Gastric Cancer
https://doi.org/10.1007/s10120-025-01705-8

ORIGINAL ARTICLE

Neoadjuvant docetaxel, oxaliplatin, and S-1 therapy for patients with large type 3 or type 4 gastric cancer: final outcomes of a multicenter, phase II study (OGSG 1902)

Shunji Endo[1] · Ryo Tanaka[2] · Toshifumi Yamaguchi[3] · Hiromichi Miyagaki[4] · Junji Kawada[5] · Takeshi Omori[6] · Naoki Takahashi[7] · Toru Masuzawa[8] · Haruna Furukawa[9] · Yuya Sato[10] · Atsushi Takeno[11] · Naoki Shinno[6] · Ryohei Kawabata[4] · Shinsuke Katsuyama[8] · Shigeyoshi Higashi[9] · Yukinori Kurokawa[12] · Toshimasa Tsujinaka[13] · Toshio Shimokawa[14] · Taroh Satoh[15]

Received: 13 October 2025 / Accepted: 10 December 2025

Abstract

Background Large type 3 (≥8 cm) and type 4 gastric cancers are associated with extremely poor prognoses. The phase III JCOG0501 trial, which evaluated neoadjuvant S-1 plus cisplatin, failed to demonstrate any survival benefits. Docetaxel, oxaliplatin, and S-1 (DOS) have been explored as more effective perioperative regimens for these tumors.

Methods Eligible patients had large type 3 or type 4 gastric cancer without distant metastases, except for positive peritoneal cytology (CY). Patients received three cycles of neoadjuvant DOS (docetaxel 40 mg/m^2, oxaliplatin 100 mg/m^2, and oral S-1 at 80 mg/m^2/day for 14 days), followed by gastrectomy with ≥D2 lymphadenectomy and one year of adjuvant docetaxel plus S-1. The primary endpoint was the 3 year progression-free survival (PFS) rate, with an expected value of 60% and a threshold of 45%. A one-sample log-rank test was performed with an α level of 0.10.

Results Of the 48 patients enrolled, 27 had type 4 tumors (56.2%), and 10 (20.8%) had CY1. Overall, 91.7% of patients completed neoadjuvant DOS. R0 resection rate was achieved in 89.6% of patients, a pathological response grade≥1b in 66.7%, and negative CY conversion in 80.0%. The 3-year PFS rate was 37.5% (95% confidence interval [CI], 24.1–50.6%; 80% CI 28.6–46.4%; $p=0.960$), and the 3-year overall survival rate was 52.1% (95% CI 37.2–65.0%).

Conclusions Although neoadjuvant DOS therapy demonstrated favorable pathological responses, the 3-year PFS did not exceed the predefined threshold, and a survival benefit was not demonstrated.

Keywords Stomach neoplasms · Docetaxel · Oxaliplatin · S-1 · Neoadjuvant therapy · Linitis plastica

✉ Toshifumi Yamaguchi
yamagu.toshifumi@gmail.com

[1] Department of Digestive Surgery, Kawasaki Medical School, Kurashiki, Japan

[2] Department of General and Gastroenterological Surgery, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

[3] Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-Machi, Takatsuki City, Osaka, Japan

[4] Department of Surgery, Osaka Rosai Hospital, Sakai, Japan

[5] Department of Surgery, Yao Municipal Hospital, Yao, Japan

[6] Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan

[7] Department of Gastroenterology, Saitama Prefectural Cancer Center, Saitama, Japan

[8] Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan

[9] Department of Gastroenterological Surgery, Rinku General Medical Center, Izumisano, Japan

[10] Department of Gastrointestinal Surgery, Institute of Science Tokyo Hospital, Tokyo, Japan

[11] Department of Surgery, NHO Osaka National Hospital, Osaka, Japan

[12] Department of Gastroenterological Surgery, The University of Osaka Graduate School of Medicine, Suita, Japan

[13] Izumi City General Hospital, Izumi, Japan

[14] Department of Biostatistics, Faculty of Medicine, Wakayama Medical University, Wakayama, Japan

[15] Center for Cancer Genomics and Precision Medicine, The University of Osaka Hospital, Suita, Japan

Published online: 21 January 2026

Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, particularly in East Asia. Among its subtypes, large type 3 (≥8 cm) and type 4 tumors are characterized by highly aggressive behavior, frequent peritoneal dissemination, and extremely poor prognosis [1].

Neoadjuvant chemotherapy (NAC) has been investigated to improve patient outcomes. The phase III JCOG0501 trial evaluated two cycles of preoperative S-1 plus cisplatin (SP) followed by surgery and postoperative S-1 compared with upfront surgery plus adjuvant S-1 in patients with large type 3 or type 4 GC [2]. Although the NAC arm achieved a higher curative resection rate (73.5% vs. 65.1%), no survival benefit was observed, with identical 3 year progression-free survival (PFS, 47.7%) and similar overall survival (OS, 62.4% vs. 60.9%). Accordingly, SP NAC may fail to provide a sufficient treatment intensity for these biologically aggressive subtypes.

Therefore, triplet regimens are garnering increasing attention. In Western countries, the fluorouracil, oxaliplatin, and docetaxel (FLOT) regimen has become the standard perioperative therapy, achieving a pathological complete response rate of 16% in the FLOT4 trial [3]. In Korea, a phase II study on neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) reported a 100% NAC completion rate, 97.6% R0 resection rate, and 19.5% pathological complete response rate [4]. The subsequent phase III PRODIGY trial demonstrated considerable improvements in both PFS and OS with neoadjuvant DOS compared to upfront surgery [5].

Based on these promising results, the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) initiated a multicenter phase II trial (OGSG1902) to evaluate neoadjuvant DOS followed by adjuvant docetaxel plus S-1 (DS) in patients with large type 3 or type 4 GC [6]. This study also included patients with positive peritoneal cytology (CY1), given that JCOG0501 enrolled such cases and that a better prognosis can be expected when surgery is performed after conversion from CY1 to negative peritoneal cytology (CY0) by chemotherapy. Short-term outcomes, including pathological response, NAC completion, R0 resection, cytological negative conversion, and safety, have been previously reported [7]. In the current study, we present the final results, focusing on the primary endpoint of 3-year PFS and the secondary endpoint of OS.

Methods

Patients

Inclusion criteria were as follows: (1) histologically confirmed adenocarcinoma of the stomach; (2) large type 3 (≥8 cm) or type 4 GC; (3) no evidence of distant metastasis except for CY1 confirmed by laparoscopy; (4) no esophageal involvement ≥3 cm; (5) age 20–80 years; (6) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (7) no prior history of chemotherapy or radiotherapy for any malignancy; (8) human epidermal growth factor receptor negative or untested; (9) adequate oral intake, with or without prior bypass surgery; and (10) adequate organ function, defined as neutrophil count ≥1500/mm^3, hemoglobin ≥8.0 g/dL (no transfusion within 14 days before registration), platelet count ≥100,000/mm^3, aspartate and alanine transaminase levels ≤100 IU, total bilirubin concentration ≤2.0 mg/dL, and creatinine clearance ≥50 mL/min. Written informed consent was obtained from all patients.

Exclusion criteria were as follows: (1) synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ; (2) infectious disease requiring systemic treatment (body temperature >38.0 °C); (3) pregnancy or lactation; (4) severe mental illness; (5) unstable angina within 3 weeks or myocardial infarction within 6 months before registration; (6) continuous systemic corticosteroid or immunosuppressant treatment; (7) treatment with flucytosine, phenytoin, or warfarin; (8) poorly controlled valve disease or dilated or hypertrophic cardiomyopathy; (9) positive for hepatitis B surface antigen; (10) interstitial pneumonia, pulmonary fibrosis, or severe emphysema on chest computed tomography (CT); (11) poorly controlled hypertension or diabetes; or (12) patients deemed unsuitable for the study by their physicians.

Staging laparoscopy and peritoneal lavage cytology (CY) were performed before enrollment to identify peritoneal metastases. Clinicopathological findings of GC were classified according to the Japanese Classification of Gastric Carcinoma (JCGC) (15th edition) [8]. Surgical procedures followed the Japanese Gastric Cancer Treatment Guidelines 2018 (5th edition) [9]. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [10]. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [11]. Performance status was assessed according to ECOG [12]. Nutritional status was evaluated using the prognostic nutritional index (PNI), calculated according to Onodera's formula: PNI = (10 × serum albumin [g/dL]) + (0.005 × total lymphocyte count [/mm^3]) [13].

Study design

This multicenter, open-label, single-arm, phase II trial was conducted to evaluate the efficacy and safety of neoadjuvant DOS and adjuvant DS therapy for large type 3 or type 4 GC. The trial was conducted in 16 institutions. Eligible patients were registered via fax at the OGSG Data Center. This study followed the Declaration of Helsinki and the Japanese Clinical Trials Act. The protocol was approved by the Certified Review Board and registered with the Japan Registry of Clinical Trials on October 11, 2019 (jRCTs 051190060).

The primary endpoint was the 3-year PFS rate, defined as the interval from the date of registration to the first occurrence of disease progression, recurrence, or death from any cause. The definitions of PFS events are provided in Supplementary Table 1. Disease progression or recurrence was evaluated every 6 months using contrast-enhanced CT and, when clinically indicated, additional CT or other imaging modalities. The date of imaging was defined as the event date. The secondary endpoints included PFS time, 3-year OS rate, pathological response rate according to the JCGC, response rate based on RECIST version 1.1, completion rate of NAC, R0 resection rate, completion rate of surgery, protocol treatment completion rate, negative conversion rate of CY1, incidence of AEs, and nutritional evaluation.

Treatment

Neoadjuvant DOS chemotherapy

The neoadjuvant DOS chemotherapy protocol has been previously described [6]. Briefly, docetaxel (40 mg/m^2) and oxaliplatin (100 mg/m^2) were administered intravenously on day 1 of a 21 day cycle. S-1 was administered orally twice daily on days 1–14, with the dose adjusted based on body surface area: <1.25 m^2, 80 mg; ≥ 1.25 to <1.5 m^2, 100 mg; and ≥ 1.5 m^2, 120 mg/day. The patient received three courses of chemotherapy prior to surgery.

Surgery

After confirming that R0 resection was possible by imaging after the final course of NAC, gastrectomy with $\geq$D2 lymphadenectomy was performed within 56 days (recommended within 28 days) of the final S-1 administration. Splenic-hilar (No.10) lymphadenectomy or splenectomy was not mandatory but was performed at the surgeon's discretion when the tumor invaded the greater curvature of the upper third of the stomach according to the Japanese Gastric Cancer Treatment Guidelines 2018 [9]. If R0 resection was not feasible or if distant metastases—including peritoneal metastases (P1), hepatic metastases (H1), or CY1—were detected during surgery, the protocol treatment was discontinued.

Adjuvant DS chemotherapy

Adjuvant DS therapy was initiated within 42 days after surgery in patients who achieved R0 resection. However, initiation within 84 days after surgery was permitted in cases of postoperative complications or delays in pathological evaluation. The adjuvant DS chemotherapy regimen was based on the START-2 study [14, 15]. Briefly, docetaxel (40 mg/m^2) was administered intravenously on day 1 of a 21-day cycle starting from the second course. S-1 was administered orally twice daily on days 1–14, beginning with the first course, with the dose adjusted based on body surface area: <1.25 m^2, 80 mg; ≥ 1.25 to <1.5 m^2, 100 mg; ≥ 1.5 m^2, 120 mg/day. After completing seven courses of DS, patients continued S-1 monotherapy at 80 mg/m^2/day on days 1–28 of a 6-week cycle for up to one year post-surgery.

Follow-up

Patients were followed up on a fixed schedule for three years after completion of accrual. Physical and blood examinations were performed every three months. Contrast-enhanced CT of the chest, abdomen, and pelvis was performed every six months. Esophagogastroduodenoscopy (EGD) was performed annually in patients who underwent distal gastrectomy.

Statistical analysis

The null hypothesis was that the 3-year PFS rate with this treatment protocol would be 45%, based on the 47.7% 3-year PFS rate of the neoadjuvant group of the JCOG0501 trial [2]. The expected value was set at 60% because three courses of neoadjuvant DOS were added, and DS therapy demonstrated a 16% increase in the 3-year relapse-free survival compared with S-1 in the START-2 study [14]. With $\alpha = 0.10$, $1-\beta = 0.8$, a two-year registration period, and a three-year follow-up period, the required sample size was 44. To account for deviations, a final target sample size of 46 was established.

The 3-year PFS rate was evaluated using a one-sample log-rank test with a one-sided significance level of 0.10. PFS and OS were estimated using the Kaplan–Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. Subgroup analyses were performed according to macroscopic classification, histological type, presence of a signet-ring cell (SRC) component, CY0 vs CY1, CY0 vs CY-negative conversion, residual tumor status, pathological

Table 1 Patient characteristics

	N = 48
Age (years), median (range)	66 (44–79)
Sex	
Male, n(%)	29 (60.4%)
Female, n(%)	19 (39.6%)
ECOG PS	
0, n(%)	38 (79.2%)
1, n(%)	10 (20.8%)
Main location	
Upper third, n(%)	17 (35.4%)
Middle third, n(%)	21 (43.8%)
Lower third, n(%)	10 (20.8%)
Macroscopic type	
3, n(%)	21 (43.8%)
4, n(%)	27 (56.2%)
Histological type	
Differentiated, n(%)	8 (16.7%)
Undifferentiated, n(%)	40 (83.3%)
Signet-ring cell component	
Present, n(%)	26 (54.2%)
Absent, n(%)	22 (45.8%)
cT	
T2, n(%)	1 (2.1%)
T3, n(%)	9 (18.8%)
T4a, n(%)	35 (72.9%)
T4b, n(%)	3 (6.3%)
cN	
N0, n(%)	15 (31.3%)
N1, n(%)	13 (27.1%)
N2, n(%)	15 (31.3%)
N3, n(%)	5 (10.4%)
Peritoneal cytology	
CY0, n(%)	38 (79.2%)
CY1, n(%)	10 (20.8%)
cStage	
I, n(%)	1 (2.1%)
IIB, n(%)	12 (25.0%)
III, n(%)	24 (50.0%)
IVA, n(%)	1 (2.1%)
IVB, n(%)	10 (20.8%)

ECOG PS Eastern Cooperative Oncology Group performance status. Clinicopathological findings of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (15th edition)

response grade, ypT, and ypN. These analyses were not prespecified in the study protocol and were therefore considered exploratory. No adjustment for multiplicity was applied.

All statistical analyses were performed at the OGSG Data Center using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

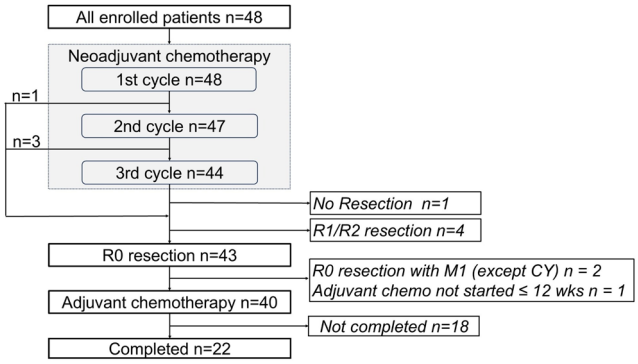

Fig. 1 CONSORT diagram

Results

Patients

Between October 2019 and February 2022, a total of 48 patients were enrolled from 16 institutions. Baseline patient characteristics are summarized in Table 1. The median age was 66 years (range, 44–79 years), and 60.4% of patients were male. ECOG PS was 0 in 79.2% and 1 in 20.8%. Twenty-one patients (43.8%) had type 3 tumors, while 27 patients (56.2%) had type 4 tumors. SRC components were identified in 26 (54.2%) patients, and CY was positive in 10 patients (20.8%). Patient enrollment and treatment flow are illustrated in Fig. 1.

Neoadjuvant DOS chemotherapy

All the patients received neoadjuvant DOS chemotherapy. As shown in Fig. 1, four patients discontinued treatment, while the remaining 44 completed all three planned courses [7]. The NAC completion rate, defined as the percentage of patients who completed all three planned courses, was 91.7% (44/48, 95% CI 80.0–97.7%). The median relative dose intensities (RDIs) were 93.0% for S-1, 94.5% for oxaliplatin, and 95.0% for docetaxel.

The chemotherapy-related AEs have been previously published [7]. The most common grade 3 or 4 toxicities were neutropenia and appetite loss (37.5% of patients). No serious AEs warranted hospitalization, or chemotherapy-related deaths were reported.

Surgery

Gastrectomy was performed in 47 patients (97.9%) after neoadjuvant DOS therapy. One patient did not undergo gastrectomy because R0 resection was not feasible. Surgical procedures and complications have been described in detail in a previous publication [7]. Total gastrectomy was performed in 32 patients (68.1%), and distal gastrectomy in 15

patients (31.9%). Seventeen patients had tumors located in the upper third of the stomach, and splenectomy was performed in 10 patients. R0 and R1 resections were achieved in 43 and 3 patients, respectively. Positive surgical margins were observed in one patient, and CY1 was observed in two patients. The R0 resection rate was 89.6% (43/48, 95% CI 77.3–96.5%).

Pathological findings

Table 2 summarizes pathological findings. A pathological response of the primary tumor graded as ≥ 1b was observed in 66.7% of patients (32/48, 95% CI 51.6–79.6%), including one patient (2.1%) who achieved a complete response. Following neoadjuvant DOS therapy, the number of patients with CY1 decreased from 10 to 2, resulting in a CY-negative conversion rate of 80% (95% CI 44.4–97.5%).

Adjuvant DS chemotherapy

Overall, 45.8% of patients (22/48, 95% CI 31.4–60.8%) completed the entire protocol, which included NAC, R0 gastrectomy, and adjuvant chemotherapy for 1 year. The completion rate of seven courses of adjuvant DS therapy was 65.0% (26/40), and that of 1 year of adjuvant therapy was 55.0% (22/40). The median RDIs were 94.2% for docetaxel and 92.4% for S-1. AEs associated with adjuvant DS therapy have been previously reported [7]. The most common grade 3 or 4 AEs were neutropenia (40.0%). No treatment-related deaths occurred.

Survival outcomes

As of the data cutoff date in February 2025, surviving patients had a minimum follow-up duration of 36 months. The median follow-up period for all enrolled patients was 36.3 months. By that time, 28 patients had died, and 30 patients had experienced disease recurrence. Recurrence occurred most frequently in the peritoneum (n = 22, 73.3%), followed by lymph nodes (n = 9, 30.0%), distant organs (n = 3, 10.0%), and locoregional sites (n = 2, 6.7%). Some patients experienced recurrence at multiple sites. Recurrence was diagnosed by imaging or EGD; none were diagnosed based solely on clinical symptoms. The 3-year PFS rate was 37.5% (95% CI 24.1–50.6%; 80% CI 28.6–46.4%) (Fig. 2a). In the one-sample log-rank test against the prespecified threshold of 45%, the result was not statistically significant ($p = 0.960$), and the primary endpoint was not met. The 3-year OS rate was 52.1%, (95% CI 37.2–65.0%) (Fig. 2b).

Exploratory subgroup analyses identified several prognostic factors (Tables 3 and 4, Fig. 3). Patients with baseline

Table 2 Pathological findings

	n = 47
ypT	
T0, n(%)	1 (2.1%)
T1a, n(%)	1 (2.1%)
T1b, n(%)	1 (2.1%)
T2, n(%)	5 (10.6%)
T3, n(%)	17 (36.2%)
T4a, n(%)	19 (40.4%)
T4b, n(%)	3 (6.4%)
ypN	
N0, n(%)	12 (25.5%)
N1, n(%)	10 (21.3%)
N2, n(%)	6 (12.8%)
N3, n(%)	18 (38.3%)
NX, n(%)	1 (2.1%)
P	
P0, n(%)	46 (97.9%)
P1, n(%)	1 (2.1%)
CY	
CY0, n(%)	45 (95.7%)
CY1, n(%)	2 (4.3%)
ypM	
M0, n(%)	41 (87.2%)
M1, n(%)	6 (12.8%)
ypStage	
IA, n(%)	2 (4.3%)
IB, n(%)	3 (6.5%)
IIA, n(%)	9 (19.6%)
IIB, n(%)	3 (6.5%)
IIIA, n(%)	8 (17.4%)
IIIB, n(%)	11 (23.9%)
IIIC, n(%)	4 (8.7%)
IV, n(%)	6 (13.0%)
Pathological response	
Grade 0, n(%)	2 (4.3%)
Grade 1a, n(%)	13 (27.7%)
Grade 1b, n(%)	15 (31.9%)
Grade 2, n(%)	16 (34.0%)
Grade 3, n(%)	1 (2.1%)

Clinicopathological findings of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (15th edition)

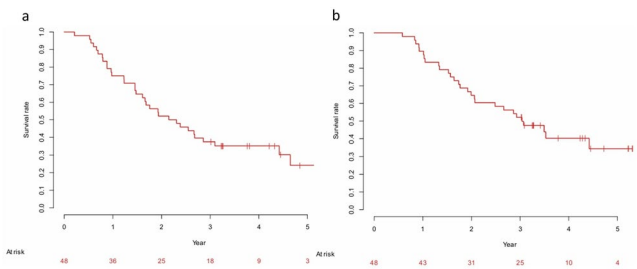

Fig. 2 Kaplan–Meier estimates of progression-free survival **a** and overall survival **b**. **a** The 3 year progression-free survival rate was 37.5% (95% CI 24.1–50.6%). **b** The 3 year overall survival rate was 52.1% (95% CI 37.2–65.0%)

Table 3 Subgroup analyses of progression-free survival

		n	Median PFS (mo) (95% CIs)	3-yr PFS (%) (95%CIs)	HR (95% CIs)	*p*-value
Sex	Male	29	30.6 (14.8–NA)	44.8 (26.5–61.6)	0.688 (0.344–1.377)	0.291
	Female	19	23.1 (14.7–32.2)	26.3 (9.6–46.8)		
Age	≥65	28	22.2 (14.7–34.3)	32.1 (16.1–49.3)	1.375 (0.673–2.809)	0.382
	<65	20	31.4 (14.8–NA)	45.0 (23.1–64.7)		
ECOG PS	0	38	22.1 (17.4–32.0)	31.6 (17.7–46.4)	2.262 (0.866–5.912)	0.095
	1	10	53.0 (11.7–NA)	60.0 (25.3–82.7)		
Macroscopic type	3	21	20.2 (10.5–NA)	33.3 (14.9–53.1)	1.245 (0.612–2.530)	0.545
	4	27	32.0 (17.4–53.0)	40.7 (22.5–58.2)		
Histology	Differentiated	8	11.1 (6.6–NA)	25.0 (3.7–55.8)	2.166 (0.911–4.918)	0.081
	Undifferentiated	40	29.6 (19.9–55.8)	40.0 (25.0–54.6)		
Signet-ring component	Yes	26	27.2 (19.3–55.8)	38.5 (20.4–56.3)	0.893 (0.448–1.780)	0.748
	No	22	25.5 (10.5–53.0)	36.4 (17.4–55.7)		
cT	2–3	10	28.7 (9.4–NA)	50.0 (18.4–75.3)	0.742 (0.305–1.802)	0.509
	4	38	26.7 (17.4–34.3)	34.2 (19.8–49.1)		
cN	0	15	37.2 (19.9–NA)	53.3 (26.3–74.4)	0.537 (0.248–1.160)	0.113
	1–3	33	20.2 (11.6–32.2)	30.3 (15.9–46.1)		
CY	1	10	11.1 (2.5–21.1)	10.0 (0.6–35.8)	2.965 (1.353–6.497)	0.006
	0	38	32.1 (20.2–55.8)	44.7 (28.7–59.5)		
CY	Negative conversion	8	14.6 (6.3–25.8)	12.5 (0.7–42.3)	2.457 (1.043–5.789)	0.039
	0	38	32.1 (20.2–55.8)	44.7 (28.7–59.5)		
Residual tumor (R)	0	43	30.6 (20.2–53.0)	41.9 (27.1–55.9)	0.275 (0.090–0.840)	0.023
	1–2	4	17.0 (8.3–NA)	–		
Pathological response	0-1a	15	23.2 (9.4–32.0)	20.0 (4.9–42.4)	Reference	
	1b	15	19.9 (7.2–30.6)	26.7 (8.3–49.6)	1.063 (0.477–2.369)	0.881
	2–3	17	55.8 (17.4–NA)	64.7 (37.7–82.3)	0.400 (0.162–0.986)	0.046
ypT	0–2	8	–	87.5 (38.7–98.1)	Reference	
	3	17	37.2 (17.4–NA)	52.9 (27.6–73.0)	6.798 (0.876–52.724)	0.066
	4a-b	22	19.6 (11.6–27.7)	9.1 (1.6–25.1)	17.42 (2.27–133.87)	0.006
ypN	0	12	—	58.3 (27.0–80.1)	Reference	
	1	10	35.7 (6.3–NA)	50.0 (18.4–75.3)	1.374 (0.418–4.513)	0.600
	2–3	24	20.1 (11.7–27.7)	20.8 (7.6–38.5)	2.787 (1.039–7.479)	0.041
PNI	<43.5	23	20.2 (14.7–55.8)	34.8 (16.6–53.7)	1.151 (0.580–2.285)	0.688
	≥43.5	25	32.0 (17.4–53.0)	40.0 (21.3–58.1)		

PFS progression-free survival, *HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *PNI* prognostic nutritional index, *NA* not available. Clinicopathological findings of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (15th edition)

CY1 had significantly worse outcomes than those with CY0 (Fig. 3 g, h), although CY-negative conversion was achieved (PFS: HR 2.457, 95% CI 1.043–5.789, Fig. 3i; OS: HR 2.610, 95% CI 1.090–6.249, Fig. 3j). Major pathological response (grade 2–3) was significantly associated with improved prognosis compared with grade 0–1a (PFS: HR 0.400, 95% CI 0.162–0.986, Fig. 3m; OS: HR 0.223, 95% CI 0.071–0.706, Fig. 3n). Advanced tumor depth (ypT4a–b) was associated with markedly worse survival than ypT0–2 (PFS: HR 17.42, 95% CI 2.27–133.87, Fig. 3o; OS: HR 13.22, 95% CI 1.71–102.28, Fig. 3p). Likewise, advanced nodal stage (ypN2–3) predicted poorer outcomes than ypN0 (PFS: HR 2.787, 95% CI 1.039–7.479, Fig. 3q; OS: HR 3.075, 95% CI 1.031–9.172, Fig. 3r).

Discussion

This multicenter phase II study evaluated the feasibility and efficacy of neoadjuvant DOS therapy followed by gastrectomy and adjuvant DS therapy in patients with large type 3 or type 4 GC. The study revealed a high NAC completion rate of 91.7%, an R0 resection rate of 89.6%, a pathological response of the primary tumor graded as≥1b in 66.7% of patients, and a CY-negative conversion rate of 80%. However, the primary endpoint, 3-year PFS, did not exceed the prespecified threshold of 45%, with an observed rate of 37.5%. The 3-year OS rate was 52.1%. These findings indicate that although neoadjuvant DOS therapy is feasible and achieves good surgical and pathological outcomes, its survival benefit may be limited in patients with this biologically aggressive disease. In the exploratory subgroup

Table 4 Subgroup analyses of overall survival

		n	Median OS (mo) (95% CIs)	3-yr OS (%) (95%CIs)	HR (95% CIs)	*p*-value
Sex	Male	29	42.3 (21.2–NA)	55.2 (35.6–71.0)	0.765 (0.356–1.642)	0.491
	Female	19	34.4 (19.7–NA)	47.4 (24.4–67.3)		
Age	≥65	28	27.3 (19.7–NA)	42.9 (24.6–60.0)	1.726 (0.784–3.801)	0.175
	<65	20	53.0 (21.2–NA)	65.0 (40.3–81.5)		
ECOG PS	0	38	33.2 (20.8–NA)	44.7 (28.7–59.5)	1.914 (0.718–5.099)	0.194
	1	10	53.0 (18.8–NA)	80.0 (40.9–94.6)		
Macroscopic type	3	21	24.8 (15.9–NA)	38.1 (18.3–57.8)	1.877 (0.878–4.015)	0.104
	4	27	42.3 (23.9–NA)	63.0 (42.1–78.1)		
Histology	Differentiated	8	14.1 (10.0–NA)	25.0 (3.7–55.8)	2.644 (1.116–6.261)	0.027
	Undifferentiated	40	41.9 (24.8–NA)	57.5 (40.8–71.0)		
Signet-ring component	Yes	26	36.8 (23.1–NA)	53.8 (33.3–70.6)	0.849 (0.403–1.789)	0.666
	No	22	35.8 (12.3–NA)	50.0 (28.2–68.4)		
cT	2–3	10	29.8 (12.6–NA)	50.0 (18.4–75.3)	0.811 (0.308–2.136)	0.670
	4	38	36.5 (23.1–53.0)	52.6 (35.8–67.0)		
cN	0	15	–	66.7 (37.5–84.6)	0.434 (0.175–1.075)	0.071
	1–3	33	34.4 (18.8–42.3)	45.5 (28.2–61.2)		
CY	1	10	20.5 (7.0–32.0)	20.0 (3.1–47.5)	2.962 (1.325–6.618)	0.008
	0	38	42.3 (29.8–NA)	60.5 (43.3–74.0)		
CY	Negative conversion	8	22.1 (7.0–41.9)	25.0 (3.7–55.8)	2.610 (1.090–6.249)	0.031
	0	38	42.3 (29.8–NA)	60.5 (43.3–74.0)		
Residual tumor (R)	0	43	41.9 (29.8–NA)	58.1 (42.1–71.2)	0.266 (0.086–0.822)	0.021
	1–2	4	20.0 (15.9–NA)	–		
Pathological response	0-1a	15	24.8 (12.6–42.3)	46.7 (21.2–68.7)	Reference	
	1b	15	32.0 (12.3–36.5)	33.3 (12.2–56.4)	1.100 (0.484–2.502)	0.819
	2–3	17	NA (29.8–NA)	76.5 (48.8–90.4)	0.223 (0.071–0.706)	0.010
ypT	0–2	8	–	87.5 (38.7–98.1)	Reference	
	3	17	53.0 (20.8–NA)	64.7 (37.7–82.3)	4.051 (0.498–32.986)	0.191
	4a-b	22	24.8 (16.1–36.5)	31.8 (14.2–51.1)	13.22 (1.71–102.28)	0.013
ypN	0	12	–	66.7 (33.7–86.0)	Reference	
	1	10	42.3 (7.0–NA)	80.0 (40.9–94.6)	1.218 (0.304–4.875)	0.780
	2–3	24	24.8 (18.3–36.5)	33.3 (15.9–51.9)	3.075 (1.031–9.172)	0.043
PNI	<43.5	23	24.7 (18.3–NA)	39.1 (19.9–58.0)	1.456 (0.690–3.074)	0.324
	≥43.5	25	41.9 (29.8–NA)	64.0 (42.2–79.4)		

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *PNI* prognostic nutritional index, *NA* not available. Clinicopathological findings of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (15th edition)

analyses, a favorable prognosis was associated with CY0 status, achievement of R0 resection, major pathological response (grade≥2), and lower ypT and ypN stages.

Given the favorable short-term outcomes, we anticipated improved long-term survival. However, the final survival results did not surpass those of the JCOG0501 trial, which used neoadjuvant SP therapy followed by adjuvant S-1 [2], despite our protocol incorporating both neoadjuvant DOS and adjuvant DS. A similar discrepancy between pathological response and survival was noted in the JCOG0501 trial. The authors noted that, although the pathological response is generally associated with improved survival in patients receiving NAC for GC, this association may not apply to type 4 or large type 3 disease. Moreover, they highlighted that the conversion from CY1 to CY0 did not necessarily improve survival.

We explored why the favorable short-term outcomes observed in our study did not translate into improved survival by comparing our results with those of the JCOG0501 trial [2]. First, while the rate of minor pathological responses (grades 1b–3) was higher in this study (66.7%) than in the JCOG0501 trial (52.3%, calculated among all patients who received NAC), the rate of major pathological responses (grades 2–3) was comparable (35.4% vs. 32.0%). Our subgroup analyses revealed that patients who achieved a major response had significantly better outcomes, whereas those with grade 1b disease had prognoses similar to those of patients with grades 0–1a disease. These findings suggest that, in large type 3 and type 4 GCs, NAC regimens must achieve at least a grade 2 pathological response to translate into a meaningful survival benefit.

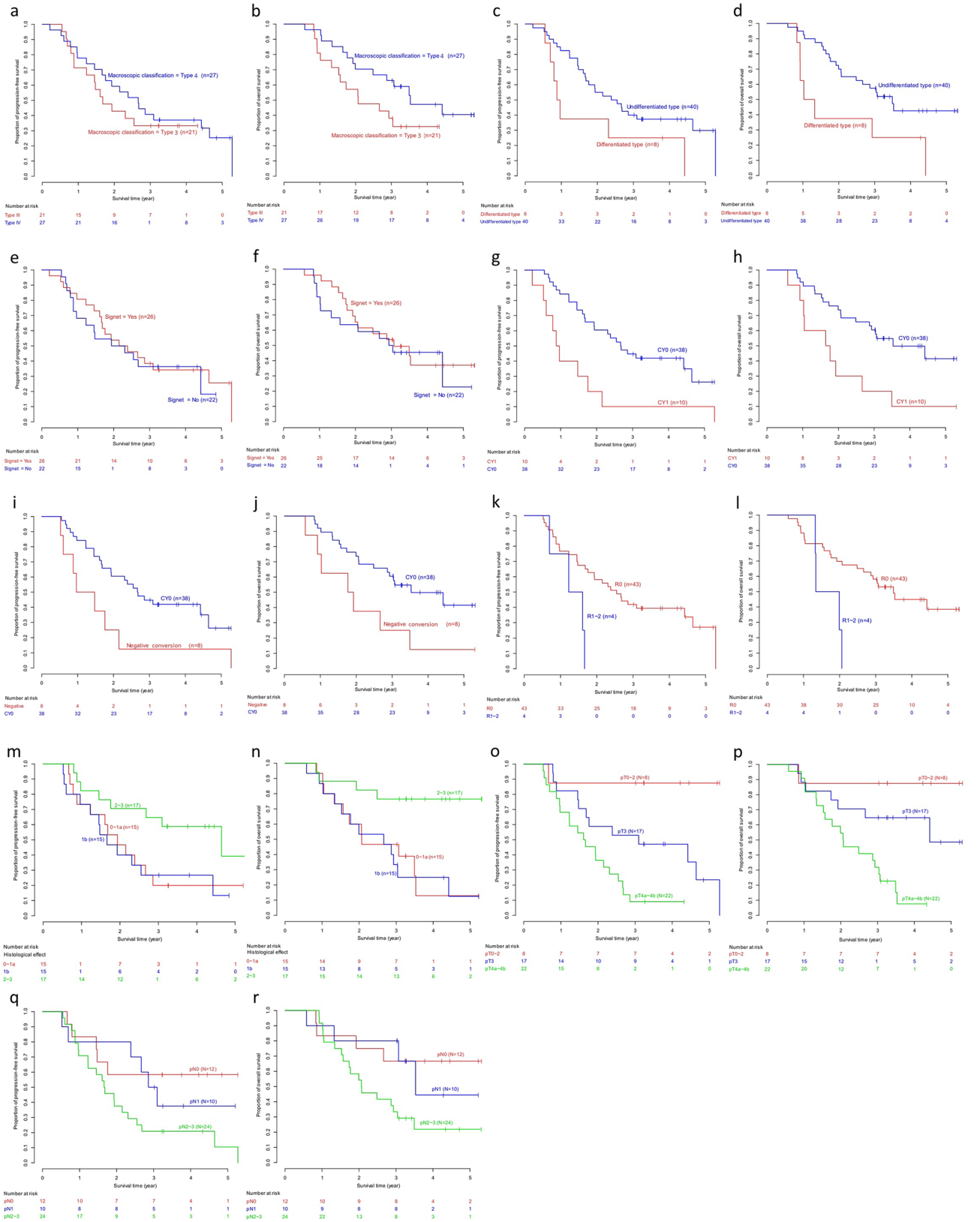

Fig. 3 Kaplan–Meier estimates of progression-free survival (PFS) curves and overall survival (OS) curves by subgroups. PFS **a** and OS **b** by macroscopic classification, PFS **c** and OS **d** by histological type, PFS **e** and OS **f** by signet-ring cell component, PFS **g** and OS **h** by CY, PFS **i** and OS **j** by CY0 vs CY negative conversion, PFS **k** and OS **l** by residual tumor (R), PFS **m** and OS **n** by pathological response grade, PFS **o** and OS **p** by ypT, and PFS **q** and OS **r** by ypN

Second, nodal control appeared to be insufficient. The proportion of pathological nodal positivity after treatment was higher in the current study (72.3%) than that reported in the JCOG0501 trial (58.3%, calculated among patients who underwent gastrectomy), with more frequent nodal recurrence observed (30% vs. 12%). As ypN2–3 disease was strongly associated with poor prognosis in our subgroup analyses, these findings suggest that the therapeutic effect of NAC must extend beyond the primary tumor response to achieve an adequate nodal response, which is critical for improving long-term survival.

Third, although CY conversion was achieved in 80% of the patients and the rate of residual CY1 was lower than that in the JCOG0501 trial (4.3% vs. 13.7%), our subgroup analysis revealed that patients with baseline CY1 disease had a persistently poor prognosis even after negative conversion. Peritoneal recurrence was observed in 22 (45.8%) patients. This contrasts with the multicenter retrospective analysis by Yamaguchi et al. [16], which reported favorable survival rates in patients who achieved P0 and CY0 after the initial chemotherapy. Nevertheless, consistent with our observations, the JACCRO GC-07 trial [15] demonstrated that, although the addition of docetaxel to S-1 significantly reduced nodal and hematogenous recurrence rates, peritoneal recurrence rates remained similar (19.6% vs. 22.7%). Despite the use of docetaxel in both the neoadjuvant and adjuvant settings in the present study, effective control of micrometastatic peritoneal disease remained challenging in large type 3 and type 4 GCs.

Although there were no substantial differences in patient characteristics between the JCOG0501 and OGSG1902 trials, including the proportion of patients with CY1 (21.2% vs. 20.8%), type 4 tumors (63.6% vs. 56.2%), or completion of adjuvant therapy (47.0% vs. 45.8%), survival outcomes were more favorable in JCOG0501. One possible explanation is the aging of the gastric cancer population; the proportion of patients aged≥65 years was 47.0% in JCOG0501, compared with 58.3% in OGSG1902. In addition, the OGSG1902 study period coincided with the COVID-19 pandemic, and differences in social and healthcare circumstances during this time may have influenced survival outcomes. Although patient accrual was delayed due to the COVID-19 pandemic, the study experienced no interruptions in protocol treatment, including surgery or adjuvant chemotherapy.

In contrast to our findings, recent studies have reported excellent survival outcomes following DOS therapy. The phase III PRODIGY trial in Korea enrolled patients with gastric or gastroesophageal junction adenocarcinoma and clinical T2–3N + or T4Nany disease [5]. Compared with upfront surgery, neoadjuvant DOS therapy significantly improved OS (adjusted HR 0.72, 95% CI 0.54–0.96; stratified log-rank $p = 0.027$). NAC also significantly improved PFS (adjusted HR 0.70, 95% CI 0.53–0.94; stratified log-rank $p = 0.016$). In Japan, the docetaxel dose was reduced from 50 mg/m^2, as used in Korea, to 40 mg/m^2 owing to concerns regarding hematologic toxicity. This dose has been explored in several clinical trials, including the present study. The Osaka University group conducted a phase II trial to determine the efficacy and safety of neoadjuvant DOS chemotherapy for clinical stage III gastric or esophagogastric junction adenocarcinoma, reporting a pathological response rate (≥grade 1b) of 63% (30/48) [17]. The 3-year PFS and OS rates were 54.2% and 68.7%, respectively. In addition, the JCOG1704 phase II trial of neoadjuvant DOS for GC with bulky nodal involvement or para-aortic lymph node metastasis reported a major pathological response rate (grade≥2a) of 57% (26/46) and a complete response rate of 24% (11/46) [18].

The influence of SRC components on the response to NAC remains controversial. In our cohort, pathological response rates were comparable between SRC-positive and SRC-negative tumors when assessed at the threshold of grade≥2 (30.8% vs. 40.9%), and notably, the only pathological complete response was observed in an SRC-positive case [7]. Survival curves stratified by SRC status also overlapped, suggesting no clear prognostic impact. In contrast, Voron et al. [19] conducted a large retrospective cohort study involving 1,799 patients, identifying SRC as an independent predictor of poor outcome and reporting lower chemosensitivity in SRC-positive disease. Similarly, the JCOG0501 trial suggested that NAC provides a limited benefit in patients with SRC-positive tumors [2]. However, some evidence suggests that taxane-based therapy may be more effective for SRC in both clinical and preclinical models [20, 21]. Taken together, our findings did not reproduce the poor NAC sensitivity reported in previous studies; however, given the limited sample size, definitive conclusions could not be drawn. Further studies are required to clarify the effects of SRC on NAC sensitivity.

This study had several limitations. First, this was a single-arm phase II trial with a relatively small sample size, which limited the generalizability of the findings and statistical power. Second, the subgroup analyses were exploratory, as they were not pre-specified in the study protocol, and therefore lacked sufficient power for definitive conclusions. Third, a central pathology review was not performed for all cases, and the assessment of SRC components and pathological responses may have been subject to inter-observer variability. Nevertheless, these data provide an important foundation for designing next-generation perioperative strategies for treating high-risk GC.

Conclusions

Neoadjuvant DOS therapy for large type 3 and type 4 GCs was feasible and achieved high R0 resection and pathological response rates. Nevertheless, the 3-year PFS did not reach the prespecified target, underscoring the inherent biological aggressiveness of these tumor types, even under intensive triplet chemotherapy. To further improve survival outcomes in this highly aggressive subgroup, more intensive approaches or the incorporation of novel strategies, such as immune checkpoint inhibitors or molecularly targeted agents, are warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-025-01705-8.

Acknowledgements We thank all of the patients, investigators, and medical staff who participated in this study, as well as the Osaka Gastrointestinal Cancer Chemotherapy Study Group data center for their contribution. We would like to thank Editage (www.editage.jp) for English language editing.

Author contributions Study concept: SE, RT, and TY. Study design: SE, RT, TY, YK, TT, TSh, and TSa. Acquisition of data: SE, RT, HM, TO, JK, NT, TM, HF, YS, AT, NS, RK, SK, and SH. Statistical analysis of data: TSh. Analysis and/or interpretation of data: SE, RT, TY, YK, TT, TSh, and TSa. Drafting the manuscript: SE. Revising the manuscript critically for important intellectual content: All authors. All authors approved the final version of the manuscript.

Funding This study was financially supported by Yakult Honsha Co., Ltd.

Declarations

Conflict of interest The authors declare the following financial interests/personal relationships, which may be considered potential competing interests: SE has received speaker honoraria from Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb Co., MSD K.K., and Takata Pharmaceutical Co., Ltd. TO has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Medtronic Japan Co., Ltd., Johnson & Johnson K.K., Ono Pharmaceutical Co., Ltd., and Bristol Myers Squibb Co. NT has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Bristol Myers Squibb Co., and AstraZeneca K.K. YK has received research funding and lecture fees from Taiho Pharmaceutical Co., Ltd outside the submitted work. TSa has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Daiichi Sankyo Co., Ltd., Bristol Myers Squibb Co., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., and MSD K.K.; and research grants or contracts from Shionogi & Co., Ltd., Prelude Therapeutics Inc., Janssen Pharmaceutical K.K., Daiichi Sankyo Co., Ltd., and Amgen K.K. All remaining authors declare no conflicts of interest.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent All patients provided written informed consent.

References

1. Sasako M, Maruyama K, Kinoshita T. Neoadjuvant chemotherapy for gastric cancer: indication and trial setting (in Japanese). Shokakigeka. 1992;15:159–67.
2. Iwasaki Y, Terashima M, Mizusawa J, Katayama H, Nakamura K, Katai H, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial. Gastric Cancer. 2021;24:492–502.
3. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17:1697708.
4. Park I, Ryu MH, Choi YH, Kang HJ, Yook JH, Park YS, et al. A phase II study of neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy followed by surgery and adjuvant S-1 chemotherapy in potentially resectable gastric or gastroesophageal junction adenocarcinoma. Cancer Chemother Pharmacol. 2013;72:815–23.
5. Kang YK, Kim HD, Yook JH, Park YK, Lee JS, Kim YW, et al. Neoadjuvant docetaxel, oxaliplatin, and S-1 plus surgery and adjuvant S-1 for resectable advanced gastric cancer: updated overall survival outcomes from phase III prodigy. J Clin Oncol. 2024;42:2961–5.
6. Endo S, Terazawa T, Goto M, Tanaka R, Kato T, Fujitani K, et al. Neoadjuvant docetaxel, oxaliplatin and S-1 therapy for the patients with large type 3 or type 4 gastric cancer (OGSG1902): protocol of a multi-center, phase II study. BMC Cancer. 2022;22:811.
7. Tanaka R, Endo S, Yamaguchi T, Miyagaki H, Kawada J, Omori T, et al. Neoadjuvant docetaxel, oxaliplatin, and S-1 therapy for patients with large type 3 or type 4 gastric cancer: short-term outcomes of a multicenter, phase II study (OGSG1902). Gastric Cancer. 2025;28:662–72.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma.15th ed. (in Japanese) Tokyo: Kanehara; 2017.
9. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines, 5th ed. (in Japanese) Tokyo: Kanehara; 2018.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
11. Japan Clinical Oncology Group. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 2017. https://jcog.jp/doctor/tool/ctcaev5/ Accessed 24 Sep 2025
12. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5:649–55.
13. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients (in Japanese with an English abstract). Nippon Geka Gakkai Zasshi. 1984;85:1001–5.
14. Yoshida K, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage III gastric cancer: interim analysis

of JACCRO GC-07, a randomized controlled trial. J Clin Oncol. 2019;37:1296–304.
15. Kodera Y, Yoshida K, Kochi M, Sano T, Ichikawa W, Kakeji Y, et al. Addition of docetaxel to S-1 results in significantly superior 5-year survival outcomes in stage III gastric cancer: a final report of the JACCRO GC-07 study. Gastric Cancer. 2023;26:1063–8.
16. Yamaguchi T, Takashima A, Nagashima K, Terashima M, Aizawa M, Ohashi M, et al. Impact of preoperative chemotherapy as initial treatment for advanced gastric cancer with peritoneal metastasis limited to positive peritoneal lavage cytology (CY1) or localized peritoneal metastasis (P1a): a multi-institutional retrospective study. Gastric Cancer. 2021;24:701–9.
17. Kurokawa Y, Kawase T, Takeno A, Furukawa H, Yoshioka R, Saito T, et al. Phase 2 trial of neoadjuvant docetaxel, oxaliplatin, and S-1 for clinical stage III gastric or esophagogastric junction adenocarcinoma. Ann Gastroenterol Surg. 2022;7:247–54.
18. Kurokawa Y, Doki Y, Kitabayashi R, Yoshikawa T, Nomura T, Tsuji K, et al. Short-term outcomes of preoperative chemotherapy with docetaxel, oxaliplatin, and S-1 for gastric cancer with extensive lymph node metastasis (JCOG1704). Gastric Cancer. 2024;27:366–74.
19. Voron T, Messager M, Duhamel A, Lefevre J, Mabrut JY, Goere D, et al. Is signet-ring cell carcinoma a specific entity among gastric cancers? Gastric Cancer. 2016;19:1027–40.
20. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. World J Gastroenterol. 2015;21:11428–38.
21. Hultman B, Mahteme H, Sundbom M, Ljungman M, Larsson R, Nygren P. Benchmarking of gastric cancer sensitivity to anticancer drugs ex vivo as a basis for drug selection in systemic and intraperitoneal therapy. J Exp Clin Cancer Res. 2014;33:110.