# Biweekly Oxaliplatin Plus S1 (SOX) As First Line Therapy For Advanced Or Metastatic Gastric Or Gastroesophageal Junction (G/GEJ) Caner In Chinese Elderly Patients: An Open-Label, Single-Arm, Phase 2 Study.

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# Abstract

**Background:** SOX (oxaliplatin and S1 every 3 weeks) is one of the most common used first line chemotherapy for advanced or metastatic G/GEJ cancer in Asia, but with significant hematological and neurological toxicity. In China, the majority of gastric cancer patients are the middle-aged and elderly with dissatisfactory tolerance to 3-weekly chemotherapy. Therefore, we aimed to assess efficacy and safety of biweekly SOX as first line treatment in patients 60 years old or older with advanced G/GEJ cancer in a single arm phase 2 study.

**Methods:** Oxaliplatin was administered intravenously on day 1 at 85 mg/$m^2$. S-1 was given at 80, 100, 120 mg/day depending on body surface area of <1.25 $m^2$, 1.25 to <1.5 $m^2$, or ≥1.5 $m^2$ two times daily on days 1-10, every 2 weeks. Eligible patients were aged 60 years old or older with histological or cytological diagnosis of advanced G/GEJ adenocarcinoma, had measurable disease according to the RECIST v 1.1 without previous treatment. The primary endpoint was objective response rate (ORR), and the secondary endpoints included progression free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR) and safety.

**Results:** Between May 2016 and Sep 2018, 42 patients were enrolled. Median follow-up time was 43.6 months. ORR and DCR were 52.4% and 85.7%, respectively. Median PFS was 4.6 months (95%CI 2.486-6.714). Median OS was 11.1 months (95%CI 8.001-14.199). The most common treatment-related adverse events (TRAEs) of any grade were thrombocytopenia (59.5%), neutropenia (57.1%), appetite loss (57.1%) and nausea (54.8%). Only two patients respectively suffered from grade 3 treatment-related neutropenia (1 patient, [2.4%]) and diarrhea (1 patient, [2.4%]). No other grade 3 or worse TRAEs occurred.

**Conclusions:** First line biweekly SOX showed promising PFS and OS with a remarkable tolerance in advanced G/GEJ cancer patients 60 years old or older preliminary worth further evaluation.

**Trial registration:** ClinicalTrials.gov ID: NCT04694404 (5/1/2021). This study was approved by the Ethical Committee of National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, (17-048/1303).


# Background

Gastric cancer is the second most common cancer and the third leading cause of cancer death in China [1–2]. The incidence of gastric cancer is 63.92 per 100, 000 aged 50 to 59 years, 143.10 per 100, 000 aged 60 to 69 years, which morbidity increased with age [3]. The majority of Chinese gastric cancer patients are the middle-aged and elderly with the average age of 64 years old. These elderly patients usually show a poor tolerance and compliance to chemotherapy due to the declination of organ functions or the existing physical illnesses such as diabetes, hypertension and other cardiac and cerebral diseases. Suspension or discontinuation of chemotherapy may decrease the objective response rate or bring an undesirable effect

on survival. Therefore, it is valuable to optimize the chemotherapy regimen for elderly advanced gastric cancer patients to improve the tolerance and efficacy of chemotherapy.

SOX (oxaliplatin and S1 every 3 weeks) is one of the standard first line treatments for the advanced gastric cancer patients recommended by the guide lines of Chinese Society of Clinical Oncology (CSCO) and Japanese Gastric Cancer Association (JGCA). Nevertheless, 3-weekly SOX regimen usually showed a high incidence of neutropenia and thrombocytopenia, reported to be 56.9-82.5% and 44.7-84.1% respectively [4–9]. The significant hematologic toxicity made more patients accepted dose reduction. The proportion was reported to be 36.1-41.5% for S1 and 41.4-48.5% for oxaliplatin, respectively, in previous phase II and III clinical trials [4–6]. Therefore, the efficacy and safety of modified 3-weekly or biweekly chemotherapy regimens with oxaliplatin and S1 or capecitabine have been evaluated in a series of clinical studies. Biweekly XELOX (oxaliplatin 85mg/$^2$ day 1, capecitabine 900-1800mg/m$^2$ bid day 1 to 10, every 2 weeks) was demonstrated that could bring a better tolerance and satisfactory therapeutic effects in the untreated advanced colorectal cancer and gastric cancer patients, especially for the elderly patients [10–11]. Furthermore, compared with the patients accepted standard 3-weekly XELOX (HR 1.10, 95% CI, 0.90-1.33), the counterparts received modified 3-weekly XELOX with does intensity reduction (HR 1.09, 95% CI, 0.89-1.32) could acquire a similar PFS benefit, in the advanced gastric cancer patients with a median age of 76 years [12]. The patients undertook 60% of the standard does showed a higher satisfaction in the quality of life and objective effectiveness (43% vs. 35%) [12]. Moreover, metronomic chemotherapy was revealed to lead a lower toxicity and satisfactory survival benefit in lung cancer and breast cancer patients by reducing single does or shortening the intermission of chemotherapy. As a consequence, we evaluated the efficacy and safety of biweekly SOX (oxaliplatin and S1) in the first line treatment of advanced or metastatic elderly gastric cancer patients, to optimize the chemotherapy for the old patients with poorer physical status.

## Methods

# Study design and aim

This is an open-label, single-arm, prospective phase II study which aims to evaluate the efficacy and safety of biweekly SOX (oxaliplatin plus S1 every two weeks) as first line treatment in patients 60 years old or older with advanced G/GEJ cancer.

# Patients

Eligible patients were aged 60 years old or older; had histological or cytological diagnosis of gastric or gastroesophageal junction adenocarcinoma; had previously untreated, unresectable advanced or metastatic disease (patients who had tumor progression after adjuvant or neoadjuvant chemotherapy completed more than 12 months were also eligible); had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); had an Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2; and had adequate hematological, hepatic, and

renal function predicted life expectancy at least 3 months. The main exclusion criteria included a diagnosis of other malignant tumors (except cured basal cell carcinoma of skin and squamous cell carcinoma of skin, or cervical carcinoma in situ) within 5 years; the total dose of previous oxaliplatin ≥800mg/$m^2$ within 2 years in the adjuvant or neoadjuvant setting; and allergic to oxaliplatin or S-1.

# Procedures

S-1 was given orally twice daily for the first 10 days of a 2-week cycle. The dose was 80 mg/day for body surface area (BSA) <1.25 $m^2$, 100 mg/day for BSA ≥1.25 to <1.5 $m^2$, and 120 mg/day for BSA ≥1.5 $m^2$. Oxaliplatin was given intravenously at a dose of 85 mg/$m^2$ on day 1 of each 2-week cycle. Treatment was continued until disease progression (defined according to RECIST, version 1.1), unacceptable toxicity, or patient withdrawal, whichever occurred first. The patients with tumor response, the oxaliplatin-based doublet chemotherapy was given for a maximum of 9 cycles, then S-1 maintenance chemotherapy was performed.

Adverse events were assessed by Common Toxicity Criteria version for Adverse Events, version 4.0. The dose of S-1 was down-regulated to the next level, if grade 4 hematological toxicities, ≥ grade 3 febrile neutropenia/leukopenia, gastrointestinal toxicities or stomatitis, or Cr>132.6μmol/L developed. In the event of ≥ grade 2 peripheral neurotoxicity continued for 7 days or any other ≥ grade 3 toxicity, the dose of oxaliplatin was reduced by the schedule from 85mg/$m^2$ to 70 mg/$m^2$ and 60mg/$m^2$.

Tumor response was evaluated every 6 weeks according to RECIST version 1.1. Contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were recommended.

The study was approved by the Ethical Committee of National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, (17-048/1303). Clinical trial information: NCT04694404 (5/1/2021).

# Statistical analysis

The objective response rate (ORR) of S1 was about 30%, the expected ORR in the current study was 50% because the protocol treatment was combination with oxaliplatin. Based on the assumption of performing a one-tailed score test with an α of 0.05, 40 patients were needed to ensure the statistical power of 80%. Considering of the drop out rate of 10%, 44 patients were needed finally. The primary endpoint was objective response rate (ORR), which was defined as the percentage of the patients who acquired complete or partial response. The secondary endpoints were progression free survival (PFS, defined as the time from the initiation of chemotherapy to the first progression or any cause of death), overall survival (OS, defined as the time from the initiation of chemotherapy to death from any cause), disease control rate (DCR), duration of response (DOR) and safety. All statistical analyses were performed using SPSS (version 25). Kaplan–Meier method was used to analyze the median PFS and OS.

# Results

# Patient characteristics

Between May 2016 and Sep 2018, 42 eligible patients received the treatment at the Department of Medicine Oncology, National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital. The characteristics of the 42 patients are shown in Table 1. The median age was 68 years (range, 60–79). ECOG was 0 in 25 patients (59.5%) and 1 in 17 patients (40.5%). The most frequent existing physical illnesses was hypertension (21.4%), diabetes (11.9%), coronary heart disease (11.9%) and cerebral infarction (7.1%).

Table 1 Patients and disease characteristics at base line.

| | No. | % |
|---|---|---|
| Gender | | |
| Male | 34 | 81.0 |
| Female | 8 | 19.0 |
| Age | | |
| 60≤<65 | 9 | 21.4 |
| 65≤<70 | 18 | 42.9 |
| 70≤<75 | 11 | 26.2 |
| ≥75 | 4 | 9.5 |
| ECOG | | |
| 0 | 25 | 59.5 |
| 1 | 17 | 40.5 |
| BMI | | |
| Low（<18.5kg/$m^2$） | 5 | 11.9 |
| Normal（18.5≤<24kg/$m^2$） | 22 | 52.4 |
| overweight（24≤<27kg/$m^2$） | 10 | 23.8 |
| Obesity（27≤<30kg/$m^2$） | 3 | 7.1 |
| Severe obesity（≥30kg/$m^2$） | 1 | 2.4 |
| Unknown | 1 | 2.4 |
| Disease status | | |
| Recurrent | 4 | 9.5 |
| Newly diagnosed | 38 | 90.5 |
| Metastatic site | | |
| Retroperitoneal lymph nodes | 25 | 59.3 |
| Supraclavicular lymph nodes | 16 | 38.1 |
| Mediastinal lymph nodes | 12 | 28.6 |
| Liver | 10 | 23.8 |
| Peritoneal | 10 | 23.8 |

| | | |
|---|---|---|
| Lung | 10 | 23.8 |
| Adrenal gland | 2 | 4.8 |
| Bone | 1 | 2.4 |
| ovary | 1 | 2.4 |
| Complication | | |
| Hypertension | 9 | 21.4 |
| Diabetes | 5 | 11.9 |
| Coronary heart disease | 5 | 11.9 |
| Cerebral infarction | 3 | 7.1 |
| Carotid artery stenosis | 2 | 4.8 |
| Arrhythmia | 2 | 4.8 |
| Liver cirrhosis | 1 | 2.4 |

# Response and survival

Objective response was observed in 22 (52.4%) of 42 patients. 14 patients (33.3%) achieved stable disease and 6 patients (14.3%) progressed during the treatment. The assessed DCR was 85.7% (36/42). Among the 22 patients who achieved an objective response, the median time to response was only 1.5 months, and the duration of response was up to 4.6 months (95%CI 2.245-6.955). Best overall response was shown in Table 2. The median follow up was 43.6 months. Median PFS was 4.6 months (95%CI 2.486-6.714, Fig. 1). Median OS was 11.1 months (95%CI 8.001-14.199, Fig. 2). Retrospective analysis showed the patients with low body mass index (BMI) (<18.5kg/$m^2$) had a shorter OS of 7.4 months, while the patients with normal BMI (18.5 to 24kg/$m^2$), overweight (BMI was 24 to 27kg/$m^2$) or obese (BMI was 27 to 30kg/$m^2$) acquired a median OS of 10.6 months, 12.6 months and 11.1 months respectively (p=0.188). Nevertheless, the severe obesity patients with BMI over 30kg/$m^2$ only developed a survival of 4.2 months. Moreover, the treatment effect was seemed greater in patients with an ECOG performance status of 0. The median OS was 12.9 months versus 10.6 months in the patients with an ECOG performance status of 0 and 1, respectively (p=0.719).

Table 2
Best overall response (N=42) in patients treated with biweekly SOX

| Best response (N=42) | No. (%) |
|---|---|
| CR | 0(0%) |
| PR | 22(52.5%) |
| SD | 14(33.3%) |
| PD | 6(14.3%) |
| ORR (CR+PR) | 22(52.5%) |
| DCR (CR+PR+SD) | 36(85.7%) |

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

# Tolerability and Adverse Events

Common treatment-related adverse events (TRAEs) of any grade were thrombocytopenia, neutropenia, gastrointestinal reaction, hyperbilirubinemia and fatigue. Most of these adverse events (AEs) were reported to be grade 1-2. The most common grade 3 TRAEs were neutropenia (n=1, 2.4%) and diarrhea (n=1, 2.4%). No febrile neutropenia and other grade 3 or worse AEs occurred. Adverse event profiles were presentation in Table 3. The median number of treatment cycles was 6, and 26 patients (61.9%) completed at least 6 cycles of chemotherapy. No TRAEs led to study discontinuation or interruption. Dose reduction occurred in 2 patients (4.8%) because of grade 2 thrombocytopenia with a long time to recovery.

Table 3
Adverse Events.

| Adverse event | Any | | Grade 1 | | Grade 2 | | ≥ Grade 3 | |
|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Appetite loss | 24 | 57.1 | 19 | 45.2 | 5 | 11.9 | 0 | 0 |
| Nausea | 23 | 54.8 | 19 | 45.2 | 4 | 9.5 | 0 | 0 |
| Vomiting | 12 | 28.6 | 7 | 16.7 | 5 | 11.9 | 0 | 0 |
| Diarrhea | 4 | 9.5 | 3 | 7.1 | 0 | 0 | 1 | 2.4 |
| Neutropenia | 24 | 57.1 | 16 | 38.1 | 7 | 16.7 | 1 | 2.4 |
| Thrombocytopenia | 25 | 59.5 | 12 | 28.6 | 13 | 31.0 | 0 | 0 |
| Increased ALT | 9 | 21.4 | 9 | 21.4 | 0 | 0 | 0 | 0 |
| Increased AST | 12 | 28.6 | 12 | 28.6 | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | 16 | 38.1 | 16 | 38.1 | 0 | 0 | 0 | 0 |
| Rash | 1 | 2.4 | 0 | 0 | 1 | 2.4 | 0 | 0 |
| Fatigue | 13 | 31.0 | 9 | 21.4 | 4 | 9.5 | 0 | 0 |
| Weight loss | 8 | 19.0 | 5 | 11.9 | 3 | 7.1 | 0 | 0 |
| Peripheral neuropathy | 8 | 19.0 | 7 | 16.7 | 1 | 2.4 | 0 | 0 |

# Second line treatment

Up to the last follow up, 38 confirmed progressions occurred in these patients. 24 patients (65%) accepted second line anti-tumor treatments including chemotherapy (n=20), local radiotherapy (n=1) and clinical trial (n=3). Chemotherapy regimens included taxanes combination with raltitrexed (n=7), apatinib (n=5), taxanes (n=3), irinotecan and apatinib (n=1), raltitrexed (n=1), oxaliplatin combined with raltitrexed (n=1), docetaxel plus S1 (n=1) and unknown (n=1). Four patients refused further treatment after progression. The information of the other ten patients whether received subsequent treatment was not clear.

# Discussion

Platinum-based drug used in combination with fluorouracil is recognized standard first-line chemotherapy for metastatic gastric cancer. S1 is a new oral drug of fluorouracil, combines tegafur with two modulators of gimeracil and oteracil [13], compared with capecitabine shows lower incidence of hand foot syndrome (HFS). S1 plus platinum has been demonstrated has favorable efficacy in Asia advanced gastric cancer patients. ORR and DCR of SOX were reported to be 32.6-58% and 75-85.2% respectively in first line randomized phase III studies. Median PFS and OS were 5.5-5.7 months and 12.9-14.1 months,

respectively [4, 5, 7]. Especially for the non-intestinal Lauren's type gastric cancer, SOX had a prolonged OS compared with SP in Chinese patients [4]. Based on the excellent efficacy and acceptable toxicity [4, 5, 14, 15], SOX is one of the most common regimens for the first line chemotherapy of advanced gastric cancer in Asia. However, elderly gastric cancer patients usually in poor performance status and complicated with underlying disease such as hypertension, diabetes and coronary heart disease. Therefore, S1 monotherapy became a choice for the patients who could not tolerate 3-weekly combination chemotherapy. Nevertheless, the effect of S1 monotherapy in first line setting was limited. ORR was only 24.7-31%, and median OS was 10.5-10.8 months [16–18], inferior to the chemotherapy with fluoropyrimidine and platinum [9]. In consequence, there is an urgent need to explore therapeutic options with satisfactory efficacy and acceptable tolerability for elderly patients of advanced gastric cancer.

This phase 2 study showed that biweekly SOX could bring out a promising survival as first-line therapy in Chinese elderly metastatic gastric cancer patients with a median age of 68 years old, preliminarily. Compared with S1 monotherapy, biweekly SOX had a tendency to improve the efficacy with higher ORR (54.2%) and DCR (85.7%). And the median PFS and OS of biweekly SOX was 4.6 months and 11.1 months, respectively, seemed to be similar with 3-weekly SOX. Furthermore, in another phase II study, the effect of biweekly SOX (oxaliplatin 85 mg/m$^2$ d1, S1 80-120mg/day d1-7, every 2 weeks) in the first line treatment was evaluated. ORR and DCR were 30.43% and 76.08%, respectively [19]. The patients with median age of 59 years old acquired a PFS of 4.4 months and OS of 10.3 months [19], who were much younger than our patients. In that study, 78.3% of patients accepted second line chemotherapy, whereas the proportion of our patients was 63.2%. In our study, 7 HER2 positive patients didn't accept trastuzumab for financial reasons, might have a negative effect on the survival. Even so, our biweekly SOX in the elderly patients showed similar effect compared with the counterpart in the previous phase II study.

A series of clinical studies demonstrated that 3-weekly SOX (oxaliplatin 130 mg/m$^2$ d1, S1 80-120mg/day d1-7, every 3 weeks) had accumulated significant hematological and neurological toxicity [6–9]. Therefore, the dose of oxaliplatin was reduced to 100mg/m$^2$ every three weeks in G-SOX phase 3 study. However, the modified 3-weekly SOX didn't show lower toxicity. Grade 3-4 neutropenia and thrombocytopenia were still reported to 19.5% and 10.1%. The rate of any grade peripheral neuropathy was up to 85.5%. As a result, 48.5% and 5% of the patients accepted dose reduction of oxaliplatin or treatment discontinuation in G-SOX phase 3 study, respectively [4]. Advanced gastric cancer patients usually suffered from weight loss, malnutrition and chronic anemia which might impair the tolerance to anti-tumor therapy, especially for the elderly patients. In our study, about 1/4 of the patients were complicated with cardiovascular or cerebrovascular disease, with high-risk of acute attack of underlying diseases if suffering from severe TRAEs. This study demonstrated well tolerance of biweekly SOX by reducing single dose of oxaliplatin and shortening treatment course of S1 in these elderly patients. Any grade neutropenia was 57.1%, similar with the result reported by previous biweekly SOX phase 2 study (54.35%) [19], and lower compared with 3-weekly SOX phase 3 studies (65.6% and 68.9%) [4–5]. Only 2.4% patients developed grade 3 neutropenia, no grade 4 neutropenia occurred. There was no ≥ grade 3

thrombocytopenia observed in this study, while the incidence was up to 7.5-17% in 3-weekly SOX [4–9]. Furthermore, this biweekly SOX seemed to show better tolerance in peripheral neurotoxicity and digestive symptoms compared with 3-weekly SOX, any grade peripheral neuropathy, nausea and vomiting were less frequent (19% vs. 34-85.5%, 54.8% vs. 61.5-74.6% and 28.6% vs. 34.9%59.9%) [4–9]. Most of these elderly patients could keep good physical conditions during treatment. As a result, biweekly SOX might bring a better quality of life in elderly advanced gastric cancer patients with lower toxicity.

Moreover, the patients with better nutritional and physical status seemed to have longer OS in this study. Compared with the ones with lower BMI, the patients of BMI≥18.5kg/$m^2$ showed longer OS of 3.2-5.2 months numerically (p= 0.188). The OS of patients with ECOG 0 and 1 were 12.9 months and 10.6 months respectively (p= 0.719). Nutritional and physical status was closely correlated with immune function and treatment tolerance [20–21], which might compromise the treatment effect. Elderly patients were usually with lower level of albumin and lymphocyte, which was associated with poorer nutritional status and immune function [22–25]. Nutritional guidance and intervention during chemotherapy were revealed to lead an increase in the CD4+ lymphocyte and alleviate the hematological and digestive toxicity [26]. Therefore, integration of nutritional supportive care into chemotherapy might be helpful to improve the tolerance and completion of anti-tumor treatment in elderly patients, subsequently prolonged the survival.

The limitation of this study was not randomized and had a small sample size undertaken in a single institution. Therefore, the anti-tumor activity results were preliminary, needing further accrual and evaluation.

# Conclusions

First line biweekly SOX showed promising PFS and OS with a remarkable tolerance in advanced or metastatic gastric or GEJ cancer patients 60 years old or older, preliminary. The incidence of grade 3 or worse AEs were low. On the base of the results, further evaluation is needed in randomized study with larger sample size.

# List Of Abbreviations

G/GEJ cancer: gastric or gastroesophageal junction (G/GEJ) caner; ORR: objective response rate; PFS: progression free survival; OS: overall survival; DCR: disease control rate; DOR: duration of response; CSCO: Chinese Society of Clinical Oncology; JGCA: Japanese Gastric Cancer Association; ECOG: Eastern Cooperative Oncology Group; BSA: body surface area; TRAEs: Common treatment-related; AE: adverse events adverse events; HFS: hand foot syndrome; BMI: body mass index.

# Declarations

### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committee of National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, (17-048/1303). Clinical trial information: NCT04694404 (5/1/2021). Written informed consent was obtained from all individual participants included in the study.

### Consent for publication

Not applicable.

### Availability of data and materials

Clinical data will be available from the corresponding author on reasonable request.

### Competing interests

None of the authors have any conflicts of interests.


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There is no funding for this study.


### Authors' contributions

ZW and ZAP developed the presented idea, design, and implemented the study. ZW supervised the project and led the writing of the final version of the manuscript. ZW, ZAP, JZC, SYK participated patients' recruitment, informed consents and data collection. JZC analyzed data, drafted the manuscript, edited the paper for English grammar and writing. ZW revised the article and provided final approval. All authors read and approved the final manuscript.


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# Figures

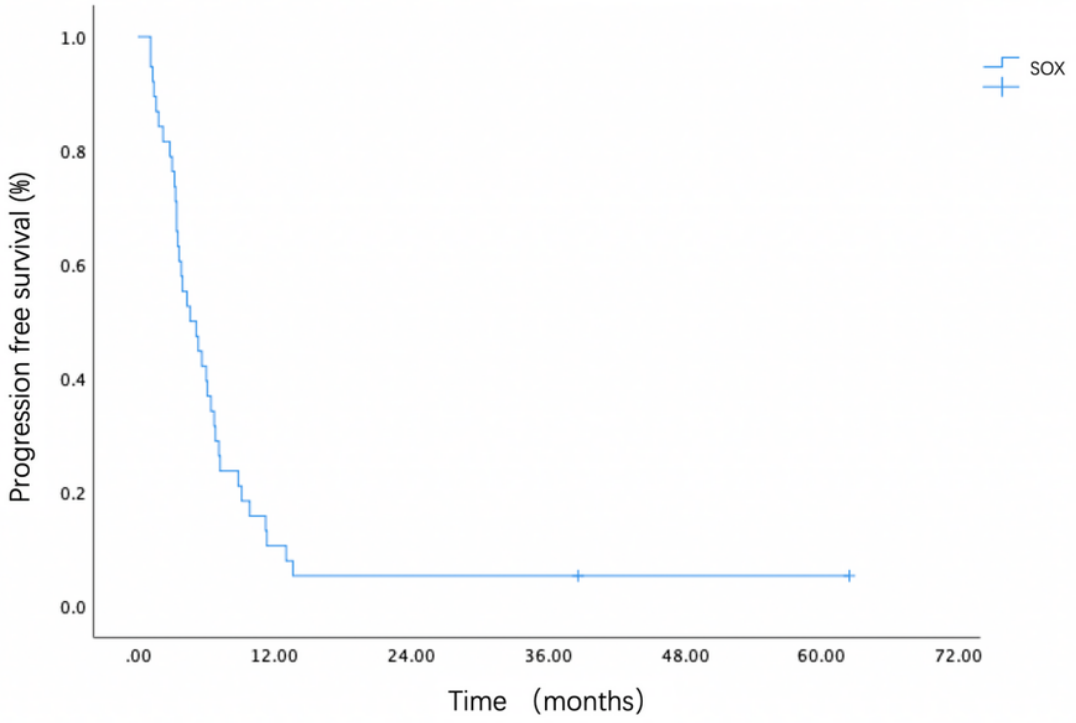
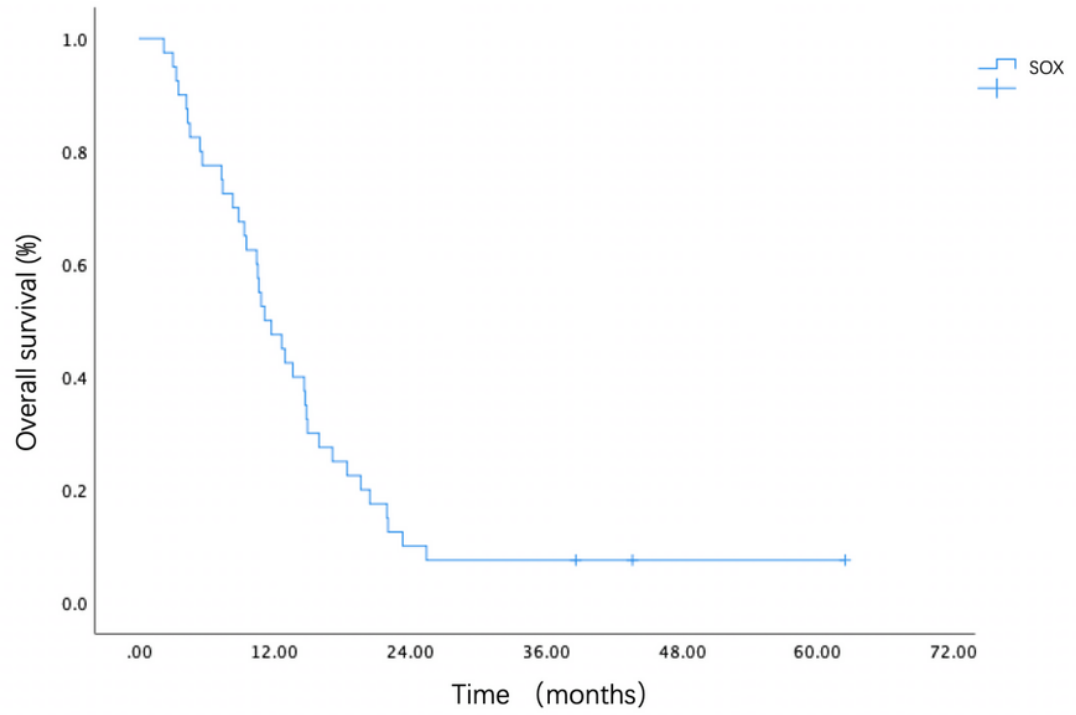



**Figure 1**

Kaplan-Meier estimates of PFS in advanced G/GEJ cancer patients treated with biweekly SOX. PFS: progression free survival; G/GEJ cancer: gastric or gastroesophageal junction caner



## Figure 2

Kaplan-Meier estimates of OS in advanced G/GEJ cancer patients treated with biweekly SOX. OS: overall survival; G/GEJ cancer: gastric or gastroesophageal junction cane