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Phase 2 study of neoadjuvant durvalumab plus docetaxel, oxaliplatin, and S-1 with surgery and adjuvant durvalumab plus S-1 for resectable locally advanced gastric cancer

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ABSTRACT

Background Based on the phase 3 PRODIGY study, neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) have emerged as a viable treatment option for Asian patients with resectable locally advanced gastric cancer (LAGC). This phase 2 study evaluated the efficacy and safety of combining neoadjuvant durvalumab with DOS, followed by surgery and adjuvant durvalumab plus S-1 chemotherapy, for resectable LAGC.

Methods Patients with LAGC with cT2/3N+or cT4Nany tumors were enrolled in this study. Patients with proficient mismatch repair protein (pMMR) tumors received three cycles of neoadjuvant durvalumab plus DOS, administered every 3 weeks, followed by surgery and adjuvant S-1 plus durvalumab (main study arm). The primary endpoints were the rate of pathologic complete regression (pCR) and safety. An exploratory arm evaluated patients with deficient mismatch repair protein (dMMR) tumors, who received three cycles of neoadjuvant durvalumab and tremelimumab, followed by surgery and adjuvant durvalumab.

Results In the main study arm, 50 pMMR patients were enrolled, and received at least one dose of neoadjuvant treatment. The median age was 63 years, with 72.0% being men. 18 and 32 patients presented with clinical stage II and III tumors, respectively. 49 (98.0%) underwent surgery, with 45 achieving R0 resection. A pCR rate of 30.0% was observed, meeting the prespecified primary efficacy endpoint. With a median follow-up of 21.8 months, the 3-year progression-free survival and overall survival rates were 69.9% and 88.1%, respectively. 10% of patients experienced predefined unacceptable severe toxicities, including febrile neutropenia (n=3) and persistent G4 neutropenia (n=2) lasting more than 7 days, thereby meeting the primary safety endpoint. Nine patients with dMMR tumors were enrolled in the exploratory arm. All nine underwent surgery, with a pCR rate of 22.2%.

Conclusions This study met its primary efficacy and safety endpoints. The combination of neoadjuvant durvalumab plus DOS, followed by surgery and adjuvant durvalumab plus S-1 chemotherapy, warrants further investigation in a phase 3 trial for Asian patients with LAGC. Clinical trial information: 04221555.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are substantial differences in adjuvant approaches for locally advanced gastric cancer (LAGC) between Asian and Western countries. Based on the phase 3 PRODIGY study, neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) have emerged as a viable treatment option for Asian patients with resectable LAGC. Combining immune checkpoint inhibitors (ICIs) with neoadjuvant chemotherapy is a promising approach for improving the outcomes of patients with gastric cancer. However, there is no established ICI-based neoadjuvant treatment for patients with LAGC.

WHAT THIS STUDY ADDS

⇒ In this non-randomized controlled, single-center, open-label phase two trial, the combination of neoadjuvant durvalumab plus DOS followed by surgery and adjuvant durvalumab plus S-1 chemotherapy was safe and efficacious. A pathologic complete response rate was 30.0%, meeting the prespecified primary efficacy endpoint. 10% experienced predefined unacceptable severe toxicities, meeting the primary safety endpoint.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study demonstrated that neoadjuvant durvalumab plus DOS followed by surgery and adjuvant durvalumab plus S-1 chemotherapy is effective in Asian patients with LAGC, highlighting the clinical feasibility of adding ICI to neoadjuvant chemotherapy in Asian patients.

BACKGROUND

Gastric cancer is the fifth most common cancer globally and the third leading cause of cancer-related deaths.[1] Surgical resection remains the cornerstone treatment for patients with locally advanced gastric cancer (LAGC), offering a potential cure. However,

due to risks of incomplete resection and high recurrence rates following surgery alone, perioperative and postoperative adjuvant therapies have been developed based on pivotal phase 3 trials and are considered standard of care. Adjuvant treatment strategies vary regionally.[2] Perioperative chemotherapy has been the standard in Western countries since the MAGIC study[3] and more recently the FLOT4 study.[4] In contrast, upfront D2 gastrectomy followed by adjuvant chemotherapy has been the standard approach in Asia based on the ACTS-GC and CLASSIC studies.[5 6]

Recent pivotal phase 3 trials have demonstrated the benefits of neoadjuvant chemotherapy in Asian patients.[7 8] The PRODIGY study showed that neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) followed by surgery and adjuvant S-1 improved both progression-free survival (PFS) and overall survival (OS) compared with upfront surgery and adjuvant S-1 in patients with LAGC.[7 9] Similarly, the RESOLVE study reported superior survival outcomes with perioperative S-1 plus oxaliplatin (SOX) compared with adjuvant capecitabine plus oxaliplatin (XELOX).[8 10] These findings establish neoadjuvant chemotherapy as a viable treatment option for LAGC in Asian patients.

Despite advancements in neoadjuvant chemotherapy, outcomes for patients with LAGC remain suboptimal, necessitating novel therapeutic strategies. The demonstrated efficacy of immune checkpoint inhibitor (ICI)-based treatments in prolonging survival for patients with metastatic gastric cancer suggests their potential benefit in the localized setting.[11–13] Moreover, neoadjuvant ICI may optimize antitumor immune responses, potentially reducing recurrence risk compared with adjuvant therapy alone.[14] Thus, combining ICIs with neoadjuvant chemotherapy is a promising approach for improving outcomes of patients with LAGC.

Therefore, this phase 2 study aims to investigate the efficacy and safety of neoadjuvant durvalumab combined with DOS, followed by surgery and adjuvant durvalumab plus S-1 chemotherapy in patients with resectable proficient mismatch repair protein (pMMR) LAGC. Additionally, as an exploratory secondary study, it examines neoadjuvant durvalumab and tremelimumab, followed by surgery and adjuvant durvalumab, in patients with deficient mismatch repair (dMMR) LAGC. This combination approach was based on the observation that while programmed cell death protein-1 (PD-1)/programmed death-ligand 1 PD-L1 inhibitors are efficacious for dMMR tumors, a significant proportion of patients with these tumors do not respond to the treatment.[15] Furthermore, clinical trials in other cancers responsive to ICIs have shown that combining PD-1 and cytotoxic T-lymphocyte associated protein 4 inhibitors improves survival outcomes.[16 17] These findings provided the rationale for employing this combination therapy in dMMR tumors.

METHODS

Study design and participants

This was a non-randomized controlled, single-center, open-label, phase 2 study evaluating neoadjuvant durvalumab plus DOS followed by surgery and adjuvant S-1 plus durvalumab in patients with pMMR resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (main study arm). An exploratory secondary study assessed the efficacy and safety of neoadjuvant durvalumab plus tremelimumab in patients with dMMR tumors. Mismatch repair (MMR) status was determined by immunohistochemistry of MLH-1 and MSH-2 on baseline tumor tissue samples, as previously described.[18] Patients were allocated to the main or exploratory study arms accordingly.

Key inclusion criteria included age ≥19 years, Eastern Cooperative Oncology Group performance status 0–1, newly diagnosed histologically confirmed primary gastric or GEJ adenocarcinoma, and clinical tumor, node, metastases (TNM) staging cT2-3N+ or cT4Nany according to the American Joint Committee on Cancer eighth edition. Baseline CT scans were centrally reviewed by a board-certified abdominal radiologist (JSL) to determine clinical TNM stage and eligibility. Clinical data were collected by investigators and research coordinators. This study was approved by the Asan Medical Center ethics committee and institutional review board, and all patients provided written informed consent.

Study procedures and assessment

For the main study arm, neoadjuvant treatment consisted of durvalumab (1,120 mg), docetaxel (50 mg/m^2), and oxaliplatin (100 mg/m^2) administered intravenously on day 1, and oral S-1 (40 mg/m^2) two times per day from days 1–14 every 3 weeks. The durvalumab dosing schedule of 1,120 mg every 3 weeks was based on its use in clinical trials for other cancer types involving durvalumab-based treatments.[19–21] After the first neoadjuvant cycle, the radiological response was assessed using Response Evaluation Criteria in Solid Tumors V.1.1. Patients with disease progression (PD) underwent surgery or received chemotherapy outside the study. Otherwise, the patient continued with the second and third neoadjuvant cycles.

Post-third cycle, a response assessment was followed by surgery within 1–3 weeks. A total or subtotal gastrectomy with D2 lymph node dissection was performed based on tumor location. A board-certified gastrointestinal pathologist (YSP, with over 10 years of experience) evaluated the histopathological tumor regression grade (TRG) of surgical specimens using Becker's criteria.[22]

Adjuvant therapy commenced within 3–6 weeks post-surgery, comprising eight cycles over 12 months. Treatment involved oral S-1 (40–60 mg two times per day, days 1–28, based on body surface area) and durvalumab (1,120 mg on day 1 and day 22) every 6 weeks. Postoperative abdominopelvic CT scans and esophagogastroduodenoscopies were conducted at 6 and 12 months, respectively, to monitor for PD.

In the exploratory arm, patients received neoadjuvant durvalumab (1,500 mg) and tremelimumab (75 mg) intravenously on day 1 every 4 weeks for three cycles. Adjuvant therapy consisted of 12 cycles of durvalumab (1,500 mg intravenously on day 1) every 4 weeks. Response evaluation and surgical procedures mirrored those of the main study arm.

Study drugs were supplied by AstraZeneca (durvalumab and tremelimumab), Boryung Pharmaceutical (docetaxel and oxaliplatin), and Taiho/Jeil Pharmaceutical (S-1).

Study endpoints

The primary endpoints of the main study were pathologic complete regression (pCR) rate and safety. Secondary endpoints included R0 resection rate, PFS, and OS. Based on the assumption that durvalumab plus DOS could improve the pCR rate to 25% (P1) compared with 10% with neoadjuvant DOS (P0),[7] a Fleming's single-stage phase 2 design with a one-sided type I error of 5% and power of 0.8 was employed. To achieve this, a pCR in 8 or more of 40 patients would meet the primary endpoint. Anticipating a 20% loss to follow-up, a total of 50 patients were required.

Safety was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0 through monitoring of adverse events (AEs) and serious AEs, routine blood tests, urinalysis, vital signs, weight, performance status, and physical examinations. Neoadjuvant durvalumab plus DOS was considered safe if fewer than 20% of patients experienced unacceptable severe toxicity during neoadjuvant chemotherapy. Unacceptable severe toxicity was defined as treatment-related AEs meeting criteria detailed in the online supplemental material, such as grade ≥3 neutropenia with fever ≥38.3°C; grade 4 neutropenia lasting more than 7 days; grade ≥3 thrombocytopenia with severe bleeding; grade 4 thrombocytopenia; grade 4 non-immune-mediated AEs; grade 4 immune-mediated AEs excluding endocrinopathies, and grade 3 non-immune-mediated AEs not recovering to grade 1 or below or baseline within 30 days of maximal conservative treatment.

Efficacy assessments were conducted on the full analysis set (FAS), which included all patients receiving at least one study drug dose and at least one tumor assessment post-baseline. The safety analysis included all patients receiving at least one study treatment dose.

Initially planned to enroll 20 patients without statistical assumptions, the exploratory study arm protocol was amended due to slow patient accrual and emerging data from phase 2 studies of dual ICIs in localized resectable gastric or GEJ cancer.[23 24] Based on the assumption that durvalumab plus tremelimumab could improve the pCR rate to 60% (P1) compared with 12.5% with neoadjuvant DOS (P0),[18] a Fleming's single-stage phase 2 design with a one-sided type I error of 5% and power of 0.8 was applied. Achieving a pCR in three or more of six patients would meet the primary endpoint.

Evaluation of PD-L1 and tumor mutation burden

PD-L1 immunohistochemistry staining was conducted on patients with available baseline tumor tissues (n=47 and 9 for the main and exploratory arms, respectively) using the Ventana PD-L1 SP263 assay, following the instructions of the manufacturers. The combined positive score (CPS) was calculated by dividing the number of PD-L1-expressing tumor and intratumoral or peritumoral inflammatory cells by the total number of tumor cells, then multiplied by 100.

Tumor mutation burden was assessed in patients from the exploratory arm with tumor tissues suitable for in-house targeted next-generation sequencing, as described previously.[25] Tumor mutation burden (TMB) was calculated by summing the number of single-nucleotide variations and insertion/deletion mutations per megabase in the targeted region.

Statistical analysis

Descriptive statistics were used to characterize patient demographics and baseline characteristics. Survival curves for PFS and OS were generated using the Kaplan-Meier method. Log-rank tests were used to compare PFS and OS in each subgroup. PFS was defined as the time from treatment initiation to PD or death, whichever occurred first. PD was determined by: (1) RECIST-defined PD during neoadjuvant chemotherapy; (2) distant metastasis detected by imaging or pathology; (3) persistence of visually observed cancer cells at resection margin (R2) or microscopic cancer cells at resection margin from postoperative histology (R1); or (4) recurrence, either local or at distant sites, during follow-up after R0 resection. OS was defined as the time from treatment initiation to death from any cause. The χ^2 test was employed to compare categorical variables between subgroups. All statistical analyses were performed using R software (V.3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients in the main study arm

A total of 50 patients with pMMR were enrolled in the main study arm between July 28, 2020, and May 23, 2023 (figure 1). All enrolled patients received at least one dose of neoadjuvant treatment and at least one tumor assessment post-baseline (FAS). Table 1 presents patient characteristics for the main study arm. The median age was 63 years, and 72.0% (n=36) of patients were men. The majority (n=46, 92.0%) had primary gastric tumors, while 8.0% (n=4) had GEJ primary tumors. Most patients (n=38, 76%) presented with cT4 tumors, with 18 (36.0%) and 32 (64.0%) having clinical stage II and III disease, respectively.

Neoadjuvant chemotherapy

Forty-eight patients (96.0%) completed three cycles of neoadjuvant treatment. One patient died after two cycles of neoadjuvant treatment due to COVID-19 pneumonia

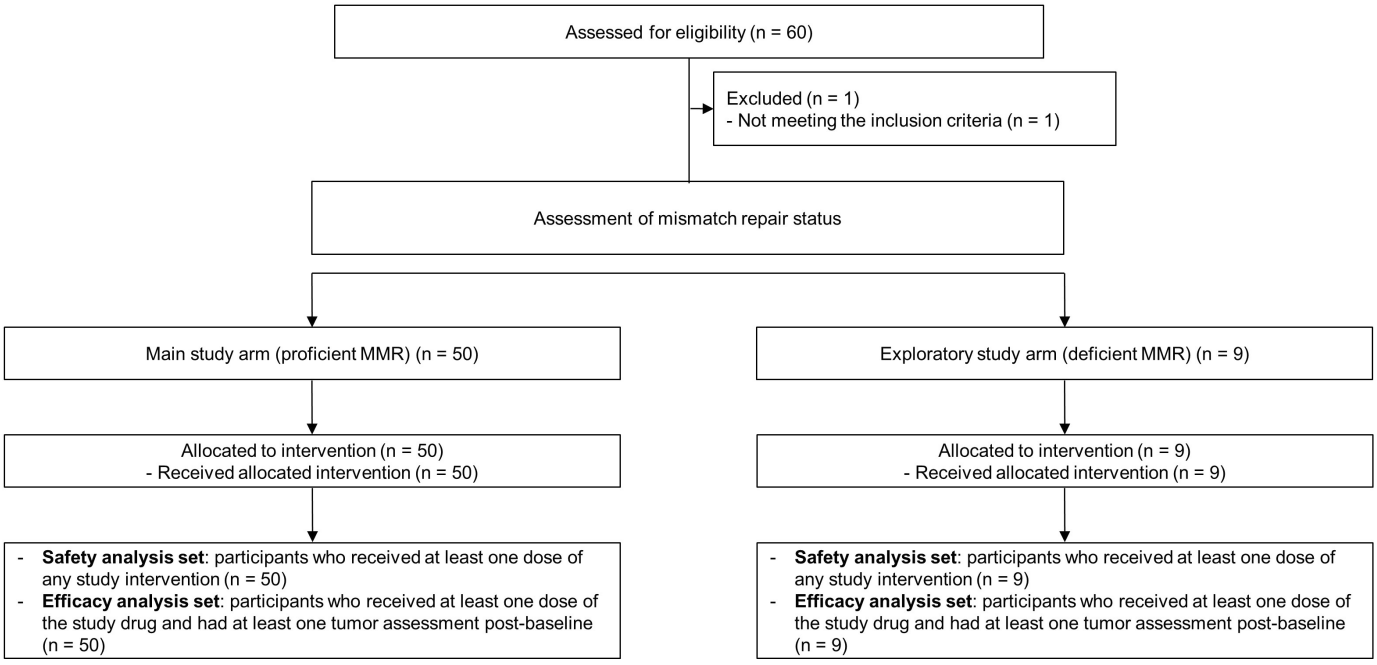

Figure 1 Consolidated Standards of Reporting Trials diagram showing the study disposition. MMR, mismatch repair.

which was assessed to be unrelated to the study treatment, and another underwent surgery after two cycles of neoadjuvant treatment due to treatment-related grade 2 enterocolitis, fatigue, anorexia, and nausea. No patients experienced radiological PD during neoadjuvant chemotherapy.

Safety profiles were assessed in all 50 patients who received at least one dose of neoadjuvant treatment (safety analysis set). The most common treatment-related AEs were fatigue (54.0%), nausea (52.0%), anorexia (48.0%), and diarrhea (46.0%) (table 2). Neutropenia was the most frequent grade 3 or higher AE. Five patients (10.0%) experienced predefined unacceptable severe toxicities: febrile neutropenia (n=3) and grade 4 neutropenia lasting at least 7 days (n=2), meeting the primary safety endpoint.

Surgical outcomes

Table 3 presents the surgical outcomes of the main study arm. Among the 50 patients in the FAS, 49 (98.0%) underwent surgery. Of these, 45 achieved a complete resection (R0). Among the 45 patients with R0 resection, D2 lymphadenectomy was performed in 44 (97.8%), with 1 patient undergoing D1+lymphadenectomy.

Pathological outcomes

Among patients in the FAS, pCR (TRG1a) was observed in 15 (30.0%, 95% CI 18.3 to 44.8) patients, meeting the primary efficacy endpoint (table 4). The pCR rate did not differ significantly between cStage II and III tumors (22.2% vs 34.4%, respectively, p=0.563). 18 patients (36.0%) exhibited TRG1b with less than 10% residual tumor. Notably, all 15 pCR cases demonstrated no residual viable lymph node metastasis, resulting in an ypT0N0 pathologic stage. 10 (20.0%), 12 (24.0%), and 8 (16.0%) patients achieved pathological stages I, II and III, respectively (online supplemental table 1).

A trend of higher pCR rate was observed in patients with higher PD-L1 CPS (39.1% vs 20.8%, p=0.293 for PD-L1 CPS≥1 vs <1; 54.6% vs 22.2%, p=0.061 for PD-L1 CPS≥5 vs <5; and 60.0% vs 22.2%, p=0.148 for PD-L1 CPS≥10 vs <10) (figure 2).

Survival outcomes

With a median follow-up of 21.8 months, neither median PFS nor OS were reached. 3-year PFS and OS rates were 69.9% (95% CI 53.4% to 83.7%) and 88.1% (95% CI 69.3% to 95.7%), respectively (online supplemental figure 1).

Patients achieving pCR (n=15) remained event-free (no PD or death) at the data cut-off. They exhibited more favorable PFS and OS trends compared with those without pCR (n=35) (p=0.019 and p=0.19 for PFS and OS, respectively) (online supplemental figure 2).

Exploratory arm

Before the planned assessment of the efficacy endpoint (pCR) in six patients, an additional three patients were enrolled, which led to the enrollment of nine patients between January 1, 2021, and September 19, 2023, in the exploratory arm (figure 1). The median age was 65 years, with 77.8% being women (online supplemental table 2). All patients presented with clinical stage III disease, with 88.9% (8/9) having clinical T4 tumors. The most common AE was skin rash (44.4%), and one patient experienced a grade 3 lipase elevation without associated symptoms (online supplemental table 3).

The nine patients underwent surgery. One patient with radiological PD after the first cycle underwent curative resection (R0), while another required an open and

Table 1 Patient characteristics of the main study arm

Characteristics (n=50)	
Age (years)	63 (39–83)
<60 years	15 (30.0)
Sex	
Male	36 (72.0)
Female	14 (28.0)
ECOG PS	
0	31 (62.0)
1	19 (38.0)
Primary tumor location	
Gastric	46 (92.0)
GEJ	4 (8.0)
Clinical T stage	
T2	3 (6.0)
T3	9 (18.0)
T4a	33 (66.0)
T4b	5 (10.0)
Clinical N stage	
N0	9 (18.0)
N1	22 (44.0)
N2	13 (26.0)
N3	6 (12.0)
Overall clinical stage	
IIA	3 (6.0)
IIB	15 (30.0)
IIIA	23 (46.0)
IIIB	8 (16.0)
IIIC	1 (2.0)

Data are presented as No. (%) or median (range).
ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction.

Table 2 Adverse events occurred in ≥5% of patients undergoing neoadjuvant chemotherapy in the main study arm

Adverse event	Any grade	Grade ≥3
Any adverse events	50 (100%)	21 (42%)
Fatigue	27 (54%)	3 (6%)
Nausea	26 (52%)	2 (4%)
Anorexia	24 (48%)	–
Diarrhea	23 (46%)	2 (4%)
Lipase increased	17 (34%)	2 (4%)
Abdominal pain	13 (26%)	–
Amylase increased	12 (24%)	–
Aspartate aminotransferase increased	10 (20%)	1 (2%)
Mucositis oral	10 (20%)	–
Neutropenia	10 (20%)	6 (12%)
Alanine aminotransferase increased	8 (16%)	2 (4%)
Alopecia	7 (14%)	–
Anemia	7 (14%)	1 (2%)
Constipation	7 (14%)	–
Dyspepsia	6 (12%)	–
Hypoalbuminemia	6 (12%)	–
Alkaline phosphatase	4 (8%)	–
Sensory neuropathy	4 (8%)	–
Skin rash	4 (8%)	–
Gamma-glutamyl transferase increased	4 (8%)	1 (2%)
Enterocolitis	3 (6%)	–
Febrile neutropenia	3 (6%)	3 (6%)
Hyperbilirubinemia	3 (6%)	1 (2%)
Palmar-plantar erythrodysesthesia	3 (6%)	–
General weakness	3 (6%)	1 (2%)
Platelet count decreased	3 (6%)	–
COVID-19 infection	3 (6%)	1 (2%)

closure procedure owing to peritoneal seeding (online supplemental table 4). pCR and TRG1b were observed in two patients each (22.2%) (online supplemental table 5). Online supplemental figure 3 presents the PD-L1 CPS and TMB for patients who achieved pCR and those who did not. Detailed postoperative pathologic stages are presented in online supplemental table 6.

Discussion/conclusion

This phase 2 study demonstrated the efficacy and safety of neoadjuvant durvalumab plus DOS neoadjuvant chemotherapy followed by surgery and adjuvant durvalumab plus S-1 chemotherapy in patients with resectable LAGC. Both primary endpoints of pCR and safety were met, supporting the clinical feasibility of this regimen. The observed pCR rate of 30.0% and manageable AEs warrant further investigation of this regimen in a phase 3 trial.

To our knowledge, this is the first study evaluating the addition of an ICI to the standard neoadjuvant DOS regimen in Asia. Following the successful results of phase 3 studies demonstrating the efficacy of ICI-based treatments in the metastatic setting,[11–13] research has focused on adding ICIs to fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)-based regimens primarily in Western populations. The phase 2 DANTE trial showed that adding atezolizumab to FLOT improved the pCR rate, leading to a phase 3 trial.[26] Similarly, the pre-planned analysis of the phase 3 MATTERHORN study reported a significant increase in pCR rates (from 7% to 19%) with the addition of durvalumab to FLOT.[27] However, the phase 3 KEYNOTE-585 study, which evaluated

Table 3 Profiles of surgery of the main study arm

Characteristics	
Surgery performed*	49 (98.0%)
Patients receiving surgery (n=49)	
R0	45 (91.8%)
R1	0 (0.0%)
R2†	2 (4.1%)
Open and closure	2 (4.1%)
Gastrectomy with R0 resection (n=45)	
Total gastrectomy	23 (51.1%)
Subtotal gastrectomy	22 (48.9%)
D2 dissection	44 (97.7%)

*One patient did not receive surgery because of due to COVID-19 pneumonia-related death during neoadjuvant chemotherapy (not related to the study treatment).
†Presence of peritoneal seeding (pathologically M1) on pathological examination of the surgical specimen.

pembrolizumab added to FLOT or 5-FU plus cisplatin (FP)/capecitabine plus cisplatin (XP), met the primary endpoint of improved pCR but failed to improve event-free survival (EFS).[28]

While some Asian patients participated in the MATTERHORN and KEYNOTE-585 studies, it is crucial to note that the FLOT and FP/XP regimens are not standard perioperative treatments in Asia. These regimens have not been proven superior to upfront surgery followed by adjuvant chemotherapy in terms of efficacy or safety in Asian populations. Coupled with the substantial differences in adjuvant approaches for LAGC between Asian and Western countries,[2] this underscores the need for ICI-based perioperative regimens tailored to Asian populations and built on chemotherapy backbones proven efficacious in this region.

Several neoadjuvant ICI-based chemotherapy regimens have shown promising outcomes in Asian populations.[29–32] However, the interpretation of these studies is limited by small sample sizes[29 32] or the use of unvalidated neoadjuvant chemotherapy backbones.[30 31] Notably, the phase 2 NEOSUMMIT-01 study (n=108) demonstrated improved pCR or near-complete response rates (TRG 0/1) with perioperative toripalimab plus SOX/XELOX compared with SOX/XELOX alone (44.4% vs 20.4%, respectively, by the National Comprehensive Cancer Network guidelines[33]) in Chinese patients, meeting the primary endpoint.[30] These findings align with our results, suggesting that adding anti-PD-1/PD-L1 to neoadjuvant chemotherapy can enhance treatment outcomes in gastric cancer. Nevertheless, the optimal chemotherapy backbone remains to be determined. It should also be noted that perioperative XELOX, used in half of the NEOSUMMIT-01 patients, is also not a standard neoadjuvant regimen.

Table 4 Pathologic response of the main study arm

Becker's criteria (n=50)	
TRG1a (No residual tumor, pCR)	15 (30.0%)
TRG1b (<10% residual tumor)	18 (36.0%)
TRG2 (10–50% residual tumor)	4 (8.0%)
TRG3 (>50% residual tumor)	10 (20.0%)
Not evaluable*	3 (6.0%)

*Not evaluable due to open and closure due to peritoneal seeding (n=2) and COVID-19 pneumonia-related death during neoadjuvant chemotherapy (n=1).
pCR, pathologic complete response; TRG, tumor regression grade.

On the other hand, the ATTRACTION-5 study showed no improvement in recurrence-free survival with adjuvant nivolumab plus chemotherapy compared with chemotherapy alone in patients with pathologic stage III disease.[34] Although there remains an issue regarding patient selection in the ATTRACTION-5 study (lower HRs in the advanced stage (ie, stage IIIC) and high PD-L1 expression subgroups),[34] the negative outcome could also be attributed to the timing of ICI administration. Mechanistically, neoadjuvant ICI therapy could optimize antitumor immune responses and prevent recurrence more effectively than adjuvant ICI.[14] Supporting evidence comes from studies in melanoma and non-small cell lung cancer, with demonstrated prolonged EFS or OS with neoadjuvant ICI compared with adjuvant ICI.[35–37] Therefore, the suboptimal results of the ATTRACTION-5 study might be related to the timing of ICI administration, further emphasizing the potential benefits of neoadjuvant ICI-based treatments.

The observed pCR rate of 30% (95% CI 18.3% to 44.8%) in this study was significantly higher than the 10% reported in patients treated with neoadjuvant DOS in the phase 3 PRODIGY study,[7] suggesting improved efficacy of the current neoadjuvant regimen. This value appears favorable when compared with the 6% pCR rate observed with neoadjuvant SOX in the RESOLVE study. However, the interpretation of these findings should be approached with caution, as the chemotherapy backbone and inclusion criterion for clinical stage (ie, cT4aN+ and cT4bNany in the RESOLVE study vs cT2-3N+and cT4Nany in the current study) differ, which may potentially affect the efficacy outcomes. Nevertheless, it should be noted that while the patient population in this study exhibited a lower proportion of cStage III tumors (64% vs 79%) and a higher proportion of cT4 tumors (76% vs 69%) compared with the PRODIGY study CSC arm. The absence of significant differences in pCR rates between stage II versus III tumors and cT2-3 versus cT4 tumors suggests that these factors did not contribute to the observed improvement in pCR. An exploratory study of the PRODIGY trial demonstrated that patients with advanced clinical T stage (cT stage) (cT4 vs cT2-3) were more likely to benefit from neoadjuvant chemotherapy than from upfront surgery followed by adjuvant chemotherapy.[38] Furthermore, patients with advanced cStage

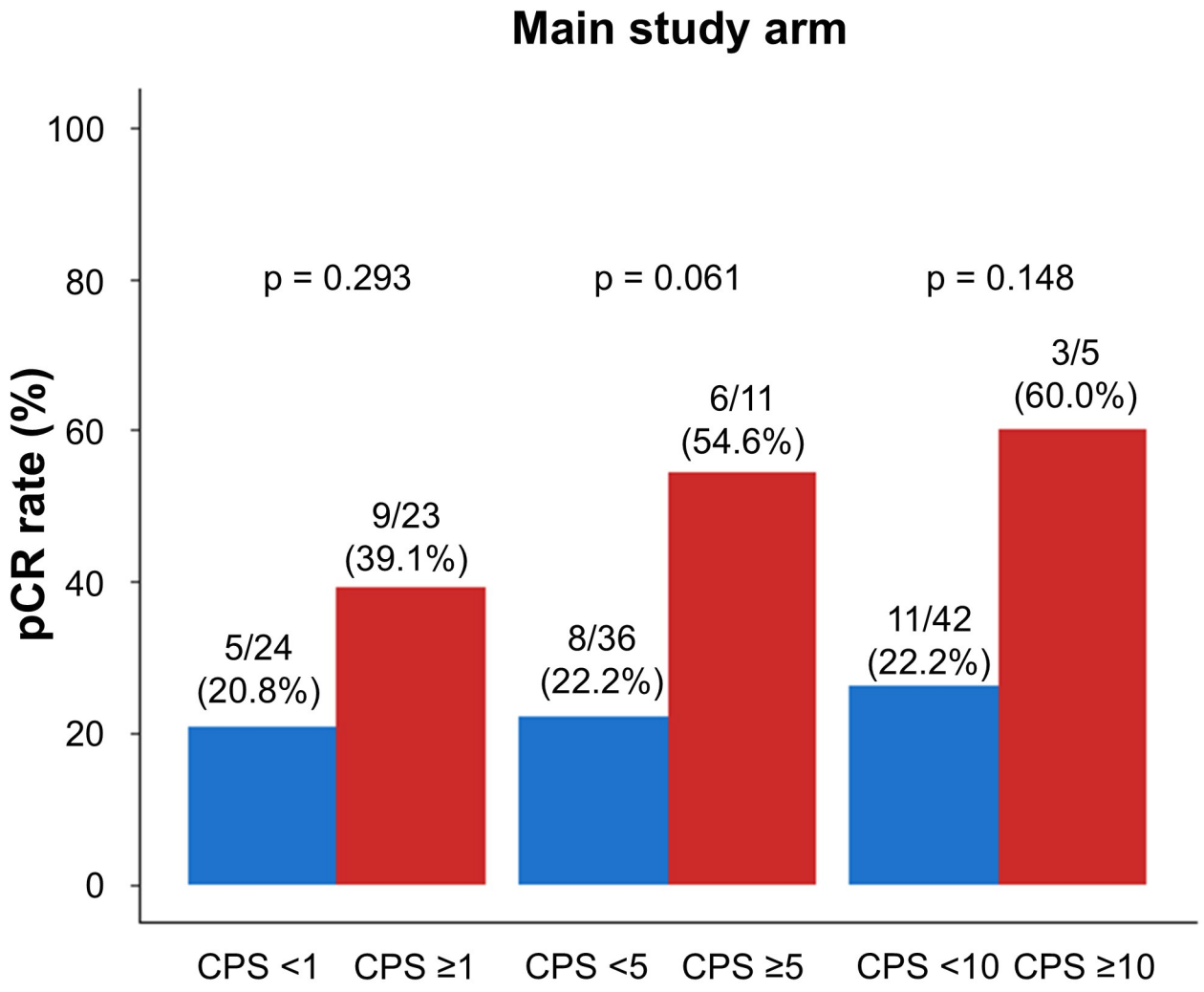

Figure 2 Pathologic complete response rate based on programmed death-ligand 1 combined positive score in the main study arm. CPS, combined positive score; pCR, pathologic complete regression.

exhibited poorer survival outcomes.[39] Therefore, the sustained pCR benefit observed in advanced stages in this study indicates that the addition of ICI to neoadjuvant chemotherapy may be particularly beneficial for patients with advanced cStage.

A trend toward a higher pCR rate was observed in patients with a high PD-L1 CPS. These findings suggest that the pCR rate may be higher in patients with a high PD-L1 CPS when treated with this regimen, consistent with those of the DANTE study.[26] However, interpreting these findings should be approached with caution due to the small sample size included in the analysis.

One distinguishing feature of this study was the incorporation of different treatment approaches based on MMR status. The pCR rate of 22.2% in the exploratory study arm was lower than the reported pCR rates (58.6–60.0%) in previous studies of dual ICIs.[23 24] However, the small sample size in this exploratory arm warrants caution in interpreting these results. The enrichment of patients with advanced clinical T stage (88.9%, cT4 tumors) in the exploratory study arm might explain the lower pCR rate, as the phase 2 INFINITY study demonstrated a correlation between pCR rate and baseline cT stage (pCR rates of 17% and 89% for cT4 and cT2-3 tumors, respectively).[24] While no significant differences in PD-L1 CPS and TMB were observed between patients who achieved pCR and those who did not, drawing definitive conclusions is challenging due to the small sample size included in the analysis. Future studies should investigate factors differentially affecting the rate of pCR in patients with dMMR/microsatellite instability (MSI)-high tumors treated with dual ICIs.

As this is currently the only Asian data on neoadjuvant dual ICIs, the lower-than-expected pCR rate in the dMMR tumor group suggests that cytotoxic chemotherapy might be necessary within the neoadjuvant regimen for these patients. While concerns exist about the potential negative impact of perioperative chemotherapy on patients with MSI-high tumors, recent studies have indicated that taxane-based triplet regimens can be efficacious in this patient population. The DANTE trial reported a pCR rate of 27.0% in MSI-high patients treated with perioperative FLOT.[40] Additionally, a multicenter observational study demonstrated improved disease-free survival in

MSI-high patients compared with microsatellite-stable patients treated with perioperative FLOT.[41] A post hoc analysis of the PRODIGY study suggested potentially better survival outcomes for dMMR patients treated with neoadjuvant DOS chemotherapy compared with pMMR patients.[18] These findings support the inclusion of taxane-based triplet regimens in neoadjuvant therapy for MSI-high/dMMR patients. Given the higher pCR rate (63.0%) observed with atezolizumab plus FLOT in MSI-high patients in the DANTE study,[40] it is plausible that the efficacy of the main study arm could have been enhanced by including dMMR patients and treating them with neoadjuvant durvalumab plus DOS. Further research is warranted to evaluate the efficacy of ICI plus DOS chemotherapy for patients with MSI-high/dMMR tumors.

The current study employed pCR as the primary endpoint, serving as a surrogate for survival outcomes. Our analysis showed favorable PFS and OS trends for patients who achieved pCR compared with those who did not, supporting the use of pCR as a surrogate endpoint in the neoadjuvant setting for gastric cancer. While pCR has established value as a surrogate in breast cancer,[42] its role in gastric cancer requires further validation. The phase 3 KEYNOTE-585 study, which showed a significant increase in pCR rate with pembrolizumab plus chemotherapy but no improvement in event-free survival, raises concerns about the reliability of pCR as a predictor of survival outcomes in the context of perioperative chemotherapy.[28] Given the widespread adoption of pCR or major pathologic response as primary endpoints in neoadjuvant studies, further research is needed to clarify the relationship between pCR and survival. On the other hand, while this study demonstrated numerically higher 3-year PFS and OS rates than those of the neoadjuvant arm of the PRODIGY study, direct comparison of survival outcomes is challenging due to differences in follow-up duration, stage distribution, and the small sample size.

This single-center phase 2 study without a control arm has inherent limitations regarding the generalizability of our findings. However, our prior experience leading the phase 3 PRODIGY study and the implementation of central radiological and pathological assessments contributed to the rigorous conduct of this study. Due to the relatively short follow-up period, definitive conclusions about long-term survival and safety outcomes require further observation.

In conclusion, neoadjuvant durvalumab plus DOS followed by surgery and adjuvant durvalumab plus S-1 demonstrated safety and efficacy in Asian patients with resectable LAGC. These findings warrant further investigation of this regimen in a phase 3 trial to confirm the benefits of this regimen in this patient population.

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