






## Research Article

# Nivolumab, Ramucirumab and Paclitaxel Combination as Second Line Therapy for Advanced Stage Gastric Cancer

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### Abstract

**Objectives:** Nivolumab immunotherapy, as well as ramucirumab with or without paclitaxel are treatment options as second line for advanced stage gastric cancer regardless of Programmed death-ligand 1 (PDL-1) status. These two tolerable treatments are not studied as combination in a phase 3 study, but phase 2. In our study, we aim to evaluate the real life data as efficacy and tolerability of this combination on gastric cancer patients.

**Methods:** Retrospective data of the patients diagnosed with gastric adenocarcinoma whose having progressive metastatic disease after first-line systemic treatment at Koc University Hospital Medical Oncology Outpatient Clinic is evaluated. Immunotherapy in the first-line treatment was the exclusion criteria.

**Results:** Patients' median age was 47 years (min 24-max 83), and PDL-1 was  $\geq 1\%$  in 50% of patients. Progression-free and overall survival were 4.9 (95% CI: 0.0-10.3) and 10.9 months (95% CI: 6.1-15.8), respectively. Disease control rate and objective response rate were found to be 80% and 50%, respectively. PDL-1 status was not related to progression-free survival, overall survival, or response rate ( $p=0.66$ , 0.32 and 0.76, respectively). The regimen was generally tolerable with manageable side effects. The most common side effects were anemia, elevated liver enzymes and neutropenia.

**Conclusion:** The combination of nivolumab along with paclitaxel and ramucirumab is a promising, effective and tolerable second line option for advanced gastric cancer. The regimen can be used irrespective of PDL-1 status, making immune checkpoints inhibitors an option for low immunogenic gastric tumors.

**Keywords:** Antiangiogenic agents, gastric cancer, nivolumab, ramucirumab, immunotherapy

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Gastric cancer represents fifth common cause of all cancer deaths worldwide, according to GLOBOCAN 2022 data.<sup>[1]</sup> At the time of diagnosis, 36% of all cases are in the metastatic stage.<sup>[2]</sup> Chemotherapy (ChT), anti-angiogenic agents, and for selected patients, anti-human epidermal growth factor receptor 2 (HER2) agents, as well as immunotherapy, are main treatment modalities for advanced-stage patients. Unfortunately, despite these

treatment modalities, which are targeting different phases of cancer development, survival improvement has not been satisfactory in stage four disease. While the average best lifespan for patients receiving first-line treatment is around one year, this period reduces to approximately six months in the second line.<sup>[3]</sup> The percentage of patients able to proceed to the third-line treatment is also only around 26%.<sup>[4]</sup>

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Programmed cell death protein 1 (PD-1) targeting pembrolizumab is recommended with ChT for the first line of advanced gastric adenocancer with Combined Positive Score (CPS) >10 based on KEYNOTE-590 trial.<sup>[5]</sup> Programmed death-ligand 1 (PDL-1) inhibitor nivolumab is indicated as a first-line treatment for patients with HER2-negative gastric adenocarcinoma who have a PDL-1 CPS greater than five, in combination with ChT, based on CheckMate-649 study.<sup>[6]</sup> These first line trials showed that only highly immunogenic gastric tumors are responsive to immune checkpoint inhibitors. For later lines, ATTRACTION-2 phase three trial evaluating nivolumab revealed improved survival outcomes in advanced gastric cancer patients when compared to those receiving a placebo.<sup>[7]</sup> In the 2-year follow-up, overall survival (OS) was higher in the nivolumab group than the placebo group, irrespective of PDL-1 status; but objective response rate (ORR) was very low (11%).<sup>[8]</sup> In another later line trial KEYNOTE-061, two-year data revealed longer OS with pembrolizumab than with paclitaxel only for the patients with PDL-1 enrichment (CPS>5% and CPS>10% subgroups).<sup>[9]</sup> In the KEYNOTE-063 trial conducted in Asian patients, it did not show any improvement in survival outcomes, despite cutting patient enrollment early after the release of KEYNOTE-061 results.<sup>[10]</sup>

Beyond immune checkpoint regulations, also vascular epidermal growth factor receptor-2 (VEGFR-2) has a pivotal role in the pathogenesis of gastric cancer. VEGFR-2 holds a major role in the control of endothelial cell growth and migration, also angiogenesis regulation. Its involvement is tied closely to the initiation, progression, and expansion of tumors, as well as the development of drug resistance.<sup>[11]</sup> The VEGFR-2 inhibitor ramucirumab, either alone or in combination with ChT, has been established as a choice in the second-line treatment for patients with metastatic gastro-oesophageal adenocarcinoma. In REGARD trial, a significant improvement in progression-free survival (PFS) and OS were observed when comparing ramucirumab to placebo.<sup>[12]</sup> Additionally, there was minimal to no impact on severe (grade 3-5) adverse events (AEs). In phase three randomized RAINBOW trial compared paclitaxel plus ramucirumab and paclitaxel, the survival benefit of combined treatment was more than paclitaxel alone.<sup>[13]</sup>

Nivolumab and ramucirumab, commonly used two agents for gastric cancer, are not studied as combination in any phase three trial. In this research, we examined the effectiveness and safety of combining ramucirumab and nivolumab along with paclitaxel chemotherapy as a second-line treatment option for patients with HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma. Combining these agents may potentially have a synergistic effect, targeting both the tumor microenviron-

ment and the immune system's response to cancer cells. Furthermore, these treatments exhibit manageable side effects, enabling their concurrent administration and providing a chance to utilize both. This is especially crucial, as a considerable number of gastric cancer patients may not have access to third-line treatment alternatives.

## Methods

We retrospectively evaluated the data from ten metastatic gastric cancer patients treated with systemic treatment between 2020 and 2023 in Koc University Hospital Medical Oncology Outpatient Clinic. Inclusion criteria were histological/cytologically diagnosis of gastric or GEJ adenocarcinoma, having progressive metastatic disease after first-line systemic treatment, and having complete medical records. The patients received immunotherapy in the first-line treatment were excluded. We enrolled the demographic, clinicopathologic features, and laboratory results of these patients from a database of medical oncology outpatient clinics. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of Koc University (No. 2024.292.IRB2.125), and informed consent was taken from all the patients.

## Systemic Treatment Protocol

Systemic treatment was performed according to the following protocol;

Paclitaxel 80 mg/m<sup>2</sup> (on days 1, 8 and 15) plus Ramucirumab 8 mg/kg (on day 1 and 15) and Nivolumab 3 mg/kg (on day 1 and 15) every four weeks until disease progression or intolerable toxicity. AEs were classified according to Common Terminology Criteria for Adverse Events version 4.0.

## Treatment Response Evaluation

Patients were followed by physical examination (H&P) each cycle, and thoraco-abdominopelvic computed tomography every two or three months. Response evaluation was conducted according to RECIST version 1.1 criteria.

## Statistical Analysis

PFS was defined as the time starting from the date of first systemic treatment till radiological progression, death, or last visit date. OS was defined as the time starting from the date of first systemic treatment until death any reason or last visit date. Data were analyzed statistically using SPSS 22.0 software (SPSS Inc., Chicago, Illinois). Chi-square and Fisher's exact tests were used for comparative data. OS and PFS were calculated using Kaplan-Meier curve and log-rank test analysis. All P values were two-sided in the tests and P<0.05 were considered statistically significant.

## Results

### Demographic and Clinicopathologic Outcomes of Patients

Eight of 10 patients were female (80%), and the median age was 47 years (min 24-max 83). Seventy percent of the patients had de novo metastatic disease. The most common site of metastasis was the peritoneum (90%) and seven (70%) patients had visceral metastases. Microsatellite status of eight (80%) patients was stable and PDL-1 was  $\geq 1\%$  in five (50%) patients. The patients received median 5.5 cycles of treatment (min 3-max 26). Data for demographic and clinicopathologic findings are reviewed in Table 1. 80% of patients received a third line treatment after progression.

### Response Rate Outcomes

The partial response was achieved in five (50%) of the patients, while three (30%) had stable disease. Disease control rate (DCR) and ORR was found to be 80% and 50%, respectively. There was no statistical difference in response rates according to PDL-1 status ( $p=0.76$ ). Median duration of response response (DoR) was 2.8 months (95% CI: 0.5-5.09). No statistical difference term of DoR in between PDL-1  $\geq 1\%$  and  $<1\%$  patients [3.6 months (95% CI: 1.1-6.05) vs 1.8 months (95% CI: 0.0-3.7),  $p=0.32$ ].

### Survival Outcomes

Median follow-up time was nine months (range 4–33 months). Ninety percent of patients (9/10) had disease progression, and 70% (7/10) passed away within the follow-up period. In the overall group, median PFS and OS were 4.9 months (95% CI: 0.0-10.3) and 10.9 months (95% CI: 6.1-15.8), respectively (shown in Fig. 1a, b). There was no statistically significant difference in terms of both PFS and OS according to PDL-1 status ( $p=0.66$  and  $0.32$  respectively, shown in Fig. 2a, b). The median PFS was statically significantly longer in patients with partial response than patients with stable disease [8.4 months (95% CI: 4.5-12.2) vs 4.9 months (95% CI: 1.6-8.1),  $p=0.01$ ]. The response rate and survival outcomes are shown in detail in Table 2. Clinical results of all patients are indicated in Figure 3.

### Adverse Events

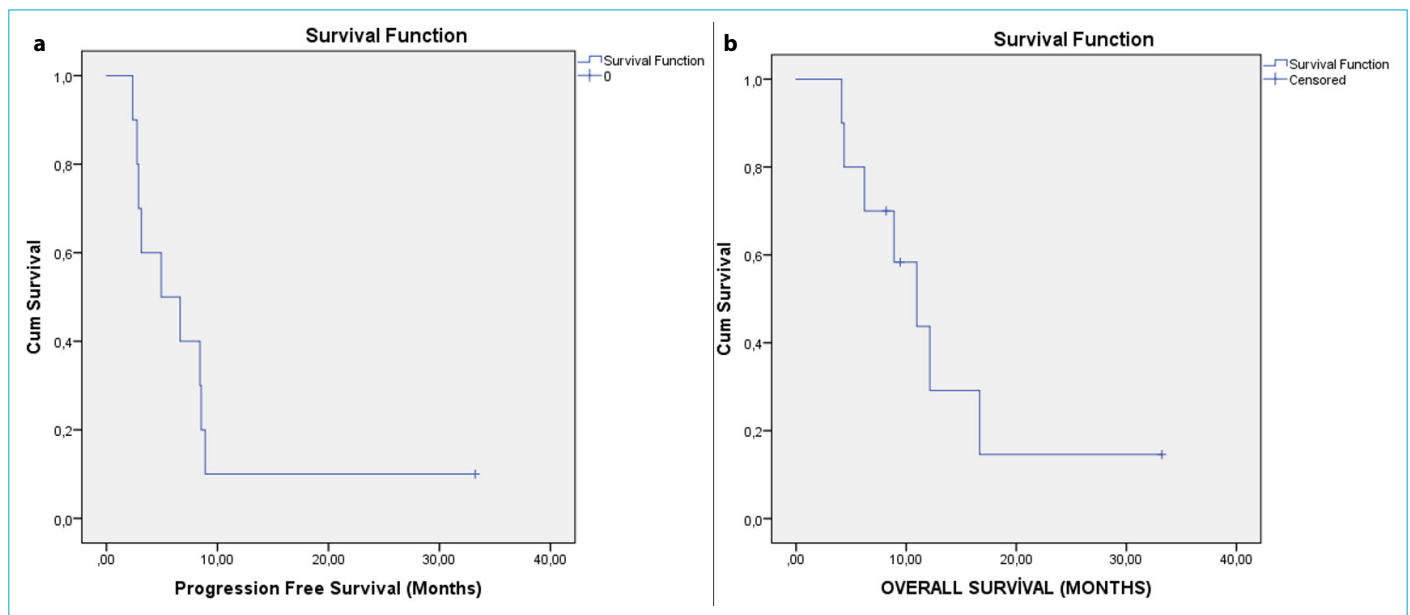
Nine of 10 patients had treatment-related AEs, seven of them were  $\geq$  grade 3. Only one patient had grade 4 adverse event, which is neutropenia. The most common side effects were anemia (60%), elevated gamma-glutamyl transpeptidase (50%) and alkaline phosphatase level (60%), neutropenia (40%). Adverse events summary is shown in Table 3.

**Table 1.** Baseline Demographics and Disease Characteristics Findings

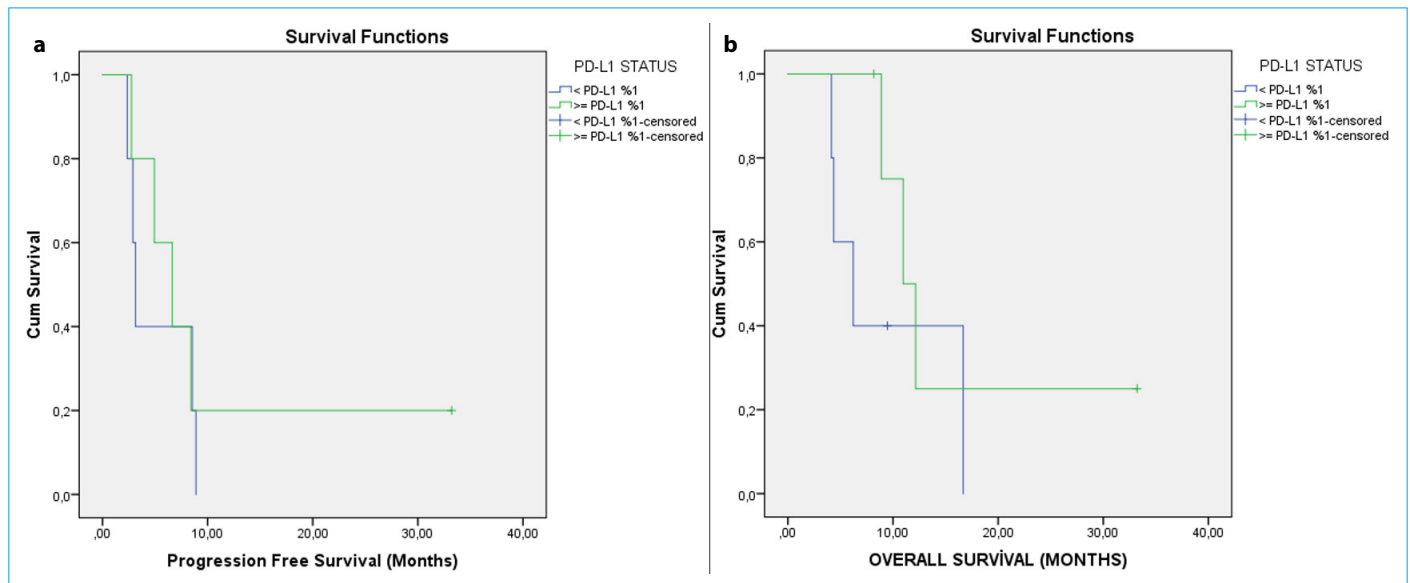
Patients	n=10 (%)
Age (median)	47 (min 24-max 83)
Gender	
Female	8 (80)
Male	2 (20)
Disease stage at diagnosis	
Stage 2	1 (9)
Stage 3	2 (18)
Stage 4	7 (70)
CEA (median)	2 (min 1-max 7766)
CA 19-9 (median)	20 (min 10.3-186)
Visceral metastasis	
Present	7 (70)
Absent	3 (30)
Peritoneal metastasis	
Present	9 (90)
Absent	1 (10)
Liver metastasis	
Present	4 (40)
Absent	6 (60)
Pathology	
Adenocarcinoma	5 (50)
Signet cell	3 (30)
Mix pathology	2 (20)
PDL-1 status (CPS)	
$<1\%$	5 (50)
$\geq 1\%$	5 (50)
MSS status	
pMMR	8 (80)
dMMR	0
Unknown	2 (20)
Treatment cycle	6 (min 3-max 50)
Disease Progression	
Present	9 (90)
Absent	1 (10)
Post-progression treatment	
Best supportive care	2 (20)
Pembrolizumab +lenvatinib	1 (10)
FOLFIRI	4 (40)
DCF	1 (10)
FOLFIRINOX	1 (10)
Status	
Alive	3 (30)
Exitus	7 (70)

## Discussion

In our study, we presented a real-life data of the combination of ramucirumab and nivolumab with paclitaxel ChT as the second line treatment of the advanced gastric cancer.



**Figure 1. (a)** Progression Free Survival Graphic by Kaplan-Meier curve. **(b)** Overall Survival Graphic by Kaplan-Meier curve.



**Figure 2. (a)** Progression Free Survival Graphic according to PDL-1 status. **(b)** Overall Survival Graphic according to PDL-1 Status.

The regimen was tolerable. Median PFS and OS were 4.9 months (95% CI: 0.0-10.3) and 10.9 months (95% CI: 6.1-15.8), respectively.

The combination of an immunotherapy with anti-VEGF agent may have a synergistic effect, inducing immunogenicity in the tumor microenvironment. Avoiding immune destruction and inducing angiogenesis are considered as two of the hallmarks of cancer. Exaggerated angiogenesis of tumors also helps for creating an immunosuppressive microenvironment.<sup>[14]</sup> Vascular endothelial growth factor-A (VEGF-A); the ligand of VEGFR-2, causes PDL-1 expression on dendritic cells and diminishes their maturation,

also activates regulatory T cells.<sup>[15]</sup> Beyond T regulatory cells, VEGF-A also increases other immunosuppressive cells in the tumor microenvironment, like tumor-associated macrophages, myeloid-derived suppressor cells, Tie-2-expressing monocytes; but antiangiogenic treatment can reverse this immunosuppressive environment.<sup>[16]</sup> Preclinical research suggests that combining inhibition of VEGFR-2 with immune checkpoint blockade could potentially boost T cell migration and improve their ability to target tumor cells.<sup>[14]</sup> Based on these findings, concurrent blockade of both VEGFR-2 and PDL-1 can enhance antitumor activity.

Table 2. Response Rate and Survival Outcomes			
Response rates	All patients, n=10 (%)	PD-L1 Status, n (%)	
		<1%	≥1 %
Complete Response (CR)	0	0	0
Partial Response (PR)	5 (50)	2 (40)	3 (60)
Stable disease (SD)	3 (30)	2 (40)	1 (20)
Progressive disease (PD)	2 (20)	1 (20)	1 (20)
Objective response rate (ORR)	50%	40%	60%
Disease control rate (DCR)	80 %	80%	80%
Duration of Response (DoR) (weeks) (median)	11 (95%CI: 1.2-20.7)	7 (95%CI:0-14,8)	14 (95%CI: 4.2-23.8)
Progression Free Survival (PFS)			
Median (Months)	4.9 (95% CI:0.0-10.3)	3.1 (95%CI:2.6-3.6)	6,6 (95%CI:2.9-10.3)
6 months rate	50%	40%	60%
Overall Survival (OS)			
Median (Months)	10.9 (95%CI:6.1-15.8)	6.2 (95%CI:2.2-10.2)	10.9 (95%CI:7.714.4)
12 Months rate	43 %	40%	50%

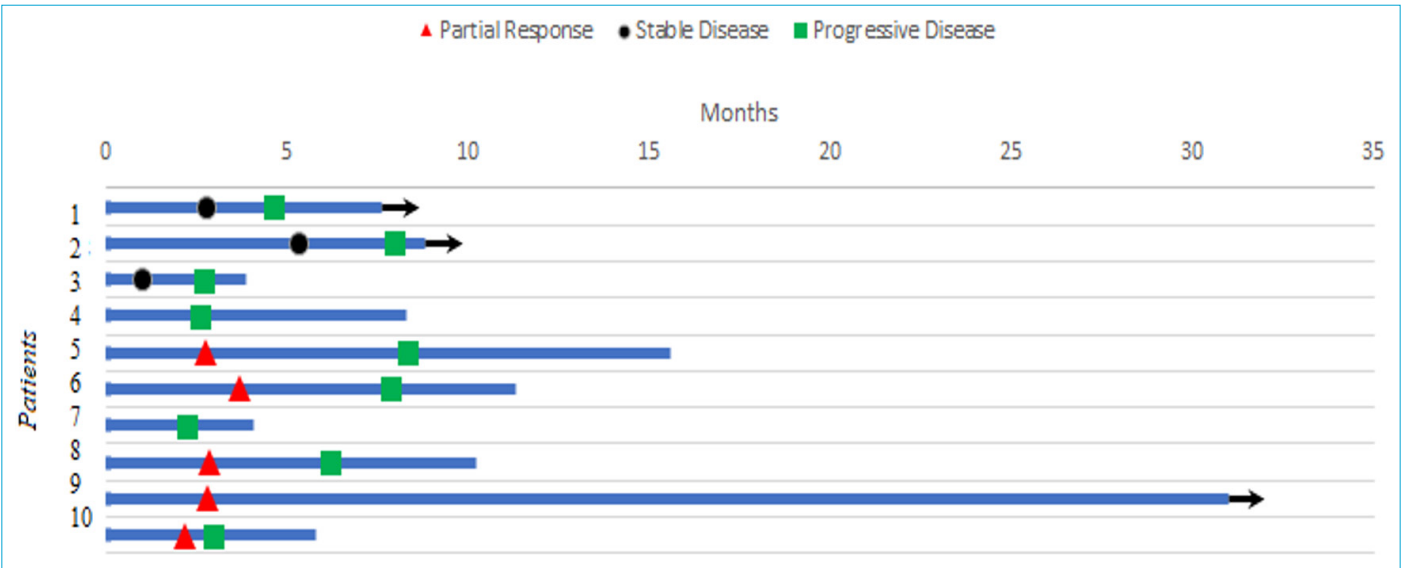


Figure 3. Clinical results of all patients in Swimmer Plot.

Table 3. Adverse Events		
Adverse Event	All Grade n (%)	Grade ≥3 n (%)
Anemia	6 (60)	2 (20)
GGT increased	6 (60)	3 (30)
ALP increased	5 (50)	-
Neutropenia	4 (40)	3 (30)
ALT/AST increased	4 (40)	1 (10)
Hypothyroidism	4 (40)	-
Nausea	2 (20)	1 (10)
Neuropathy	1 (10)	1 (10)
Hypertension	1 (10)	1 (10)
Infection	1 (10)	1 (10)

GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

There are also some effectiveness reports from early phase trials for gastric cancer. Current studies investigating the efficacy of combined treatment in gastric cancer patients are outlined in Table 4.

In a multicenter phase I/II study from Japan, the effectiveness and safety of nivolumab with paclitaxel plus ramucirumab as second line treatment was investigated.<sup>[17]</sup> There were forty-three patients totally, median PFS was 5.1 months, median OS was 13.1 months, 90.7% of patients had serious AEs, and more than one-third of these were immune-related AEs. The most frequent grade 3 or more adverse event was neutropenia, followed by leukopenia. Survival data was comparable to ours, but serious adverse event rate was higher than our study and RAINBOW trial,

**Table 4.** Review of current trial investigating the clinical efficacy of combined treatment in patients with advanced gastric cancer

Trial	Design	Outcomes		
		ORR % (95% CI)	PFS Median, months (95% CI)	OS Median, months (95% CI)
Nagahima et al. <sup>[17]</sup>	Multicenter Phase I/II Study (n=43) Paclitaxel plus Ramuricumab plus Nivolumab	37.2 (23.0-53.5) CPS ≥ 1: 46.2 (26.6–66.6) CPS <1: 30.8 (9.1–61.4)	5.1 (4.5–6.5) CPS ≥ 1: 6.4 (4.2–7.9) CPS <1: 5.1 (2.6–6.7)	13.1 (8.0–16.6) CPS ≥ 1: 13.8 (8.0–19.5) CPS <1: 8.0 (4.8–24.1)
RAP trial <sup>[18]</sup>	Multicenter, nonrandomized Phase 2 (n=59) Paclitaxel plus Ramuricumab plus Avelumab	30.5 CPS status not determined	5.4 (4.2-6.6) CPS ≥ 5: 4.5(2.4-6.6) CPS <5: 5.7 (4.7-6.7)	10.6 (8.4-12.8) CPS ≥ 5: 14.0 (6.0-22.1) CPS <5: 9.4 (7.2-11.7)
JVDF trial <sup>[19]</sup> (gastric cohort)	Multicenter, multicohort, nonrandomized Phase 1a/b (n=41) Ramucirumab plus Pembrolizumab	7 (1.5-19.9) CPS ≥ 1: 9 (1.1-29.2) CPS <1: 6 (0.1-28.7)	2.5 (1.5-4.2) CPS ≥ 1: 4.6 (2.3-8.5) CPS <1: 1.7 (1.3- 4.0)	5.9 (4.4-10.6) CPS ≥ 1: 12.6 (4.7- 20.3) CPS <1: 5.2 (1.3- 8.6)
JVDJ trial <sup>[20]</sup> (gastric cohort)	Multicenter, multicohort, nonrandomized Phase 1a/b (n=29) Ramucirumab plus Durvalumab	21 High PDL-1*: 36 Low PDL-1: 0	2.6 (1.5-7) High PDL-1*: 5.5 (1.8-16.8) Low PDL-1: 1.5 (1.4-2.6)	12.4 (5.5-16.9) High PDL-1*: 14.8 (7.2-NE) Low PDL-1: 5.5 (3.3-16.2)
Our trial Retrospective (n=10)	Single center, Paclitaxel plus Ramuricumab plus Nivolumab	50 CPS ≥ 1: 60 CPS <1: 40	4.9 (0.0-10.3) CPS ≥ 1: 6.6 (2.9-10.3) CPS <1: 3.1 (2.6-3.6)	10.9 (6.1-15.8) CPS ≥ 1: 10.9 (7.7-14.4) CPS <1: 6.2 (2.2-10.2)

\*High PDL-1 expression is defined as ≥25% immune cell or tumor cell staining.

probably because of patient's characteristics. Consistent with our study, although PFS and OS were better for PDL-1 positive patients, there was not statistically difference between survival and PDL-1 status.

In a phase II nonrandomized controlled trial from Germany, the RAP trial, PDL-1 inhibitor avelumab was studied with ramucirumab plus paclitaxel (18). 42.9% of total fifty-nine patients had five or more CPS, but also 67.8% had prior taxane treatment and 48.2% was GEJ tumors. Median PFS and OS was 5.4 and 10.6 months, respectively. For those with five or greater CPS, median OS was 14.0 months, this was numerically higher, but it did not reach statistically significance. The combination was generally well tolerated. Most common AEs were hematologic, grade 3-4 neutropenia occurred in 23.7% of patients. Although another immune checkpoint inhibitor, avelumab was studied, this study is also importantly confirmative with our finding that PDL-1

status is not relevant to survival when immune checkpoint inhibitors are combined with anti-VEGF agent and ChT.

Beyond these studies, there are some early phase trials investigating the effectiveness of ramucirumab with different immune checkpoint inhibitors without ChT for the treatment of a group of cancer types, including gastro-oesophageal cancer. In phase 1a/b JVDF trial ramucirumab plus pembrolizumab combination for previously treated non-small cell lung cancer, urothelial cancer and gastro-oesophageal cancer was studied.<sup>[19]</sup> Forty-one of 92 patients were gastric or GEJ carcinoma. For this cohort, ORR was 7%, median PFS and OS was 2.5 months and 5.9 months, respectively. Shorter survival result than other trials is probably because of high percentage of patients who had two prior systemic treatment lines before. Most common adverse event was grade 1-2 fatigue, seen in 39% of this cohort. According to these trials results, PDL-1 positive



gastric cancers had numerically better OS and PFS, but the groups were not statistically compared.

Phase Ia/b study JVDJ was studying durvalumab and ramucirumab effectivity in the second line and beyond for the metastatic stage non-small cell lung cancer, hepatocellular carcinoma and gastric/GEJ adenocarcinoma.<sup>[20]</sup> There were totally 85 patients, and 29 of them had gastric/GEJ cancer. ORR was 21%, median PFS and OS were 2.6 and 12.4 months respectively, for this group of patients. 37.9% of them experienced grade 3 or more AEs, the most observed all-grade adverse event was hypertension and headache. PDL-1 high subgroup was defined as  $\geq 25$  percentage immune cell or tumor cell staining, and they had longer median PFS and a similar trend for longer median OS, probably because of very high immunogenic group selection.

In our study, all patients' CPS status was lower than 5% except for two patients, half of the patients PDL-1 was greater than 1%. There was numerically, but not statistically significant difference in terms of both PFS and OS according to PDL-1 status ( $P=0.66$  and  $0.32$  respectively), likewise most of the above-mentioned studies. With these results, we can speculate there is a higher synergism of these drugs in PDL-1 overexpressing cancers, but an increase of immunogenicity for patients' low CPS levels with the use of anti-VEGF agent and ChT is possible, which creates a chance for utilizing checkpoint inhibition.

In RAINBOW trial and ATTRACTION-2 trial for the patients in the experimental arm median OS was 9.6 months and 5.26 months, respectively. Although direct comparison is not possible, combining these study agents seems like a favourable treatment choice, as in our trial median OS was 10.9 months.

The study regimen was generally well tolerated. Cytopenia was the most seen adverse event, as expected from a combination with a myelosuppressive chemotherapy agent. There was only one grade 4 neutropenia, but no neutropenic fever was seen. Asymptomatic elevated liver enzyme level was relatively common.

There are some limitation factors in our study. This was a single center retrospective study with a limited number of patients. Comprehensive randomized prospective trials are needed before recommendation of this regimen.

## Conclusion

In the context of treating advanced gastric cancer, the combination of nivolumab along with paclitaxel and ramucirumab has shown encouraging effectiveness and tolerability, irrespective of PDL-1 status. This regimen can be a promising second-line treatment option.

## Disclosures

**Ethics Committee Approval:** This study was approved by Koc University Ethics Committee (Date: 13/08/2024, Number: 2024.292.IRB2.125).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Authorship Contributions:** Concept – S.A., F.S.; Design – S.A., F.S.; Supervision – F.S.; Materials – S.L., B.K.; Data collection&/processing – S.L., B.K., B.B.K.; Analysis and/or interpretation – S.A., O.A.; Literature search – S.A., B.B.K.; Writing – S.A., O.A.; Critical review – F.S.

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