (1.6)	1 (0.5)
Proteinuria	16 (10.9)	2 (1.4)	4 (2.9)	0 (0.0)	39 (21.7)	2 (1.1)	16 (8.3)	0 (0.0)
Renal failure	7 (4.8)	3 (2.0)	4 (2.9)	2 (1.5)	15 (8.3)	3 (1.7)	10 (5.2)	1 (0.5)
Infusion related reaction	6 (4.1)	1 (0.7)	5 (3.7)	0 (0.0)	13 (7.2)	1 (0.6)	7 (3.6)	0 (0.0)
Venous thromboembolic events	6 (4.1)	3 (2.0)	9 (6.6)	4 (2.9)	7 (3.9)	5 (2.8)	9 (4.7)	7 (3.6)
Congestive heart failure	4 (2.7)	1 (0.7)	2 (1.5)	2 (1.5)	4 (2.2)	1 (0.6)	2 (1.0)	0 (0.0)
Gastrointestinal perforation	2 (1.4)	2 (1.4)	1 (0.7)	0 (0.0)	2 (1.1)	2 (1.1)	0 (0.0)	0 (0.0)

Values are presented as number of participants (%).
LM = liver metastasis; LM+/− = with/without liver metastasis; RAM = ramucirumab; PAC = paclitaxel; PL = placebo; AE = adverse event; GI = gastrointestinal.

This is illustrated through the level of subsequent therapies in several recent global phase 3 trials, including the RAINFALL (48%), KEYNOTE-062 (47%), and CheckMate-649 trials (38%) [18]. As 50% of patients who progress after first-line therapy are candidates for further treatment, the data presented in this study suggest that while RAM+PAC cannot be used as a second-line treatment option for all patients, it should be considered for those with LM [19]. In Japan, conversion surgery—resection in initially unresectable patients after response to chemotherapy—is used to treat eligible late-stage patients with mGEA [20]. The data presented in this study show a higher ORR in the LM+ group (38%) than that in the LM− group (19%). The active use of RAM+PAC may provide new opportunities for improved treatment outcomes in patients with LM, as they are potential candidates for conversion surgery [21].

This post -hoc analysis aimed to report the efficacy, safety, and biomarker outcomes of RAM+PAC treatment in patients with and without LM at baseline. Due to several factors, including the small sample size, the prognostic association of LM with OS in this study is inconsistent with previously published data. The literature shows that the presence of LM is associated with poor survival in patients with mGEA [4,22] owing to the impairment of vital organ function and increasing tumor burden to lethal levels [3,23]. This leads to lower 1-year (LM+ vs. LM−, 12.5% vs. 43.3%) and 2-year (LM+ vs. LM−, 5.6% vs. 43.3%) survival rates [24]. In addition, a lower 5-year median OS has been reported compared with that in patients without LM (LM+ vs. LM−, 6.5% vs. 17.5%). The prognostic significance of LM has been evaluated in several reports [22,24-27]. Among patients with mGEA who underwent chemotherapy, the presence of LM was determined to be a negative prognostic factor for

https://doi.org/10.5230/jgc.2023.23.e15

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Table 5. Occurrence of treatment-emergent AEs (>10%) by the presence of LM

AE	LM+				LM−			
	RAM+PAC (n=147)		PL+PAC (n=136)		RAM+PAC (n=180)		PL+PAC (n=193)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grage ≥3	Any grade	Grade ≥3
Neutropenia	81 (55.1)	65 (44.2)	38 (27.9)	27 (19.9)	97 (53.9)	68 (37.8)	64 (33.2)	35 (18.1)
Anemia	48 (32.7)	11 (7.5)	49 (36.0)	10 (7.4)	63 (35.0)	19 (10.6)	68 (35.2)	24 (12.4)
Leukopenia	44 (29.9)	25 (17.0)	27 (19.9)	10 (7.4)	67 (37.2)	32 (17.8)	42 (21.8)	12 (6.2)
Thrombocytopenia	18 (12.2)	3 (2.0)	9 (6.6)	3 (2.2)	25 (13.9)	2 (1.1)	11 (5.7)	3 (1.6)
Decreased appetite	58 (39.5)	3 (2.0)	36 (26.5)	2 (1.5)	73 (40.6)	7 (3.9)	69 (35.8)	11 (5.7)
Fatigue	55 (37.4)	11 (7.5)	37 (27.2)	6 (4.4)	75 (41.7)	12 (6.7)	69 (35.8)	7 (3.6)
Nausea	46 (31.3)	3 (2.0)	38 (27.9)	2 (1.5)	69 (38.3)	3 (1.7)	70 (36.3)	6 (3.1)
Epistaxis	44 (29.9)	0 (0.0)	7 (5.1)	0 (0.0)	56 (31.1)	0 (0.0)	16 (8.3)	0 (0.0)
Alopecia	41 (27.9)	0 (0.0)	45 (33.1)	0 (0.0)	66 (36.7)	0 (0.0)	82 (42.5)	1 (0.5)
Diarrhea	40 (27.2)	5 (3.4)	28 (20.6)	3 (2.2)	66 (36.7)	7 (3.9)	48 (24.9)	2 (1.0)
Edema peripheral	40 (27.2)	1 (0.7)	18 (13.2)	1 (0.7)	42 (23.3)	4 (2.2)	27 (14.0)	1 (0.5)
Abdominal pain	39 (26.5)	5 (3.4)	26 (19.1)	5 (3.7)	62 (34.4)	13 (7.2)	41 (21.2)	6 (3.1)
Hypertension	37 (25.2)	25 (17.0)	6 (4.4)	3 (2.2)	41 (22.8)	21 (11.7)	10 (5.2)	5 (2.6)
Constipation	36 (24.5)	0 (0.0)	27 (19.9)	1 (0.7)	34 (18.9)	0 (0.0)	44 (22.8)	1 (0.5)
Asthenia	35 (23.8)	12 (8.2)	18 (13.2)	4 (2.9)	34 (18.9)	6 (3.3)	27 (14.0)	2 (1.0)
Vomiting	32 (21.8)	3 (2.0)	23 (16.9)	1 (0.7)	56 (31.1)	7 (3.9)	45 (23.3)	11 (5.7)
Peripheral sensory neuropathy	30 (20.4)	3 (2.0)	10 (7.4)	1 (0.7)	27 (15.0)	3 (1.7)	26 (13.5)	2 (1.0)
Pyrexia	27 (18.4)	2 (1.4)	19 (14.0)	1 (0.7)	32 (17.8)	1 (0.6)	18 (9.3)	0 (0.0)
Stomatitis	25 (17.0)	0 (0.0)	5 (3.7)	1 (0.7)	39 (21.7)	2 (1.1)	19 (9.8)	1 (0.5)
Cough	23 (15.6)	0 (0.0)	11 (8.1)	0 (0.0)	17 (9.4)	0 (0.0)	14 (7.3)	0 (0.0)
Dyspnea	21 (14.3)	5 (3.4)	16 (11.8)	2 (1.5)	21 (11.7)	3 (1.7)	15 (7.8)	0 (0.0)
Neuropathy peripheral	19 (12.9)	5 (3.4)	11 (8.1)	1 (0.7)	28 (15.6)	5 (2.8)	19 (9.8)	6 (3.1)
Weight decreased	18 (12.2)	1 (0.7)	15 (11.0)	0 (0.0)	27 (15.0)	5 (2.8)	34 (17.6)	4 (2.1)
Headache	18 (12.2)	0 (0.0)	1 (0.7)	0 (0.0)	14 (7.8)	0 (0.0)	21 (10.9)	1 (0.5)
Rash	16 (10.9)	0 (0.0)	10 (7.4)	0 (0.0)	19 (10.6)	0 (0.0)	16 (8.3)	0 (0.0)
Proteinuria	16 (10.9)	2 (1.4)	4 (2.9)	0 (0.0)	39 (21.7)	2 (1.1)	16 (8.3)	0 (0.0)
Malignant neoplasm progression	19 (12.9)	18 (12.2)	23 (16.9)	23 (16.9)	33 (18.3)	29 (16.1)	37 (19.2)	36 (18.7)

Values are presented as number of participants (%).
LM = liver metastasis; LM+/− = with/without liver metastasis; RAM = ramucirumab; PAC = paclitaxel; PL = placebo; AE = adverse event.

Table 6. Biomarker treatment effect (RAM+PAC vs. PL+PAC) for OS and PFS using Cox regression within patients with or without LM

Biomarker	OS				PFS			
	LM+	Interaction	LM−	Interaction	LM+	Interaction	LM−	Interaction
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
VEGF-C		0.5144		0.3736		0.6090		0.5290
High	0.63 (0.39–1.03)		0.83 (0.54–1.29)		0.39 (0.23–0.64)		0.77 (0.51–1.16)	
Low	0.80 (0.48–1.34)		1.11 (0.71–1.76)		0.46 (0.28–0.75)		0.63 (0.42–0.97)	
VEGF-D		0.4333		0.6565		0.7568		0.5857
High	0.60 (0.35–1.05)		1.05 (0.60–1.85)		0.40 (0.23–0.69)		0.79 (0.46–1.35)	
Low	0.80 (0.51–1.27)		0.90 (0.63–1.30)		0.44 (0.28–0.70)		0.66 (0.47–0.93)	
VEGFR-1		0.2526		0.5502		0.6563		0.2387
High	0.57 (0.34–0.95)		1.04 (0.69–1.57)		0.39 (0.23–0.65)		0.81 (0.54–1.22)	
Low	0.87 (0.52–1.47)		0.86 (0.54–1.35)		0.46 (0.28–0.76)		0.57 (0.38–0.87)	
VEGFR-2		0.2995		0.6982		0.4671		0.6200
High	0.58 (0.35–0.97)		0.87 (0.57–1.34)		0.36 (0.22–0.60)		0.62 (0.42–0.92)	
Low	0.85 (0.51–1.40)		0.98 (0.64–1.51)		0.47 (0.28–0.77)		0.72 (0.48–1.08)	

Thresholds: For LM+: VEGF-C (cut-off point=352.70 pg/mL), VEGF-D (cut-off point=590.49 pg/mL), VEGFR-1 (cut-off point=130.40 pg/mL), VEGFR-2 (cut-off point=11,925.00 pg/mL); For LM−: VEGF-C (cut-off point=364.25 pg/mL), VEGF-D (cut-off point=590.49 pg/mL), VEGFR-1 (cut-off point=113.70 pg/mL), VEGFR-2 (cut-off point=11,480.00 pg/mL).
RAM = ramucirumab; PAC = paclitaxel; PL = placebo; OS = overall survival; PFS = progression-free survival; LM = liver metastasis; LM+/− = with/without liver metastasis; HR = hazard ratio; CI = confidence interval; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

survival [22,25,26]. The presence of LM is an independent poor prognostic factor even after hepatic resection [28]. In a multicenter study involving 200 patients treated with third-line nivolumab, the presence of LM was prognostic for PFS in both univariate (HR, 1.55; 95% CI, 1.12–2.14; P=0.008) and multivariate (HR, 2.01; 95% CI, 1.40–2.89; P<0.001) analyses. Similarly, Tokumaru et al. [29] observed significantly worse PFS rates among patients with

https://doi.org/10.5230/jgc.2023.23.e15

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LM treated with nivolumab than among other patients (1-year PFS: 0.0 vs. 24.4%, respectively; P=0.005). The results obtained in our study are inconsistent with published data for OS, and our data showed that the presence of LM was not prognostic for OS (HR, 1.13; 95% CI, 0.95–1.35; P=0.1575), but it was for PFS (HR, 1.36; 95% CI, 1.15–1.61; P=0.0003). These results suggest a different and stronger effect of LM on PFS than on OS. Patients with LM were estimated to have a 36% greater risk of disease progression or death overall than those without LM (total HR, 1.36), and this observation was statistically significant (P=0.0003). More importantly, this observation appears to have been driven mostly by the effect of LM within the PL group, where LM+ was observed to have a 68% increased risk of disease progression or death (HR, 1.68; P=0.0001). The PFS results suggested that RAM+PAC may lower the risk of disease progression or death in patients with LM. VEGF has previously been associated with the development and growth of LM [8,30]. Additionally, an in vivo mouse model with LM treated with anti-angiogenesis agents, including VEGFR tyrosine kinase inhibitors or DC101 (VEGFR-2 antibody), demonstrated lower liver weights (a gross measure of hepatic tumor burden), inhibited tumor growth and vascularity, and induced endothelial cell apoptosis [31,32]. A similar phenomenon has been reported in clinical trials of RAM [33-35].

The patient demographics and disease characteristics reported in this study are consistent with other reports, as the following factors were more prevalent among patients with LM: intestinal type, higher number of metastatic sites, non-Asian sex, and male [1-3]. The LM+ vs. LM− groups varied significantly along with other clinical features, including ascites rate, histology, and sex. Additionally, the LM+ group was enriched for white patients, which likely reflects the intestinal type and more proximal cancers.

A retrospective analysis involving 1,355 patients with mGEA who received treatment at the Aichi Cancer Center Hospital from 2005 to 2019 showed a remarkable improvement (from 14.3 to 19.3 months) among those with LM after the approval of RAM and nivolumab (from 2015 to 2019) [15]. This improvement was statistically significant in the multivariate analyses (HR, 0.45; 95% CI, 0.31–0.65; P<0.001). An improved benefit was also observed within the phase 3 RAINBOW-Asia LM subgroup analysis, as patients with LM tended to receive more benefit from RAM+PAC treatment than those without LM [16]. Similar results were observed in our analyses as improvements in mOS and mPFS were observed among patients treated with RAM+PAC irrespective of LM status, with greater benefit observed in those with OS LM (HR, 0.71; 95% CI, 0.54–0.93) than those without LM (HR, 0.88; 95% CI, 0.69–1.11) and mPFS LM (HR, 0.47; 95% CI, 0.36–0.60) than those without LM (HR, 0.76; 95% CI, 0.61–0.96). Regarding safety, the occurrence of adverse events was well-balanced between patients with and without LM, with lower incidences of vomiting and proteinuria reported for patients with LM.

There were no major differences regarding liver injuries between patients with (any grade: 16%; grade ≥3:4%) and without LM (any grade: 17%; grade ≥3:5%) treated with RAM+PAC. These results showed that treatment with RAM+PAC did not increase the risk of liver injury in patients with or without LM.

VEGF expression in cancer cells can serve as a pertinent prognostic indicator in both early and mGEA and has been identified as a risk factor for LM [8-10]. In a pre-clinical study, Yang et al. [36] showed that discontinuation of anti-VEGF cancer therapy can promote LM; however, the results within the human population remain to be seen. The prognostic [37-39] and predictive [40,41] values of VEGF ligand and subtype expression have been demonstrated in several studies involving patients with mGEA. In particular, VEGF-C expression is strongly

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correlated with poor prognosis [39,42], with 5-year survival rates of 48% for patients expressing VEGF-C versus 66% for those without VEGF-C expression; however, in this study, the difference was not statistically significant [39]. Similarly, in multivariate analysis, the expression of VEGFR-1 and -2 in stromal vessels was an independent predictor of poor outcomes among patients with GEA [40].

Although several studies have investigated the plasma biomarkers of anti-VEGF antibodies, there are few reproducible results. In colorectal cancer, VEGF-D could be a predictive biomarker of RAM, according to a sub-analysis of the RAISE trial [43]. In the RAINBOW study, no predictive markers for RAM in gastric cancer were identified. In the present study, we searched for plasma biomarkers separately for the presence or absence of LM.

As these studies were not powered for LM subgroup analyses, the prognostic effects of VEGF-C/D and VEGFR-1/2 biomarkers among patients with and without LM were investigated in our analyses. Similar mOS and mPFS were observed for patients irrespective of LM status; however, the biomarker data were limited, and there was insufficient evidence for a predictive relationship between any marker and treatment effect (all P-values >0.05).

In this exploratory analysis, the presence of LM may be a negative prognostic factor for PFS, especially in patients treated with PL+PAC, and a positive interaction was observed between the presence of LM and RAM treatment (P=0.0061). Irrespective of the presence of LM, RAM provided a significant benefit, with a numerically stronger effect observed in patients with LM. No new safety signals were observed. These results indicate that RAM+PAC is a viable therapeutic option for patients with mGEA and LM as well as for those without LM.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Louise McGrath and Elaine Jennings employees of Eli Lilly and Company for providing editorial and process support, and Dana Schamberger of Syneos Health for providing editorial support.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Summary of liver failure/injury AEs

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Supplementary Table 2
Biomarker level in patients with or without LM

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Supplementary Table 3
Cox regression for OS and PFS for high or low expression of VEGF-C

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Supplementary Table 4
Cox regression for OS and PFS for high or low expression of VEGF-D

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Supplementary Table 5
Cox regression for OS and PFS for high or low expression of VEGFR-1

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Supplementary Table 6
Cox regression for OS and PFS for high or low expression of VEGFR-2

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Supplementary Fig. 1
CONSORT diagram

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Supplementary Fig. 2
RAINBOW clinical trial design. Dosing schedules for every 4-week cycle: RAM and PL = Days 1 and 15; PAC = Days 1, 8, and 15.

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