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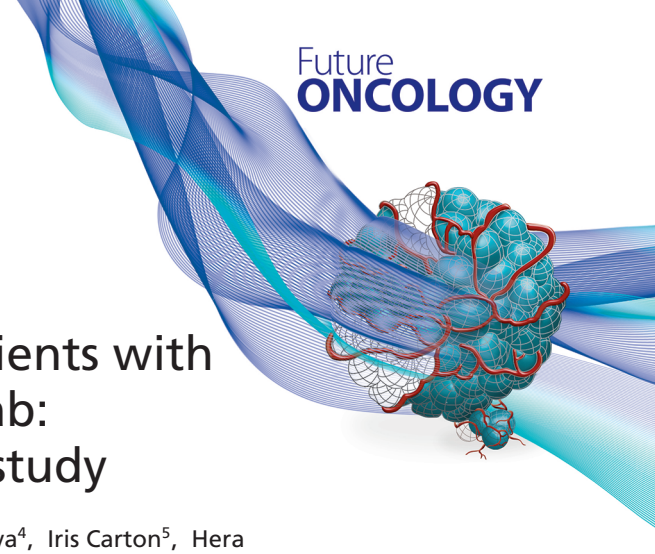

Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study

Ferdinando De Vita*[,1], Christophe Borg[2], Gabriella Farina[3], Ravit Geva[4], Iris Carton[5], Hera Cuku[6], Ran Wei[7] & Kei Muro[8]

[1]Division of Medical Oncology, Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Naples, 80138, Italy
[2]Department of Medical Oncology, University Hospital of Besançon, Besançon, 25000, France
[3]Department of Medical Oncology, Fatebenefratelli Sacco Hospital, Milan, 20121, Italy
[4]Oncology Division, Tel Aviv University, Tel Aviv, 6997801, Israel
[5]Eli Lilly & Company, Brussels, 1000, Belgium
[6]Eli Lilly & Company, Florence, 50019, Italy
[7]Eli Lilly & Company, Indianapolis, IN 46285, USA
[8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, 464-8681, Japan
*Author for correspondence: ferdinando.devita@unicampania.it

Aim: This subgroup analysis of the RAINBOW study evaluated the efficacy and safety of ramucirumab in patients with gastric cancer/gastroesophageal junction adenocarcinoma who received prior trastuzumab therapy. **Patients & methods:** Of adult patients enrolled in the RAINBOW study, 39 had received prior trastuzumab therapy. Of these, 20 patients were treated with ramucirumab plus paclitaxel and 19 patients with placebo plus paclitaxel within the RAINBOW trial. **Results:** Overall survival was longer with ramucirumab plus paclitaxel (11.4 months; 95% CI: 7.0–17.9) versus placebo plus paclitaxel (7.0 months; 95% CI: 3.4–14.6), hazard ratio: 0.68 (0.33–1.41); p = 0.30. Longer progression-free survival, higher objective response were observed in ramucirumab combination group. **Conclusion:** Ramucirumab plus paclitaxel demonstrated efficacy benefits with manageable safety profile in a subgroup of patients pretreated with trastuzumab.

Clinical trial registration number: NCT01170663.

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Keywords: gastric cancer • HER-2 inhibitor • prior trastuzumab • ramucirumab plus paclitaxel • targeted therapy • VEGFR-2 inhibitor

Gastric cancer is the fifth most common malignancy in the world with 1 million cases diagnosed in 2018 per GLOBOCAN estimates. It is also the third leading cause of cancer mortality in both sexes across the globe [1]. Surgical resection of the tumor is potentially curative at early stages; however, 50–80% of patients still relapse following resection. The majority of patients with gastric cancer are diagnosed at an advanced stage or develop recurrence after surgery, and combined therapies are the standard of care for stage 1B or higher gastric cancer [2,3]. Irrespective of recent advances in diagnosis, surgical techniques and new therapies, the overall clinical outcome in patients with advanced gastric cancer is poor [4]. Survival rates depend on the extent of disease. The 5-year survival rate is 31%, reflecting the fact that most patients are being diagnosed after the cancer has already spread to other body parts.

As per the National Comprehensive Cancer Network, European Society for Medical Oncology, and Pan-Asian European Society for Medical Oncology guidelines, established first-line treatments for advanced gastric cancer are platinum- and fluoropyrimidine-based combinations [2,5–7]. These guidelines also stated that ramucirumab plus paclitaxel is the preferred second-line treatment option for patients with metastatic gastric cancer, who failed first-line treatment with platinum- and fluoropyrimidine-based combinations or trastuzumab in combination with cisplatin and 5-fluorouracil/cisplatin and capecitabine [2,6,7].

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Trastuzumab and ramucirumab are the only globally approved targeted therapies, targeting HER-2 and VEGFR-2, respectively.

Trastuzumab is approved first-line treatment for patients with advanced gastric/gastroesophageal junction (GEJ) adenocarcinoma with HER-2 overexpression. However, many patients progress with this therapy [8]. A prospective, randomized study failed to show the clinical benefits of further trastuzumab treatment in patients with advanced gastric/GEJ, who progressed during first-line trastuzumab containing therapy [9].

Ramucirumab is a human IgG1 monoclonal antibody receptor antagonist designed to bind to the extracellular domain of VEGFR-2, thereby blocking the binding of multiple VEGF ligands and inhibiting receptor activation [10]. Ramucirumab is approved by the US FDA, the European Medical Association, and regulatory authorities from other counties for the treatment of advanced gastric or GEJ adenocarcinoma in patients who have progressed to a first-line chemotherapy [11].

RAINBOW trial reported that ramucirumab is the only biological treatment given in combination with paclitaxel that has shown clinical benefits over chemotherapy alone in patients with advanced gastric cancer, who have progressed after first-line chemotherapy [10]. In REGARD trial, ramucirumab has also shown efficacy as a monotherapy in patients with advanced or GEJ adenocarcinoma [12]. A retrospective study reported significantly longer durations of disease control than expected in patients with HER-2 positive GEJ adenocarcinoma, who progressed on trastuzumab-based combination therapy and subsequently received combination therapy with ramucirumab and paclitaxel. Overall, 50% (five of ten) of the patients had stable disease and one patient achieved complete response, and the median duration of disease control was 8 months with ramucirumab-based therapy [13]. The results of this retrospective study are suggestive of a crosstalk between HER-2 signaling and angiogenesis. Indeed, published data based on breast cancer showed a relationship between HER-2 overexpression and VEGF upregulation. Even if those data are not available for gastric cancer, HER-2 overexpression through VEGF upregulation might support angiogenesis and tumor growth [13,14]. Moreover, the VEGF pathway highlighting the role of antiangiogenic therapy, might mediate resistance to anti-HER-2 therapies [14].

The objective of this study was to evaluate the efficacy and safety of ramucirumab plus paclitaxel in a subgroup of patients with gastric cancer/GEJ adenocarcinoma from the RAINBOW trial who received prior trastuzumab therapy.

Patients & methods

Study design

RAINBOW was a randomized, multicenter, double-blind, placebo-controlled, Phase III study [10]. Patients aged 18 years or above with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma were included. Other eligibility criteria were documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line therapy; an Eastern Cooperative Oncology Group performance status score of 0 or 1; and measureable or nonmeasurable evaluable disease (defined with Response Evaluation Criteria In Solid Tumors, version 1.1). Excluded patients had squamous or undifferentiated gastric cancer; had undergone major surgery within 28 days prior to randomization; had gastrointestinal perforation, fistulae or any arterial thromboembolic event within 6 months prior to randomization; had a history of deep vein thrombosis, pulmonary embolism or any other significant thromboembolism; and had poorly controlled hypertension.

Treatment

Patients were randomized in a 1:1 ratio to receive ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab (8 mg/kg) was administered as an intravenous infusion on days 1 and 15, or in combination with paclitaxel (80 mg/m^2) administered on days 1, 8 and 15 of a 28-day cycle. Patients received study treatment until disease progression, unacceptable adverse events (AEs) or withdrawal of consent. Crossover was not allowed between treatment groups.

Outcomes

This subgroup analysis included patients with gastric cancer/GEJ adenocarcinoma who had received first-line therapy with trastuzumab. The efficacy end points were progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and disease control rate (DCR). The PFS is defined as the time from randomization to progressive disease or death, whichever happens first. OS is defined as the time from randomization to death. Patients who were lost to follow-up or discontinued the study were censored. The ORR is defined as the proportion

of patients who had a best response of complete response or partial response; DCR is defined as the proportion of patients who had a best response of complete response, partial response or stable disease.

Assessments

Tumor assessments were done at baseline and every 6 weeks thereafter until disease progression. The Kaplan–Meier method was used to generate time-to-event curves for PFS and OS. Median PFS and OS, and the associated 95% CI were estimated using the Kaplan–Meier method. Hazard ratio (HR) of the treatment effect was estimated using unstratified Cox PH model, while the p-value was calculated by unstratified log-rank test. A two-sided Cochran–Mantel–Haenszel test was used to compare ORR and DCR (adjusted for randomization strata; geographical region, disease measurability, time to progression as per IVRS/IWRS). AEs were recorded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE; version 4.02). Treatment-emergent AEs reported in ≥20% of patients were summarized using preferred term.

Ethics

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.

Results

Efficacy and safety results of the RAINBOW study have been published previously [10]. The RAINBOW study enrolled 665 patients who were randomized to ramucirumab plus paclitaxel (n = 330) or placebo plus paclitaxel (n = 335) [10]. Of these, 39 patients had received prior trastuzumab therapy; 20 were placed in the ramucirumab plus paclitaxel group and 19 in the placebo plus paclitaxel group.

In the subgroup of patients who received prior trastuzumab therapy, baseline demographics and disease characteristics were compared between treatment arms (Table 1). Most of the characteristics investigated appeared to be balanced between treatment arms, except median duration of disease from diagnosis to randomization, which was longer in ramucirumab plus paclitaxel group compared with placebo plus paclitaxel group (10.25 vs 7.20 months).

Efficacy

Overall survival

For patients who received prior trastuzumab therapy, 14 and 16 deaths were reported in the ramucirumab plus paclitaxel and placebo plus paclitaxel groups, respectively. Median OS was longer with ramucirumab plus paclitaxel treatment (11.4 months; 95% CI: 7.0–17.9) compared with placebo plus paclitaxel (7.0 months; 95% CI: 3.4–14.6); unstratified HR: 0.68 (0.33–1.41); p = 0.30 (Figure 1). Numerical benefit in OS was observed but no statistical significance can be concluded due to the limited sample size in this *post hoc* subgroup analysis. For patients treated with ramucirumab plus paclitaxel, median OS was numerically longer in the subgroup of patients who received prior trastuzumab treatment compared with the overall RAINBOW population (median: 9.6; 95% CI: 8.2–10.8).

Progression-free survival

For patients who received prior trastuzumab therapy, 17 and 19 PFS events were reported in the ramucirumab plus paclitaxel and placebo plus paclitaxel groups, respectively. Median PFS was higher with the ramucirumab and paclitaxel treatment combination (4.2 months; 95% CI: 2.8–7.6) compared with placebo plus paclitaxel (2.7 months; 95% CI: 1.4–3.0); un-stratified HR: 0.40 (0.19–0.82); p = 0.01 (Figure 2). Due to the small sample size, no statistical significance conclusion can be made for the treatment benefit on PFS. PFS in both treatment arms for patients who received prior trastuzumab therapy was consistent with the corresponding treatment arms in overall population.

Objective response & disease control

Higher ORR and DCR were reported with ramucirumab plus paclitaxel treatment versus placebo plus paclitaxel; nine patients (45.0%) versus two patients (10.5%), p = 0.07, and 16 patients (80.0%) versus 11 patients (57.9%), p = 0.03, respectively.

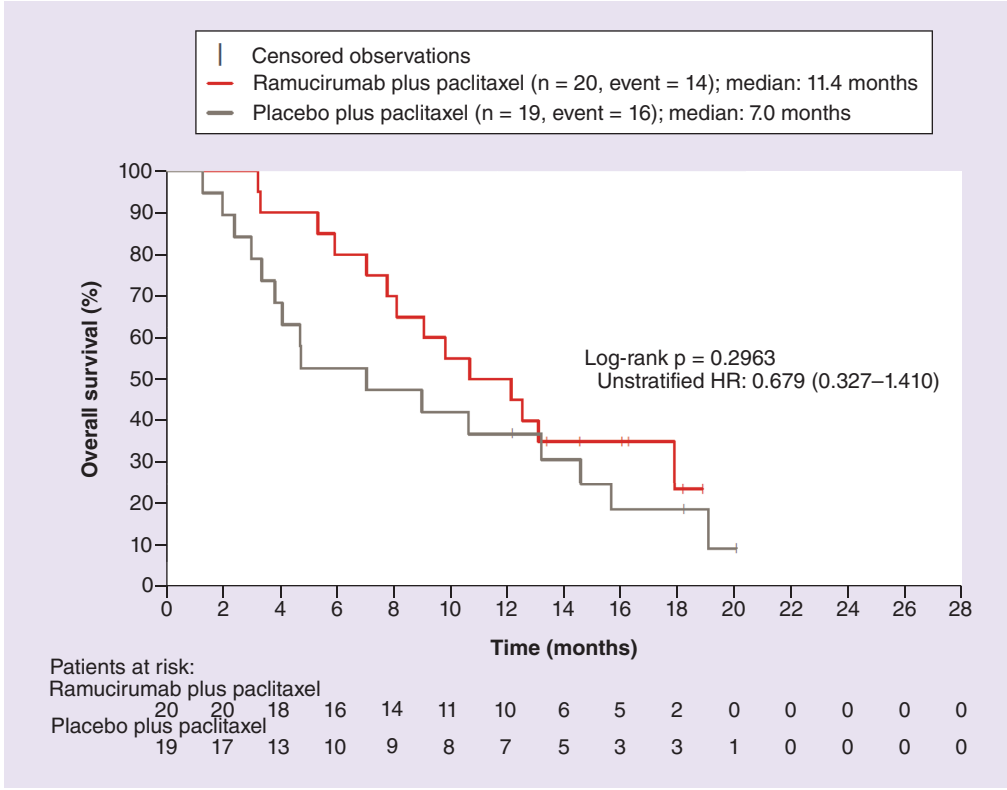

Figure 1. Overall survival in patients with previous trastuzumab therapy.

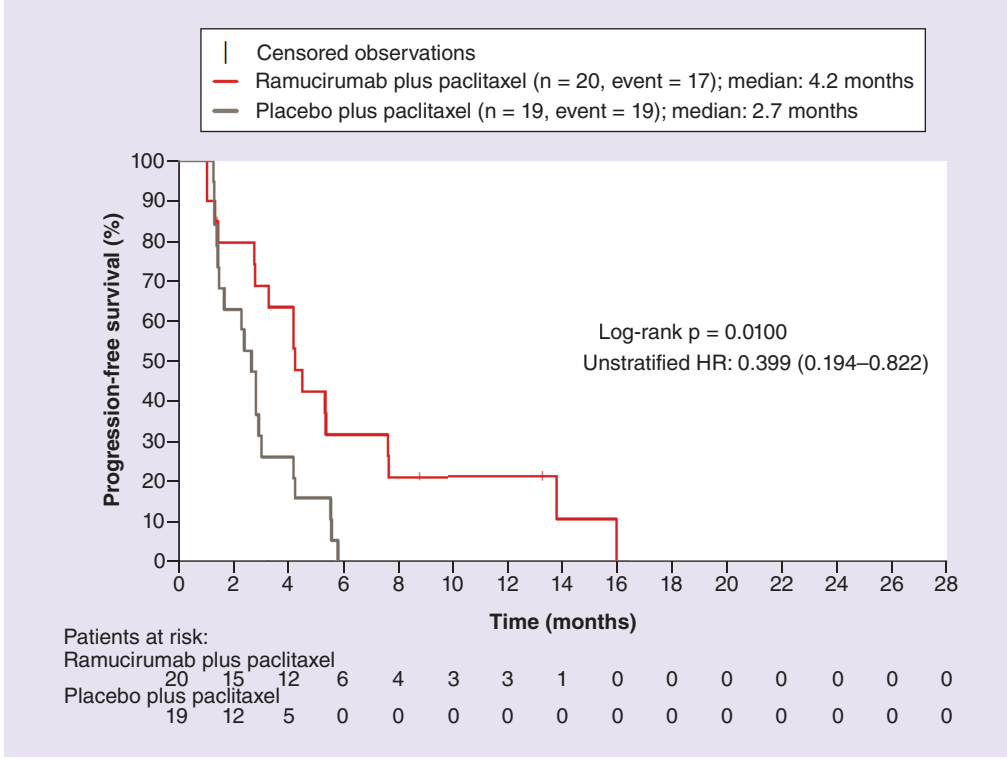

Figure 2. Progression-free survival in patients with previous trastuzumab therapy.

Table 1. Baseline demographics and disease characteristics.

Parameter	Ramucirumab plus paclitaxel N = 20	Placebo plus paclitaxel N = 19
Median age, years	60.5	58.0
Male, n (%)	15 (75.0)	11 (57.9)
Race n (%):		
– White	14 (70.0)	11 (57.9)
– American Indian or Alaska native	0	1 (5.3)
– Asian	6 (30.0)	7 (36.8)
ECOG PS, n (%):		
– 0	8 (40.0)	10 (52.6)
– 1	12 (60.0)	9 (47.4)
Disease measurability, n (%):		
– Measurable	17 (85.0)	15 (78.9)
– Nonmeasurable	3 (15.0)	4 (21.1)
Duration of disease (median), months	10.25	7.2
Primary tumor location, n (%):		
– Gastric	13 (65.0)	15 (78.9)
– Gastroesophageal junction	7 (35.0)	4 (21.1)
Primary tumor present, n (%)	14 (70.0)	14 (73.7)
Histological/pathological type, n (%):		
– Intestinal	10 (50.0)	7 (36.8)
– Diffuse	6 (30.0)	7 (36.8)
– Mixed	0	2 (10.5)
– Unknown/missing	4 (20.0)	3 (15.8)
Grade, n (%):		
– Well differentiated	2 (10.5)	1 (5.3)
– Moderately differentiated	6 (30.0)	10 (52.6)
– Poorly differentiated	12 (60.0)	6 (31.6)
– Unknown/missing	0	2 (10.5)
Number of metastatic sites involved, n (%):		
– 1	1 (5.0)	4 (21.1)
– 2	10 (50.0)	6 (31.6)
– ≥3	9 (45.0)	9 (47.4)
Site of metastatic disease, n (%):		
– Any	20 (100.0)	19 (100.0)
– Lung	8 (40.0)	3 (15.8)
– Liver	11 (55.0)	10 (52.6)
– Bone	1 (5.0)	3 (15.8)
– Skin	0	1 (5.3)
– Lymph nodes	16 (80.0)	14 (73.7)
– Pleural	2 (10.0)	4 (21.1)
– Peritoneal	9 (45.0)	5 (26.3)
– Other	3 (15.0)	7 (36.8)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Safety

Patients who were receiving ramucirumab plus paclitaxel and placebo plus paclitaxel combinations experienced at least one AE of any grade. AEs reported in this analysis are consistent with the overall population of the RAINBOW study. The most common AEs of any grade in both groups (listed in order of frequency) were: epistaxis, neutropenia, alopecia, fatigue, decreased appetite, leukopenia, nausea, constipation, hypertension, peripheral sensory neuropathy, vomiting, anemia, cough, peripheral neuropathy, peripheral edema and pyrexia (Table 2). Grade ≥3 AEs in the

Table 2. Treatment-emergent adverse events reported in ≥20% of patients.

Preferred term	Ramucirumab plus paclitaxel N = 20, n (%)		Placebo plus paclitaxel N = 19, n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any patients with TEAE	20 (100.0)	15 (75.0)	19 (100.0)	12 (63.2)
Epistaxis	10 (50.0)	0	3 (15.8)	0
Neutropenia	10 (50.0)	9 (45.0)	7 (36.8)	3 (15.8)
Alopecia	8 (40.0)	0	10 (52.6)	0
Fatigue	8 (40.0)	1 (5.0)	9 (47.4)	0
Decreased appetite	7 (35.0)	0	4 (21.1)	1 (5.3)
Leukopenia	7 (35.0)	4 (20.0)	3 (15.8)	0
Nausea	7 (35.0)	1 (5.0)	5 (26.3)	0
Constipation	6 (30.0)	0	4 (21.1)	1 (5.3)
Hypertension	6 (30.0)	1 (5.0)	1 (5.3)	1 (5.3)
Peripheral sensory neuropathy	5 (25.0)	2 (10.0)	4 (21.1)	1 (5.3)
Vomiting	5 (25.0)	1 (5.0)	2 (10.5)	0
Anemia	4 (20.0)	2 (10.0)	5 (26.3)	0
Cough	4 (20.0)	0	1 (5.3)	0
Neuropathy peripheral	4 (20.0)	1 (5.0)	2 (10.5)	1 (5.3)
Edema peripheral	4 (20.0)	0	4 (21.1)	0
Pyrexia	4 (20.0)	0	3 (15.8)	0
Adverse events of special interest associated with VEGF pathway				
Bleeding/hemorrhage events	12 (60.0)	2 (10.0)	6 (31.6)	0
Hypertension	6 (30.0)	1 (5.0)	1 (5.3)	1 (5.3)
GI hemorrhage events	4 (20.0)	2 (10.0)	0	0
Proteinuria	2 (10.0)	0	0	0
Congestive heart failure	0	0	1 (5.3)	1 (5.3)
Renal failure	0	0	2 (10.5)	1 (5.3)

GI: Gastrointestinal; TEAE: Treatment emergent AEs.

ramucirumab plus paclitaxel arm versus placebo plus paclitaxel arm were neutropenia (45.0 vs 15.8%), leukopenia (20.0 vs 0.0%), anemia (10.0 vs 0.0%) and peripheral sensory neuropathy (10.0 vs 5.3%), respectively.

AEs of special interest

AEs associated with the VEGF pathway and common with ramucirumab plus paclitaxel treatment were hemorrhagic events, hypertension, gastrointestinal hemorrhage events and proteinuria. The frequencies of AEs are presented in Table 2.

Discussion

The REGARD and RAINBOW studies reported improved OS with ramucirumab, either administered as monotherapy or in combination with paclitaxel in respective trials. Recent therapeutic advances in gastric cancer have targeted only VEGFR-2 and HER-2 [8,15]. Available preclinical data based on HER-2-positive breast cancer indicates a relationship between HER-2 overexpression and activation of the angiogenic pathway in tumor cells. Overexpression of HER-2 in tumor cells is associated with expression of VEGF and increased angiogenesis, and may support sustaining and promoting of tumor survival [13,16]. Ramucirumab is a VEGFR-2 antagonist monoclonal antibody that prevents ligand-binding and receptor-mediated pathway activation in endothelial cells [17]. Trastuzumab resistance might be overcome by inhibiting angiogenesis pathways by VEGFR-2 inhibitors such as ramucirumab, as it stops the crosstalk between HER-2 and angiogenesis for tumor survival [13].

There is some controversy about trastuzumab as a second-line therapy beyond disease progression. A recently published study by Palle *et al.* has suggested that continuation of trastuzumab beyond progression has clinical benefit in patients with HER2-positive advanced gastric cancer [18]. However, prospective and retrospective studies have indicated no significant differences in OS and PFS with second-line trastuzumab combination in patients who

progressed on first-line trastuzumab and chemotherapy combination [9,15,18]. Finally, as reported in the GATSBY trial, an agent such as trastuzumab emtansine (T-DM1), different from trastuzumab, also failed to improve OS or PFS in patients with HER-2 positive advanced gastric and gastroesophageal cancer, previously treated with anti-HER-2 agents [19].

In this RAINBOW subgroup analysis of patients who received prior trastuzumab therapy, second-line ramucirumab and paclitaxel combination reported higher median OS (11.4 months; 95% CI: 7.0–17.9) compared with the placebo plus paclitaxel group (7.0 months; 95% CI: 3.4–14.6). PFS was prolonged in the ramucirumab and paclitaxel group versus placebo and paclitaxel. ORR and DCR were also higher with ramucirumab and paclitaxel combination compared with placebo plus paclitaxel. At present, no biomarker predictor of response is available for ramucirumab; hence, it is difficult to select patients with a higher probability of response to the treatment.

AEs of special interest associated with the VEGF pathway were hemorrhage events, hypertension, GI hemorrhage events and proteinuria. Limitations of this subgroup analysis were the small sample size and the fact that this was a *post hoc* retrospective analysis that was not sufficiently powered. The observed numerical difference in efficacy and safety across treatment arms cannot be deemed as statistically significant, and is further challenged in interpretation by the fact that patients were not randomized within the subgroup of prior trastuzumab therapy. Our subgroup analysis, although limited by sample size, revealed numeric clinical benefits of ramucirumab-based therapy. Further investigation in prospective clinical trials is required to confirm the clinical benefits of ramucirumab-based combination therapy in patients who received prior trastuzumab.

Conclusion

Recent trials showed that trastuzumab failed to demonstrate clinical benefits beyond disease progression, and options remain limited beyond first-line therapy for the treatment of HER+ patients. Findings of this subgroup analysis suggest that ramucirumab in combination with paclitaxel is effective with a manageable safety profile for the treatment of patients who received first-line therapy with trastuzumab. Ramucirumab in combination with paclitaxel remains a standard of care for patients who progress on prior platinum based chemotherapy, regardless of prior trastuzumab therapy.

Summary points

- Gastric cancer is one of the leading causes of cancer-related mortality. Early stage disease is curable with surgical resection; however, many patients still relapse. Combined therapies are standard of care for ≥stage 1B gastric cancer.
- Published research states the relation between HER-2 overexpression and activation of the angiogenic pathway in tumor cells. Overexpression of HER-2 via VEGFR-2 upregulation may support angiogenesis for tumor survival; hence, HER-2 and VEGFR-2 may be the valid target to treat gastric cancer.
- Ramucirumab is the only biological treatment given in combination with paclitaxel that has shown clinical benefits over chemotherapy alone in patients with advanced gastric cancer who have progressed after first-line chemotherapy. Ramucirumab has also shown efficacy as a monotherapy in patients with advanced or gastroesophageal junction adenocarcinoma.
- The objective of this study was to assess the efficacy and safety of ramucirumab plus paclitaxel in a RAINBOW subgroup of patients with gastric cancer/gastroesophageal junction adenocarcinoma who received prior treatment with trastuzumab therapy.
- Longer median overall survival was reported with ramucirumab and paclitaxel combination (11.4 months; 95% CI: 7.0–17.9) versus placebo plus paclitaxel (7.0 months; 95% CI: 3.4–14.6); un-stratified hazard ratio: 0.68 (0.33–1.41); $p = 0.30$.
- Median progression-free survival was improved with ramucirumab and paclitaxel combination (4.2 months; 95% CI: 2.8–7.6) versus placebo plus paclitaxel (2.7 months; 95% CI: 1.4–3.0); un-stratified hazard ratio: 0.40 (0.19–0.82); $p = 0.01$.
- Higher objective response and disease control were seen in patients treated with ramucirumab plus paclitaxel compared with placebo plus paclitaxel.
- Adverse events were consistent with the overall population of the RAINBOW study.
- Ramucirumab and paclitaxel combination was effective in patients who received first-line therapy with trastuzumab.

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Authors' contributions

F de Vita, C Borg, G Farina, R Geva, I Carton, H Cuku, R Wei and K Muro were involved in conception of the work, critical revision of the manuscript for important intellectual content, participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and provided final approval of the manuscript to be submitted to *Future Oncology*.

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Financial & competing interests disclosure

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Writing support was provided by VK Ranka, an employee of Eli Lilly and Company.

Ethical conduct of research

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.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: NCT01170663 [10]. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com

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