



Real-world efficacy of ramucirumab plus paclitaxel with or without nivolumab in patients with advanced gastric and gastroesophageal junction cancers

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■ MAIN POINTS

- Ramucirumab plus paclitaxel demonstrates consistent efficacy as a second-line treatment for advanced gastric/GEJ cancers in real-world settings.
- Although response rates were numerically higher with the addition of nivolumab to this combination, no statistically significant clinical benefit was observed.
- Ramucirumab plus paclitaxel (\pm ICI) may serve as an effective third-line treatment option in patients with good performance status.

■ ABSTRACT

Aim: This study primarily aimed to assess the efficacy of second-line ramucirumab (RAM) plus paclitaxel (PTX) in patients with advanced gastric and gastroesophageal junction (GEJ) cancers and to compare its outcomes with those of RAM+PTX plus immune checkpoint inhibitor (ICI) in real-world practice. The secondary objective was to assess the safety of RAM+PTX (\pm ICI) and to explore its efficacy in later-line settings.

Materials and Methods: This single-center study retrospectively analyzed the clinicopathologic data of patients with advanced gastric/GEJ cancer treated with RAM+PTX, with or without an ICI, in second-line or later settings between January 2018 and September 2024. Efficacy was evaluated based on the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). We analyzed efficacy outcomes by treatment line.

Results: We identified 46 patients (female, 54.3%) who received RAM+PTX (\pm ICI). In the second-line setting, 27 patients (58.7%) received RAM+PTX, and 10 patients (21.7%) received RAM+PTX plus nivolumab. The ORRs were 18.5% and 30.0% ($p=0.66$), and the DCRs were 55.6% and 80% ($p=0.26$), respectively. The addition of nivolumab did not significantly improve survival outcomes (median PFS, 4.3 vs. 3.1 months; HR, 0.93; 95% CI, 0.44-1.98; $p=0.85$; median OS, 7.8 vs. 9.6 months; HR, 0.82; 95% CI, 0.35-1.91; $p=0.64$). Age ≥ 50 years (HR, 2.90; 95% CI, 1.24-6.78; $p=0.014$) and the presence of ascites (HR, 2.86; 95% CI, 1.14-7.16; $p=0.025$) were independently associated with poorer OS.

Conclusion: The real-world efficacy of RAM+PTX as second-line therapy in advanced gastric/GEJ cancers is consistent with the results of randomized trials, though grade ≥ 3 adverse events were more frequent. While adding nivolumab did not confer a statistically significant benefit, a numerical improvement in ORR and DCR indicates potential value that warrants further prospective evaluation.

Keywords: Immunotherapy, Stomach neoplasms, VEGFR-2, Ramucirumab

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■ INTRODUCTION

Globally, gastric and gastroesophageal junction (GEJ) cancers are the fifth most common cause of cancer-related death [1]. Current first-line systemic therapy for advanced gastric/GEJ cancers consists of platinum- and fluoropyrimidine-based chemotherapy, with the addition of human epidermal growth factor receptor 2 (HER2)-targeted agents and/or immune checkpoint inhibitors (ICIs) for selected patients [2]. Following failure of first-line therapy, subsequent systemic therapies demonstrate limited efficacy, and only 14–27% of

patients are able to receive third-line systemic therapy in real-world practice [3,4]. The development of more effective second-line therapeutic options and combination strategies is essential to improve oncologic outcomes in advanced gastric/GEJ cancers.

Ramucirumab (RAM) is a fully human IgG1 monoclonal antibody that specifically binds to and blocks vascular endothelial growth factor receptor-2 (VEGFR-2) [5]. In the pivotal phase III RAINBOW trial, second-line treatment with RAM plus paclitaxel (PTX) improved overall survival (OS)

compared with PTX monotherapy, and this combination has become one of the recommended second-line treatment options for advanced gastric/GEJ cancers [2,6]. The efficacy and safety of incorporating immune checkpoint inhibitors (ICIs) into this regimen remain unclear and have been investigated only in small early-phase studies [7,8]. Despite the encouraging results of early-phase studies combining ICIs with RAM+PTX, evidence regarding their efficacy in the second-line treatment of advanced gastric/GEJ cancer remains limited. We conducted a retrospective study to explore the potential benefit of adding ICI to RAM+PTX. The primary objective of this study was to evaluate the efficacy of second-line RAM+PTX and to compare its outcomes with those of RAM+PTX combined with an ICI in real-world clinical practice. The secondary objective was to assess the safety profile of this regimen and to explore the efficacy of RAM+PTX in later-line settings.

■ MATERIALS AND METHODS

In this single-center study, we retrospectively analyzed the clinical and pathological data of patients with metastatic gastric/GEJ adenocarcinoma treated with RAM+PTX, with or without an ICI, in second-line or later settings between January 2018 and September 2024. Adult patients aged ≥ 18 years with metastatic gastric/GEJ adenocarcinoma who had experienced disease progression during first-line therapy were included. Patients who received RAM+PTX (\pm ICI) in later lines were also included. ICI was added to RAM+PTX at the discretion of the treating physicians, particularly for patients with programmed cell death ligand-1 combined positive score (PD-L1 CPS) ≥ 1 , based on the results of early-phase studies [7,8]. As RAM and nivolumab are not reimbursed for second-line or later treatment of metastatic gastric/GEJ adenocarcinoma in Türkiye, only a limited number of patients are able to access RAM+PTX (\pm ICI). All eligible patients receiving these regimens in the second-line or later settings were included in the study. Patients were administered RAM at 8 mg/kg on days 1 and 15, PTX at 80 mg/m² on days 1, 8, and 15, and nivolumab at 3 mg/kg on days 1 and 15 of each 4-week cycle, continuing until disease progression or unacceptable toxicity. Each 4-week interval was counted as one treatment cycle. Data collected from these patients included baseline characteristics, treatment details, tumor response, treatment-related adverse events (TRAEs), laboratory results, and survival status. Efficacy was determined using the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and OS. Tumor responses were evaluated by investigators following the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [9]. ORR represented the proportion of patients achieving a complete response (CR) or partial response (PR), while DCR included those with CR, PR, or stable disease (SD) as their best overall outcome. PFS was measured from the initiation of RAM+PTX (\pm ICI) to the date of disease

progression or death. OS was measured from the initiation of RAM+PTX (\pm ICI) to death or the date of last follow-up for surviving patients. For patients with unknown survival status, survival data were censored at the most recent date on which the patient was confirmed to be alive based on medical documentation. Safety was assessed through TRAE analysis. All TRAEs were categorized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [10]. We analyzed efficacy outcomes by treatment line, whereas TRAEs were evaluated across the entire study cohort.

This study adhered to the principles of Good Clinical Practice and was approved by the local institutional review board (Koç University Ethics Committee, Approval ID: 2025.096.IRB2.044). The institutional review board exempted the study from the requirement to obtain individual informed consent given the retrospective design of the study.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software version 25.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were reported as medians with interquartile ranges (IQR), whereas categorical variables were presented as frequencies with percentages. Chi-squared or Fisher's exact tests were applied to compare percentages, as appropriate, based on sample size and expected cell counts. The follow-up duration was determined by the reverse Kaplan–Meier method, and PFS and OS were assessed via Kaplan–Meier estimates. Cox proportional hazards regression was used for the univariate and multivariate analyses. Variables showing an association at $p < 0.10$ in univariate analysis, as well as the treatment arm (the primary exposure variable), were entered into the multivariate model to adjust for potential confounders while minimizing the risk of overfitting. A two-sided p value < 0.05 was statistically significant.

■ RESULTS

We identified 46 patients (female, 54.3%) with metastatic gastric/GEJ adenocarcinoma who received RAM+PTX (\pm ICI) as second-line or later therapy. In the second-line setting, 27 (58.7%) patients received RAM+PTX alone, and 10 (21.7%) patients received RAM+PTX combined with nivolumab. In the third-line setting ($n=9$, 19.6%), 7 (15.2%) patients received RAM+PTX alone, whereas 2 (4.3%) received the same regimen combined with nivolumab.

In the second-line setting, the median (IQR) age was 50 (44–59) years for patients treated with RAM+PTX alone and 49 (38–62) years for those treated with RAM+PTX plus nivolumab ($p=0.62$) (Table 1). The majority of patients had tumors with diffuse histology (66.7% in the RAM+PTX group vs. 80.0% in the RAM+PTX+nivolumab group; $p=0.73$) and HER2-negative disease (88.9% vs. 100.0%;

Table 1. Patient characteristics in the second-line and third-line groups and comparison of these features among the second-line treatment arms.

Variables	2L		P value	3L
	RAM+PTX (n = 27)	RAM+PTX+ICI (n = 10)		All patients (n = 9)
Age, median (IQR)	50 (44-59)	49 (38-62)	0.62 ^a	51 (46-58)
Female, n (%)	14 (51.9)	6 (60.0)	0.73 ^b	5 (55.6)
ECOG PS, n (%)				
0-1	24 (88.9)	9 (90.0)	1.0 ^b	9 (100.0)
≥2	3 (11.1)	1 (10.0)		0
Primary tumor location, n (%)				
Cardia	9 (33.3)	2 (20.0)	0.63 ^c	1 (11.1)
Corpus	11 (40.7)	4 (40.0)		3 (33.3)
Antrum	7 (25.9)	4 (40.0)		4 (44.4)
Unknown	0	0		1 (11.1)
Histological subtype, n (%)				
Diffuse	18 (66.7)	8 (80.0)	0.73 ^c	5 (55.6)
Intestinal	4 (14.8)	1 (10.0)		0
Unknown	5 (18.5)	1 (10.0)		4 (44.4)
HER2 status, n (%)				
Negative	24 (88.9)	10 (100.0)	0.55 ^b	9 (100.0)
Positive	3 (11.1)	0		0
MMR status, n (%)				
pMMR	23 (85.2)	10 (100.0)	0.56 ^c	8 (88.9)
dMMR	0	0		1 (11.1)
Unknown	4 (14.8)	0		0
PD-L1 status, n (%)				
CPS<1	19 (70.4)	5 (50.0)	0.059 ^c	3 (33.3)
CPS≥1	4 (14.8)	5 (50.0)		5 (55.6)
Unknown	4 (14.8)	0		1 (11.1)
Time to metastasis, n (%)				
Synchronous	18 (66.7)	7 (70.0)	1.0 ^b	9 (100.0)
Metachronous	9 (33.3)	3 (30.0)		0
Peritoneal metastases, n (%)				
Yes	14 (51.9)	9 (90.0)	0.097 ^c	5 (55.6)
No	9 (33.3)	1 (10.0)		4 (44.4)
Unknown	4 (14.8)	0		0
Liver metastases, n (%)				
Yes	5 (18.5)	5 (50.0)	0.094 ^b	3 (33.3)
No	22 (81.5)	5 (50.0)		6 (66.6)
Unknown	0	0		0

^a Mann–Whitney U test, ^b Fisher’s exact test, ^c Chi-square test. CPS, combined positive score; dMMR, deficient MMR; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IQR, interquartile range; MMR, mismatch repair; PD-L1, programmed cell death ligand-1; pMMR, proficient MMR; PTX, paclitaxel; RAM, ramucirumab.

Table 2. The best overall response.

	2L		P value	3L
	RAM+PTX (n = 27)	RAM+PTX+ICI (n = 10)		All patients (n = 9)
Best overall response, n (%)				
Complete response (CR)	0	0		1 (11.1)
Partial response (PR)	5 (18.5)	3 (30.0)		2 (22.2)
Stable disease (SD)	10 (37.0)	5 (50.0)		3 (33.3)
Progressive disease (PD)	12 (44.4)	2 (20.0)		3 (33.3)
Objective response rate, n (%)	5 (18.5)	3 (30.0)	0.66 ^a	3 (33.3)
Disease control rate, n (%)	15 (55.6)	8 (80.0)	0.26 ^a	6 (66.7)

^a Fisher’s exact test.

Table 3. Univariate and multivariate analyses assessing factors influencing overall survival in patients treated with second-line ramucirumab plus paclitaxel, with or without an immune checkpoint inhibitor.

Variables	Median OS, months (95% CI)	Univariate Analysis HR (95% CI)	P value ^a	Multivariate Analysis HR (95% CI)	P value ^a
Gender					
Female	9.6 (3.8-15.4)	0.74 (0.35-1.57)	0.43		
Male	8.9 (4.7-13.1)				
Age					
<50 years	11.0 (8.6-13.4)	2.53 (1.11-5.76)	0.027	2.90 (1.24-6.78)	0.014
≥50 years	6.3 (4.5-8.1)				
ECOG PS					
0-1	9.0 (5.2-12.9)	2.88 (0.96-8.66)	0.059	2.71 (0.85-8.65)	0.091
≥2	4.4 (2.8-5.9)				
Peritoneal metastases					
Yes	8.9 (5.3-12.5)	1.24 (0.52-2.96)	0.63		
No	9.0 (5.2-12.9)				
Liver metastases					
Yes	7.8 (2.3-13.3)	1.62 (0.71-3.68)	0.25		
No	8.9 (5.7-12.0)				
Ascites					
Yes	6.3 (4.1-8.5)	2.81 (1.23-6.43)	0.014	2.86 (1.14-7.16)	0.025
No	11.0 (7.9-14.1)				
CEA, µg/L					
<ULN	9.6 (4.2-14.9)	0.65 (0.28-1.50)	0.31		
≥ULN	9.0 (4.7-13.4)				
CA 19-9, U/mL					
<ULN	9.6 (7.1-12.1)	1.13 (0.49-2.63)	0.77		
≥ULN	5.5 (2.9-8.1)				
Treatment arm					
RAM+PTX	7.8 (4.2-11.3)	0.82 (0.35-1.91)	0.64	1.51 (0.56-4.08)	0.42
RAM+PTX+ICI	9.6 (7.6-11.5)				
PIV					
<460.46	9.6 (3.1-16.1)	1.16 (0.55-2.43)	0.70		
≥460.46	7.8 (4.9-10.6)				
PNI					
<37.01	6.3 (5.2-7.4)	0.61 (0.29-1.29)	0.19		
≥37.01	11.0 (8.3-13.7)				

^a Cox proportional hazards regression. CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PIV, pan-immune inflammation value; PNI, prognostic nutritional index; PTX, paclitaxel; RAM, ramucirumab; ULN, upper limit of normal.

Table 4. Treatment-related adverse events during treatment with ramucirumab plus paclitaxel, with or without immune checkpoint inhibitor.

Adverse events	Any grade, n (%)	Grade ≥3, n (%)
Anemia	42 (91.3)	18 (39.1)
Neutropenia	24 (52.2)	15 (32.6)
Thrombocytopenia	24 (52.2)	6 (13.0)
AST/ALT increased	27 (58.7)	5 (10.9)
Infection	12 (26.1)	9 (19.6)
Nausea-diarrhea	3 (6.5)	2 (4.3)
Neuropathy	2 (4.3)	0
Thrombosis/bleeding	7 (15.2)	4 (8.7)
Perforation/Fistula	3 (6.5)	2 (4.3)
Others	6 (13.0)	4 (8.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

p=0.55). Mismatch repair deficiency (dMMR) was not detected in any patient. PD-L1 CPS was <1 in most patients (70.4%) treated with RAM+PTX alone, whereas it was ≥1

in half of the patients (50.0%) treated with RAM+PTX plus nivolumab (p=0.059). The percentages of patients with synchronous metastases were 66.7% and 70.0%, respectively

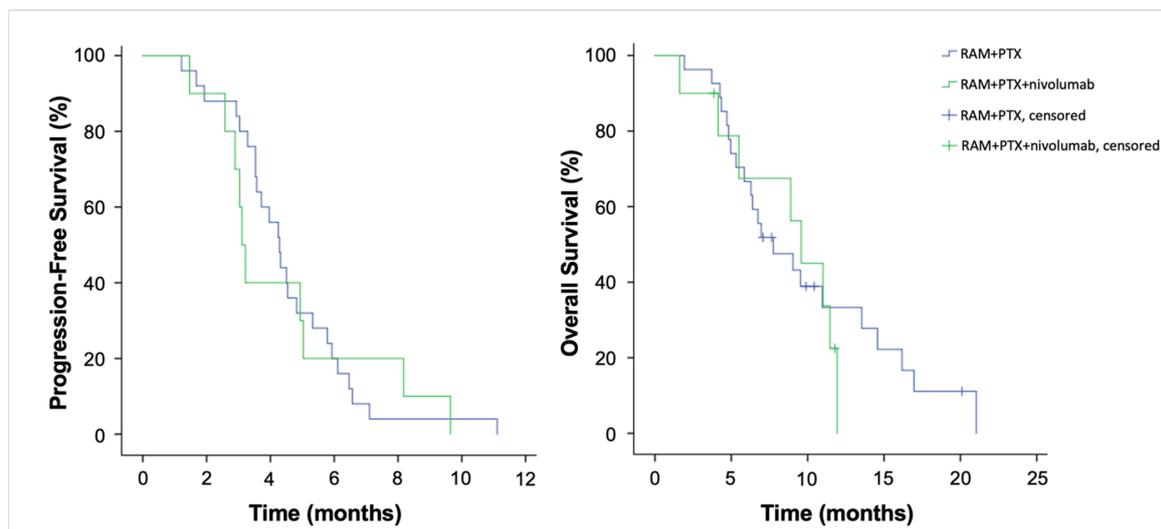


Figure 1. Progression-free survival and overall survival analyses of patients who received ramucirumab plus paclitaxel and those who received ramucirumab plus paclitaxel plus nivolumab as second-line treatment.

($p=1.0$). Patients treated with RAM+PTX plus nivolumab showed higher frequencies of peritoneal (51.9% vs. 90.0%; $p=0.12$) and liver (18.5% vs. 50.0%; $p=0.094$) metastases, although not statistically significant. The median age in the third-line setting was 51 (46-58). Diffuse histology was observed in 55.6% of the patients, and all patients had HER2-negative disease. dMMR was observed in only one patient (11.1%), while 55.6% of patients had a PD-L1 CPS of ≥ 1 . All patients had synchronous metastases, including peritoneal metastases in 55.6% and liver metastases in 33.3%.

In the second-line setting, the median follow-up duration was 20.1 months (95% confidence interval [CI], 8.1-32.1). The median (IQR) numbers of RAM and PTX cycles were both 4 (3-5) in RAM+PTX group. The median (IQR) numbers of cycles among those treated with RAM+PTX plus nivolumab were 5 (3-6) for RAM, 4 (3-6) for PTX, and 4 (3-6) for nivolumab. No significant differences in response rates or survival outcomes were observed between patients treated with RAM+PTX alone and those receiving RAM+PTX plus nivolumab. The ORRs were 18.5% and 30.0% in the RAM+PTX and RAM+PTX plus nivolumab groups, respectively ($p=0.66$) (Table 2). The DCRs were 55.6% and 80.0% in the RAM+PTX and RAM+PTX plus nivolumab groups, respectively ($p=0.26$). The median PFS was 4.3 months (95% CI 3.7-4.9) in the RAM+PTX group and 3.1 months (95% CI 2.8-3.4) in the RAM + PTX plus nivolumab group (hazard ratio [HR], 0.93; 95% CI, 0.44-1.98; $p=0.85$) (Figure 1). The median OS was 7.8 months (95% CI, 4.2-11.3) in the RAM+PTX group and 9.6 months (95% CI, 7.6-11.5) in the RAM+PTX plus nivolumab group (HR, 0.82; 95% CI, 0.35-1.91; $p=0.64$).

The median follow-up duration in the third-line setting was 10.0 months (95% CI, 0.0-36.5). The median (IQR) numbers of RAM and PTX cycles were 4 (3-7) and 4 (3-6), respectively. The ORR and DCR were 33.3% and 66.7%, respectively (Ta-

ble 2). The median PFS was 6.6 months (95% CI, 0.0-17.1), and the median OS was 7.4 months (95% CI, 2.0-12.7).

In multivariate analyses of patients receiving second-line RAM+PTX (\pm ICI), age ≥ 50 years (HR, 2.90; 95% CI, 1.24-6.78; $p=0.014$) and the presence of ascites (HR, 2.86; 95% CI, 1.14-7.16; $p=0.025$) were independently associated with worse OS (Table 3).

The most common ($>10\%$) grade 3 TRAEs while receiving RAM+PTX (\pm ICI) were anemia (39.1%), neutropenia (32.6%), infections (19.6%), thrombocytopenia (13.0%), and alanine aminotransferase and/or aspartate aminotransferase increase (10.9%) (Table 4). Seven patients (15.2%) experienced any-grade thrombosis and/or bleeding, while three patients (6.5%) experienced any-grade gastrointestinal perforation and/or fistula formation. Four patients (10.8%) receiving second-line treatment and two patients (22.2%) receiving third-line treatment discontinued therapy due to TRAEs.

DISCUSSION

Our results indicate that the real-world efficacy of RAM+PTX as second-line therapy for advanced gastric/GEJ cancers is consistent with the outcomes observed in randomized clinical trials. Nevertheless, grade ≥ 3 TRAEs were more common in our cohort. Our results also showed no clear benefit from adding an ICI to this regimen, despite numerically higher ORR and DCR in patients who received RAM+PTX plus ICI. Furthermore, our results indicate that RAM+PTX (\pm ICI) may serve as an effective third-line treatment option in patients with good performance status.

The therapeutic landscape of advanced gastric/GEJ cancers has been rapidly evolving in recent years with the incorporation of ICIs based on PD-L1 expression, microsatellite instability, and tumor mutational burden, as well as novel targeted agents directed against HER2, Claudin 18.2 (CLDN18.2),

and fibroblast growth factor receptor 2 (FGFR2) [11]. However, available treatment options are still limited following progression on first-line platinum- and fluoropyrimidine-based chemotherapy with or without ICIs and/or targeted therapy, especially for patients ineligible for targeted agents or ICIs [2,11]. The phase III REGARD trial demonstrated that second-line RAM monotherapy significantly prolonged both PFS and OS compared with placebo (median PFS, 2.1 vs. 1.3 months; HR, 0.48; $p < 0.0001$; median OS, 5.2 vs. 3.8 months; HR, 0.78; $p = 0.047$), confirming the clinical relevance of VEGFR-2 inhibition in advanced gastric/GEJ cancer [12]. In the pivotal phase III RAINBOW trial, the combination of RAM+PTX significantly improved both PFS and OS compared with PTX monotherapy (median PFS, 4.4 vs. 2.9 months; HR, 0.64; $p < 0.0001$; median OS, 9.6 vs. 7.4 months; HR, 0.81; $p = 0.017$), establishing this regimen as one of the recommended second-line treatments for advanced gastric/GEJ cancers [13]. In our cohort, while the median PFS was comparable to that observed in the RAINBOW trial, the ORR, DCR, and median OS were numerically lower, with the RAINBOW trial reporting ORR and DCR of 28% and 80%, respectively [13]. Differences in histological subtype distribution may partly explain these findings. In the RAINBOW trial, the clinical benefit of adding RAM to PTX was more pronounced in patients with intestinal-type histology [13]. Consistently, in a real-world analysis, Fountzilias et al. reported that the OS advantage of second-line RAM+PTX was confined to the intestinal subtype, with no significant benefit in diffuse or mixed histologies [14]. In our study, intestinal-type tumors represented only 14.8% of patients in the second-line RAM+PTX group, compared with 44% in the RAINBOW cohort [13].

Based on the results of the CheckMate-649 and KEYNOTE-859 trials, the addition of nivolumab for patients with PD-L1 CPS ≥ 5 or pembrolizumab for patients with PD-L1 CPS ≥ 10 to first-line platinum- and fluoropyrimidine-based combination chemotherapy has become the standard of care in advanced gastric/GEJ cancers [15,16]. However, the efficacy and safety of adding ICI to second-line RAM+PTX in patients who did not receive ICI in the first-line setting remain under investigation. A phase I/II trial reported encouraging efficacy with the combination of RAM+PTX and nivolumab, particularly among patients with PD-L1 CPS ≥ 1 , representing 60.5% of the study population ($n = 43$) [7]. Patients with PD-L1 CPS ≥ 1 showed higher ORR (46.2% vs. 30.8%), longer median PFS (6.4 vs. 5.1 months), and longer median OS (13.8 vs. 8.0 months) than those with CPS < 1 . Notably, grade ≥ 3 TRAEs occurred in 90.7% of patients. Another phase II study investigating the efficacy and safety of avelumab with RAM+PTX as second-line treatment reported a 6-month OS rate of 71.2% and a median OS of 10.4 months [8]. The ongoing phase II/III SWOG S2303 (PARAMUNE) trial is assessing the efficacy and safety of adding nivolumab to RAM+PTX compared

with RAM+PTX alone in patients with advanced-stage gastric and esophageal cancers with PD-L1 CPS ≥ 1 [17]. To the best of our knowledge, our study is the first retrospective analysis comparing the efficacy of second-line RAM+PTX versus RAM+PTX plus nivolumab. Despite the absence of a statistically significant clinical benefit with the addition of an ICI, we observed numerically higher ORR, DCR, and median OS in the RAM+PTX plus nivolumab group. The lack of statistical significance may be partly explained by the small sample size and the fact that only 50% of the patients in the RAM+PTX plus nivolumab group had PD-L1 CPS ≥ 1 , as the benefit of adding nivolumab appears to be primarily confined to patients with PD-L1 CPS ≥ 1 in the previous phase I/II study [7]. The median PFS was numerically lower in the RAM+PTX plus nivolumab group than in the RAM+PTX group. This may be partly explained by the modest ORR of 30%, as ICIs may prolong PFS by inducing durable responses in a subset of patients, and by the small sample size in this cohort. This finding might also reflect assessment-time bias because unscheduled early imaging (e.g., due to adverse events or comorbidities) could have led to the earlier documentation of progression than planned.

In our study, older age (≥ 50 years) and the presence of ascites were identified as independent poor prognostic factors for OS. These findings are consistent with those of previous studies. The exploratory analysis of the RAINBOW trial demonstrated that the median OS was shorter in patients with ascites (median OS for the RAM+PTX group: 7.2 vs. 11.4 months) [18]. However, the efficacy of the RAM+PTX combination was comparable between patients with and without ascites [18]. Similarly, in a real-world study, Chen et al. reported that the presence of ascites was associated with worse OS in both the RAM monotherapy group (median OS: 3.9 vs. 6.8 months) and the RAM+PTX group (median OS: 7.3 vs. 15.5 months) [19]. Our results support previous evidence indicating that the presence of ascites before RAM+PTX treatment is a poor prognostic factor.

In our cohort, we observed higher rates of grade ≥ 3 anemia and thrombocytopenia in real-world practice than in clinical trials [13]. Moreover, thromboembolic events, gastrointestinal perforation, and fistula formation were more frequent in our cohort. These findings underscore the importance of close clinical monitoring to enable early detection and management of potentially life-threatening adverse events associated with RAM+PTX combination.

Limitations

This study has several limitations. The primary limitations of this study are the small sample size in the second-line treatment arms and the retrospective, single-center design. Currently, RAM and ICIs are not reimbursed for second-line treatment of advanced gastric/GEJ cancers in Türkiye, which largely explains the limited number of patients who could receive these combinations. Nevertheless, our real-world data

may serve as supportive evidence for future prospective studies in this patient population, where therapeutic options remain limited.

■ CONCLUSION

In conclusion, the real-world efficacy of RAM+PTX as second-line therapy in advanced gastric/GEJ cancers is consistent with the results of pivotal randomized trials. However, grade ≥ 3 TRAEs were more frequent in clinical practice. Although the addition of an ICI did not yield a statistically significant benefit, the ORR and DCR numerically improved. Further prospective studies, particularly in patients with PD-L1-positive tumors, are needed to clarify the potential benefit of adding an ICI. Moreover, RAM+PTX (\pm ICI) appears to be a reasonable third-line treatment option for patients with preserved performance status.

Ethics Committee Approval: The Ethics Committee of Koç University approved this study (Approval ID: 2025.096.IRB2.044, February 26, 2025).

Informed Consent: The study was retrospective, informed consent was not required from the patient.

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■ REFERENCES

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263. doi: [10.3322/caac.21834](https://doi.org/10.3322/caac.21834).
- Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(10):1005-1020. doi: [10.1016/j.annonc.2022.07.004](https://doi.org/10.1016/j.annonc.2022.07.004).
- Le DT, Ott PA, Korytowsky B, Le H, Le TK, Zhang Y, et al. Real-world Treatment Patterns and Clinical Outcomes Across Lines of Therapy in Patients With Advanced/Metastatic Gastric or Gastroesophageal Junction Cancer. *Clin Colorectal Cancer.* 2020;19(1):32-38.e3. doi: [10.1016/j.clcc.2019.09.001](https://doi.org/10.1016/j.clcc.2019.09.001).
- Chan W, Lam K, So T, Lee VH, Kwong LD. Third-line systemic treatment in advanced/metastatic gastric cancer: a comprehensive review. *Ther Adv Med Oncol.* 2019;11:1758835919859990. doi: [10.1177/1758835919859990](https://doi.org/10.1177/1758835919859990).
- Oholendt AL, Zadlo JL. Ramucirumab: A New Therapy for Advanced Gastric Cancer. *J Adv Pract Oncol.* 2015;6(1):71-5. doi: [10.6004/jadpro.2015.6.1.8](https://doi.org/10.6004/jadpro.2015.6.1.8).
- Wilke H, Muro K, Cutsem EV, Oh S-C, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-35. doi: [10.1016/S1470-2045\(14\)70420-6](https://doi.org/10.1016/S1470-2045(14)70420-6).
- Nakajima TE, Kadowaki S, Minashi K, Nishina T, Yamanaka T, Hayashi Y, et al. Multicenter Phase I/II Study of Nivolumab Combined with Paclitaxel Plus Ramucirumab as Second-line Treatment in Patients with Advanced Gastric Cancer. *Clin Cancer Res.* 2021;27(4):1029-1036. doi: [10.1158/1078-0432.CCR-20-3559](https://doi.org/10.1158/1078-0432.CCR-20-3559).
- Thuss-Patience P, Högner A, Goekkurt E, Stahl M, Kretzschmar A, Götze T, et al. Ramucirumab, Avelumab, and Paclitaxel as Second-Line Treatment in Esophagogastric Adenocarcinoma: The Phase 2 RAP (AIO-STO-0218) Nonrandomized Controlled Trial. *JAMA Netw Open.* 2024;7(1):e2352830. doi: [10.1001/jamanetworkopen.2023.52830](https://doi.org/10.1001/jamanetworkopen.2023.52830).
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228–47. doi: [10.1016/j.ejca.2008.10.026](https://doi.org/10.1016/j.ejca.2008.10.026).
- Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.
- Taieb J, Bennouna J, Penault-Llorca F, Basile D, Samalin E, Zaanan A. Treatment of gastric adenocarcinoma: A rapidly evolving landscape. *Eur J Cancer.* 2023;195:113370. doi: [10.1016/j.ejca.2023.113370](https://doi.org/10.1016/j.ejca.2023.113370).
- Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39. doi: [10.1016/S0140-6736\(13\)61719-5](https://doi.org/10.1016/S0140-6736(13)61719-5).
- Wilke H, Muro K, Van Cutsem E, Oh S-C, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-35. doi: [10.1016/S1470-2045\(14\)70420-6](https://doi.org/10.1016/S1470-2045(14)70420-6).
- Fountzilas E, Souglakos J, Alafis J, Dadouli K, Koumariou A, Tsoukalas N, et al. Real-world efficacy and toxicity data of paclitaxel and ramucirumab compared with other treatment regimens in patients with advanced gastric cancer. *ESMO Gastrointest Oncol.* 2024;5:100073. doi: [10.1016/j.esmogo.2024.100073](https://doi.org/10.1016/j.esmogo.2024.100073).
- Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* 2021;398(10294):27-40. doi: [10.1016/S0140-6736\(21\)00797-2](https://doi.org/10.1016/S0140-6736(21)00797-2).
- Rha SY, Oh D-Y, Yañez P, Bai Y, Ryu M-H, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2023;24(11):1181-1195. doi: [10.1016/S1470-2045\(23\)00515-6](https://doi.org/10.1016/S1470-2045(23)00515-6). Erratum in: *Lancet Oncol.* 2024;25(12):e626. doi: [10.1016/S1470-2045\(24\)00650-8](https://doi.org/10.1016/S1470-2045(24)00650-8).

17. Saeed A, Colby S, Oberstein PE, Duda DG, Park R, Agarwal R, et al. S2303: phase II/III trial of paclitaxel + ramucirumab ± nivolumab in gastric and esophageal adenocarcinoma (PARAMUNE). *Future Oncol.* 2025;21(11):1325-1331. doi: [10.1080/14796694.2025.2485020](https://doi.org/10.1080/14796694.2025.2485020).
18. Muro K, Jen M-H, Cheng R. Is ramucirumab and paclitaxel therapy beneficial for second-line treatment of metastatic gastric or junctional adenocarcinoma for patients with ascites? Analysis of RAINBOW phase 3 trial data. *Cancer Manag Res.* 2019;11:2261-2267. doi: [10.2147/CMAR.S193739](https://doi.org/10.2147/CMAR.S193739).
19. Chen Y, Katayose T, Nagaoka S, Piao Y, Yamaguchi K, Asou H. A post-marketing observational study of ramucirumab in patients with gastric cancer in Japan. *Gastric Cancer.* 2021;24(6):1320-1329. doi: [10.1007/s10120-021-01199-0](https://doi.org/10.1007/s10120-021-01199-0).