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Perioperative Nivolumab Combined with Neoadjuvant Chemotherapy in Locally Advanced Gastric/Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Objective: The exact role of nivolumab in the perioperative systemic treatment of locally advanced-gastric/gastroesophageal junction (LA-G/GEJ) adenocarcinoma remains unclear. This study aimed to evaluate the real-world effectiveness and safety of perioperative nivolumab in patients with LA-G/GEJ adenocarcinoma.

Material and Methods: Clinical and pathological data were retrospectively collected for previously untreated patients with human epidermal growth factor receptor 2-negative, clinical stage T2-4bN0-3M0 (stage II-III) G/GEJ adenocarcinoma, either microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) or microsatellite stable (MSS)/proficient MMR (pMMR) with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) of ≥5, who received perioperative nivolumab in combination with chemotherapy or ipilimumab between January 2021 and April 2025. Kaplan-Meier survival analysis was used to estimate disease-free survival (DFS) and overall survival (OS).

Results: Fifteen eligible patients were identified among 134 with stage II-III G/GEJ adenocarcinoma. Seven patients (46.7%) were classified as MSI-H/dMMR, and 11 patients (73.3%) had a PD-L1 CPS of ≥5. The median numbers of immunotherapy and chemotherapy cycles prior to surgery were 6 (range, 3-8) and 8 (range, 1-8), respectively. Objective response and disease control rates were 60% and 100%, respectively. All patients underwent surgical resection, and the R0 resection rate was 93.3%. Pathological complete response and major pathological response rates were both 71.4% in the MSI-H/dMMR subgroup, compared to 25% and 37.5%, respectively, in MSS/pMMR patients with a PD-L1 CPS ≥5. During follow-up [median 17.0 months (95% confidence interval: 13.0-20.9)], four patients experienced tumor recurrence, and three died. All cases of disease recurrence and death occurred in the MSS/pMMR subgroup, with 18 months DFS and OS rates of 35.7% and 47.6%, respectively.

Conclusion: For the treatment of LA-G/GEJ adenocarcinoma, perioperative nivolumab combined with total neoadjuvant chemotherapy might be effective for both MSI-H/dMMR patients and MSS/pMMR patients with a PD-L1 CPS of ≥5, and have an acceptable safety profile.

Keywords: Neoadjuvant therapy; immunotherapy; perioperative treatment; gastric cancer

INTRODUCTION

Gastric/gastroesophageal junction (G/GEJ) cancers account for approximately 5% of newly diagnosed malignancies and remain a major global cause of cancer-related mortality, ranking fifth worldwide.[1] Adenocarcinoma is the predominant subtype, comprising nearly 95% of all cases.[2] While surgical resection remains a key component of curative-intent treatment, high recurrence rates exceeding 60% and poor survival outcomes following upfront surgery have prompted

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a shift towards perioperative therapy, which has become the standard of care in locally advanced-G/GEJ (LA-G/GEJ) adenocarcinoma.[3,4] The incorporation of both neoadjuvant and adjuvant chemotherapy has been shown to improve tumor regression, increase the likelihood of complete (R0) resection, and raise pathological complete response (pCR) rates, overall survival (OS), and disease-free survival (DFS).[5-7]

Recent advances have highlighted the potential of immune checkpoint inhibitors (ICIs) in the neoadjuvant treatment of various solid tumors, prompting interest in their application to G/GEJ adenocarcinomas.[8] In a meta-analysis of 33 studies including 1,074 patients whose tumors were either microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) or microsatellite stable (MSS)/proficient MMR (pMMR) tumors, neoadjuvant immunotherapy was associated with promising outcomes, including a pCR rate of 24%, a major pathological response (MPR) rate of 49%, and an R0 resection rate of 89%.[9] A pooled analysis of phase I and II trials evaluating neoadjuvant ICIs in MSS/pMMR LA-G/GEJ adenocarcinoma also reported encouraging rates of pCR (21%), MPR (47%), and R0 resection (92%).[10] Consistent with these findings, a meta-analysis of randomized controlled trials including 2,718 patients showed that adding ICIs to perioperative chemotherapy significantly increased pCR rates compared to chemotherapy alone.[11] The addition of durvalumab to the perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) regimen has led to improved survival outcomes and pathological response rates, establishing this combination as the current standard of care.[12,13] Despite these promising results, the optimal incorporation of ICIs into the systemic treatment of LA-G/GEJ adenocarcinoma has yet to be clearly defined. Furthermore, nivolumab was infrequently used in these trials, underscoring a notable gap in evidence specific to this agent.

In this study, we aimed to assess the real-world effectiveness and safety of perioperative nivolumab administered in combination with either chemotherapy or ipilimumab in patients with LA-G/GEJ adenocarcinoma.

MATERIAL AND METHODS

Patient Selection

This study included previously untreated patients with clinical stage T2-4bN0-3M0 (stage II-III) G/GEJ adenocarcinoma who received neoadjuvant ICIs at two tertiary centers between January 2021 and April 2025. Eligibility criteria included histologically confirmed human epidermal growth factor receptor 2 (HER2)-negative G/GEJ adenocarcinoma, MSI-H/dMMR status or a programmed death-ligand 1 (PD-L1) combined positive score (CPS) of ≥5 in patients with MSS/pMMR tumors, clinical stage T2-4bN0-3M0 per the 8th edition of the American Joint Committee on Cancer (AJCC) gastric cancer staging system, age ≥18 years, Eastern Cooperative Oncology Group performance status of 0-1, and administration of neoadjuvant ICI therapy, either alone or in combination with chemotherapy. Patients with coexisting malignancies or compromised organ function were excluded.

Ethical Approval

The study was approved by the Koç University Ethics Committee (approval number: 2025.036.IRB2.024, date: 22.01.2025); the requirement for informed consent was waived because of its retrospective design. The study was performed in compliance with the principles of the Declaration of Helsinki.

Treatment Protocols

Neoadjuvant chemotherapy regimens included FLOT (oxaliplatin 85 mg/m^2 on day 1, docetaxel 50 mg/m^2 on day 1, leucovorin 200 mg/m^2 on day 1, and fluorouracil 2,600 mg/m^2 as a 24 hours continuous infusion, administered biweekly) and FOLFOX (fluorouracil 400 mg/m^2 as a bolus on day 1 followed by 2,400 mg/m^2 as a 46 hours continuous infusion, leucovorin 400 mg/m^2 on day 1, oxaliplatin 85 mg/m^2, administered biweekly). One patient with GEJ adenocarcinoma received concurrent chemoradiotherapy with weekly carboplatin (area under the curve 2 mg/mL/min) and paclitaxel (50 mg/m^2). Immunotherapy regimens included nivolumab (240 mg biweekly), either combined with chemotherapy or administered as dual immune checkpoint blockade with ipilimumab (1 mg/kg every six weeks). Although total neoadjuvant therapy (TNT) is not currently standard for LA-G/GEJ adenocarcinoma, participating institutions adopted a center-specific approach in which all planned perioperative systemic treatment was administered before surgery. The rationale for this approach was to maximize treatment completion and minimize the risk of postoperative treatment omission. Tumor response was assessed two weeks after the final neoadjuvant systemic treatment using computed tomography (CT) scans of the abdomen and chest, magnetic resonance imaging of the abdomen, and/or floride 18-fluorodeoxyglucose positron emission tomography-CT scan.

All patients underwent gastrectomy with lymphadenectomy following neoadjuvant systemic treatment. The surgical extent was individualized based on tumor characteristics to ensure negative margins. Of the 15 patients, 12 completed chemotherapy in the neoadjuvant setting (the total neoadjuvant chemotherapy approach), and none received adjuvant chemotherapy. The only adjuvant immunotherapy

regimen was nivolumab, administered as either 240 mg every two weeks or 480 mg every four weeks. Regardless of pathological response status, continuation of nivolumab for a treatment duration of one year was recommended in routine clinical practice. Routine follow-up included CT scans at three-month intervals.

Outcome Assessment

Radiologic and pathologic responses were defined as the primary endpoints of the study. Radiologic response to neoadjuvant therapy was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 and classified as CR, partial response (PR), stable disease (SD), or progressive disease.[14] The objective response rate (ORR) and the disease control rate (DCR) were defined as the proportions of patients achieving CR or PR and CR, PR, or SD, respectively. Surgical specimens were evaluated for pathological response using the Becker tumor regression grade (TRG) criteria, defined as follows:[15] TRG1a (no residual tumor cells), TRG1b (<10% residual tumor cells), TRG2 (10-50% residual tumor cells), and TRG3 (>50% residual tumor cells). TRG1a was classified as pCR, and TRG1a/1b was classified as MPR. cTNM staging was determined based on the 8th edition of the AJCC staging system.

Secondary outcomes included OS, defined as the time from initiation of neoadjuvant therapy to death from any cause, and DFS, defined as the time from initiation of neoadjuvant therapy to disease recurrence or death from any cause. Treatment-related adverse events (TRAEs) were graded using the Common Terminology Criteria for Adverse Events, version 5.0.[16]

MSI/MMR status was determined by immunohistochemistry for MSH2, MSH6, MLH1, and PMS2. PD-L1 expression was assessed through immunohistochemical staining with the SP263 anti-PD-L1 antibody (VENTANA PD-L1 Assay, Roche), and expression levels were quantified by the CPS. CPS was calculated as the ratio of PD-L1-expressing cells (including tumor cells, lymphocytes, and macrophages) to the total number of viable tumor cells, multiplied by 100. HER2 expression was assessed by immunohistochemistry.

Statistical Analysis

SPSS software version 24.0 (IBM SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables were presented as medians with ranges, while categorical variables were reported as frequencies with percentages. The reverse Kaplan-Meier approach was applied to estimate follow-up duration. DFS and OS were calculated using Kaplan-Meier methods.

RESULTS

Patient Characteristics

Of the 134 patients with previously untreated clinical stage T2-4bN0-3M0 (stage II-III) G/GEJ adenocarcinoma, 24 underwent upfront surgery, whereas 110 received neoadjuvant systemic treatment. Among them, 15 eligible patients who received perioperative nivolumab, either in combination with chemotherapy or with ipilimumab, were included in the analysis. The median age was 60 years (range, 55-70), and 12 patients (80.0%) were male (Table 1). Gastric adenocarcinoma was diagnosed in 13 patients (86.7%); only two patients (13.3%) had tumors located at the GEJ. All patients were HER2 negative; seven (46.7%) were classified as MSI-H/dMMR; and 11 (73.3%) had a PD-L1 CPS of ≥5. Six patients (40.0%) had signet ring cell carcinoma.

The median time interval between the initiation of neoadjuvant treatment and surgery was 4.3 months (range, 2.1-4.9 months). Median numbers of immunotherapy and chemotherapy cycles prior to surgery were 6 (range, 3-8) and 8 (range, 1-8), respectively. One patient with MSI-H/dMMR gastric adenocarcinoma received only dual immunotherapy with nivolumab and ipilimumab after a prolonged hospitalization for febrile neutropenia following the first cycle of the FLOT regimen. All other patients were treated with both chemotherapy and immunotherapy before surgery. Additionally, one patient with GEJ adenocarcinoma received radiotherapy in the neoadjuvant setting, along with immunotherapy and concomitant chemotherapy.

Tumor Response and Survival Outcomes

Radiological evaluation after the last cycle of neoadjuvant therapy revealed that two patients (13.3%) achieved CR and seven patients (46.7%) achieved PR. SD was observed in six patients (40%), with no cases of progressive disease. ORR and DCR were 60% and 100%, respectively. All patients underwent surgical resection, with an R0 resection rate of 93.3% (14 out of 15 patients). The median interval between completion of neoadjuvant treatment and surgery was 25 days (range, 16-43 days). Pathological examination showed rates of TRG1a, TRG1b, TRG2, and TRG3 of 46.7%, 6.7%, 13.3%, and 33.3%, respectively; the corresponding pCR and MPR rates were 46.7% and 53.3%.

Within our cohort, we observed a notably high pCR rate of 71.4% (5 out of 7) in the MSI-H/dMMR subgroup (Table 1). One patient with MSI-H/dMMR gastric adenocarcinoma and a PD-L1 CPS of 60 experienced grade 4 febrile neutropenia following the first cycle of the FLOT regimen. Subsequently, treatment was switched to dual immunotherapy with nivolumab and ipilimumab, without chemotherapy (Patient 7 in Table 1).

TABLE 1: Data on clinical and pathological characteristics for the entire cohort.

	Age/ sex	Clinical stage	Histological diagnosis	Tumor location	MSI status	PD-L1 CPS	Neoadjuvant treatment	Pathological response	Adjuvant treatment	FU (months)	DFS (months)	OS (months)	Last status
1	58/M	cT3N0	Adenocarcinoma, moderately differentiated	Antrum	MSI-H/ dMMR	0	8x FLOT + 7x nivolumab	TRG1a	Nivolumab	25.4	N/A	N/A	Remission
2	57/M	cT3N0	Adenocarcinoma, moderately differentiated	Antrum	MSI-H/ dMMR	Unknown	8x FLOT + 6x nivolumab	TRG1a	Nivolumab	47.6	N/A	N/A	Remission
3	59/M	cT3N+	Adenocarcinoma, poorly differentiated	GEJ	MSS/pMMR	10	2x FOLFOX + 1x nivolumab, then 5x weekly carboplatin plus paclitaxel concurrent with radiotherapy, then 2x FOLFOX + 2x nivolumab	TRG1a	Nivolumab	8.9	N/A	N/A	Remission
4	70/M	cT3N+	Adenocarcinoma, moderately differentiated	Corpus	MSI-H/ dMMR	5	8x FLOT + 7x nivolumab	TRG1a	Not received	10.3	N/A	N/A	Remission
5	54/F	cT3N+	Signet ring cell carcinoma	Antrum	MSS/pMMR	21	8x FLOT + 5x nivolumab	TRG1b	Nivolumab	16.1	10.2	16.1	Exitus
6	55/M	cT3N+	Tubulopapillary adenocarcinoma	Antrum	MSI-H/ dMMR	0	3x FOLFOX + 3x nivolumab	TRG2	Nivolumab	14.3	N/A	N/A	Remission
7	65/F	cT4aN+	Adenocarcinoma, poorly differentiated	Antrum	MSI-H/ dMMR	60	1x FLOT, then 6x nivolumab + 2x ipilimumab	TRG1a	Nivolumab	24.8	N/A	N/A	Remission
8	55/M	cT4aN+	Signet ring cell carcinoma	Corpus	MSS/pMMR	5	8x FLOT + 3x nivolumab	TRG3	Not received	9.5	8.3	9.5	Exitus
9	85/M	cT4bN+	Signet ring cell carcinoma	Antrum	MSS/pMMR	5	8x FOLFOX + 7x nivolumab	TRG3	Nivolumab	10.0	8.9	10.0	Exitus
10	60/M	cT4aN+	Adenocarcinoma, poorly differentiated	Antrum	MSS/pMMR	30	8x FLOT + 7x nivolumab	TRG3	Nivolumab (postoperative radiotherapy due to R2 resection)	15.3	14.4	N/A	Receiving subsequent treatment
11	81/M	cT4bN+	Signet ring cell carcinoma	Corpus	MSS/pMMR	7	7x FOLFOX + 6x nivolumab	TRG1a	Not received	34.1	N/A	N/A	Remission
12	40/M	cT3N+	Signet ring cell carcinoma	Corpus	MSS/pMMR	15	8x FLOT + 8x nivolumab	TRG2	Nivolumab	18.0	N/A	N/A	Remission
13	67/M	cT3N+	Adenocarcinoma, poorly differentiated	Corpus	MSI-H/ dMMR	70	8x FLOT + 7x nivolumab	TRG1a	Nivolumab	17.0	N/A	N/A	Remission
14	66/F	cT3N+	Signet ring cell carcinoma	Antrum	MSI-H/ dMMR	0	8x FLOT + 5x nivolumab	TRG3	Not received	11.7	N/A	N/A	Remission
15	70/M	cT2N+	Adenocarcinoma, moderately differentiated	GEJ	MSS/pMMR	13	6x FOLFOX + 4x nivolumab	TRG3	Not received	10.1	N/A	N/A	Remission

DFS: Disease-free survival; F: Female; FU: Follow-up; GEJ: Gastroesophageal junction; M: Male; MPR: Major pathological response; N/A: Not applicable; OS: Overall survival; pCR: Pathological complete response; TRG: Tumor response grade; MSI: Microsatellite instability; MSS: Microsatellite stable; MMR: Mismatch repair.

pCR was achieved in this patient, and adjuvant nivolumab monotherapy was continued for up to 1 year following surgery. One patient with MSI-H/dMMR gastric adenocarcinoma underwent surgery after three cycles of FOLFOX and nivolumab because of chemotherapy-induced myelosuppression, following the multidisciplinary tumor board's recommendation (Patient 6). Post-surgical pathology revealed a TRG2 response, and adjuvant nivolumab monotherapy was continued for up to 1 year. In the MSI-H/dMMR subgroup, a TRG3 response was observed in a single patient, who was also the only individual with signet ring cell carcinoma (Patient 14).

In MSS/pMMR patients with a PD-L1 CPS ≥5, the pCR and MPR rates remained modest, observed in only 25% (2 out of 8) and 37.5% (3 out of 8) of cases, respectively. One patient with GEJ adenocarcinoma (Patient 3) received neoadjuvant radiotherapy in addition to chemotherapy and nivolumab and achieved pCR. Only one patient with an R2 resection received adjuvant radiotherapy (Patient 10). Of the four patients with a poor pathological response to neoadjuvant therapy (TRG3 response), three experienced recurrence (Patients 8, 9, and 10) and two (Patients 8 and 9) died from cancer progression, with OSs of 9.5 and 10 months, respectively. A patient with a TRG1b response to neoadjuvant therapy (Patient 5) also experienced disease recurrence and died from cancer progression, with an OS of 16.1 months. Signet-ring cell carcinoma was present in three of the four patients with disease recurrence (Patients 5, 8, and 9). Across the cohort, three of the six patients with signet ring cell carcinoma (Patients 11, 12, and 14) were in remission at last follow-up.

By the data cut-off date of April 30, 2025, the median follow-up duration was 18.0 months [95% confidence interval (CI): 10.5-25.5) in the MSS/pMMR subgroup and 17.0 months (95% CI: 13.0-20.9) in the MSI-H/dMMR subgroup. During this period, four patients experienced tumor recurrence, three died, and all other patients remained in remission. All cases of disease recurrence and death occurred in the MSS/pMMR subgroup, with 18 months DFS and OS rates of 35.7% and 47.6%, respectively (Figure 1). In contrast, no recurrences or deaths were observed in the MSI-H/dMMR subgroup, resulting in 100% DFS and OS at 18 months. Although the number of patients was limited in each subgroup, the log-rank test demonstrated a statistically significant difference in DFS (p=0.034) between the MSI-H/dMMR and MSS/pMMR subgroups and a trend toward better OS (p=0.062) in the MSI-H/dMMR subgroup.

Safety

TRAEs were observed in all patients during neoadjuvant treatment (Table 2). The most common TRAEs (>10%) were anemia (93.3%), thrombocytopenia (80%), fatigue (80%), neutropenia (60%), increased aspartate aminotransferase (60%), increased alanine aminotransferase (53.3%), peripheral neuropathy (46.7%), nausea or vomiting (20%), and fever (13.3%). Neutropenia accounted for the largest proportion of grade 3 or higher TRAEs (46.7%), while other grade 3 or higher TRAEs were anemia (20%), thrombocytopenia (20%), febrile neutropenia (6.7%), diarrhea (6.7%), peripheral neuropathy (6.7%), fever (6.7%), and myasthenia gravis (6.7%).

DISCUSSION

This retrospective analysis demonstrated that perioperative nivolumab combined with neoadjuvant chemotherapy for patients with LA-G/GEJ adenocarcinoma may improve pathological responses and is associated with an acceptable safety profile. This benefit might be particularly notable in

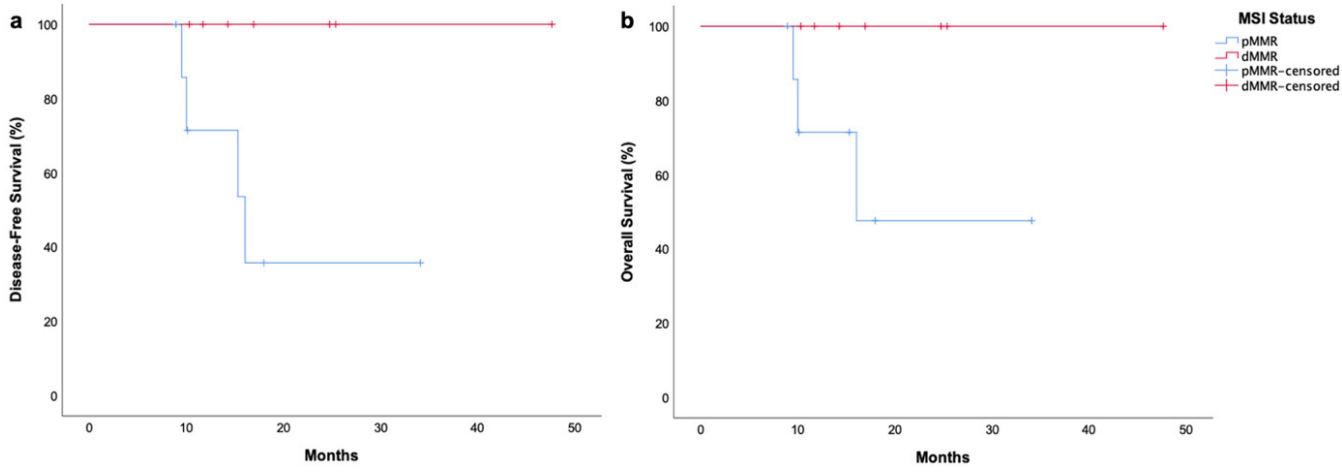

FIGURE 1: Kaplan-Meier curves for **(a)** disease-free survival and **(b)** overall survival according to microsatellite instability status

MSI: Microsatellite instability; MMR: Mismatch repair

TABLE 2: Treatment-related adverse events during neoadjuvant treatment.			
	Grade 1-2	Grade 3	Grade 4
All events	15 (100%)	11 (73.3%)	2 (13.3%)
Anemia	11 (73.3%)	3 (20.0%)	0
Thrombocytopenia	9 (60.0%)	3 (20.0%)	0
Neutropenia	2 (13.3%)	5 (33.3%)	2 (13.3%)
Febrile neutropenia	0	0	1 (6.7%)
Alanine aminotransferase increase	8 (53.3%)	0	0
Aspartate aminotransferase increase	9 (60.0%)	0	0
Nausea or vomiting	3 (20.0%)	0	0
Diarrhea	0	1 (6.7%)	0
Peripheral neuropathy	6 (40.0%)	1 (6.7%)	0
Fever	1 (6.7%)	1 (6.7%)	0
Fatigue	12 (80.0%)	0	0
Rash	2 (13.3%)	0	0
Pneumonitis	1 (6.7%)	0	0
Hypophysitis	1 (6.7%)	0	0
Myasthenia gravis	0	1 (6.7%)	0

MSI-H/dMMR patients and in MSS/pMMR patients with a PD-L1 CPS of ≥5. A total neoadjuvant chemotherapy approach, rather than perioperative chemotherapy, might further enhance both pathological and radiological outcomes.

The current standard of care for LA-G/GEJ adenocarcinoma is perioperative therapy. Following the results of the phase II/III FLOT4 trial (NCT01216644), which demonstrated a significant improvement in OS with perioperative FLOT compared to epirubicin, cisplatin, fluorouracil/epirubicin, cisplatin, capecitabine, FLOT has become the preferred perioperative chemotherapy regimen.[7] Nevertheless, fewer than half of patients diagnosed with LA-G/GEJ adenocarcinoma survive beyond five years.[7,17] Given the efficacy of perioperative immunotherapy across different tumor types, clinical trials were initiated to evaluate the safety and efficacy of adding ICIs to perioperative systemic treatment in patients with LA-G/GEJ adenocarcinoma.[8,18,19] In phase II/III DANTE trial (NCT03421288), Lorenzen et al.[20] reported that adding atezolizumab to perioperative FLOT improved tumor downstaging and increased the pCR rate (24% vs. 15%), particularly in patients with PD-L1 CPS ≥10 (33% vs. 12%) and MSI-H/dMMR tumors (63% vs. 27%). The Phase III KEYNOTE-585 study (NCT03221426) evaluated the efficacy of combining pembrolizumab with either perioperative cisplatin-based doublet chemotherapy (main cohort) or FLOT (FLOT cohort).[21] Although the addition of pembrolizumab increased pCR rates both in the main cohort (13.4% vs. 2.0%) and the main plus FLOT cohort (14.2% vs. 2.8%), there was no benefit in event-free survival (EFS) or OS.[22] However, it should be noted that pembrolizumab demonstrated a trend toward improved EFS in patients with PD-L1 CPS ≥10 (hazard ratio: 0.69; 95% CI: 0.48-1.01), despite the majority of patients receiving cisplatin-based doublet chemotherapy rather than the FLOT regimen.[21] Recently, the MATTERHORN study (NCT04592913) demonstrated that adding durvalumab to perioperative FLOT significantly improved EFS, OS, and the pCR rate (19.2% vs. 7.2%).[12,13] The survival benefit of adding durvalumab was observed regardless of the PD-L1 tumor area positivity score.[13] Based on these data, durvalumab in combination with the FLOT regimen received U.S. Food and Drug Administration approval for perioperative treatment of resectable G/GEJ adenocarcinoma.[23]

Neoadjuvant ICIs are significantly more efficacious in patients with MSI-H/dMMR disease than in patients with MSS/pMMR LA-G/GEJ adenocarcinoma, in whom only limited but encouraging pathological responses have been observed. The phase II GERCOR NEONIPIGA study (NCT04006262), assessing the efficacy of dual immune checkpoint blockade with nivolumab and ipilimumab in patients with resectable MSI-H/dMMR G/GEJ adenocarcinoma, successfully met its primary endpoint, achieving a pCR rate of 58.6%.[24] The Phase II INFINITY trial (NCT04817826), evaluating the combination of durvalumab plus tremelimumab in patients with resectable MSI-H/dMMR G/GEJ adenocarcinoma, recently reported a PCR rate of 60% and an MPR rate of 80%.[25] These findings suggest that patients with resectable MSI-H/dMMR G/GEJ adenocarcinoma may be suitable candidates for non-operative management using dual immune checkpoint blockade in future treatment strategies. Within our cohort, only one patient with MSI-H/dMMR gastric adenocarcinoma

received dual immune checkpoint blockade with nivolumab and ipilimumab, and this patient achieved pCR.

In the Phase III CheckMate 649 study (NCT02872116), the addition of nivolumab to chemotherapy significantly improved both OS and progression-free survival in patients with previously untreated advanced G/GEJ adenocarcinoma, with a more substantial benefit observed in those with PD-L1 CPS ≥5.[26] Although nivolumab has been widely used in patients with advanced G/GEJ adenocarcinoma, particularly in those with PD-L1 CPS ≥5 based on these data, its efficacy in the preoperative or perioperative setting in patients with LA-G/GEJ adenocarcinoma remains unclear. Currently, only a few studies are investigating the addition of neoadjuvant nivolumab to perioperative chemotherapy in patients with LA-G/GEJ adenocarcinoma. In the phase II single-arm STIMULATE-01 trial (n=46), perioperative nivolumab combined with the SOX regimen (oxaliplatin and S-1) for LA-G/GEJ adenocarcinoma yielded a pCR rate of 28.3%, an MPR rate of 41.3%, and a 100% R0 resection rate, following three cycles of preoperative nivolumab plus SOX.[27] PD-L1 CPS status (≥5 vs. <5) was not associated with significant differences in MPR (42.9% vs. 38.9%, p=0.79). A large-scale observational study (NCT06235164) is currently underway to assess the efficacy and safety of neoadjuvant chemotherapy combined with immunotherapy, including nivolumab, in patients with cT2-4a and/or node-positive gastric cancer.[28]

Although adjuvant nivolumab significantly improved DFS in patients with resected esophageal or GEJ cancer who had residual disease following neoadjuvant chemoradiotherapy, it did not demonstrate a similar benefit as adjuvant treatment for gastric cancer.[29,30] The efficacy of adding nivolumab to adjuvant chemotherapy in patients with pathological stage III disease who underwent upfront gastrectomy with D2 or a more extensive lymph node dissection was evaluated in the ATTRACTION-5 (NCT03006705) study; no improvement in 3 years relapse-free survival was observed.[30] However, a majority of patients in this trial had low PD-L1 expression, and subgroup analysis suggested that patients with PD-L1 expression of ≥1% might benefit from the addition of nivolumab. Lower PD-L1 expression has been consistently associated with reduced therapeutic benefit from the addition of ICIs across various trials.[26,31] This observation could partly explain the negative outcomes in the ATTRACTION-5 study, as a significant reduction in PD-L1-positive tumor cells after surgery could limit nivolumab's ability to effectively activate the immune system in the postoperative adjuvant setting. Moreover, neoadjuvant chemotherapy, rather than adjuvant therapy, could enhance immunogenic cell death and promote antigen release, potentially improving treatment outcomes when combined with nivolumab.[32]

Therefore, using nivolumab in the perioperative setting, combined with chemotherapy, particularly in patients with PD-L1 CPS ≥5, might yield better results than its use as postoperative adjuvant treatment.

Taken together, the previously discussed data indicate that the primary rationale for choosing nivolumab as an ICI in combination with perioperative chemotherapy is the inability to reliably exclude peritoneal metastases in every patient with LA-G/GEJ adenocarcinoma because diagnostic laparoscopy was used selectively. Hence, extrapolating the results of the CheckMate 649 study to treat this subgroup characterized by PD-L1 CPS ≥5 or MSI-H/dMMR is a reasonable approach. Additionally, ICIs are not currently reimbursed for LA-G/GEJ adenocarcinoma by Türkiye's healthcare system, and nivolumab is more financially accessible to patients than other ICIs. However, some otherwise eligible patients with MSI-H/dMMR tumors or MSS/pMMR tumors with a PD-L1 CPS ≥5 may still not have received this treatment because of financial constraints. Consequently, selection bias related to treatment accessibility cannot be excluded.

In our cohort, another important approach that could potentially increase pCR rates is completing all planned chemotherapy cycles before surgery as TNT rather than perioperative (neoadjuvant and adjuvant) chemotherapy. TNT has been adopted in locally advanced rectal cancer due to its potential advantages including a higher likelihood of completing all planned chemotherapy cycles, more effective management of micro-metastatic disease, enhanced tumor downstaging, and a greater chance of achieving R0 resection.[33,34] This approach also seems to be applicable to LA-G cancer.[35-37] Despite the historically low pCR rates, several studies have reported that achieving pCR could be a useful surrogate endpoint for predicting long-term survival in patients with LA-G/GEJ adenocarcinoma.[38,39] While this retrospective study involved a limited number of patients, our findings suggest that perioperative nivolumab combined with total neoadjuvant chemotherapy may increase pCR rates in MSI-H/dMMR patients and in MSS/pMMR patients with a PD-L1 CPS of ≥5.

Study Limitations

Despite these encouraging findings, several important limitations should be acknowledged. The retrospective nature of the study and its restriction to two centers may introduce selection bias, while unmeasured confounders may have impacted the observed outcomes. In addition to the retrospective design, the small sample size, variability in chemotherapy regimens, and heterogeneity in histopathological characteristics may further limit the robustness of the conclusions. Furthermore, the survival

findings should be interpreted cautiously because the survival data remain immature, with limited follow-up duration and a small number of events. Although continuation of adjuvant nivolumab to complete a total treatment duration of one year was recommended, access to treatment was influenced by financial constraints. As a result, not all patients were able to receive the planned duration of adjuvant immunotherapy, which may also have affected long-term outcomes. PD-L1 assessment was performed using the SP263 assay, primarily because of local availability, rather than the more commonly used 22C3 assay employed in G/GEJ cancer clinical trials. Although previous studies have demonstrated a high degree of concordance between these assays for PD-L1 assessment in G/GEJ adenocarcinomas, minor differences in CPS classification may occur in individual cases.[40] Large, well-designed prospective trials are needed to further clarify the potential impact of perioperative nivolumab in combination with total neoadjuvant chemotherapy on pathological responses and survival outcomes.

CONCLUSION

In the treatment of LA-G/GEJ adenocarcinoma, perioperative nivolumab combined with total neoadjuvant chemotherapy might be an effective approach for both MSI-H/dMMR patients and MSS/pMMR patients with a PD-L1 CPS of ≥5, with an acceptable safety profile.

Ethics

Ethics Committee Approval: The study was approved by the Koç University Ethics Committee (approval number: 2025.036.IRB2.024, date: 22.01.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., C.İ.K., F.K., N.D., P.F.Y., Ş.L., M.K., N.M.M., F.S., Concept: B.K., F.S., Design: B.K., F.S., Data Collection or Processing: B.K., C.İ.K., F.K., R.E., N.D., Analysis or Interpretation: B.K., C.İ.K., F.K., R.E., N.D., Literature Search: B.K., Writing: B.K., C.İ.K., F.K., R.E., Ö.A., N.D., P.F.Y., Ş.L., M.K., N.M.M., F.S.

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REFERENCES

1. Bray F, Laversanne M, Sung H, 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. [Crossref] [PubMed]
2. Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. Nat Rev Dis Primers. 2017;3:17036. [Crossref] [PubMed]
3. Liu D, Lu M, Li J, et al. The patterns and timing of recurrence after curative resection for gastric cancer in China. World J Surg Oncol. 2016;14(1):305. [Crossref] [PubMed] [PMC]
4. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg. 2004;240(5):808-816. [Crossref] [PubMed] [PMC]
5. Cunningham D, Allum WH, Stenning SP, et al.; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20. [Crossref] [PubMed]
6. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-1721. [Crossref] [PubMed]
7. Al-Batran SE, Homann N, Pauligk C, et al.; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948-1957. [Crossref] [PubMed]
8. Boydell E, Sandoval JL, Michielin O, Obeid M, Addeo A, Friedlaender A. Neoadjuvant immunotherapy: a promising new standard of care. Int J Mol Sci. 2023;24(14):11849. [Crossref] [PubMed] [PMC]
9. Wang J, Tong T, Zhang G, et al. Evaluation of neoadjuvant immunotherapy in resectable gastric/gastroesophageal junction tumors: a meta-analysis and systematic review. Front Immunol. 2024;15:1339757. [Crossref] [PubMed] [PMC]
10. Dennehy C, Khan AF, Zaidi AH, Lam VK. The evolving landscape of neoadjuvant immunotherapy in gastroesophageal cancer. Cancers (Basel). 2024;16(2):286. [Crossref] [PubMed] [PMC]
11. Huang D, Sun F, Ke L, Li S. Perioperative immune checkpoint inhibitors combined with chemotherapy versus chemotherapy for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma: a systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol. 2024;138:112576. [Crossref] [PubMed]
12. Janjigian YY, Al-Batran SE, Wainberg ZA, et al.; MATTERHORN Investigators. Perioperative durvalumab in gastric and gastroesophageal junction cancer. N Engl J Med. 2025;393(3):217-230. [Crossref] [PubMed]
13. Tabernero J, Al-Batran S-E, Wainberg ZAA, et al. LBA81 Final overall survival (OS) and the association of pathological outcomes with event-free survival (EFS) in MATTERHORN: a randomised, phase III study of durvalumab (D) plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric / gastroesophageal junction (G / GEJ) adenocarcinoma. Ann Oncol. 2025;36(Suppl 2):S1623-S1624. [Crossref]
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247. [Crossref] [PubMed]
15. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer. 2003;98(7):1521-1530. [Crossref] [PubMed]
16. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE): version 5.0 [Internet]. Bethesda (MD): National Cancer Institute; 2017. [Crossref]
17. Nakayama I, Ohashi M, Nunobe S. Perioperative or neoadjuvant chemotherapy for locally advanced gastric or gastroesophageal junction cancer: from independent evidence in the West, the East,

and Japan to global collaboration. Chin Clin Oncol. 2024;13(1):8. [Crossref] [PubMed]

18. Liu X, Ma B, Zhao L. Neoadjuvant chemoimmunotherapy in locally advanced gastric or gastroesophageal junction adenocarcinoma. Front Oncol. 2024;14:1342162. [Crossref] [PubMed] [PMC]
19. Lin F, Chen Y, Huang B, et al. Application of immune checkpoint inhibitors for resectable gastric/gastroesophageal cancer. Front Pharmacol. 2024;15:1391562. [Crossref] [PubMed] [PMC]
20. Lorenzen S, Götze TO, Thuss-Patience P, et al.; AIO and SAKK Study Working Groups. Perioperative atezolizumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable esophagogastric cancer: interim results from the randomized, multicenter, phase II/III DANTE/IKF-s633 trial. J Clin Oncol. 2024;42(4):410-420. [Crossref] [PubMed]
21. Shitara K, Rha SY, Wyrwicz LS, et al.; KEYNOTE-585 investigators. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. Lancet Oncol. 2024;25(2):212-224. [Crossref] [PubMed]
22. Shitara K, Rha SY, Wyrwicz L, et al.; KEYNOTE-585 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy as perioperative therapy in locally advanced gastric and gastroesophageal junction cancer: final analysis of the randomized, phase III KEYNOTE-585 study. J Clin Oncol. 2025;43(29):3152-3159. [Crossref] [PubMed]
23. U.S. Food and Drug Administration. FDA approves durvalumab for resectable gastric or gastroesophageal junction adenocarcinoma [Internet]. 2025. [Crossref]
24. André T, Tougeron D, Piessen G, et al. Neoadjuvant Nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. J Clin Oncol. 2023;41(2):255-265. [Crossref] [PubMed] [PMC]
25. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: a multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). J Clin Oncol. 2023;41(Suppl 4):358-358. [Crossref]
26. Janjigian YY, Shitara K, Moehler M, 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. [Crossref] [PubMed] [PMC]
27. Cheng X, Xu Z, Hu C, et al. Preoperative nivolumab plus SOX in patients with locally advanced gastric or gastro-esophageal junction cancer: a phase 2, single-arm trial. J Clin Oncol. 2024;42(Suppl 16):4074. [Crossref]
28. Huang CM. The safety and efficacy of neoadjuvant immunochemotherapy followed by laparoscopic gastrectomy for gastric cancer: a multicenter real-world clinical study. clinicaltrials.gov; 2024. [Crossref]
29. Kelly RJ, Ajani JA, Kuzdzal J, et al.; CheckMate 577 Investigators. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191-1203. Erratum in: N Engl J Med. 2023;388(7):672. [Crossref] [PubMed]
30. Kang YK, Terashima M, Kim YW, et al. Adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy for stage III gastric or gastro-oesophageal junction cancer after gastrectomy with D2 or more extensive lymph-node dissection (ATTRACTION-5): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2024;9(8):705-717. Erratum in: Lancet Gastroenterol Hepatol. 2025;10(4):e7. [Crossref] [PubMed]
31. Yoon HH, Jin Z, Kour O, et al. Association of PD-L1 expression and other variables with benefit from immune checkpoint inhibition in advanced gastroesophageal cancer: systematic review and meta-analysis of 17 phase 3 randomized clinical trials. JAMA Oncol. 2022;8(10):1456-1465. [Crossref] [PubMed] [PMC]
32. Lote H, Chau I. Immunotherapy in gastrointestinal cancers. Cancer Treat Res. 2024;192:277-303. [Crossref] [PubMed]
33. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546-2556. [Crossref] [PubMed] [PMC]
34. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol. 2018;4(6):e180071. [Crossref] [PubMed] [PMC]
35. Yang J, Greally M, Strong VE, et al. Perioperative versus total neoadjuvant chemotherapy in gastric cancer. J Gastrointest Oncol. 2023;14(3):1193-1203. [Crossref] [PubMed] [PMC]
36. Rencuzogullari A, Karahan SN, Ates MI, et al. Preliminary outcomes of total (FLOT8) vs standart neoadjuvant (FLOT 4+4) therapy for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma:a propensity-matched comparison. EJSO. 2024;50(2):107856. [Crossref]
37. Villanueva L, Anabalon J, Butte JM, et al. Total neoadjuvant chemotherapy with FLOT scheme in resectable adenocarcinoma of the gastro-oesophageal junction or gastric adenocarcinoma: impact on pathological complete response and safety. Ecancermedicalscience. 2021;15:1168. [Crossref] [PubMed] [PMC]
38. Chen Y, He J, Zheng J, et al. Impact of pathological complete response on survival in gastric cancer after neoadjuvant chemotherapy: a propensity score matching analysis. BMC Gastroenterol. 2025;25(1):11. [Crossref] [PubMed] [PMC]
39. Kaltenmeier C, Althans A, Mascara M, et al. Pathologic complete response following neoadjuvant therapy for gastric adenocarcinoma: a national cancer database analysis on incidence, predictors, and outcomes. Am Surg. 2021;87(7):1145-1154. [Crossref] [PubMed] [PMC]
40. Klempner SJ, Cowden ES, Cytryn SL, et al. PD-L1 immunohistochemistry in gastric cancer: comparison of combined positive score and tumor area positivity across 28-8, 22C3, and SP263 assays. JCO Precis Oncol. 2024;8:e2400230. [Crossref] [PubMed]