





# Effects of an oral elemental nutritional supplement in gastric cancer patients with adjuvant S-1 chemotherapy after gastrectomy: A multicenter, open-label, single-arm, prospective phase II study (OGSG1108)

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## Abstract

**Aim:** Post-surgical weight loss influences chemotherapy compliance and may be a risk factor for survival. Intake of an oral elemental nutritional supplement (OENS) can reduce weight loss after gastric cancer (GC) surgery. We assessed whether therapy completion levels would increase in patients receiving postoperative adjuvant chemotherapy in combination with an OENS.

**Methods:** This was a multicenter, open-label, single-arm, phase II study in GC patients who underwent curative total or distal gastrectomy (TG/DG) and received adjuvant S-1 chemotherapy. The primary endpoint was the S-1 completion rate for 1 year with a relative performance (RP) value of  $\geq 70\%$ ; secondary endpoints included

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factors affecting the completion rate of S-1, RP value after eight S-1 courses, S-1 and OENS persistence rates, nutritional index, OENS compliance, and safety.

**Results:** In 71 efficacy-evaluable patients, the S-1 completion rate was 69.0% (TG, 68.0%; DG, 69.6%) and the RP value was 87.5 (TG, 89.1; DG, 87.5). Over eight treatment courses, median persistence rates were 89.0% for S-1 and 93.8% for the OENS. The mean OENS compliance was 81.8% at the fourth S-1 course and 52.9% at the eighth course. The incidence of Grade 3 or 4 adverse events was 27.2%, most commonly neutropenia (12.3%).

**Conclusions:** The completion rate of S-1 for 1 year in patients who could take the OENS exceeded the pre-defined threshold level. Randomized controlled trials are warranted to confirm the role of OENS in adjuvant chemotherapy.

#### KEYWORDS

adjuvant chemotherapy, gastrectomy, gastric cancer, supplemental nutrition

## 1 | INTRODUCTION

In 2018, there were more than 1 million new gastric cancer (GC) cases worldwide. GC is the fifth most common cancer, and it is also the third leading cause of cancer death.<sup>1</sup> Currently, the only curative treatment for GC is surgical resection.<sup>2-5</sup> However, locally advanced GC, such as stage II or III GC, may recur after curative gastrectomy (R0) with D2 lymphadenectomy.<sup>6,7</sup>

In East Asia, gastrectomy with D2 lymphadenectomy and subsequent adjuvant chemotherapy is the standard treatment for stage II or III GC, based on the results of two phase III trials, ACTS-GC<sup>8,9</sup> and CLASSIC,<sup>10,11</sup> showing the survival benefit of adjuvant chemotherapy compared with surgery alone. However, owing to toxicity and adverse events (AEs), it is difficult for patients to start adjuvant chemotherapy immediately after surgery and to continue treatment over long durations.<sup>12,13</sup> In S-1-treated patients in the ACTS-GC trial, the 1-year treatment completion rate (excluding relapse and death) was 65.8%.<sup>8</sup> Even when treatment was continued for 1 year, dose reduction was required in 46.5% of patients. In the CLASSIC trial, the treatment completion rate in the capecitabine plus oxaliplatin group was 66.5%, and treatment interruption or dose reduction due to AEs was reported in 89.9% of patients.<sup>10</sup>

Since reductions of adjuvant chemotherapy strength and treatment continuity have been demonstrated to negatively impact survival in patients with other types of cancer,<sup>14-16</sup> it is important to maintain the dose intensity of adjuvant chemotherapy. The results of a retrospective analysis in 103 patients who underwent curative D2 surgery for GC followed by adjuvant S-1 suggested that short-term post-surgical weight loss was the critical factor influencing compliance with adjuvant treatment.<sup>17</sup> In a follow-up analysis, loss of body weight was also reported to be a risk factor for survival.<sup>18</sup> In a recent randomized, controlled clinical trial, we demonstrated that an

oral elemental nutritional supplement (OENS) significantly reduced short-term weight loss after radical gastrectomy.<sup>19</sup>

This multicenter, cooperative, prospective phase II study aimed to determine whether therapy completion levels would increase in patients receiving postoperative adjuvant chemotherapy in combination with intake of an OENS.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This open-label, single-arm, clinical phase II study was conducted at 16 hospitals from the Osaka Gastrointestinal Cancer Chemotherapy Study Group (Supplementary material) between September 2011 and September 2015. The study comprised two stages. In the first stage, patients with clinical stage II or III GC R0 were registered and assessed to evaluate their suitability (tolerance and compliance) for OENS (Elental<sup>®</sup> 300 kcal/d) treatment for  $\geq 14$  days during the time-period after surgery to the initiation of S-1, which usually commenced 8 weeks after the operation. One pack of the OENS (80 g) was dissolved in 250 mL of water, resulting in 300 mL of solution at 1 kcal/mL. Patients with an intake of  $\geq 60\%$  of the planned dose were considered compliant and were eligible for registration into the second stage of the study. In the second stage, only patients with pathological stage II or III cancer as they were receiving adjuvant S-1 treatment were included. One pack per day of the OENS was then administered from the first day after the second stage registration for 6 months. After the planned 6-month administration, patients could decide whether or not to continue the OENS for up to 1 year.

S-1 compliance and OENS consumption were recorded daily by the patients themselves in a diary distributed to the patient at the beginning of the second stage. The attending physicians checked the

patient diary and confirmed S-1 compliance and OENS consumption at each visit.

This trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000006872). The institutional review board of each participating hospital approved the study protocol. All patients provided written informed consent.

## 2.2 | Patients

All patients who underwent curative distal gastrectomy (DG) or total gastrectomy (TG) for gastric adenocarcinoma at participating hospitals between February 2012 and July 2014 were potentially eligible for study participation.

The key inclusion criteria were age  $\geq 20$  years; histologically confirmed GC via pathological examination; postoperative status; clinical stage II or stage III at surgery; R0 gastrectomy; Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2; no history of chemotherapy or radiation therapy; good oral intake and ability to receive OENS; informed consent for trial participation; and no serious postoperative complications.

The key exclusion criteria were synchronous and metachronous multiple cancer; contraindications for the administration of S-1 or the OENS; presence of active infection, uncontrollable hypertension or diabetes, clinically significant cardiovascular disease, or severe lung disorder (interstitial pneumonia, pulmonary fibrosis, severe pulmonary emphysema); history of mental disorder or central nervous system damage; pregnancy or lactation; participation in another clinical study; or being judged as inappropriate for this trial by the investigator.

Eligibility for the second stage required patients to satisfy the following criteria in addition to the original inclusion criteria: pathological stage II (excluding T1 and T3 N0) or stage III cancer according to the third English edition of the Japanese Classification of Gastric Cancer<sup>20</sup>; good compliance ( $\geq 60\%$ ) to the OENS; meeting prespecified laboratory test criteria: white blood cells  $\geq 2500/\text{mm}^3$ , neutrophil count  $\geq 1200/\text{mm}^3$ , platelet count  $\geq 75\,000/\text{mm}^3$ , hemoglobin  $\geq 8.0$  g/dL, total bilirubin  $\leq 1.5$  mg/dL, aspartate aminotransferase (AST)  $\leq 100$  IU/L, alanine aminotransferase (ALT)  $\leq 100$  IU/L, creatinine clearance (Ccr)  $\geq 40$  mL/min, and ability to receive S-1 as postoperative adjuvant chemotherapy.

To minimize bias due to changing stage definitions from the ACTS-GC trial, patients with stage II (excluding T1 and T3 N0) and III were included in the study.

## 2.3 | Surgical procedures

DG or TG with lymphadenectomy was performed according to the Japanese Gastric Cancer Treatment Guidelines.<sup>20</sup> Briefly, D1 lymphadenectomy plus suprapancreatic node dissection (D1 +

dissection) was performed in patients with cT1, N0 tumors. D2 lymphadenectomy was performed in patients with cT1, N+ tumors, and with cT2-4 tumors. The reconstruction method and surgical approach (i.e. open or laparoscopic) were not prespecified. The operative methods and pathology results were recorded according to the 14th edition of the Japanese Classification of Gastric Carcinoma.<sup>20</sup> Patients were generally allowed to return home around 2 weeks after surgery; however, some remained hospitalized for  $>2$  weeks.

## 2.4 | Adjuvant S-1 chemotherapy

The initial dose of S-1 (80-120 mg/body/d divided into two doses) was determined based on body surface area (BSA) and Ccr criteria. For BSA  $< 1.25$  m<sup>2</sup>, the initial dose was 80 mg/day; for BSA  $\geq 1.25$  to  $< 1.5$  m<sup>2</sup>, 100 mg/d; and for BSA  $\geq 1.5$  m<sup>2</sup>, 120 mg/d. For Ccr  $\geq 60$  mL/min the standard dose was applied; for Ccr  $\geq 40$  to  $< 60$  mL/min, the dose was reduced by one step (from 120 mg/d to 100 mg/d, from 100 mg/d to 80 mg/d, or from 80 mg/d to 50 mg/d); patients with Ccr  $< 40$  mL/min were ineligible for study participation. Subsequent S-1 doses were adjusted based on tolerability. The criteria for dose reduction and toxicity were described previously.<sup>8</sup> Specifically, if patients had Grade 3 or Grade 4 hematological toxicity or Grade 2, Grade 3, or Grade 4 non-hematological toxicity, their daily dose was reduced by one step. One course of S-1 consisted of 28 days, followed by 14 days of rest. This 42-day course was repeated eight times during the first year after surgery.

## 2.5 | Study endpoints

The primary endpoint was the S-1 completion rate, defined as the proportion of patients who entered the second registration and continued eight consecutive courses of S-1 for 1 year with a relative performance (RP; administered/planned S-1 doses  $\times 100\%$ ) value of  $\geq 70\%$ . Secondary endpoints included RP value at 1 year of S-1 treatment (including that of patients who did not continue S-1 treatment up to 1 year), S-1 persistence rate, the nutritional index for patients entering the second stage (body weight and serum levels of albumin, total protein, total cholesterol, C-reactive protein [CRP], and Ccr), factors contributing to the completion rate of S-1, compliance with the OENS during the first and second registrations, persistence rate of the OENS, and safety of S-1.

## 2.6 | Study measures and assessments

The persistence rate (%) of S-1 was calculated as follows: the actual number of days that the patient took S-1 treatment/planned number of days that the patient took S-1 treatment. The persistence rate (%) of OENS was calculated as follows: the actual number of days that the patient took OENS treatment/planned number of days per eight courses (336 days) of S-1 treatment. The median persistence

rate was calculated for patients who started S-1. Compliance with the OENS was calculated at the fourth and eighth course of S-1 in patients who had compliance records at those time points, as follows: actual number of packs of the OENS that the patient took/planned number of packs of the OENS. Average compliance (%) of the relevant courses was also calculated.

AEs were recorded throughout the study and for <30 days following the end of treatment and were coded and graded according to the Common Toxicity Criteria of the National Cancer Institute (version 4.0). Blood samples for evaluation of efficacy and safety were regularly collected during the study and were analyzed by the study site laboratory.

## 2.7 | Statistical analyses

The sample size calculations are provided in the Supplementary material. The full analysis set (FAS) consisted of all patients who were eligible for the second registration, excluding those with protocol deviations. The per protocol set (PPS) comprised FAS patients who received treatment according to the study implementation plan, but excluded patients who relapsed, died, were lost to follow-up, or had protocol deviations. Efficacy analyses were conducted in the PPS. Safety analyses were performed in the FAS.

The treatment completion rate of S-1 (primary endpoint) was assessed by a one-sample binomial test with 56.6% (treatment completion rate reported for S-1 monotherapy in the ACTS-GC trial<sup>8,9</sup>; Taiho Pharmaceutical Co., Ltd. Study report. No. 717, 2017) as the

threshold value with 95% confidence intervals (CIs). If the one-sided *P*-value was <.05, the S-1 + OENS was judged to be effective.

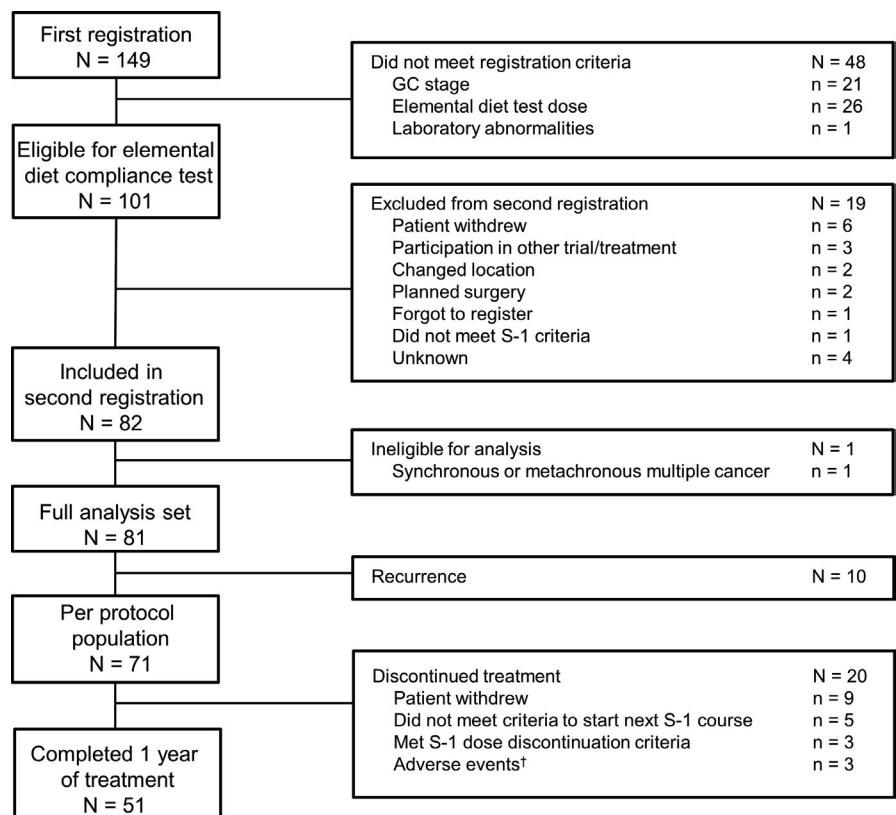
Summary statistics and changes in values from the start of the secondary registration were calculated for the nutritional index at each evaluation point during the test period. The statistical significance levels were calculated using the Mann-Whitney *U*-test. No adjustments were made for multiplicity for exploratory evaluation. Summary statistics were also calculated for S-1 RP values up to the end of 1 year, OENS compliance (during adjuvant chemotherapy), and OENS acceptance rates (during the first registration). These endpoints were analyzed using a binomial test for categorical outcomes and Wilcoxon test for continuous outcomes.

Missing data were excluded from the analysis, and no data were imputed. No statistical methods were used to control for confounding as this study was not a randomized controlled trial. The statistical analyses were performed using R version 3.5.1 (The R Foundation for Statistical Computing).

## 3 | RESULTS

### 3.1 | Patients

The patient disposition is shown in Figure 1. From February 2012 to July 2014, 149 patients with clinical stage II or III GC after R0 were registered in the first stage and began the OENS compliance test. Twenty-six patients did not show acceptability (>60% intake) of the OENS in the test for at least 14 days. The compliance with the OENS of



**FIGURE 1** Patient disposition. GC, gastric cancer. †Adverse events leading to discontinuation were rash, neutrophils decreased, and pyelonephritis. The Registration Center (Cancer medication research group) judged patients' appropriateness for the study

all patients registered in the first stage was 82.3% (95% CI: 77.5-87.2). Overall, 13 patients had  $\geq 1$  AE during the first registration period (diarrhea,  $n = 9$ ; abdominal pain,  $n = 5$ ; vomiting,  $n = 2$ ; anorexia and fatigue,  $n = 1$  each). All AEs were Grade  $\leq 2$ , and none were found to be clinically significant according to the investigator's judgment. Twenty-one patients did not have GC in pathological stage II or III.

A total of 82 patients met the eligibility criteria for the second registration. Excluding one patient who was found to be ineligible after registration (due to a history of bladder cancer and treatment), 81 patients were included in the FAS. Of those, after excluding 10 patients who had a recurrence during adjuvant chemotherapy, 71 patients were included in the PPS, and 51 completed 1 year of treatment (Figure 1).

The baseline characteristics of all 82 patients who entered the second registration are shown in Table 1. There was a slight preponderance of male patients (50/82; 61.0%), with a median age of 70.0 years, and median body weight 52.2 kg. Over half of the patients (45/82; 54.9%) had an ECOG PS of 0; no patients had an ECOG PS of 2. Around one-third of patients (27/82; 32.9%) had TG, and 55/82 (67.1%) had DG.

### 3.2 | Primary endpoint: S-1 completion rate

In the PPS, the S-1 completion rate was 69.0% (95% CI: 56.9-79.5). When stratified by surgical method, S-1 completion rates were 68.0% (95% CI: 46.5-85.1) for TG and 69.6% (95% CI: 54.2-82.2) for DG.

### 3.3 | Secondary efficacy endpoints

#### 3.3.1 | S-1 RP and persistence rate after eight courses

The RP value of S-1 in the PPS was 87.5 (interquartile range [IQR] 60.7-100.0, Table 2). RP values of S-1 by the surgical method were 89.1 (IQR 54.0-100.0) for TG and 87.5 (IQR 66.1-100.0) for DG. The median S-1 persistence rate throughout eight courses was 89.0% (IQR 46.4-92.8, Table 2).

#### 3.3.2 | Nutritional parameters and serum measurements

The median body weight before treatment was 52.7 kg (IQR: 31.0-79.0) and after adjuvant S-1 treatment was 50.5 kg (IQR: 31.4-84.0), indicating that significant loss of body weight was observed during treatment despite supplementation with the OENS (1.60 kg, IQR: -9.40-10.00; 4.06%, IQR: -0.70-7.94,  $P < .0001$ ) in Table 3. Significant weight loss was observed with both TG (2.00 kg, IQR: -3.30-10.00; 4.06%, IQR: -0.48-7.26,  $P = .008$ ) and DG (1.55 kg, IQR: -9.40-9.80; 3.94%, IQR: -1.05-8.01,  $P = .002$ ).

Changes in serum measurements are shown in Table 3. Median serum albumin was 3.9 g/dL (IQR: 3.6-4.1) before treatment and 4.0 g/dL (IQR: 3.7-4.2) after treatment, indicating a significant change of -0.1 g/dL (IQR: -0.50-0.15;  $P = .021$ ). Median serum total protein, total cholesterol, and Ccr were not significantly changed after treatment. Median CRP was 0.1 mg/dL (IQR: 0.0-0.3) before treatment and 0.0 mg/dL (IQR: 0.0-0.1) after treatment, indicating a significant reduction of 0.1 (IQR 0.0-0.2;  $P = .001$ ).

### 3.3.3 | Compliance and persistence with the OENS

The mean compliance with the OENS at the fourth course of S-1 postoperative adjuvant chemotherapy in the PPS was 81.8% (95% CI: 74.8-88.9). The results according to the surgical method were 85.3% (95% CI: 73.1-97.5) and 80.0% (95% CI: 71.0-89.1) for TG and DG, respectively. The mean compliance with the OENS at the eighth course of S-1 was 52.9% (95% CI: 39.2-66.6). The results according to the surgical method were 56.4% (95% CI: 31.8-80.9) and 50.7% (95% CI: 33.0-68.4) for TG and DG, respectively. The OENS persistence rate in the PPS (over the entire eight courses of S-1 treatment) is shown in Figure 2. The median persistence rate was 93.8% (IQR 48.2-100).

### 3.4 | Safety of S-1

The AE profile for the FAS population is shown in Table 4. The overall incidence of AEs of any Grade was 98.8%. The incidence of Grade 3 or 4 AEs was 22/81 (27.2%), with neutropenia (12.3%) the most commonly observed, followed by anorexia (3.7%), diarrhea (3.7%), and nausea (1.2%).

## 4 | DISCUSSION

We found that the completion rate of S-1 in this study (69.0%) was considerably higher than that reported in a previous study of adjuvant S-1 in GC patients.<sup>8</sup> The lower limit of the 95% CI (56.9%) was higher than that of the S-1 group in the ACTS-GC trial<sup>8,9</sup> (56.6%,  $P = .022$ ; Taiho Pharmaceutical Co., Ltd. Study report. No. 717, 2017), indicating that supplementation with the OENS may significantly improve the completion rate of adjuvant S-1 after gastrectomy.

Compared with patients undergoing surgery for rectal cancer, the intensity and frequency of AEs associated with adjuvant S-1 treatment seemed stronger after gastrectomy, likely due to increased frailty resulting from postoperative damage. Major AEs in S-1-treated patients in the ACTS-GC trial included anorexia (all grades, 61.1% and Grade  $\geq 3$ , 6.0%), diarrhea (59.8% and 3.1%, respectively), and nausea (39.1% and 3.7%, respectively).<sup>8</sup> In the ACTS-RC randomized phase III trial in patients with rectal cancer, major AEs in the S-1 group were anorexia (all grades, 27.7% and Grade  $\geq 3$ , 2.6%), diarrhea (18.5% and 2.6%, respectively) and nausea (17.4% and 1.3%,

**TABLE 1** Baseline characteristics of patients entering the second registration (N = 82)

Characteristic	Patients (N = 82)
Male	50 (61.0)
Age, median (range)	70.0 (42-85)
ECOG PS	
0	45 (54.9)
1	37 (45.1)
Gastrectomy	
TG	27 (32.9)
DG	55 (67.1)
GC stage	
IIA	9 (11.0)
IIB	18 (22.0)
IIIA	24 (29.3)
IIIB	14 (17.1)
IIIC	17 (20.7)
Body weight (kg), median (range)	52.2 (31-79)
Body mass index (kg/m <sup>2</sup> ), median (range)	20.8 (13.4-29.0)
Serum levels, median (range)	
Albumin (g/dL)	3.9 (2.5-4.7)
Protein (g/dL)	6.8 (5.7-8.7)
Cholesterol (mg/dL)	160 (101-211)
CRP (mg/dL)	0.135 (<0.02-4.04)
Creatinine clearance (mL/min)	64.8 (38.6-121.4)

Note: Data are shown as n (%) unless otherwise stated.

Abbreviations: CRP, C-reactive protein; DG, distal gastrectomy; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; TG, total gastrectomy.

**TABLE 2** S-1 RP and persistence rate after eight courses (PPS; N = 71)

S-1	Surgery	Median [interquartile range]
RP	All	87.5 [60.7, 100.0]
	TG	89.1 [54.0, 100.0]
	DG	87.5 [66.1, 100.0]
Persistence rate (%)	All	89.0 [46.4, 92.8]

Abbreviations: DG, distal gastrectomy; PPS, per protocol set; RP, relative performance; TG, total gastrectomy.

respectively).<sup>22</sup> Post-gastrectomy loss of body weight has been reported to influence adjuvant chemotherapy compliance<sup>17</sup> and survival outcomes<sup>18</sup> in GC patients. Prior analyses demonstrated that post-gastrectomy intake of the OENS significantly reduced weight loss both in patients who underwent curative DG and TG in the short term<sup>19</sup> and in patients who underwent TG after 1 year,<sup>23</sup> implying that short-term OENS administration can bring long-term efficacy

for body weight loss prevention. In the present phase II study, body weight data were not obtained preoperatively, only before and after taking S-1, so it is not possible to discuss the relationship between S-1 compliance and the degree of weight loss. However, this study did investigate whether adjuvant S-1-treated GC patients could continue treatment for longer durations for 1 year with the help of the nutritional support with the OENS and the results indicated that treatment completion rates were improved compared with the historical data from the ACTS-GC trial.<sup>8,9</sup>

In a prospective pilot study for the prevention of oral mucositis associated with adjuvant S-1 chemotherapy, supplementation with OENS significantly increased cumulative S-1 continuation rates (log-rank  $P = .047$ ).<sup>24</sup> Reduction of body weight loss and drug-induced toxicities could allow GC patients to continue postoperative adjuvant chemotherapy.<sup>24</sup> Recently, not only S-1 alone<sup>8</sup> but also more toxic doublets, such as S-1 + DTX,<sup>25</sup> capecitabine + L-OHP,<sup>10,11,26</sup> and S-1 + L-OHP,<sup>27,28</sup> have been used for postoperative adjuvant chemotherapy in Japan. Our trial results indicate that supplementation with the OENS may contribute to an increase in the completion rate of more toxic adjuvant therapies.

Mean compliance with the OENS at the fourth course of S-1 was 81.8%. Nevertheless, the protocol-prescribed period of OENS administration was 6 months, and the mean compliance with the OENS was 52.9% at the eighth course of S-1. The median OENS persistence rate over the entire eight courses was high (93.8%). This is likely owing to the explanation of the importance of the OENS by the study investigators; patients who understood this importance were found to continue the OENS beyond the protocol-prescribed period.

It was assumed that maintaining high compliance with the OENS is key to preventing weight loss and increasing rates of continuous adjuvant S-1 chemotherapy after gastrectomy. Prior to initiating this study, we had concerns about the difficulty of intake of the OENS after gastrectomy, therefore we adopted the two-stage trial design. First, OENS compliance of all patients registered in the first stage was evaluated, where a compliance rate of 82.3% was recorded in the 149 patients, suggesting that most patients had no difficulties ingesting this hyperosmolar nutritional supplement. Although no severe or clinically significant AEs were reported during this part of the study, 26 patients had inadequate compliance (i.e. <60%) and could not be registered for the second stage. Thus, the high compliance and longer-term persistence rates for the OENS in the selected patients for the second stage undoubtedly contributed to the S-1 RP of 87.5 and persistence rate of 89.0% after eight courses.

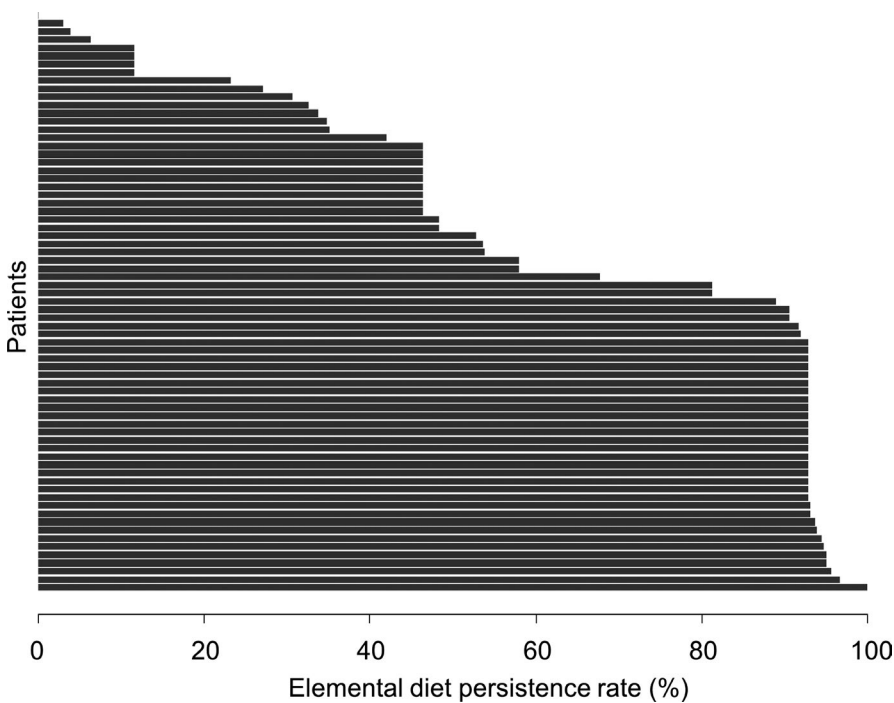
The main limitation of this study was the single-arm design. There was also a difference in the historical background of the two studies; ACTS-GC included patients treated between 2001 and 2004, while this study included patients treated between 2011 and 2015, 10 years later. During this period, there have been various changes in perioperative management in Japanese surgical practice, including improvements in laparoscopic surgery, clinical pathways, Enhanced Recovery After Surgery, and supportive care for postoperative

**TABLE 3** Changes in nutritional parameters, serum measurements (PPS; N = 71)

Variable	Surgery	Median [interquartile range]		Change	P-value
		Before treatment	After treatment		
Body weight (kg)	All	52.7 [31.0, 79.0]	50.5 [31.4, 84.0]	1.60 [-9.40, 10.00]	<.001
	TG	54.2 [33.7, 79.0]	51.0 [37.0, 73.0]	2.00 [-3.30, 10.00]	.008
	DG	51.7 [31.0, 78.3]	49.3 [31.4, 84.0]	1.55 [-9.40, 9.80]	.002
Body mass index (kg/m <sup>2</sup> )		20.8 [18.6-22.7]	19.9 [17.9-21.7]	0.76 [-0.16-1.83]	<.001
Serum albumin (g/dL)		3.9 [3.6, 4.1]	4.0 [3.7, 4.2]	-0.1 [-0.5, 0.2]	.021
Serum total protein (g/dL)		6.8 [6.4, 7.0]	6.8 [6.5, 7.2]	-0.1 [-0.4, 0.2]	.091
Serum whole cholesterol (mg/dL)		160.0 [139.8, 181.3]	156.0 [135.8, 177.0]	-2.5 [-10.5, 11.0]	.901
CRP (mg/dL)		0.1 [0.0, 0.3]	0.0 [0.0, 0.1]	0.1 [0.0, 0.2]	0.001
Creatinine clearance (mL/min)		64.1 [54.3, 83.1]	64.9 [51.6, 80.5]	0.7 [-2.7, 9.7]	.107

Note: P-values were calculated using Mann-Whitney's U test.

Abbreviations: CRP, C-reactive protein; DG, distal gastrectomy; PPS, per protocol set; TG, total gastrectomy.

**FIGURE 2** OENS continuation rate (PPS, N = 71). OENS, oral elemental nutritional supplement; PPS, per protocol set

chemotherapy. Laparoscopic surgery has been shown to improve early postoperative quality of life after gastrectomy. However, the 12-month compliance with S-1 medication in ACTS-GC was 65.8%, compared with 56% in the JACCRO GC-07 study<sup>25</sup> (2013-2017) S-1-only group. Although there are different patient and study backgrounds across these studies, we recognize that S-1 compliance does not necessarily improve over time. This study was conducted with as much caution as possible due to differences in study design and the heterogeneity of the patients, so we believe that while direct comparisons with historical data have major limitations, they are not meaningless. For further investigation of the role of OENS on adjuvant chemotherapy compliance and patient outcomes, multicenter, randomized, controlled trials are warranted. Another limitation of this study is that patients who had better postoperative courses

and could consume the OENS in the early period after operation were enrolled for the second stage. These patients might have had a higher motivation for taking S-1 treatment, which may have affected our findings.

In conclusion, the completion rate of S-1 for 1 year in patients who could take the OENS exceeded the pre-defined threshold level. Randomized controlled trials are warranted to confirm the role of OENS in adjuvant chemotherapy.

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**TABLE 4** Summary of adverse events (FAS, N = 81)

Events <sup>a</sup>	Any grade, n (%)	Grade 3 or 4, n (%)
Leukopenia	38 (46.9)	1 (1.2)
Neutropenia	42 (51.9)	10 (12.3)
Thrombocytopenia	23 (28.4)	1 (1.2)
Anemia	63 (77.8)	3 (3.7)
Creatinine increased	8 (9.9)	1 (1.2)
Total bilirubin increased	24 (29.6)	1 (1.2)
AST increased	17 (21.0)	0
ALT increased	14 (17.3)	0
Anorexia	40 (49.3)	3 (3.7)
Nausea	26 (32.1)	1 (1.2)
Vomiting	12 (14.8)	1 (1.2)
Abdominal pain	11 (13.6)	0
Diarrhea	43 (53.1)	3 (3.7)
Fatigue	20 (24.7)	1 (1.2)
Watering eyes	8 (9.9)	1 (1.2)
Mucositis oral	21 (25.9)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAS, full analysis set.

<sup>a</sup>No cases of febrile neutropenia (of any grade) were reported.

## DISCLOSURE

Ethical considerations: The protocol for this research project has been approved by the suitably constituted ethics committees at each institution and it conforms to the provisions of the Declaration of Helsinki. All patients provided written informed consent. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000006872).

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## DATA AVAILABILITY STATEMENT

Data are available from the authors upon reasonable request.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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