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RESEARCH

Does HER2 status influence in the benefit of ramucirumab and paclitaxel as second line treatment of advanced gastro-esophageal adenocarcinoma? Data from the AGAMENON-SEOM registry

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Abstract

Purpose This study aimed to compare ramucirumab-paclitaxel versus chemotherapy in second-line (2L) advanced gastroesophageal cancer (aGEC) based on HER2 status and analyze prognostic factors.

Methods The study includes patients from the AGAMENON-SEOM registry with aGEC and known HER2 status who received 2L between 2016 and 2021. The Kaplan–Meier method was used to calculate progression-free survival (PFS) and overall survival (OS) and multivariable Cox regression analysis was done to adjust for confounding variables.

Results Of the 552 patients who met the selection criteria, 149 (26.9%) had HER2-positive aGEC, 89 were treated with chemotherapy, and 60 with ramucirumab-paclitaxel, and 403 had an HER2-negative aGEC, 259 were treated with chemotherapy, and 144 with ramucirumab-paclitaxel.

In the whole sample, 2L PFS was 3.0 months (95% CI 2.8–3.2), 2L OS, 5.7 months (5.2–6.3), and ramucirumab-paclitaxel versus chemotherapy was associated with increased PFS (HR 0.64, 95% CI 0.53–0.78, $p<0.0001$) and OS (HR 0.68, 0.55–0.83, $p=0.0002$). Median PFS of ramucirumab- paclitaxel versus chemotherapy was 3.5 vs 2.8 months (HR 0.67, 0.54–0.83, $p=0.0004$) in HER2-negative, and 4.7 vs 2.7 months (HR 0.57, 0.40–0.82, $p=0.0031$) in HER2-positive aGEC, respectively. Median OS for ramucirumab-paclitaxel versus chemotherapy was 6.6 vs 5 months (HR 0.67, 0.53–0.85, $p=0.0007$) in HER2-negative, and 7.4 vs 5.6 months (HR 0.70, 0.53–1.04, $p=0.083$) in HER2-positive aGEC, respectively. ECOG-PS, tumor burden, Lauren subtype, and neutrophil–lymphocyte ratio were prognostic factors.

Conclusions In patients with an aGEC from the AGAMENON-SEOM registry, 2L treatment with ramucirumab-paclitaxel was superior to chemotherapy in PFS, OS and response rate, independent of HER2 status.

Keywords Gastroesophageal adenocarcinoma · HER2 · Prognosis · Ramucirumab · Survival

Introduction

Advanced gastric cancer (aGC) is the third leading cause of cancer death worldwide (Ferlay et al. 2015). Chemotherapy (CT) improves overall survival (OS) and quality of life for individuals with aGC compared to best supportive care (BSC) (Wagner et al. 2017). In first line, platinum-fluoropyrimidine schedules are the most widely

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used options (Smyth et al. 2016). In case of patients with tumors that amplify or overexpress human epidermal growth factor receptor-2 (HER2+) the standard of care is the combination of trastuzumab and platinum-fluoropyrimidine (Bang et al. 2010). The benefit of first-line therapy is limited; with 25–30% of patients with progressive disease at their first evaluation of response (Yamada et al. 2019), median progression-free survival (PFS) of 4–7 months (Wagner et al. 2017), and approximately 50% of patients in suitable conditions to receive second-line (2L) treatment after progression (Thuss-Patience et al. 2011; Kang et al. 2012).

Numerous drugs have proven limited activity in 2L for aGC (Hironaka et al. 2013; Lee et al. 2019). A small, randomized trial (NCT00144378) confirmed for the first time that the use of irinotecan versus (vs) BSC in 2L discreetly prolonged OS (Thuss-Patience et al. 2011). In the COUGAR-2 study, docetaxel increased OS and demonstrated a benefit in quality of life vs BSC (Ford et al. 2014). Both drugs also improved OS compared to BSC in a phase 3 trial (Kang et al. 2012), while the WJOG-4007 study detected no differences between paclitaxel and irinotecan [9]. More recently, the phase 3 RAINBOW trial showed an increase in OS with ramucirumab plus paclitaxel (RAM-PAC) vs paclitaxel in 2L (Wilke et al. 2014). For its part, the REGARD study demonstrated a gain in OS with ramucirumab vs BSC (Fuchs et al. 2014). Both studies with ramucirumab were bolstered by favorable quality of life analyses, as well as real-world data (di Bartolomeo et al. 2018; Paulson et al. 2018; Jung et al. 2018). This positioned ramucirumab as the recommended 2L strategy, whether in combination with paclitaxel or monotherapy (Muro et al. 2019). There are minimal data concerning how the use of the various alternatives available for 2L treatment have evolved, in addition to their efficacy in actual clinical practice (Choi et al. 2018; Cotes Sanchís et al. 2020). Moreover, pembrolizumab has shown higher activity than CT in esophageal and gastroesophageal junction (GEJ) carcinoma in the pre-specified PDL1-CPS ≥ 10 subgroup in 2L (KEYNOTE-181 phase 3 trial) (Kojima et al. 2020), while efficacy in 2L was unproven for advanced gastric or GEJ adenocarcinoma with PD-L1 CPS of 1 or higher (KEYNOTE-061 phase 3 trial) (Shitara et al. 2018b).

Based on retrospective analysis, certain individuals who do not maintain first-line treatment until progression might profit from reintroducing platinum-fluoropyrimidine doublets, when the treatment-free interval exceeds three months (Okines et al. 2010; Cotes Sanchís et al. 2020). Despite the fact that this subgroup of patients is excluded from most recent 2L clinical trials for aGC (Fuchs et al. 2014; Wilke et al. 2014), updated ESMO clinical guideline consider reintroduction of the first-line to be an appropriate alternative (Muro et al. 2019). Likewise, treatment options with proven efficacy exist in third-line scenario where there is also the option of alternatives not used in previous lines such as irinotecan (Kang et al. 2012, 2017; Shitara et al. 2018a).

Treatment in second and successive lines for HER2+ tumors does not currently differ from the rest, given the absence of evidence in favor of anti-HER2 therapy based on phase 3 trials (Satoh et al. 2014; Thuss-Patience et al. 2017). Nevertheless, these tumors are molecularly dissimilar and their optimal treatment after progression to CT and trastuzumab remains unclear. Phase 3 studies investigating the use of HER2-targeted therapies in the 2L in aGC, including the TyTAN and GATSBY trials, which evaluated lapatinib and ado-trastuzumab, respectively, have not demonstrated a significant survival benefit (Satoh et al. 2014; Thuss-Patience et al. 2017). In patients with metastatic breast cancer, however, several trials have shown benefit from continuing trastuzumab beyond progression (Bartsch et al. 2007; von Minckwitz et al. 2009). A small retrospective study has suggested that continuation of trastuzumab after progression may lead to improved clinical outcomes when compared with CT alone in patients with HER2+ aGC (Palle et al. 2017). In addition, trastuzumab deruxtecan activity data based on a phase 2 trial are awaiting confirmation in the ongoing phase 3 study (DESTINY-gastric04) and to date, there have been no studies comparing HER2-targeted therapies with the current standard 2L treatment, ramucirumab and CT, in HER2+ aGC.

In this analysis, we used data from a real-world registry to describe 2L treatment in patients with advanced gastroesophageal cancer (aGEC), compare RAM-PAC vs CT based on HER2 status, and probe into associated prognostic factors.

Materials and methods

Study design and patients

AGAMENON-SEOM (Spanish Society of Medical Oncology) is a consecutive registry of esophageal, GEJ, and gastric cancer supported by the SEOM with 40 Spanish participating centers (Carmona-Bayonas et al. 2016, 2018a, b, 2019, 2022; Jiménez-Fonseca et al. 2017; Custodio et al. 2017; Jiménez Fonseca et al. 2017; Visa et al. 2018; Cotes Sanchís et al. 2020; Jimenez-Fonseca et al. 2021a, b; Alvarez-Manceñido et al. 2021; Zaragoza-Huesca et al. 2022). The study was conducted in compliance with the Good Clinical Practice guidelines and the latest version of the Declaration of Helsinki and was approved by the Ethics Committee of each institution and by the Spanish Agency of Medicines and Health Products. All patients still alive at the time of data collection provided written, signed, informed consent.

This study involved adult patients (> 18 years), with histologically confirmed unresectable locally advanced and

metastatic distal esophageal, GEJ and gastric adenocarcinoma, with known HER2 status, who received RAM-PAC or CT in 2L between December 2016 and December 2021 and with at least 3 months of follow-up after the start of 2L treatment.

Variables

Epidemiological, histopathological, clinical, and treatment related variables were obtained from the clinical history at the beginning of the first and 2L (Annex Table 1 in Supplementary material and Table 1). Clinical variables related to weight and nutritional status, the presence of symptoms and the number of chronic and symptom control medications were assessed before starting 2L. The data were registered on a website (www.agamenonstudy.com) that consists of filters and a system of queries to guarantee data reliability and control for missing and inconsistent data, with telephone and online monitoring (PJF).

Treatment related outcomes were overall response rate (ORR) per locally assessed RECIST 1.1 criteria, PFS, OS, and toxicity, classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. OS and PFS were defined as the time between initiation of 2L and all-cause mortality or progression, censuring those subjects without any event at last follow-up.

Statistics

Survival was calculated using the Kaplan–Meier method. To control for confounding bias, multivariable Cox proportional hazards regression models were fitted for PFS and OS. These multivariable models were specified with the following covariates: therapeutic regimen (RAM-PAC vs CT), prior first-line therapy, HER2 subtype (positive vs negative), number of metastatic sites ($\leq$ vs >2), neutrophil-to-lymphocyte ratio (NLR), bone metastases, Lauren subtype (intestinal vs diffuse), histological grade (1 vs others), and performance status (ECOG-PS $\leq$ vs >1). Criteria for selection of these factors were theoretical, based on the literature review and in consultation with the AGAMENON-SEOM registry investigators, and were not based on results observed in this sample.

To estimate the effect based on HER2 subtype, the interaction between therapy and this variable was assessed and hazard ratios (HR) were obtained for each subgroup. The Bayesian alternative of the Cox model was used under the same specification and under weakly informative priors for all covariates (normal ~ mean = 0, standard deviation = 10) to quantify uncertainty. The aim of these Bayesian versions was to evaluate the hypothesis of directionality of effect (probability that RAM-PAC improves prognosis with HR < 1). Analyses were performed using R v4.05 statistical software, including the rms and brms library (Harrel FE. Jr; Bürkner 2017; Team R. C. 2022).

Results

Baseline characteristics before first-line

The database contains 3088 patients with aGEC, of which 552 meet the eligibility criteria for this study (Fig. 1, flow chart). Of these, 204 (36.9%) received RAM-PAC and 348 (63.0%) received other 2L CT schemes. In this cohort, there are 403 subjects (73.0%) with a HER2-negative and 149 (26.9%) with HER2+ aGEC. All patients with HER2+ neoplasia received trastuzumab-based therapy as first-line.

Annex Table 1 in Supplementary material shows the characteristics of patients before starting first-line systemic treatment according to HER2 status. The median age was 63 years, and the majority were men (70%) with no differences between HER2+ and HER2-negative populations. The most frequent comorbidity was diabetes mellitus present in 13.5%, followed by cardiovascular (10.4%) and peripheral vascular disease (7.9%). The most common primary tumor site was the stomach (76%), although it is worth noting the higher frequency of neoplasms in GEJ in HER2+ vs HER2-negative cancer (25% vs 12%). There are also differences between the two groups according to Lauren's classification, with a higher number of intestinal tumors in HER2+ vs HER2-negative (58% vs 31%), and an inverse relationship in the diffuse type, with a higher percentage in HER2-negative tumors (44%) than in HER2+ (14%).

The most frequent first-line treatment was platinum/fluoropyrimidine-based CT doublet (72%) with less frequent use of platinum/fluoropyrimidine and anthracycline-based CT triplet (15%) or docetaxel-based regimen (6%, $n = 34$).

Baseline characteristics before 2L

Of the 403 HER2-negative aGEC patients, 64% ($n = 259$) were treated with CT and 36% ($n = 144$) with RAM-PAC in 2L; while of the 149 with HER2+ aGEC, 60% ($n = 89$) and 40% ($n = 69$) received CT and RAM-PAC in 2L, respectively (Table 1). The majority had a good performance status, especially those subjects with HER2+ aGEC treated with RAM-PAC (ECOG PS 0–1, 81%). There were no differences in weight, nutritional status or symptoms at 2L initiation, the most frequent being anorexia (30%, $n = 170$), pain (28%, $n = 155$) and cachexia (9%, $n = 52$). Most had one or two metastatic sites (32% and 39%, respectively), with slight variations in the pattern of dissemination according to HER2. Thus, lymph node followed by liver were the most frequent metastatic sites in the complete series, with more frequent peritoneal metastases in HER2-negative tumors, and higher

Table 1 Baseline characteristics at 2L initiation

Baseline Characteristics	All, *N* (%)	HER2-negative, *N* (%)		HER2+, *N* (%)	
	N = 552 (100%)	*N* = 403 (100%)		*N* = 149 (100%)	
2L Treatment	All	RAM-PAC, *N* (%)	CT, *N* (%)	RAM-PAC, *N* (%)	CT, *N* (%)
		N = 144 (100)	*N* = 259 (100)	*N* = 60 (100)	*N* = 89 (100)
Sex, male	388 (70.2)	95 (66.0)	176 (68.0)	46 (76.7)	71 (79.8)
Age, median (range)	63 (20–86)	59 (20–83)	65 (30–85)	62 (31–81)	64 (23–86)
ECOG-PS (2L)					
0	85 (15.4)	31 (21.5)	23 (8.9)	18 (30.0)	13 (14.6)
1	344 (62.3)	84 (58.3)	171 (66.0)	35 (58.3)	54 (60.7)
2	120 (21.7)	29 (20.1)	63 (24.3)	7 (11.7)	21 (23.6)
3	3 (0.5)	0	2 (0.8)	0	1
4	0	0	0	0	0
Weight, median (range)	65 (34–140)	66 (40–110)	65 (34–140)	64.5 (40–100)	66 (40–106)
Weight loss (Kg) in 3 months, median (range)	2.2 (0–24.4)	2.0 (0–17.6)	2.0 (0–20)	3.4 (0–15.1)	2.6 (0–24.4)
BMI, median (range)	23.3 (13.4–47.3)	23.2 (14.5–37.9)	23.2 (13.5–47.3)	23.5 (13.5–33.8)	23.6 (15.2–34.2)
Nutritional assessment					
Not done	281 (50.9)	69 (47.9)	131 (60.6)	33 (55.0)	48 (53.9)
Well-nourished patient	113 (20.4)	27 (18.8)	55 (21.2)	13 (21.7)	18 (20.2)
Malnourished patient	158 (28.6)	48 (33.3)	73 (28.2)	14 (23.3)	23 (25.8)
Nutritional intervention					
Not done	345 (62.5)	83 (57.6)	164 (63.3)	42 (70.0)	56 (62.9)
Before 2L	179 (32.4)	57 (39.6)	78 (30.1)	16 (26.7)	28 (31.5)
At the beginning of 2L	28 (5.0)	4 (2.8)	17 (6.6)	2 (3.3)	5 (5.6)
Symptoms					
Anorexia	170 (30.0)	40 (27.8)	96 (37.1)	28 (46.7)	44 (49.4)
Pain	155 (28.0)	37 (25.9)	76 (29.3)	18 (30.0)	24 (27.0)
Cachexia	52 (9.4)	16 (11.1)	25 (9.7)	4 (6.7)	7 (7.9)
High GI stenosis	50 (9.0)	11 (9.0)	25 (9.7)	2 (3.3)	10 (11.2)
Low intestinal sub/occlusion	37 (6.7)	17 (11.8)	18 (6.9)	2 (3.3)	0
Number of metastatic sites					
1	176 (31.8)	40 (28.8)	96 (37.1)	17 (28.3)	23 (25.8)
2	217 (39.3)	62 (43.1)	98 (37.8)	21 (35.0)	36 (40.4)
3	100 (18.1)	32 (22.2)	40 (15.4)	11 (18.3)	17 (19.1)
4	59 (10.6)	10 (6.9)	25 (9.7)	11 (18.3)	13 (14.6)
Metastatic sites					
Liver	231 (41.9)	49 (34.0)	94 (36.3)	34 (56.7)	54 (60.7)
Unresected locoregional lymph nodes	323 (58.5)	76 (52.8)	157 (60.6)	35 (58.3)	55 (61.8)
Distant lymph nodes	277 (50.1)	62 (43.1)	141 (54.4)	36 (60.0)	38 (42.7)
Peritoneum	282 (51.1)	87 (60.4)	145 (56.0)	22 (36.7)	28 (31.5)
Ascites	165 (29.9)	57 (39.6)	85 (32.8)	10 (16.7)	13 (14.6)
Lung	106 (19.2)	28 (18.1)	43 (16.6)	18 (30.0)	19 (21.3)
Bone	66 (13.8)	23 (16.0)	32 (12.4)	9 (15.0)	12 (13.5)
Hepatic tumor burden					
< 25%	111 (45.6)	24 (49.0)	49 (49.5)	10 (27.8)	28 (47.5)

Table 1 (continued)

Baseline Characteristics	All, *N* (%)	HER2-negative, *N* (%)		HER2+, *N* (%)	
	N = 552 (100%)	*N* = 403 (100%)		*N* = 149 (100%)	
2L Treatment	All	RAM-PAC, *N* (%)	CT, *N* (%)	RAM-PAC, *N* (%)	CT, *N* (%)
		N = 144 (100)	*N* = 259 (100)	*N* = 60 (100)	*N* = 89 (100)
25–50%	103 (42.3)	21 (42.9)	40 (40.4)	18 (50.0)	24 (40.7)
51–75%	23 (9.4)	4 (8.2)	8 (8.1)	4 (11.1)	7 (11.9)
> 75%	6 (2.4)	0	2 (2.0)	4 (11.1)	0
None	309	95	160	24	30
Laboratory					
Hemoglobin	11.9 (5.9–17.8)	12.0 (8.1–15.0)	11.8 (6.8–15.5)	12.1 (7.9–15.3)	11.1 (7.9–17.8)
Neutrophils	4320 (390–114,000)	4155 (1020–18,600)	4225 (790–11,400)	3710 (1000–12,100)	4795 (1500–22,400)
Lymphocytes	1500 (200–12,200)	1475 (400–4450)	1490 (400–5240)	1650 (250–3940)	1330 (540–3220)
NLR	3 (0.5–11)	2.8 (0.7–15)	3.1 (0.5–11)	2.31 (0.6–48.4)	3.5 (0.5–21)
Platelets	228,000 (1630–801,000)	229,550 (83,000–620,000)	224,500 (74,000–75,700)	215,000 (91,000–456,000)	233,000 (114,000–620,000)
LDH	270 (18–15,386)	285 (18–2346)	228 (100–2456)	314 (101–2547)	268 (123–1742)
Alkaline phosphatase	108 (17–2136)	122 (17–1139)	101 (32–1400)	108 (40–1842)	106 (33–1270)
Bilirubin	0.5 (0–6.3)	0.5 (0–2.2)	0.5 (0–2.8)	0.6 (0.2–2.6)	0.5 (0–3.7)
Albumin	3.8 (1.6–4.6)	3.8 (2–4.6)	3.8 (1.6–5.2)	4 (2.6–7.1)	3.9 (2–4.1)
Sodium	140 (124–143)	140 (124–147)	140 (126–150)	140 (127–146)	140 (124–145)
Potassium	4.3 (2.7–6)	4.3 (3.3–6)	4.3 (2.8–5.9)	4.3 (3.3–5.4)	4.3 (3.2–6)
CEA	5.3 (0–11,113)	4.2 (0.5–11,113)	4.3 (0–1345)	19.7 (0.6–60,010)	12 (0.9–930)
Number of medications	4 (0–18)	4 (0–18)	4 (0–14)	4 (0–12)	3 (0–13)
Number of medications for symptom control	2 (0–10)	2 (0–10)	2 (0–10)	2 (0–7)	2 (0–10)
Therapy in 2L					
RAM-PAC	204 (36.9)	144 (100)	–	60 (100)	–
Paclitaxel	155 (28.0)	–	115 (44.4)	–	40 (44.9)
Irinotecan	61 (11.0)	–	45 (17.4)	–	16 (18.0)
FOLFIRI	54 (9.7)	–	49 (18.9)	–	5 (5.6)
Docetaxel	28 (5.0)	–	49 (18.9)	–	16 (18.0)
Other CT	50 (8.4)	–	39 (15.1)	–	12 (13.5)

2L second line, *RAM-PAC* ramucirumab-paclitaxel, *CT* chemotherapy, *BMI* body mass index, *GI* gastrointestinal, *NLR* neutrophil–lymphocyte ratio, *LDH* lactate dehydrogenase

tropism for the lung in HER2+ aGEC. Laboratory variables showed similar medians and ranges in the groups except for CEA which was higher in HER2+ aGEC patients. The median number of chronic medications per patient was four drugs, including two for symptom control.

Across the whole population, RAM-PAC was the most used therapy as 2L (37%, $n = 204$), followed by paclitaxel monotherapy (28%, $n = 155$), irinotecan (11%, $n = 61$), FOLFIRI (10%, $n = 54$), and docetaxel (5%, $n = 28$). In HER2-negative aGEC patients treated with CT, 44% received paclitaxel, 17% irinotecan, 19% FOLFIRI and 19% docetaxel. In patients with HER2+ aGEC treated with CT, the percentage receiving paclitaxel, irinotecan, FOLFIRI and docetaxel were 45%, 18%, 6% and 18%, respectively. Eighteen patients (3.2%) underwent surgery for metastases, 17 of them during the first-line. The median number of lines of treatment received was two in 326 patients (59%), three in 157 patients (30%) and > 3 in 59 patients (11%) with no difference between HER2-negative vs HER2+ aGEC patients ($p = 0.41$).

Efficacy and toxicity

With a median follow-up of 34 months, 530 events of progression (96%) and 487 of death (88%) were detected. The median 2L PFS was 3.0 months (95% CI 2.8–3.2) and 2L

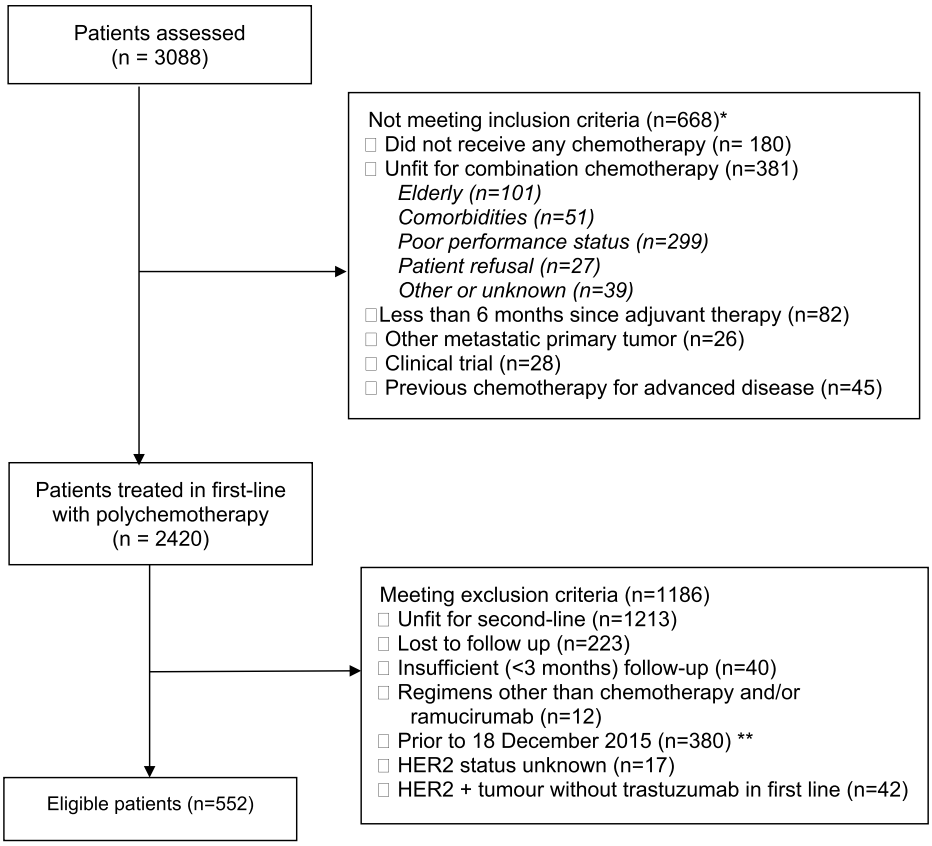

Fig. 1 Flowchart of the study. *Categories were not mutually exclusive, **Date when ramucirumab was approved in Spain

OS, 5.7 months (95% CI 5.2–6.3) (Annex Fig. 1 in Supplementary material). The pattern of progression was as new lesions in 31% ($n=164$), or growth of previous lesions in 69% (n = 366).

In the complete sample ($n=552$), RAM-PAC compared to CT was associated with increased PFS with HR 0.64 (95% CI 0.53–0.78), $p<0.0001$. Figure 2A, B depicts PFS stratified by treatment based on HER2. In HER2-negative, median PFS with RAM-PAC vs CT was 3.5 (95% CI 3.2–4.7) vs 2.8 months (95% CI 2.6–3.1), respectively (HR 0.67, 95% CI 0.54–0.83, $p=0.0004$). In HER2+ aGEC, median PFS with RAM-PAC vs CT was 4.7 (95% CI 3.3–5.9) vs 2.7 months (95% CI 2.5–3.1), respectively (HR 0.57, 95% CI 0.40–0.82, $p=0.0031$). The interaction test found no evidence that the benefit with RAM-PAC vs CT was different based on HER2 status (interaction test $p=0.459$).

Across the whole series, RAM-PAC increased OS over other CT regimens with HR 0.68 (95% CI 0.55–0.83), $p=0.0002$. Figure 3A, B represents OS stratified by treatment based on HER2. In HER2-negative, median OS with RAM-PAC vs CT was 6.6 (95% CI 5.7–8.5) vs 5 months (95% CI 4.2–5.7), respectively (HR 0.67, 95% CI, 0.53–0.85, p = 0.0007). In HER2+ aGEC, median OS with RAM-PAC vs CT was 7.4 (6.1–12) vs 5.6 months (95% CI 5.1–8), respectively (HR 0.70, 95% CI 0.53–1.04, $p=0.083$). The interaction test found no evidence of differences based on HER2 status in OS ($p=0.822$). In the Bayesian version of this analysis adjusting for the same variables, the posterior probability of benefit with RAM-PAC in HER2+ aGEC (HR < 1) was 83%.

Computed tomography for response assessment was performed every 6–8 weeks in 149 patients (27%), every 9–12 weeks in 274 patients (50%), > 12 weeks in 59 patients (11%) and not performed due to clinical deterioration or early death in 70 patients (12%). The 2L ORR was 12% ($n=62$), and stabilization occurred in 19% ($n=105$) with a disease control rate (responses and stabilization) of 31%. Annex Table 2 illustrates ORR based on 2L strategy and HER2 status. In HER2-negative aGEC, the ORR and disease control rate were 17% and 38% for RAM-PAC vs 7% and 26% for CT, respectively. In HER2+ aGEC, the ORR and disease control rate were 28% and 47% for RAM-PAC vs 9% and 24% for CT, respectively.

In terms of safety, RAM-PAC was associated with more ramucirumab related adverse effects than CT, such as hypertension (23% vs 1%, grade 3–4 in 2% vs 0%), bleeding (21% vs 10%, grade 3–4 in 2% vs 4%), proteinuria (9% vs 2%, grade 3–4 in 2% vs 0%), thrombosis (6% vs 3%, grade 3–4 in 4% vs 1%), and gastrointestinal perforation (3% vs 0%, grade 3–4 in 1% vs 0%), respectively (Table 2). RAM-PAC vs CT also had more neutropenia (44% vs 21%, grade 3–4 in 19% vs 7%), thrombopenia (17% vs 8%, grade 3–4 in 2%

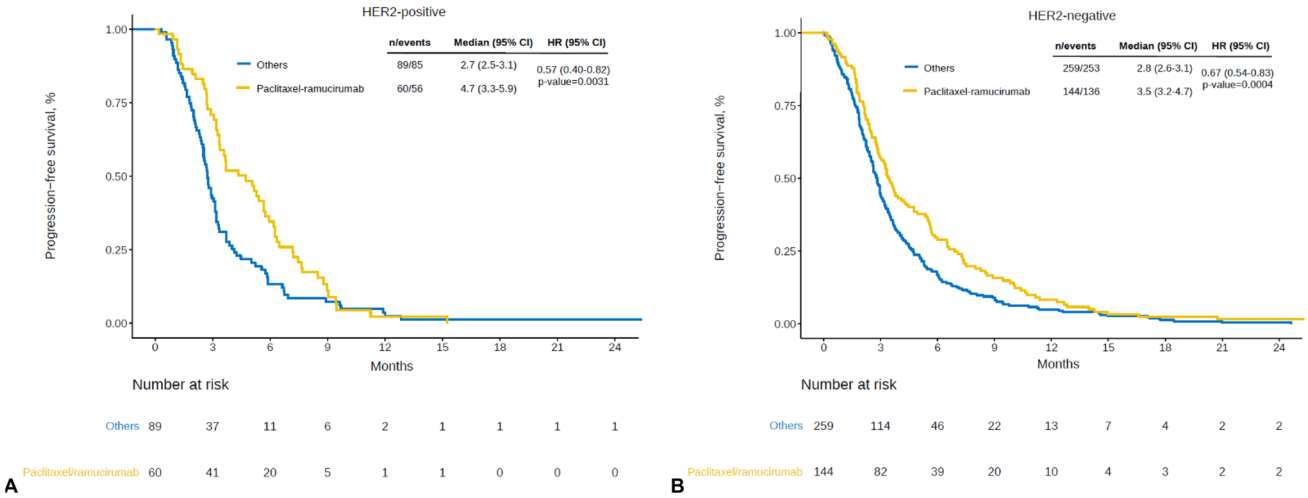

Fig. 2 PFS stratified by treatment in HER2+ (**A**) and negative (**B**) aGEC

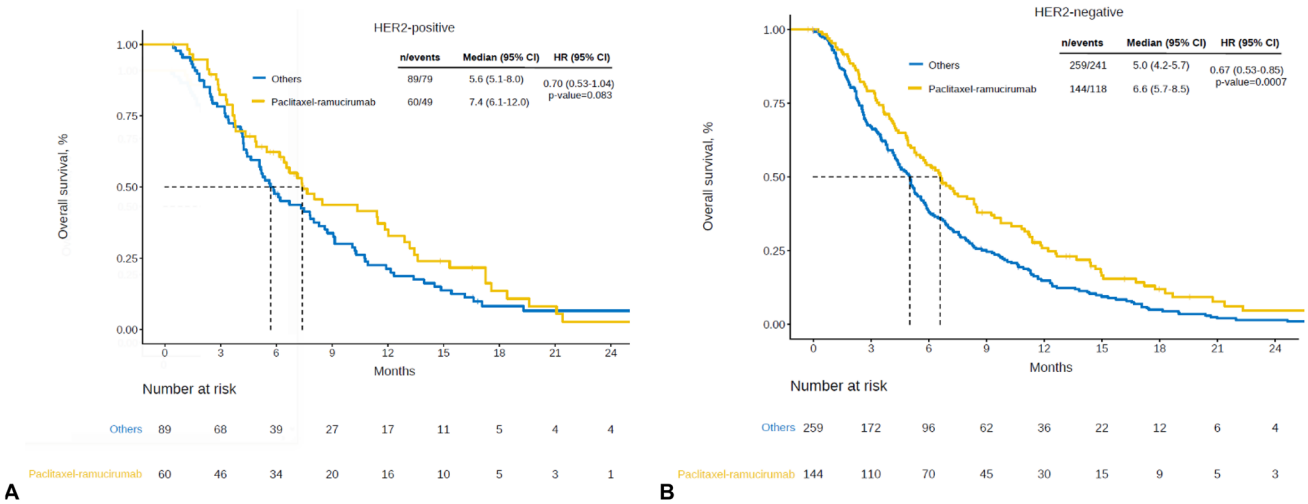

Fig. 3 OS stratified by treatment in HER2+ (**A**) and negative (**B**) aGEC

vs 0%), and neuropathy (55% vs 34%, grade 3–4 in 3% vs 2%), respectively. Diarrhea was higher with CT vs RAM-PAC, 28% vs 21% with little grade 3–4 diarrhea, 2% vs 1%, respectively.

Prognostic factors for PFS and OS

The prognostic models for PFS and OS are shown in Fig. 4A, B, respectively. RAM-PAC therapy (HR 0.64, 95% 0.53–0.78), ECOG-PS > 1 (HR 1.87, 95% CI, 1.5–2.33), liver burden disease 25–50% vs none (HR 1.38, 1.06–1.79), diffuse Lauren subtype (HR 1.36, 1.11–1.67) and NLR 4.2 vs 1.9 (HR 1.04, 1–1.07) were associated with PFS (Fig. 4A). For OS, an ECOG-PS > 1 (HR 1.89, 1.5–2.37), liver burden disease 25–50% vs none (HR 1.37, 1.04–1.80) or 51–75% vs none (HR 1.81, 1.13–2.90), and diffuse Lauren subtype (HR 1.42, 95% CI, 1.14–1.76) were variables associated with worse prognosis. Treatment with RAM-PAC vs CT (HR 0.69, 0.55–0.83) and < 2 metastatic sites (HR 0.78, 0.63–0.96) was associated with better OS (Fig. 4B).

Discussion

In this real-life analysis based on the AGAMENON-SEOM registry we have confirmed a greater benefit of PAC-RAM vs CT in ORR, PFS and OS, independent of HER2 status.

The rationale for this study is that the optimal therapy upon progression to trastuzumab-CT is not well established. Currently, there are no phase 3 clinical trials that

Table 2 Toxicity

Adverse event	RAM-PAC, *N* (%) *N* = 204 (100)	CT, *N* (%) *N* = 348 (100)
Hypertension		
0	76.6	98.6
1	13.9	0.9
2	7.0	0.6
3	2.0	0
4	0.5	0
Proteinuria		
0	91.5	98.3
1	6.5	1.7
2	1.5	0
3	0.5	0
Bleeding		
0	79.1	90.1
1	14.4	4.3
2	4.0	1.2
3	2.0	3.8
4	0.5	0.3
5	0	0.3
Gastrointestinal perforation		
0	97.0	99.7
1	1.5	0.3
2	0.5	0
3	0.5	0
4	0.5	0
5	0.5	0
Thrombosis		
0	94.0	97.4
1	0	0
2	1.5	1.4
3	4.0	1.2
4	0.5	0
Anemia		
0	42.3	39.1
1	36.3	35.5
2	17.4	15.7
3	3.0	9.3
4	1.0	9
5	0	0.3
Neutropenia		
0	56.2	78.8
1	14.9	10.1
2	10.0	4.3
3	12.4	4.1
4	6.5	2.6
Thrombocytopenia		
0	82.6	91.9
1	12.4	6.1
2	3.0	1.7
3	1.5	0.3
4	0.5	0
Nausea		
0	53.7	54.4
1	35.8	36.2
2	9.5	8.1
3	1.0	0.9
NA (no available)	0	0.3
Vomiting		
0	77.1	73.6
1	15.9	17.4
2	5.5	5.8
3	1.0	2.6
NA	0.5	0.6
Diarrhea		
0	79.1	72.2
1	15.9	21.2
2	4.0	4.6
3	0.5	1.4
NA	0.5	0.6
Stomatitis		
0	75.1	76.2
1	15.9	17.1
2	7.0	5.5
3	2.0	1.2
Fatigue		
0	75.1	76.2
1	15.9	17.1
2	7.0	5.5
3	2.0	1.2
Skin Toxicity		
0	88.6	93.3
1	10.4	5.8
2	0	0.6
3	0	0.3
NA	1.0	0
Peripheral neuropathy		
0	45.3	66.4
1	32.8	22.6
2	18.9	9.0
3	2.5	1.4
NA	0.5	0.6
Alopecia		
0	53.7	57.1
1	24.4	18.8
2	16.9	18
NA	5.0	6.1

RAM-PAC ramucirumab-paclitaxel, *CT* chemotherapy, *NA* no available

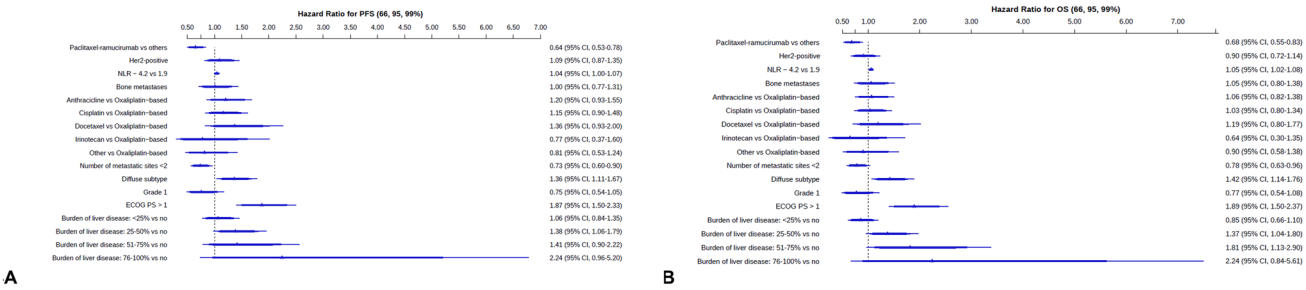

Fig. 4 PFS (**A**) and OS (**B**) prognostic models. *NLR* neutrophils/lymphocytes ratio; *ECOG PS* Eastern Cooperative Oncology Group Performance status. Chemotherapy regimens are those administered in the first line. For the categorical variable "burden of liver disease" the contrast is between each level and the rest. The neutrophil-to-lymphocyte ratio variable has been modeled by means of a restricted cubic splines, illustrating here the prognostic effect of the increase from 2.2 to 5.1 (25% and 75% percentiles, respectively)

have demonstrated the utility of extending HER2 blockade beyond first-line in HER2+ aGEC (Satoh et al. 2014; Thuss-Patience et al. 2017). The randomised phase 2 DESTINY-gastric02 study supports that trastuzumab deruxtecan could be a 2L HER2-targeted therapy option (E. Van Cutsem et al. 2021). However, the confirmatory phase 3 trial (DESTINY-gastric04) is ongoing (Shitara et al. 2021). In this setting, standard therapy after progression to trastuzumab-CT in HER2+ is the same as in HER2-negative aGC with RAM-PAC being the most widely recommended regimen, and the schedule with the highest level of evidence (Wilke et al. 2014; Muro et al. 2019; Martín-Richard et al. 2020). The RAINBOW trial showed a significant increase in OS with RAM-PAC compared with paclitaxel, considering it a new standard 2L for aGC patients [11]. However, a peculiarity of this clinical trial was the under-representation of patients with HER2+ tumors, 5.8% (n = 39) in RAINBOW trial vs 26.9% in our series. Analysis of this under-represented subgroup of patients in the RAINBOW study found no signal to support that the benefit in HER2+ aGC was different from that reported globally (de Vita et al. 2019). Nevertheless, uncertainty has persisted to date, even conditioning the selection of the control arm (at the investigator's discretion) in the DESTINY-gastric02 trial (E. Van Cutsem et al. 2021).

Our study supports the efficacy of RAM-PAC compared to CT in 2L regardless of HER2 status with the largest series of real-life Western patients in this setting. Bayesian modelling suggests that the most plausible hypothesis is RAM-PAC superiority in both HER2+ and HER2-negative aGEC. While the statistical evidence is limited (posterior probability of benefit [HR < 1] of 83%), these data are consistent with the rest of the available literature. Thus, the Korean study KCSG-ST19-16 ($n = 994$) evaluating 2L RAM-PAC has reported that the ORR may be higher in HER2+ ($n = 163$) vs HER2-negative aGC (23% vs 15%, $p = 0.025$) with comparable PFS (4.3 vs 3.7 months, $p = 0.054$) and OS (9.8 vs 10.1 months, $p = 0.564$) (Kim et al. 2022). Our data are also similar to those of the Italian RAMoss study (RAM-PAC, $n = 150$) that found a PFS and OS of 4.4 and 7.9 months (CI not reported) with RAM-PAC in HER2+ aGC ($n = 45$) that in our series was, 4.7 (95% CI 3.3–5.9) and 7.4 months (95% CI 6.1–12) in HER2+ aGEC (n = 60), respectively (di Bartolomeo et al. 2018). Likewise, our results are comparable to those of the Spanish RAMIS study (RAM-PAC, $n = 297$) that reported a PFS and OS of 4.9 (95% CI 3.5–7.4) and 9.7 months (95% CI 7.4–22.7) with RAM-PAC in HER2+ aGC ($n = 43$), respectively (Longo et al. 2021).

Regarding the applicability conditions, there are several aspects that need to be considered. Firstly, in contrast to the other studies that included patients with aGC (stomach and GEJ), our study involved 10.7% of HER2+ advanced esophageal adenocarcinoma. Consistent with a previous study of the AGAMENON-SEOM registry, advanced esophageal adenocarcinoma has clinicopathological features, prognostic factors, and treatment outcomes comparable to those of gastric and GEJ adenocarcinoma (Alvarez-Manceñido et al. 2021). Molecular analysis by TCGA (The Cancer Genome Atlas Research Network) supports that esophageal adenocarcinoma is reasonably similar to gastric adenocarcinoma (Kim et al. 2017). In fact, phase 3 trials with immunotherapy follow this trend grouping by histology (advanced gastroesophageal adenocarcinoma) rather than by location (Janjigian et al. 2021; Cohen et al. 2022). Secondly, our study, in contrast to the RAINBOW trial, included 11.7% of patients with HER2+ aGEC treated with RAM-PAC who presented with poor performance status (ECOG 2). The percentage is similar to that reported in the full sample of the RAMoss (11.3%) and RAMIS (9.4%) studies reflecting clinical practice. Although this small sample size does not allow assessment of a subgroup effect, these patients have a poorer prognosis, which should be considered in the therapeutic decision (di Bartolomeo et al. 2018; Longo et al. 2021). Thirdly, these patients come from the era before immunotherapy was prescribed in clinical practice. Currently, there is no evidence of a modification of the effect of RAM-PAC in patients who have previously received checkpoint inhibitors but data

from preliminary studies suggest that survival outcomes are superior with RAM-PAC after immunotherapy (Sasaki et al. 2020; Kankeu Fonkoua et al. 2021).

Our study has identified several prognostic factors that may be useful in the selection of 2L, including performance status, tumor burden (hepatic, number of metastatic sites), diffuse Lauren subtype, and NLR. In essence, these findings are comparable to those reported by the other studies with the caveat that the Korean and Spanish studies contributed some additional specific factors such as alkaline phosphatase and albumin (KCSG trial); unmeasurable disease (RAMIS study) and ascites (both studies) (Jung et al. 2018; Longo et al. 2021; Kim et al. 2022).

This study has several limitations. Firstly, the most conspicuous being the observational, retrospective design and the choice of treatment at the investigator's discretion, without randomization. Although attempts were made to control for major confounders, residual confounding bias cannot be completely ruled out, especially when the number of events is relatively low, and the model therefore supports limited covariates. Nevertheless, the results are consistent with those of the RAINBOW trial in each HER2 subtype and therapeutic group (Wilke et al. 2014; de Vita et al. 2019). Secondly, CT was pooled given the diversity of 2L regimens used, without being able to establish whether any of them had advantages over the others. However, to date, no 2L clinical trial that has compared CT regimens has demonstrated the superiority of any of them (Kang et al. 2012; Hironaka et al. 2013). Indeed, in the 2L DESTINY-gastric02 clinical trial, the comparator was chosen at the investigator's discretion (Van Cutsem et al. 2021).

In conclusion, the results of the AGAMENON-SEOM registry analysis of 2L treatment (RAM-PAC vs CT) efficacy in aGEC based on HER2 status are consistent, in the largest series in a Western population, with those previously published in this same context, and in an Eastern sample. RAM-PAC was superior to CT in PFS, OS and response rate, independent of HER2 status. These results justify the choice of PAC-RAM as a standard 2L treatment regardless of HER2 status, and its selection as the control arm of clinical trials in this setting.

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Author contributions SV, JG, ACB and PJF, developed the project, analyzed the data, and drafted the manuscript. The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript. All authors participated in the interpretation and discussion of data, and the critical review of the manuscript.

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Data availability Available upon request to the authors.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest JG declares he has received honoraria for advisory consulting and speaking role from Lilly, Servier and BMS. PJF declares she has received honoraria for advisory consulting and speaking from Lilly, MSD and BMS. VA declares she has received honoraria for advisory consulting and speaking role from Lilly, MSD and BMS. AFM declares she has received honoraria for advisory consulting and speaking role from Lilly, Servier, Pierre Fabre, Merck, MSD and BMS. RVT declares she has received honoraria for advisory consulting and speaking from Amgen, Merck, Sanofi, Servier, Bristol-MS, Bayer and Roche and has received support for educational, scientific activities and travel from Amgen, Roche, Lilly, Sanofi, Bristol-MS, Pierre-Fabre and Servier. The other authors declare that they have no conflict of interest regarding the scope of this article.

Ethics approval and consent to participate 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 or a substitute for it was obtained from all patients before they were included in the study. Ethics committee Hospital General Universitario Morales Meseguer approved the study (C.P.AGAMENON-C.I.EST:30/14, 26 November 2014).

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