NCT Number: NCT01515748

Protocol

Drug Substances: Docetaxel, Oxaliplatin, S-1(Tegafur, Gimeracil, Oteracil)

A Phase III, Open-labelled, Randomised Study of Neoadjuvant Docetaxel+Oxaliplatin+S-1 (DOS) + Surgery + Adjuvant S-1 Versus Surgery + Adjuvant S-1 in Patients With Resectable Advanced Gastric Cancer

Study No.: EFC13833

Abbreviated title: PRODIGY (PReOperative Dos Investigation in Gastric malignancY)

Version No.: v8.0
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Sponsor: Sanofi Group

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1. CLINICAL TRIAL OUTLINE

Drug substances: Docetaxel, Oxaliplatin, S-1 (Tegafur, Gimeracil, Oteracil)
Clinical trial number: EFC13833

Title	A Phase III, Open-labelled, Randomised Study of Neoadjuvant Docetaxel+Oxaliplatin+S-1 (DOS) + Surgery + Adjuvant S-1 Versus Surgery + Adjuvant S-1 in Patients With Resectable Advanced Gastric Cancer
Study objectives	**Primary objective:** • To compare the 3-year Progression-Free Survival (PFS) between two groups **Secondary objectives:** To assess and compare the followings between two groups: • Overall survival (OS) • Post-operative pathological stage • R0 (complete) resection rate • Safety assessment
Study design	A multicenter, open-label, randomized (1:1), phase 3 clinical study
Study population ***Key inclusion criteria:***	**Inclusion criteria:** 1. Patients who provide voluntary written consent using the Informed Consent Form before participating in this study 2. Patients with new histologically confirmed primary gastric or gastroesophageal junction adenocarcinoma amenable to curative resection 3. Patients with TNM Stage T2,3/N (+) or any T4/N stage (according to the AJCC 7th Edition) (lymph node positive: irrespective of the lymph node shape, if the short axis is ≥8 mm, it is defined as lymph node metastasis positive)
Key exclusion criteria:	**Exclusion criteria:** • **Methods** 1. Patients aged less than 20 years or over 76 years old (inclusive) 2. Patients with the Eastern Cooperative Oncology Group (ECOG) Performance Status ≥2 3. Patients with the past medical history of gastric cancer (gastroesophageal junction included) (including all of the following cases) − Patients who had surgery for gastric cancer (gastroesophageal junction included) − Patients who received adjuvant chemotherapy, or pre-operative chemotherapy and/or radiotherapy and/or immunotherapy for treatment of gastric cancer (gastroesophageal junction included) 4. Patients with the past medical history of other malignancy However, patients with the followings can be included in this study − Adequately treated basal cell or squamous cell carcinoma, in situ cervical carcinoma − Other cancer that exceeded 5 years after completion of chemotherapy and remained disease-free for 5 years or more 5. Patients with a distant metastasis (M1) including a distant lymph node (retro-pancreatic, para-aortic, peri-portal, retro-peritoneal, mesenteric lymph nodes) of gastric or gastroesophageal junction adenocarcinoma

6. Patients who cannot undergo curative resection at the discretion of a surgeon
- Patients with T4b with completely resectable involvement of the surrounding organ with no distant metastasis can be enrolled

7. Patients who participated in another study or administered another investigational product within 30 days prior to signing the Informed Consent Form
8. Patients who had any of the followings within 6 months prior to signing the Informed Consent Form: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass surgery, NYHA Class III or IV congestive heart failure, stroke or transient ischemic attack
9. Patients who had deep vein thrombosis within 4 weeks prior to signing the Informed Consent Form
10. Patients with the previous medical history of uncontrolled seizure, CNS or psychological disorder which is so clinically significant that it is impossible to obtain the Informed Consent Form or the severity may interfere with oral administration of medication
11. Patients with uncontrolled active infection or sepsis, previously known acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, previously known active hepatitis B or C
12. Patients with severe acute or chronic disease that may limit the ability to participate in the study or make it difficult to interpret results of the study
13. Patients who have not fully recovered from other procedure
14. Patients who may experience a problem with absorption after oral administration of the investigational product, as follows:
- Patients with intolerability with oral administration, malabsorption, or absorption disorder
- Patients who have not recovered from the lack of physical completeness of the upper gastrointestinal tract
- Ileus
- Chronic inflammatory bowel disease
- Extensive small bowel resection and other diseases that limit drug absorption (example: gastric dumping syndrome, rapid intestinal transit, malabsorption after bowel surgery)

15. In case of female subjects of childbearing potential or male subjects with a female partner of childbearing potential, patients who do not consent to use of generally accepted effective contraception during the investigational product administration period or for at least 6 months after completion of the investigational product administration
16. Breastfeeding or pregnant women. Women of childbearing potential with a positive pregnancy test

- **Investigational product administration**

17. Inadequate bone marrow and organ function prior to administration of the investigational product:
    I. Absolute neutrophil count <1.5 x 10^9/L
    II. Platelet <100 x 10^9/L
    III. Hemoglobin ≤ 9 g/dL
    IV. AST >2.5 x ULN, ALT >2.5 x ULN
    V. ALP >2.5 x ULN
    VI. Total bilirubin >1.5 x ULN
    VII. Serum creatinine >1.5 x ULN

    Creatinine clearance is calculated by using the Cockcroft-Gault formula with 24 hr urine collection; patients with creatinine clearance <60 mL/min will be excluded.

<table>
<tr><td></td><td>18. Peripheral neuropathy with Grade ≥2 (NCI CTCAE v4.03) clinical symptoms
19. Grade ≥2 (NCI CTCAE v4.03) hearing loss
20. Grade ≥2 (NCI CTCAE v4.03) severe tumor bleeding
21. Past medical history of the hypersensitivity reaction to the investigational product (Docetaxel, Oxaliplatin, S-1 (Tegafur, Gimeracil, Oteracil))
22. Patients using immunosuppressants and prohibited concomitant medication</td></tr>
<tr><td>Expected total number of subjects:</td><td>530 subjects</td></tr>
<tr><td>Expected number of sites:</td><td>Approximately 20 sites</td></tr>
<tr><td>Investigational products</td><td>Docetaxel,
Oxaliplatin,
S-1 (Tegafur, Gimeracil,Oteracil)</td></tr>
<tr><td>Formulation:</td><td>Injection (Docetaxel and Oxaliplatin) and orally administered tablet (S-1)</td></tr>
<tr><td>Dosing route:</td><td>Intravenous injection and oral administration</td></tr>
<tr><td>Administration method:</td><td>Neo-adjuvant chemotherapy administration method (DOS):
• Docetaxel 50 mg/m² intravenous injection for at least 1 hr on Day 1 of every 3 weeks
• Oxaliplatin 100 mg/m² intravenous injection for at least 2 hrs on Day 1 of every 3 weeks
• S-1 40 mg/m² oral administration twice daily from Day 1 ~ Day 14 every 3 weeks (total 80 mg/m² per day)

Table 1. Neo-adjuvant chemotherapy S-1 by BSA

<table>
<tr><th>Initial dose</th><th colspan="2">40mg/m²</th></tr>
<tr><th>BSA (m²)</th><th>Calculated dose (mg)</th><th>Actual dose (mg)</th></tr>
<tr><td>≤ 1.11</td><td>≤ 44.4</td><td>40 (20,20)</td></tr>
<tr><td>1.12-1.17</td><td>44.8-46.8</td><td>45 (20,25)</td></tr>
<tr><td>1.18-1.42</td><td>47.2-56.8</td><td>50 (25,25)</td></tr>
<tr><td>1.43-1.57</td><td>57.2-62.8</td><td>60 (20,20,20)</td></tr>
<tr><td>1.58-1.67</td><td>63.2-66.8</td><td>65 (20,20,25)</td></tr>
<tr><td>1.68-1.82</td><td>67.2-72.8</td><td>70 (20,25,25)</td></tr>
<tr><td>1.83-1.92</td><td>73.2-76.8</td><td>75 (25,25,25)</td></tr>
<tr><td>≥ 1.93</td><td>≥ 77.2</td><td>80 (20,20,20,20)</td></tr>
</table>

Total 3 cycles will be administered and 1 cycle consists of 3 weeks (2 weeks administration + 1 week wash-out).

Surgery:
Surgery type is determined according to the location and extent of the primary cancer at the discretion of</td></tr>
</table>

	the investigator and based on the Surgical Manual (Appendix 26.3). Re-staging before surgery will be conducted only in the neo-adjuvant chemotherapy group, and the staging should be performed after completion of total 3 cycles of neo-adjuvant chemotherapy and within 1 week prior to surgery. **Adjuvant chemotherapy:** Subjects who underwent curative resection will receive S-1 treatment for 8 cycles (approximately 1 year) as adjuvant chemotherapy. Adjuvant chemotherapy will start 3 ~ 6 weeks after surgery. For S-1 adjuvant chemotherapy, 1 cycle consists of 6 weeks, with 4 weeks of administration and 2 weeks of wash-out. Table 2. Adjuvant chemotherapy S-1 by BSA

Initial dose	**40mg/m^2**	
BSA (m^2)	Calculated dose (mg)	Actual dose (mg)
≤ 1.24	≤ 49.6	40
1.25 - 1.49	50 – 59.6	50
≥ 1.5	≥ 60	60

Efficacy criteria	**Primary endpoint** **To compare the 3-year Progression-Free Survival (PFS) between two groups.** PFS is defined as the time from randomization to the objective tumor progression assessed according to the RECIST 1.1 Criteria, or recurrence or death. **Secondary endpoints** (1) **Overall survival (OS):** OS is defined as the time from randomization to death for any cause. The survival period is calculated based on the last day that the subject is known to be alive or the data cut-off date, whichever is earlier. (2) **Post-operative pathological stage:** Post-operative pathological stage is determined and the difference between two groups is compared. (3) **R0 resection rate:** All resected tissues will be microscopically examined after surgery, and the difference in the complete resection rate is compared between two groups.
Safety criteria	**Safety data are collected as follows:** • For treatment-emergent adverse events, type (according to the MedDRA), frequency, severity (according to the NCI CTCAE v4.03), seriousness, and relationship are assessed. • Abnormal findings from clinical laboratory tests are assessed according to the NCI CTCAE v4.03. • Other clinical examination (physical examination, blood pressure, BSA, body weight, ECOG PS) will be assessed.

Assessment schedule	**Baseline:** It is necessary to get the written Informed Consent Form signed by a patient prior to any study-related procedure. Within 14 days prior to randomization, inclusion/exclusion criteria check, clinical examination (physical examination, blood pressure, height, body weight, ECOG PS), clinical laboratory tests (hematology and blood chemistry test, coagulation test, renal function test), pregnancy test, 12-lead ECG, medical history and surgical history, concomitant medication/treatment check, demographic data review, chest X-ray, abdominal-pelvic CT for clinical staging of advanced gastric cancer, and other tests to rule out M1 should be conducted. Gastroduodenoscopy and histology findings for confirmation of advanced gastric adenocarcinoma within 3 months prior to randomization should be checked. **Neo-adjuvant chemotherapy: DOS + surgery + S-1 treatment group only** Within 7 days prior to start of each 3-week chemotherapy cycle, clinical examination (physical examination, blood pressure, body weight, ECOG PS) and clinical laboratory tests should be conducted. Radiological tests for tumor assessment (abdominal-pelvic CT and additional test at the discretion of the investigator) are conducted **within 5 days of Cycle 2 initiation and after Cycle 3 completion, before surgery**. **Surgery:** Within 14 days before surgery, clinical examination (physical examination, blood pressure, body weight, ECOG PS), clinical laboratory tests, 12-lead ECG, and chest X-ray should be conducted. Pathological stage and R0 resection should be confirmed after surgery. **Adjuvant chemotherapy:** Within 7 days prior to start of each 6-week chemotherapy cycle, clinical examination (physical examination, blood pressure, body weight, ECOG PS), clinical laboratory tests, and chest X-ray should be conducted. Total 8 cycles of treatment will be implemented for about 1 year. Adverse events should be continuously monitored from the time the subject signs the Informed Consent Form for this study, during the study treatment phase, and until 30 days after the last dose of the investigational product according to the NCI CTCAE v4.03. For details of assessment, see Study flow chart. **Follow-up after the End-of-Treatment (EOT):** Follow-up is conducted every 3 months for the first year after the End-of-Treatment (EOT), and subsequently, every 6 months up to 5 years. Clinical examination (physical examination, blood pressure, ECOG PS) and survival status should be checked. As tumor assessment, physical examination, abdominal-pelvic CT, and gastroduodenoscopy will be conducted; abdominal-pelvic CT will be conducted every 6 months (±2 weeks) and gastroduodenoscopy will be performed every 12 months (±2 weeks) from the date of surgery. In case of suspected disease progression at the discretion of the investigator, tests for tumor assessment can be immediately performed irrespective of the relevant schedule, and clinically necessary tests other than tumor assessment can be conducted. In case of following survival/death status only, follow the survival status with in-person visits or phone calls every 6 months.
Statistical considerations	**Analysis sets:** Intent-to-treat (ITT) Set includes all randomized subjects. Full Analysis Set (FAS) is defined as all randomized subjects who satisfied the inclusion/exclusion criteria and had at least one tumor assessment after the Baseline visit. While the CSC (**Chemotherapy + Surgery + Chemotherapy**) Arm includes subjects who administered at least one dose of the DOS investigational products, the SC (**Surgery + Chemotherapy**) Arm will include subjects who had

surgery.

Per-Protocol (PP) Set includes all randomized subjects who have no major protocol deviation and satisfy the following conditions.

1) For the neo-adjuvant chemotherapy + surgery + adjuvant chemotherapy S-1 (CSC Arm), subjects who completed the entire total 3 cycles of DOS administration as neo-adjuvant chemotherapy, had surgery, and then started adjuvant chemotherapy (S-1) according to this protocol

2) For the surgery + adjuvant chemotherapy (SC Arm), subjects who had surgery and then started adjuvant chemotherapy (S-1) according to this protocol

Note: Subjects who intended to receive postoperative S-1 adjuvant chemotherapy but did not start it at the discretion of the investigator based on consideration of the patient's medical condition such as toxicity will be included in the PP Set. Serious protocol deviations will be specified in the Statistical Analysis Plan (SAP).

Main analysis will be conducted in the FAS and all efficacy analyses will be also conducted using the ITT Set and the PP Set to confirm robustness of this study.

Safety Analysis Set includes subjects who administered at least one dose of the investigational product. Medication compliance/administration and all clinical safety data will be summarized using the Safety analysis set. All analyses using this population will be based on the actually administered drug.

Efficacy analysis:
The primary endpoint, 3-year Progression-Free Survival is compared between two treatment groups using a log rank test stratified by stratification factors (site, TNM stage (T2/N+, T3-4/N+, T4/N-) specified at randomization at the overall 5% significance level. Survival curve is estimated using the Kaplan-Meier estimate. Median and the corresponding 95% confidence interval, and the 3-year Progression-Free Survival will be presented by treatment group.

Safety analysis:
For analysis of safety data, adverse events, hematological toxicity, routine physical examination, and laboratory data will be described and analyzed using the Safety analysis set defined in Section 12.4.2. Safety data will be also summarized by cycle (if applicable). For each safety variable, Baseline will be defined as the last level or assessment measured prior to the first treatment in the study.

Interim analysis and final analysis:
The interim analysis will be conducted upon occurrence of at least 122 PFS events (50% information rate). The efficacy boundaries will use the O'Brien-Fleming method, and the significance level to consider study completion based on the difference in efficacy at interim analysis will be 0.0031. If a statistically significant difference is observed between two groups at interim analysis, the study may be discontinued; otherwise, the study will continue until the final completion.

Interim analysis will be conducted under supervision of the Independent Data Monitoring Committee (IDMC).

The final analysis will be conducted once 244 PFS events occur or median follow-up reaches a minimum of 3 years, and the significance level to demonstrate superiority of the CSC Arm at final analysis is 0.0490.

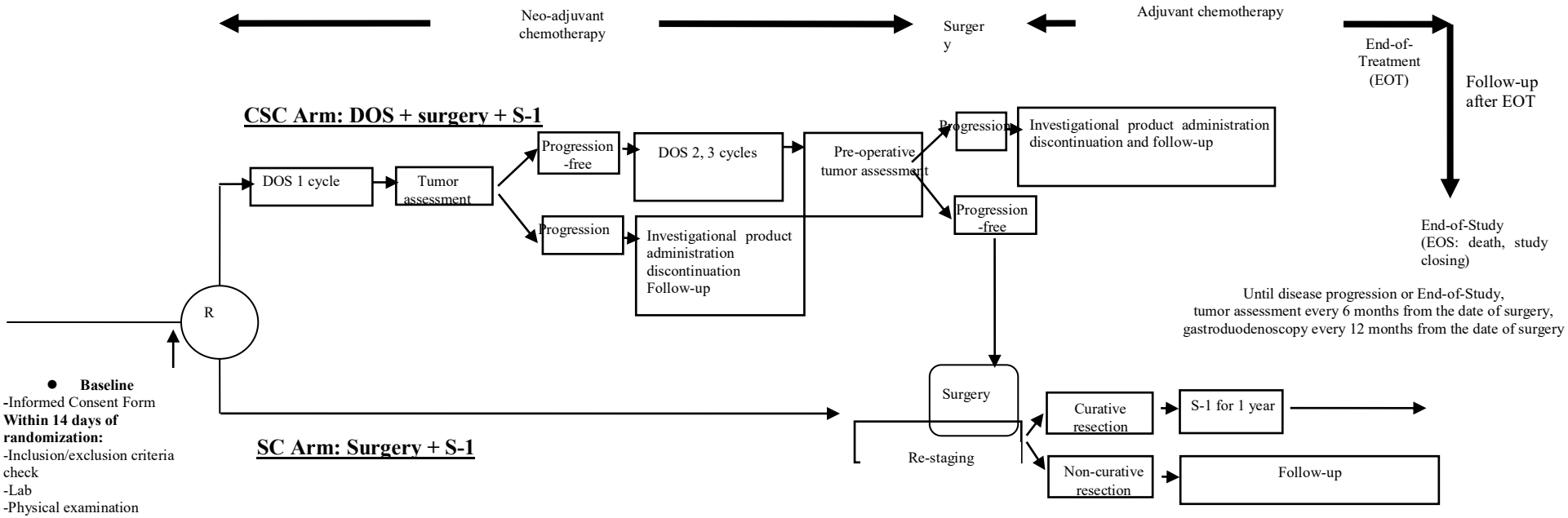
OS will be compared between two groups in the same way as PFS.

For the postoperative pathological stage and the R0 resection rate, frequency and percentage will be

	presented, and comparatively analyzed by using the Cochran-Mantel-Haenszel test stratified by the specified stratification factors (site, stage (T2/N+, T3-4/N+, T4/N-) at randomization. For all statistical tests, a two-sided significance level of 5% will be used. **Sample size determination:** Based on the assumption of the 3-year Progression-Free Survival (PFS) of 70% in the CSC Arm and 60% in the SC Arm (i.e. HR=0.698), a total of 244 events and at least 238 subjects per group are required for comparison of PFS distribution between two groups with the 80% power. Given the dropout rate of 10%, a total of 530 subjects are required. This calculation was carried out by considering one interim analysis, using the group sequential approach with efficacy boundaries suggested by the O'Brien-Fleming alpha spending function. To compare the Progression-Free Survival (PFS) distribution between two groups, a two-sided 5% significance level and up to 7.5 years of follow-up were assumed, including 4.5 years of enrollment period. Therefore, in case superiority is not demonstrated at interim analysis, the database will be closed when the total number of events reaches a minimum of 244 or median follow-up reaches a minimum of 3 years.
Study period	All subjects will be followed after EOT (End-of-Treatment) until death or study closing date, whichever is earlier. In case only survival/death status is followed, confirmation of disease progression, initiation of new anticancer treatment, and subject's consent withdrawal on follow-up are included. The maximum study period and the final follow-up completion date for survival will be completed when a minimum of 244 recurrence or death occurs or the median follow-up reaches a minimum of 3 years. However, the duration of the study for a survival follow-up will be up to 5 years from randomization.

2. FLOW CHART

2.1 Study Design



- **Baseline**

-Informed Consent Form
Within 14 days of randomization:
-Inclusion/exclusion criteria check
-Lab
-Physical examination
-ECG
-Demographics
-Medication/surgical history/concominant medication
-Chest X-ray
-Tumor assessment

Within 3 months of randomization:
-Gastroduodenoscopy
-Histopathology results

CSC = Chemotherapy + Surgery + Chemotherapy
SC = Surgery + Chemotherapy
DOS = Docetaxel, Oxaliplatin, S-1
R = Randomization
EOT = End-of-Treatment
EOS = End-of-Study

2.2 Study flow chart

Visit	Baseline	Randomization	Neo-adjuvant chemotherapy (DOS) (a)			Surgery	Adjuvant chemotherapy (S-1) (c) 8 cycle	EOT Treatment completion and study withdrawal	Follow-up		End-of-Study
			Cycle 1	Cycle 2	Cycle 3						
Visit number	**BAS**	**RAN**	**D01**	**D02**	**D03**	**OPR**	**S01~S08**	**EOT**	**F01~**		**EOS**
Visit window			(d)	**±3 days**	**±3 days**	(b)	**Week 6 ±3 days**	**30 days (+1 week) after the last dose**	**Every 3 months ±1 week for the first year**	**Every 6 months ±2 weeks**	
Informed Consent Form	Prior to the study procedure	**Randomization**									
Inclusion/exclusion criteria	Within 14 days										
Prior medical/surgical history	Within 14 days										
Prior/concomitant medication	Within 14 days		X	X	X	X	X	X			
Demographics	Within 14 days										
Clinical examination (e)	Within 14 days		X	X	X	X	X	X	X	X	
Clinical laboratory tests (f)	*Within 14 days		X	X	X	**X	X	X			
Pregnancy test (if applicable) (g)	Within 14 days										
12-lead ECG	Within 14 days					X					
Adverse event (h)			X	X	X	X	X	X	X	X	
Chest X-ray (i)	Within 14 days					X	X				
Gastroduodenoscopy	Within 3 months						X (every 12 months ± 2 weeks from the date of surgery)				
Tumor assessment (j)	Within 14 days		X			X	X (every 6 months ± 2 weeks from the date of surgery)				
Survival status									X	X (k)	X
Investigational product administration			X	X	X		X				

Footnote for the study flow chart

(a) **Neo-adjuvant chemotherapy** is administered to the CSC Arm only, and consists of the followings. For toxicity, it can be delayed for up to 3 weeks.
Docetaxel 50 mg/m^2 intravenous injection, Day 1 of each cycle
Oxaliplatin 100 mg/m^2 intravenous injection, Day 1 of each cycle
S-1 40 mg/m^2 oral, twice daily, Day 1-14 of each cycle

(b) Surgery is scheduled 1~3 weeks after completion of neo-adjuvant chemotherapy for subjects in the CSC Arm, and within 2 weeks after randomization for subjects in the SC Arm.

(c) **Adjuvant chemotherapy** starts within 3~6 weeks after surgery; S-1 40 mg/m^2 is orally administered twice daily, Day 1~28 of each cycle. For toxicity, each cycle can be delayed for up to 3 weeks. The actual dose follows the dose per BSA in the dose table in 9.2.2.3.

(d) **Within 7 days of randomization,** neo-adjuvant chemotherapy Cycle 1 is initiated.

(e) **Clinical examination:** Physical examination, blood pressure, height (at Baseline only), body weight (including body surface area calculation), ECOG PS

(f) **Clinical laboratory tests:** To be conducted prior to initiation of treatment in each cycle
Hematology: Hemoglobin, WBC, ANC, Platelet count.
Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Creatinine clearance, Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose
* Baseline test addition: Hematocrit, RBC, PMN, LYM, PT (INR), aPTT (sec),
** Pre-operative test addition: Hematocrit, RBC, PMN, LYM, PT (INR), aPTT (sec)

(g) **Pregnancy test:** Menopause is defined as maintenance of the menopausal condition for 1 year since the last menstruation.

(h) **Adverse events:** Safety observation is recorded from the patient's signature of the Informed Consent Form until 30 days (+1 week) after the last dose of the investigational product. During follow-up, all adverse events that occurred previously and are ongoing, and newly occurring adverse events related with the investigational product or determined by the investigator as having a reasonable possibility of being caused by the investigational product are recorded, and of these, serious adverse events are all reported. Serious adverse events ongoing at the time of completion of the investigational product administration will be followed during the follow-up period until resolved or stabilized irrespective of the relationship with the investigational product (see Section 10.4).

(i) **Chest X-ray:** During pre-operative and adjuvant chemotherapy, chest X-ray results within 14 days can be used, if available.

(j) **Tumor assessment:** Tumor assessment will be conducted with (1) physical examination, (2) abdominal-pelvic CT scan, and (3) gastroduodenoscopy. In case of suspected M1, other protocol-specified test can be conducted. Abdominal-pelvic CT scan will be conducted within 14 days prior to randomization, and subsequently, after neo-adjuvant chemotherapy Cycle 1 and before start of Cycle 2, after Cycle 3 before surgery, and subsequently, during the adjuvant chemotherapy period and follow-up, every 6 months (±2 weeks) from the date of surgery until progressive disease, upon development of suspected progressive disease, and at the follow-up completion visit. At each assessment, the same method will be used for follow-up. For the SC Arm, the same schedule will be implemented as the CSC Arm after surgery.

(k) **Survival status:** In case of following only survival/death status, the survival status is followed with phone calls or in-person visits.

* Visit window is based on calendar days

3. ABBREVIATIONS

5-FU	5-fluorouracil
5-HT3	5-hydroxytriptamine
AE	Adverse event
AESI	Adverse event of special interest
AGC	Advanced gastric cancer
ALT	Alanine aminotransferase
ALP	Alkaline phosphatise
AST	Aspartate aminotransferase
AUC	Area under the curve
CDHP	5-chloro-2, 4-dihydroxypyridine (gimestat)
CRF	Case Report Form
CSC	Chemotherapy-Surgery-Chemotherapy
CSF	Colony stimulating factor
CT	Computed tomography
DOS	Docetaxel, oxaliplatin and S-1
DPD	Dihydropyrimidine dehydrogenase
DRF	Discrepancy Resolution Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EUS	Endoscopic ultrasound
FAS	Full Analysis Set
FDA	Food and Drug Administration
FT	Tegafur
GI	Gastrointestinal
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
ITT	Intent-to-treat
LYM	Lymphocyte
NCI CTC	National Cancer Institute Common Terminology Criteria
ORR	Objective response rate
OS	Overall survival
Oxo	Oteracil potassium
PFS	Progression-Free Survival
PMN	Poly-Morgho-Nuclear Leukocytes. Human Neutrophil
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Surgery-Chemotherapy
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal

4. INTRODUCTION AND THEORETICAL BACKGROUND

Pre-operative anticancer adjuvant therapy and adjuvant chemotherapy for treatment of gastric cancer

Gastric cancer remains the second leading cause of cancer deaths globally, with more than 600,000 deaths caused by gastric cancer every year[1-3]. Surgery is a potentially curative treatment option in locally advanced gastric cancer (AGC) with no distant metastasis, and achievement of R0 resection (potentially curative resection in the absence of cancer cells at the margin) is necessary. However, prognosis is still poor for patients with locally advanced gastric cancer even after potentially curative resection, and the risk is high for recurrence at a local or distant site.[4]

Globally, almost 60% of patients who had R0 resection experience recurrence, and according to several large-scale multinational studies, overall 5-year survival for resectable gastric cancer patients ranged 10%~71.4%[5-7, 14], varying greatly in reported survival depending on the study method. While results from the meta analysis consistently suggest small but clear benefits of adjuvant chemotherapy in AGC patients[8-13], such treatment effects in AGC still remain controversial. Nevertheless, well-designed, large-scale recent studies provided reliable data on the effects of adjuvant treatment in AGC.

Three pivotal studies that investigated adjuvant treatment in AGC are the US Intergroup study (INT-0116)[14] of the postoperative chemoradiotherapy, MAGIC study[15] of pre-operative/immediate postoperative chemotherapy, and a study in Japan[16] that examined adjuvant chemotherapy using S-1 (ACTS-GC).

The first study, i.e. the US Intergroup study (INT-0116) investigated the role of postoperative chemoradiotherapy, and reported significantly improved OS and RFS in patients in the chemoradiotherapy group compared to observation-only patients[14]. In the INT-0116 study, the 5-year survival in the chemoradiotherapy group was 42%, which was not superior to 45~47% observed after the D1/D2 procedure only in a study in the Netherlands, and significantly inferior to 71.4%, survival achieved after the D2/D3 surgery only in the JCOG 9501 study[17]. Inferior results from the INT-0116 study were attributable to inappropriate surgery. Most patients were eligible for D0 (54%) or D1 (36%) surgery, and only 10% underwent the D2 procedure as originally planned. Therefore, while chemoradiotherapy is used as standard adjuvant treatment after curative resection for gastric cancer in the US, a number of oncologists in East Asia where the D2 procedure is a standard and frequently performed procedure, raise questions on the role of appropriate additional D2 postoperative chemoradiotherapy even though it may benefit patients who had inappropriate surgery (D0 or D1).

The second one, the UK MAGIC study investigated the effect of pre-operative/immediately postoperative chemotherapy in operable gastroesophageal cancer patients. This study has clearly demonstrated the effect of pre-operative/immediate postoperative chemotherapy compared to surgery alone. Pre-operative/immediate postoperative chemotherapy group showed significantly improve results for 5-year OS and 5-year PFS compared to the surgery alone (5-year OS: 36% *vs* 23%, 5-year PFS 32% *vs* 15%).[15] Based on such findings, pre-operative/immediate postoperative chemotherapy using chemotherapy became standard adjuvant treatment for operable advanced gastric cancer in the UK and several Western countries. However, this study faced similar criticism as that of the US Intergroup study. In other words, the 5-year survival of

the pre-operative/intra-operative/immediate postoperative chemotherapy group was only 36%. Such poor results were also attributable to the low percentage (38%) of patients who had the appropriate D2 procedure. Another criticism is feasibility of the proposed treatment. Overall, only 42% of patients completed 3 cycles of planned pre-operative/immediate postoperative chemotherapy, reflecting low tolerability of the platinum-containing triplet chemotherapy after gastric resection. The optimal timing for adjuvant chemotherapy (i.e. pre-operative, postoperative, or both pre- and postoperative) has not been established yet. Furthermore, in case of using pre-operative/immediate adjuvant chemotherapy, there is a risk that treatment may be excessive for a very early stage in operable gastric cancer patients. This is due to the incomplete accuracy of determination of the pre-operative clinical stage. In fact, approximately 13.5% of subjects in the MAGIC study (hereafter 'subjects') are estimated to have TNM Stage 1 gastric cancer. Six cycles of chemotherapy can obviously represent excessive treatment in such Stage 1 gastric cancer patients.

The third study, the ACTS-GC study in Japan included 1,059 Stage 2 and 3 (Japan classification) gastric cancer patients who received R0- resection after the D2 procedure, and assessed the effect of 1-year administration of adjuvant chemotherapy S-1 compared to the observation group[16]. This study was closed after the first interim analysis in 2006.06, since analysis results clearly showed significantly higher 3-year OS in the study group compared to the observation group (HR, 0.68; 95% CI, 0.52–0.87; p=0.0024). After results from this study were presented, adjuvant chemotherapy using S-1 became standard treatment after curative resection for gastric cancer in Japan and other Asian countries where the D2 procedure is performed.

In summary, while the promising role of the adjuvant therapy in AGC was demonstrated, selected methods differed by region. While studies showed that chemoradiotherapy or pre-operative/immediate adjuvant chemotherapy is recommended in the US and Europe where a limited procedure is the standard, it may be appropriate to use adjuvant chemotherapy only in Asian countries including Japan where more extensive procedures are frequently used.

Based on these studies, it is required to investigate how to further improve the treatment effect of the standard adjuvant chemotherapy S-1 in Asian region in the future.

First, the addition of radiotherapy such as the US Intergroup study can be considered; as mentioned previously, nevertheless, most oncologists are skeptical about adding another local therapy to effective local treatment such as the D2 procedure. However, a phase 3 study (ARTIST) has been conducted in one site in Korea for several years that compared adjuvant chemotherapy (XP) after the D2 procedure *vs* adjuvant chemotherapy (XP) + radiotherapy, and if the results are presented, it may be possible to reach a conclusion on whether additional radiotherapy is effective even after the D2 procedure.

Next, intensity of adjuvant chemotherapy may be raised by adding platinum to S-1. Intensified adjuvant chemotherapy with combination of Fluoropyrimidine and platinum was compared with the observation only group in several previous phase 3 studies in Western countries; not only sample sizes were small but also no improved treatment effects were detected compared to the observation group. Such failure is attributable to intolerability of therapy including postoperative Cisplatin by most patients.

The AMC 0201 study compared MMC administration followed by 3 months of Doxifluridine (Mf arm) with a group that added 6 doses of Cisplatin every 4 weeks and extended

administration of Doxifluridine for 12 months (MFP arm) in 855 Stage 2–4 (M0) gastric cancer patients who had R0-resection[18]. However, 3-year RFS and OS did not differ between these two groups. In other words, it was not effective to intensify adjuvant chemotherapy by simply adding Cisplatin or extending the treatment period.

In addition, the US CALGB 80101 study investigated whether the intensified chemotherapy can improve the treatment effect by substituting chemotherapy with ECF therapy that added Epirubicin and Cisplatin to 5-FU in combination chemoradiotherapy using postoperative 5-FU Leucovorin (CCRT) for which effects were demonstrated in the previous Intergroup study. However, results presented at the 2011 ASCO suggested that this strategy was not effective at all.[19]

In a recent CLASSIC study in Asian countries including Korea, 1035 patients after the D2 procedure were compared by being divided into the observation group and 8 cycles of XELOX therapy (Capecitabine + Oxaliplatin); from the interim analysis results presented at the 2011 ASCO, while effects were not demonstrated in terms of overall survival, the treatment group showed significant effects in the primary endpoint, 3-year disease free survival, so that XELOX was recognized as another effective adjuvant chemotherapy.[20]

However, from comparison of results between this study and the ACTS-GC study, almost the same treatment effect was shown, with a 13~14% improvement of the 3-year disease free survival in the treatment group (ACTS-GC 72%, CLASSIC 74%) compared to that of the control group (ACTS-GC 59.6%, CLASSIC 60%) in the patient population that had the almost same stage distribution (Stage 2 approximately 50%, Stage 3A approximately 30~36%, Stage 3B 10~14%). Meanwhile, 170 of 517 patients in the S-1 treatment group of the ACTS-GC study discontinued treatment prior to 12 months; 143 of them discontinued due to side effects other than recurrence or consent withdrawal. In the CLASSIC study, 212 of 520 patients in the XELOX group discontinued treatment before the planned treatment period; other than 11 who discontinued due to recurrence, 201 discontinued due to treatment refusal or side effect or consent withdrawal. Such result may suggests inferior treatment compliance of XELOX therapy to S-1 monotherapy as expected.

Unlike the AMC0201 study, the AMC 0101 study randomized 640 patients amenable to curative resection for whom tumor was determined to have involved the gastric serosa during surgery in the operating room, and in the study group (iceMFP arm), intraperitoneal chemotherapy using Cisplatin was conducted, adjuvant chemotherapy was started with MMC injection from the next day of surgery, 6 doses of Cisplatin was administered at 4-week intervals and Doxifluridine was administered for 12 months. In the control group, same as the AMC0201 study, MMC was injected 3 weeks after the surgery, followed by 3 months of Doxifluridine administration.[21] In this AMC0101 study, in order to intensify adjuvant chemotherapy, Cisplatin was added, and 2 more strategies were used compared to the AMC0201 study that used extended administration of Doxifluridine for 12 months: the first was the addition of intraperitoneal chemotherapy in order to lower the risk of peritoneal recurrence, and the second was early initiation of adjuvant chemotherapy, i.e. from the next day of surgery. As a result, unlike results from the AMC 0201 study, the study group in the AMC 0101 study achieved a significantly improved treatment effect (RFS and OS) compared to the control group. The 3-year RFS was iceMFP group 60.2%, Mf group 50.0%, and HR was 0.695 (95% CI, 0.536–0.902; p=0,006). The 3-year OS was iceMFP group 71.2%, Mf group 59.6%, and HR was 0.710 (95% CI, 0.531–0.950; p=0.02). Along with negative findings from the AMC 0201 study, positive results of the AMC 0101 study suggest that rather than simply adding Cisplatin or extending the treatment period, early

initiation of adjuvant chemotherapy or addition of intraperitoneal chemotherapy represents an effective strategy to improve the effect of adjuvant chemotherapy.
Therefore, if early initiation of adjuvant chemotherapy is effective, it would be reasonable to consider neo-adjuvant chemotherapy as the adjuvant chemotherapy that starts earliest.

Docetaxel

Mechanism of action and pharmacokinetics

The key mechanism of Docetaxel was increasing polymerization of tubulin into the stable microtubule while also reducing depolymerization, without changing the number of protofilaments in the microtubule during such actions. Pharmacokinetic characteristics are as follows: (1) Pharmacokinetic profile was established in a phase 1 study that treated cancer patients at 20~115 mg/m^2, and (2) the response rate profile of Docetaxel is not dose-dependent. (3) Plasma concentrations followed the third order reaction rate, (4) Docetaxel's half-life in blood was $t_{½}\alpha$ = 4 min, $t_{½}\beta$ = 36 min, $t_{½}$ = 11.1 hr, and (5) Docetaxel's pharmacokinetics were not affected by age or sex of cancer patients.

Docetaxel in treatment of gastric cancer

Docetaxel has been demonstrated to be effective in AGC treatment. Activity of Docetaxel in this disease was known in the early 1990s, and Docetaxel monotherapy showed a 18-24% response rate as the first-line treatment, and similar results were also shown as the second-line treatment.[22]

Investigation of combination therapy focused on the Docetaxel and Cisplatin and/or 5-FU combination therapy. The reasons were as follows: Pharmacological mechanisms did not overlap between drugs, there was no cross-resistance, and there were no overlapping side effects. In the study by Roth and Ajani,[22] 48 gastric cancer patients were treated with Docetaxel (85 mg/m^2) and Cisplatin (75 mg/m^2) combination therapy. The response rate was 56% (including 2 events of a complete response), median time to progression was 6.6 months, and median OS was 9 months. However, 9 patients developed substantial hematological toxicities and febrile neutropenia. Ridwelski et al.[23] conducted a phase 2 study of low dose Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 treatment in 39 patients. While the 37.2% response rate was slightly lower than what was reported in the Roth et al. study, the time to progression (6.1 months) and OS (10.4 months) were comparable. Hematological toxicity was significantly lower, and there was no febrile neutropenia. Nevertheless, 2 patients developed irreversible ear toxicity.

In a recent phase 3 study, addition of Docetaxel to Cisplatin and 5-FU resulted in a significant improvement of the time to cancer progression (5.6 *vs* 3.7 months, P <0.001) and overall survival (Docetaxel, Cisplatin, 5-FU group 1-year survival 40% *vs* Cisplatin, 5-FU group 32%) compared to the Cisplatin and 5-FU only group.[24] In 2006, based on results of this study, the Food and Drug Administration (FDA) approved combination therapy of Docetaxel with Cisplatin and 5-FU as treatment of AGC including gastroesophageal junction cancer. Such improved efficacy should be balanced with increased toxicity; for Docetaxel, Cisplatin, 5-FU triplet combination therapy, approximately 20% of patients experienced Grade 3 non-hematological toxicities including lethargy, stomatitis, and diarrhea. The risk of infection was also high. Grade 3/4 neutropenia occurred in approximately 80% of patients and about 30% of

patients had neutropenic fever and infection. Therefore, despite improved efficacy, Docetaxel, Cisplatin, and 5-FU therapy was considered by many physicians as too toxic to be used in clinical settings.

Other studies were also conducted that investigated methods other than the addition of Docetaxel to 5-FU and Cisplatin combination. A phase **1/2 study of Docetaxel, Capecitabine, Cisplatin triplet combination therapy was conducted in Korean advanced gastric patients.[25] Recommended doses of Docetaxel (60 mg/m^2 on Day 1), Capecitabine (1,875 mg/m^2/day on Day 1-14), and Cisplatin (60 mg/m^2 on Day 1) were used for the 3-week cycle therapy of Docetaxel, Capecitabine, and Cisplatin. Docetaxel, Capecitabine, and Cisplatin combination therapy was highly active and tolerable as the first-line chemotherapy of AGC. Of 40 patients treated in the** phase **2 part of this study, 4 patients showed a complete response, 23 reported a partial response, and the response rate was 68%. Median time to progression was 7.8 months and median OS was 16.9 months. Of subjects showing favorable responses, 10 had received resection of the primary gastric cancer, and achieved 4 pathological complete responses. What is more promising is the improved safety profile: 40% of patients had Grade 3/4 neutropenia and 10% experienced neutropenic fever. This represented much greater tolerability that what was reported for Docetaxel, Cisplatin, and 5-FU therapy[24]. Therefore, by reducing the Docetaxel and Cisplatin dose and replacing 5-FU with oral Fluoropyrimidine and Capecitabine, toxicities were remarkably reduced while maintaining efficacy of triplet combination therapy in advanced gastric cancer patients.**

Recently, Sym et al. reported a phase 2 study of neoadjuvant chemotherapy using the same Docetaxel, Capecitabine, and Cisplatin therapy in locally advanced unresectable or intraperitoneal metastatic gastric cancer patients.[26] R0 resection rate in this patient population was 63%, and the toxicity profile was favorable. Only 4% of patients experienced febrile neutropenia.

Oxaliplatin

Mechanism of action and pharmacokinetics

Oxaliplatin is a diaminocyclohexane platinum derivative with a similar molecular mechanism of action with Cisplatin: these two compounds form a DNA conjugate or DNA cross link between the Guanine base pairs (GG or GNG), or between Guanine and Adenine base pairs adjacent within the DNA single strand. Compared to Cisplatin, Oxaliplatin has a slightly wider spectrum of action, possibly due to its ability to form a conjugate in a different way, especially, coping with some mechanisms of platinum resistance based on mismatch repair deficiency and replication bypass.

Pharmacokinetic characteristics are as follows: (1) After infusion for 2 hr, 15% of platinum remain in circulation, and the remaining 85% is promptly distributed into the tissue or eliminated via urine. (2) Half-life is determined by the natural regeneration period of RBC and serum albumin due to the irreversible binding with RBC and plasma binding in such distribution compartment between cells. (3) Accumulation of platinum was not observed in the ultrafiltrated plasma after administration of 85 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks. (4) Platinum is usually eliminated via the kidneys. Approximately 54% of the total dose was

excreted via urine on Day 5, and less than 3% was eliminated via feces. (5) In case of limited renal function, clearance may be clearly lowered from 17.6 ± 2.18 l/hr to 9.95 ± 1.91 l/hr, and the volume of distribution may greatly decrease from 330 ± 40.9 L to 241 ± 36.1 L. (6) The effect of seriously limited renal function on the plasma elimination rate has not been investigated.

Oxaliplatin in treatment of gastric cancer

Oxaliplatin is an anticancer agent approved for adjuvant chemotherapy **in advanced colorectal cancer and colon cancer. In 5-FU-resistant tumor patients, Oxaliplatin monotherapy achieved a 10% response rate.[27,28] Oxaliplatin is also actively investigated in gastroesophageal cancer treatment. Various therapies were investigated in** phase **2 studies and the response rate for all of them ranged 40~67%, and median survival was 8~15 months.[28-36]**

Therapeutic effects of Oxaliplatin in gastric cancer treatment was demonstrated in two phase 3 studies.

One of them was a study that compared Fluorouracil, Leucovorin, and Oxaliplatin combination therapy with 5-FU infusion + Cisplatin combination therapy; 220 advanced gastric cancer patients were randomized in this study. Time to progression was comparable between Fluorouracil, Leucovorin, and Oxaliplatin *vs* 5-FU infusion + Cisplatin (5.7 months *vs* 3.8 months, log rank P = 0.081), and the response rate was 34% *vs* 24%, respectively. While Oxaliplatin containing therapy was associated with significantly lower grade nausea, alopecia, fatigue, and renal toxicity, more peripheral neuropathy events were reported as expected. In addition, compared to the 5-FU infusion + Cisplatin group, the Fluorouracil, Leucovorin, and Oxaliplatin group reported a slightly lower adverse event (AE) incidence. This study had an intent-to-treat design and was powered to test superiority of Fluorouracil, Leucovorin, and Oxaliplatin for the time to progression.

As the other study, Cunningham et al. **reported results of a randomized** phase **3 study that compared Fluorouracil and Capecitabine combination *vs* Cisplatin and Oxaliplatin combination in 1002 treatment-naïve advanced gastroesophageal cancer patients.[5] Compared to the standard therapy of Epirubicin, Cisplatin, and Fluorouracil, Epirubicin, Oxaliplatin, and Capecitabine therapy showed significantly better median OS as the first-line treatment of gastric cancer. Strength of such efficacy was associated with reduced** Grade **3/4 neutropenia. Compared to Cisplatin, Oxaliplatin was associated with significantly less** Grade **3 or 4 neutropenia and alopecia, but significantly more** Grade **3 or 4 diarrhea and peripheral neuropathy. Compared to the Cisplatin group, the Oxaliplatin group tended to show a lower creatinine concentration elevation and a significantly lower rate of thromboembolic events. By adding the 3rd generation platinum compound Oxaliplatin and oral Fluoropyrimidine Capecitabine to Epirubicin, increased OS was achieved compared to standard therapy. Such data suggest that Oxaliplatin is as effective as Cisplatin in combination therapy for advanced gastroesophageal cancer subjects.**

S-1

Mechanism of action and pharmacokinetics

S-1 is an orally administered new anticancer agent consisting of Tegafur (FT), 5-chloro-2,

4-dihydroxypyridine (gimestat [CDHP])], and Oteracil potassium (Oxo) at the 1:0.4:1 mole ratio.

Its pharmacokinetic characteristics are as follows: (1) Tegafur is a prodrug of 5-FU. After orally administered, Tegafur remains in blood for a long time, and is gradually converted to 5-FU in the presence of the liver enzyme P-450 in body. (2) After oral administration of Tegafur, the blood concentration of 5-FU is low. It is due to degradation by the liver enzyme dihydropyrimidine dehydrogenase(DPD). Therefore, Tegafur was conjugated with a potent DPD inhibitor (CDHP) to maintain a higher 5-FU blood concentration and potentially enhance the anticancer efficacy. (3) The anticancer effect of 5-FU depends on the drug concentration in blood and tumor tissue. The activity of DPD (enzyme that degrades 5-FU) is inhibited by CDHP, and the efficacy is 180-fold higher than Uracil. This allows maintenance of the 5-FU concentration in blood and tumor for a longer time. CDHP has substantially low toxicity and has no anticancer activity. (4) After orally administered, Oxo is present at a high concentration in the gastrointestinal tract, and selectively inhibits phosphorylation by orotate phosphoribosyltransferase which is the first route. Figure 1 depicts the mechanism.[37] S-1 was developed by combining CDHP and Oxo with Tegafur as an orally administered treatment that can effectively maintain the 5-FU plasma concentration.

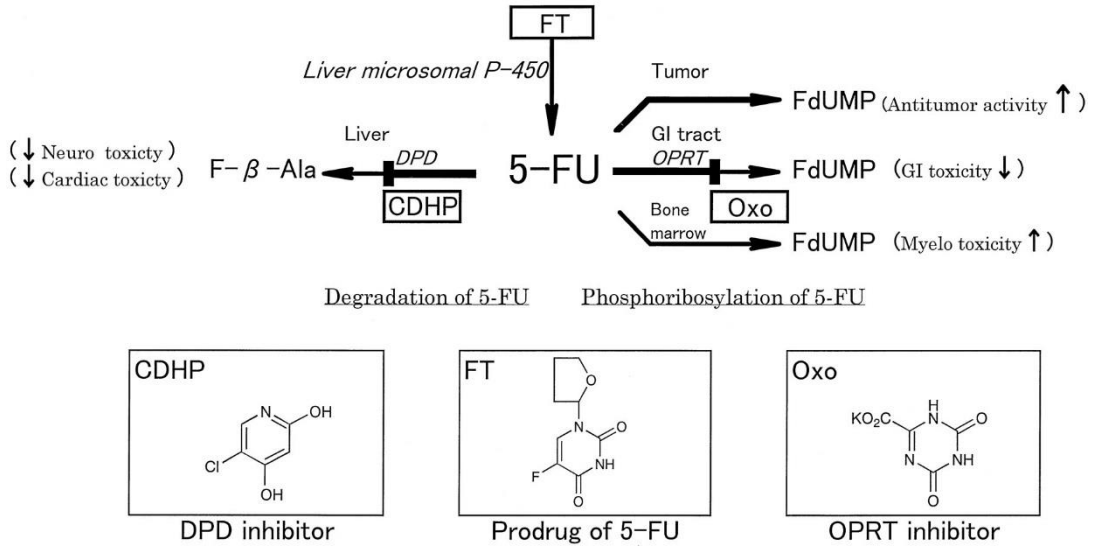


Figure 1. Mechanism of action of S-1: S-1 consists of FT, CDHP, and Oxo to enhance oral efficacy of FT, a prodrug of 5-FU.

Dose determination process for a drug:

After administration of S-1 at the dose with the same toxicity as Uracil+FT in a murine model, the 5-FU concentration was higher in the S-1 treatment group, and pharmacokinetic measures were (1) area under the curve for 1 day for 5-FU in plasma (AUC_{0-24}) (3.5-fold), (2) AUC_{0-24} of 5-FU incorporated into tumor RNA (1.3-fold), and (3) the tumor thymidylate synthase inhibition rate (B20%).

In a phase 1 clinical study, the once daily and twice daily (b.i.d.) dosing schedules were implemented for 28 continuous days. The maximum allowed dose was 150~200 mg/m^2/day for once daily administration or 75~100 mg/m^2/day for twice daily administration[38].

Pharmacokinetics were examined at 25, 50, 100, 150, and 200 mg/body. Results of this study were linear for unchanged S-1 after a single-dose, and the maximum plasma concentration and AUC of the active metabolite 5-FU were dose-dependent. Based on such results, the recommended dose for the phase 2a clinical study was determined as 75 mg/body twice daily for 28 consecutive days, followed by 14 days of wash-out (1 cycle). Phase 2a study was conducted at 50 or 75 mg/body[39], and the recommended dose for the phase 2b study was determined as 80 mg/m^2/day. Hirata et al. investigated pharmacokinetics for S-1 single dose (40mg/m^2) and 8-day continuous administration (80 mg/m^2/day, divided into 2 doses). Mean single dose per body surface area was 35.9 mg/m^2 (31.7-39.7 mg/m^2). Pharmacokinetic parameters for 5-FU in plasma were as follows: (1) maximum plasma concentration, 128.5 ± 41.5 ng/mL, (2) time to the maximum plasma concentration, 3.5 ± 1.7 hr, (3) AUC_{0-14}, 723.9 ± 272.7 ng*h/mL, (4) $t_{1/2}$, 1.9 ± 0.4 hr. (5) No variability or drug accumulation was observed for 28-day continuous therapy. Such results suggest that pharmacokinetics of orally administered S-1 are comparable to that of 5-FU administered with continuous intravenous infusion[10].

S-1 in treatment of gastric cancer

From two phase 2 studies of S-1 monotherapy in Japan, a high objective response rate (ORR; 44~49%) was observed after 4 weeks of 80 mg/m^2/day administration, followed by 2 weeks of wash-out[41,42] Such high objective response rate was not reproduced in the subsequent Korean study[43].

Based on the synergistic effect of S-1 and Cisplatin observed in a pre-clinical study, combination therapy of these two drugs was developed[44-48]. In a study conducted in Japan, 20 patients administered S-1 for 2 weeks, followed by 1 week wash-out + Cisplatin (20 mg/m^2) on Day 1 and Day 8, and achieved high ORR of 78%[46]. In a US study[47,48], 42 patients administered S-1 50 mg/m^2/day for 3 weeks, followed by 1 week wash-out + Cisplatin 75 mg/m^2 on Day 1 of each 4-week cycle, and achieved ORR 48%, median Progression-Free Survival (PFS) 5.3 months, and median OS 10.9 months. Toxicities of this therapy mostly developed in the third week of continuous administration, and in order to reduce such toxicities, a new administration schedule was developed. In other words, S-1 was continuously administered for 2 weeks during a 3-week cycle and the Cisplatin dose was 60 mg/m^2. In a Korean study using this schedule, the recommended dose for S-1 was 90 mg/m^2/day, and lowered to 80 mg/m^2 to improve feasibility. In addition, Cisplatin was administered on Day 1. The resultant ORR was 48% and median PFS was 5.3 months[45].

Recently, results were reported from several phase 3 studies of S-1 in advanced gastric cancer treatment.[8,49-51] Most of all, S-1 had comparable efficacy with intravenously infused 5-FU. Furthermore, addition of Cisplatin to S-1 resulted in a significant improvement of ORR and survival compared to S-1 monotherapy[50]; therefore in Japan, S-1 + Cisplatin combination therapy became standard treatment in advanced gastric cancer, and also in the Asian region including Korea, S-1 and Cisplatin combination therapy became standard therapy.

Docetaxel, Oxaliplatin, and S-1 combination therapy in gastric cancer

In advanced gastric cancer patients, the role of Docetaxel, Oxaliplatin and/or S-1 combination chemotherapy was evaluated.

Two phase **1/2 studies of Docetaxel and S-1 combination therapy were conducted in advanced gastric cancer patients. Yamaguchi et al.[13] reported a 46% response rate and the tolerable toxicity profile (Docetaxel 40 mg/m^2 on Day 1 + S-1 40 mg/m^2 twice daily, Day 1-14 of every 3 weeks) for this combination therapy. The most common** Grade **3/4 toxicity was neutropenia (67% of subjects) which was predictable and manageable. In the other study, 48 advanced gastric cancer patients administered intravenous Docetaxel 40 mg/m^2 on Day 1 and oral S-1 80 mg/m^2/day on Day 1~14 every 3 weeks. This study reported a 93.8% tumor suppression rate and tolerable toxicities[52]. This therapy showed moderate toxicity and promising activity in treatment of advanced gastric cancer.**

A phase **1/2 study of S-1 and fixed dose Oxaliplatin (130 mg/m^2) combination therapy was conducted in Asian patients with advanced gastric cancer[53]. The recommended dose was determined as S-1 100 mg/m^2/day on Day 1-14 and Oxaliplatin 130 mg/m^2 on Day 1 of a 3-week treatment cycle in Korean advanced gastric cancer patients. Pharmacokinetics of S-1 ingredients or its active metabolite did not differ between S-1 monotherapy and combination with Oxaliplatin. For patient treatment, the objective response rate was observed as 61% (95% CI, 53~73%). Stable disease was achieved in 30% of patient and the median follow-up was 12.1 months, median PFS was 6.5 months, and median OS was 12.2 months. Grade 3/4 toxicities included thrombocytopenia (39%), neutropenia (28%), anemia (17%), febrile neutropenia (8%), asthenia (8%), and decreased appetite (8%). Therefore, Oxaliplatin + S-1 combination therapy showed great activity in treatment of advanced gastric cancer, with a favorable toxicity profile in patients.**

Docetaxel + Oxaliplatin combination therapy was investigated for treatment of advanced gastric cancer. Kim et al.[54] reported the efficacy and safety of Docetaxel + Oxaliplatin combination therapy in 42 treatment-naïve metastatic or recurrent measurable gastric cancer patients. Patients administered intravenous Docetaxel 65 mg/m^2 + Oxaliplatin 120 mg/m^2 on Day 1 based on a 3-week cycle. ORR was 45.2% and the median time to progression and median OS was 5.7 months. Richards et al.[55] reported manageable toxicity after administration of Docetaxel 60 mg/m^2, followed by Oxaliplatin 130 mg/m^2 on Day 1 of each 3-week cycle. Results were promising, including the response rate 36%, the clinical benefit rate 40%, and mean survival 8.5 months, similar to that of standard first-line therapy. Furthermore, a phase **2 study by Sym et al.[26] demonstrated a favorable toxicity profile of the Docetaxel, Capecitabine and Cisplatin triplet adjuvant chemotherapy and achievement of the promising R0 resection rate in unresectable locally advanced gastric cancer or abdominal metastatic gastric cancer patients.**

A dose-finding study of Docetaxel, Oxaliplatin, and S-1 (DOS) was conducted in advanced gastric cancer patients. Docetaxel 52.5 mg/m^2 and Oxaliplatin 105 mg/m^2 on Day 1 and S-1 80 mg/m^2 on Day1-14 of each 21-day cycle were reported as the recommended dose of the 21-day cycle DOS therapy in advanced gastric cancer patients[56]. Most patients reported Grade **3/4 neutropenia, and febrile neutropenia occurred at 56%. Most non-**

hematological toxicities were Grade **1/2 decreased appetite, diarrhea, neuropathy, and fatigue, and they were all reversible.**

In a phase **2 study of Docetaxel (50 mg/m^2), Oxaliplatin (100 mg/m^2), and S-1 (80 mg/m^2)** neo-adjuvant chemotherapy **in locally advanced gastric cancer or gastroesophageal cancer conducted by Dr. Kang, 39 events of R0 resection were reported from 41 advanced gastric cancer patients who received** neo-adjuvant chemotherapy **and surgery. Furthermore, 4 patients showed a pathological complete response after surgery. In this study,** Grade **3 neutropenia (24%),** Grade **3 thrombocytopenia (27%), and** Grade **3 febrile neutropenia (10%) were reported as hematological toxicities of DOS. As non-hematological toxicities of DOS, Grade 3 decreased appetite (2%) and diarrhea (2%) were reported, so that a subsequent study could be conducted[57].**

In conclusion, the role of neo-adjuvant chemotherapy in advanced gastric cancer is becoming increasingly important, and investigation of new therapy with a more favorable toxicity profile is crucial for the success of the approach to treatment. Given results of studies so far, the pre-operative Docetaxel, Oxaliplatin, and S-1 triplet chemotherapy and postoperative S-1 alone chemotherapy are expected to present one of optimal treatment methods in advanced gastric cancer patients amenable to curative resection.

5. STUDY OBJECTIVES

5.1 Primary objective

To compare the 3-year Progression-Free Survival (PFS) between two groups in advanced gastric cancer patients amenable to curative resection who are randomized and treated in the pre-operative DOS chemotherapy + surgery + adjuvant chemotherapy S-1 arm (hereafter CSC Arm) and the surgery + adjuvant chemotherapy S-1 arm (hereafter SC Arm).

5.2 Secondary objectives

To assess and compare the followings between two groups:

- Overall survival (OS)
- Post-operative pathological stage
- R0 (complete) resection rate
- Safety assessment (NCI CTCAE v4.03)

6. STUDY DESIGN

6.1 Description of protocol

This is a randomized (1:1, CSC Arm and SC Arm), open-label, multicenter, comparative, phase 3 clinical study in advanced gastric cancer patients amenable to curative resection. For details of the study procedure, see Section 8 Study procedure.

6.2 Study period

Patients who signed the Informed Consent Form and are randomized are considered participating in this study. According to the Study diagram and the Study flow chart (Section 2.1 and 2.2), the CSC Arm starts neo-adjuvant chemotherapy within 7 after randomization, administers the investigational product for a total of 3 cycles, and undergoes surgery within 1~3 weeks, and the SC Arm undergoes surgery within 2 weeks after randomization; both groups will receive adjuvant chemotherapy for 8 cycles (for about 1 year) within 3~6 weeks after surgery, and have the safety assessment on Day 30 after the last dose of the investigational product, and follow-up (site visit every 3 months for the first year and subsequently, every 6 months, and after disease progression, only survival status will be checked with a phone call or in-person visit every 6 months).

During the Baseline period, the relevant procedures (see Section 2 and Section 8) should be performed within specified periods (including Section 7.2 and Section 7.3 Inclusion/exclusion criteria review).

Subjects in the CSC Arm will initiate neo-adjuvant chemotherapy within 7 days after randomization, receive treatment for a total of 3 cycles (1 cycle is 3 weeks, 2 weeks of administration + 1 week wash-out), and undergo surgery within 1~3 weeks after completion of neo-adjuvant chemotherapy. Administration of the investigational product should continue every 3 weeks unless the subject meets the administration discontinuation criteria described in Section 11. In case of unresolved toxicity, the study can be delayed for up to 3 weeks in each cycle. If disease progression is confirmed from pre-operative tumor assessment, the investigational product administration can be discontinued and surgery and other treatment can be considered.

Subjects in the SC Arm will undergo surgery within 2 weeks after randomization.

Both groups will receive S-1 adjuvant chemotherapy (1 cycle is 6 weeks, 4 weeks of administration + 2 weeks of wash-out) for 8 cycles (for about 1 year) within 3~6 weeks after surgery. Administration of the investigational product should continue every 6 weeks unless the subject meets the administration discontinuation criteria described in Section 11, and subjects should be followed for safety for at least 30 days after the last dose of the investigational product. In case of unresolved toxicity, the study can be delayed for up to 3 weeks in each cycle until the dose day in the next cycle, and any investigational product-related adverse event and any serious adverse event of subjects should be followed until resolved/stabilized. Adverse events possibly related with the investigational product recognized by the investigator should be reported to Monitoring Team at any time after discontinuation of the investigational product.

All subjects will be followed after the End-of-Treatment (EOT) until death or study closing date, whichever is earlier.

The study data cutoff date will be the day of occurrence of approximately 244 disease progression or death events or at least 3 years of median follow-up.

6.3 Steering Committee

Steering Committee will be involved in this study and provide scientific and strategic guidance for the study, and will assume the overall responsibility for the study design, conduct, and publication.

In addition, the Steering Committee has the responsibility to assure high quality performance and management of the study.

Steering Committee will approve the study criteria and guidelines before study initiation (e.g., protocol).

Steering Committee will meet periodically to report and discuss the study progress.

6.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) consisting of independent external members not associated with the study conduct or other study Committees has the responsibility to periodically monitor safety of patients exposed to the investigational product and assess efficacy of the study at the interim analysis. DMC procedure will be fully described in the DMC charter and should be approved by DMC members.

7. SUBJECT SCREENING

7.1 Prearranged sample size

Approximately 530 patients (265 per group) will be enrolled and treated in this study. It is planned that approximately 20 sites would enroll these subjects in about 54 months.

7.2 Inclusion criteria

Patients who satisfy all of the following criteria can be randomized in this study:

1. Patients who provide voluntary written consent using the Informed Consent Form before participating in this study
2. Patients with new histologically confirmed primary gastric or gastroesophageal junction adenocarcinoma amenable to curative resection

Patients with TNM Stage T2,3/N (+) or any T4/N stage (according to the AJCC 7th Edition) (lymph node positive: irrespective of the lymph node shape, if the short axis is ≥8 mm, it is defined as lymph node metastasis positive)

7.3 Exclusion criteria

Patients who satisfy any of the following criteria cannot be randomized in this study:

- **Methods**

1. Patients aged less than 20 years or over 76 years old (inclusive)

2. Patients with the Eastern Cooperative Oncology Group (ECOG) Performance Status ≥2
3. Patients with the past medical history of gastric cancer (gastroesophageal junction included) (including all of the following cases)

– Patients who had surgery for gastric cancer (gastroesophageal junction included)
– Patients who received adjuvant chemotherapy, or pre-operative chemotherapy and/or radiotherapy and/or immunotherapy for treatment of gastric cancer (gastroesophageal junction included)

4. Patients with the past medical history of other malignancy

However, patients with the followings can be included in this study.

- Adequately treated basal cell or squamous cell carcinoma, in situ cervical carcinoma
- Other cancer that exceeded 5 years after completion of chemotherapy and remained disease free for 5 years or more

5. Patients with a distant metastasis (M1) including a distant lymph node (retro-pancreatic, para-aortic, peri-portal, retro-peritoneal, mesenteric lymph nodes) of gastric or gastroesophageal junction adenocarcinoma
6. Patients who cannot undergo curative resection at the discretion of a surgeon

- Patients with T4b with completely resectable involvement of the surrounding organ with no distant metastasis can be enrolled

7. Patients who participated in another study or administered another investigational product within 30 days prior to signing the Informed Consent Form
8. Patients who had any of the followings within 6 months prior to signing the Informed Consent Form: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass surgery, NYHA Class III or IV congestive heart failure, stroke or transient ischemic attack
9. Patients who had deep vein thrombosis within 4 weeks prior to signing the Informed Consent Form
10. Patients with the previous medical history of uncontrolled seizure, CNS or psychological disorder which is so clinically significant that it is impossible to obtain the Informed Consent Form or the severity may interfere with oral administration of medication
11. Patients with uncontrolled active infection or sepsis, previously known acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, previously known active hepatitis B or C
12. Patients with severe acute or chronic disease that may limit the ability to participate in the study or make it difficult to interpret results of the study
13. Patients who have not fully recovered from other procedure
14. Patients who may experience a problem with absorption after oral administration of the investigational product, as follows:

- Patients with intolerability with oral administration, malabsorption, or absorption disorder
- Patients who have not recovered from the lack of physical completeness of the upper gastrointestinal tract

- Ileus
- Chronic inflammatory bowel disease
- Extensive small bowel resection and other diseases that limit drug absorption (example: gastric dumping syndrome, rapid intestinal transit, malabsorption after bowel surgery)

15. In case of female subjects of childbearing potential or male subjects with a female partner of childbearing potential, patients who do not consent to use of generally accepted effective contraception during the investigational product administration period or for at least 6 months after completion of the investigational product administration
16. Breastfeeding or pregnant women. Women of childbearing potential with a positive pregnancy test

- **Investigational product administration**

17. Inadequate bone marrow and organ function prior to administration of the investigational product:
    I. Absolute neutrophil count <1.5 x 10^9/L
    II. Platelet <100 x 10^9/L
    III. Hemoglobin ≤9 g/dL
    IV. AST >2.5 x ULN, ALT>2.5 x ULN
    V. ALP >2.5 x ULN
    VI. Total bilirubin >1.5 x ULN
    VII. Serum creatinine >1.5 x ULN
    Creatinine clearance is calculated by using the Cockcroft-Gault formula with 24 hr urine collection; patients with creatinine clearance <60 mL/min will be excluded.
18. Peripheral neuropathy with Grade ≥2 (NCI CTCAE v4.03) clinical symptoms
19. Grade ≥2 (NCI CTCAE v4.03) hearing loss
20. Grade ≥2 (NCI CTCAE v4.03) severe tumor bleeding
21. Past medical history of the hypersensitivity reaction to the investigational product (Docetaxel, Oxaliplatin, S-1 (Tegafur, Gimeracil, Oteracil))
22. Patients using immunosuppressants and prohibited concomitant medication

8 STUDY PROCEDURE

8.1 Baseline

To determine eligibility for participation in this study, potential patients will be examined prior to start of the study.

- **Informed Consent Form** should be necessarily signed by the patient prior to any study-related procedure. However, all Baseline tests can be substituted with results for the relevant test within the allowed window, if available.

The following results should be confirmed within 14 days prior to randomization.

- Inclusion/exclusion criteria check

- Clinical examination: Physical examination, blood pressure, height and body weight for BSA calculation, ECOG PS
- Clinical laboratory safety assessment:
  Hematology: Hemoglobin/Hematocrit, RBC, WBC, PMN, LYM, ANC, Platelet count
  Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Creatinine clearance (using the Cockcroft-Gault calculation method), Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose
  Coagulation test: PT (INR), aPTT (sec)
  For women of childbearing potential, pregnancy test: Urine β-hCG

  24 hr urine test: Creatinine in urine (optionally conducted for Creatinine Clearance calculation)
- 12-lead ECG
- Demographics: Age, sex
- Concomitant medication: For drugs that have been used from previously, record medications that are used as of 14 days prior to randomization.
- Chest X-ray: Record abnormal pulmonary findings.
- Tumor assessment: Abdominal-pelvic CT and the following tests for exclusion of M1 can be used as source data at the discretion of the investigator, even if they were conducted at another site.
  - Brain MRI: In case of symptoms of suspected brain metastasis
  - Chest CT: In case of suspected a pulmonary metastasis from physical examination and chest X-ray
  - Laparoscopy: In case of suspected peritoneal dissemination from abdominal-pelvic CT, confirm with laparoscopy at the discretion of the investigator (mini laparoscopy is also acceptable)

Results of the following tests conducted within 3 months prior to randomization should be confirmed.

- **Gastric adenocarcinoma confirmation result:** Gastroduodenoscopy results and histology results can be used as source data at the discretion of the investigator, if conducted at another site.

Prior medical history, surgical history, and other comorbidities should be confirmed within 6 months prior to obtaining the informed consent.

8.2 Randomization

A subject who consents to participation in this study will complete all Baseline procedures, and based on the results, the investigator will determine eligibility of the relevant subject and then the subject will be randomized. Subject will be randomized 1:1 to the CSC Arm or the SC Arm.

8.2.1 Assignment of subjects to treatment groups

Subjects will be assigned to treatment groups by the IWRS (Interactive Web-Response System) according to the computer-generated randomization list. Subjects who satisfy all inclusion/exclusion criteria will be randomized 1:1 to the CSC Arm or the SC Arm, with the site and TNM stage according to the AJCC 7th Edition (T2/N+, T3-4/N+, T4/N-) as stratification factors. The investigator should record it in the Case Report Form, and it is the investigator's responsibility to ensure that subjects assigned to each group receive the planned treatment for the assigned group.

8.3 Treatment period

8.3.1 Neo-adjuvant chemotherapy

Administration of the neo-adjuvant chemotherapy is initiated within 7 days after randomization. During this period, subject will administer DOS at a 3-week interval (for the detailed administration method, see Section 9.2).

The following tests to be conducted in each cycle should be performed within 7 days prior to start of each cycle.

- Clinical examination before each cycle: ECOG PS, physical examination, blood pressure, body weight
- Concomitant medication
- All adverse events
- Clinical laboratory safety assessment:
  Hematology: Hemoglobin, WBC, ANC, Platelet count
  Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Creatinine clearance (using the Cockcroft-Gault calculation method), Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose.
- Other tests as clinically necessary

* **Tumor assessment**: To follow the target lesion confirmed at Baseline, pre-operative abdominal-pelvic CT will be conducted within 5 days prior to start of Cycle 2 and after completion of Cycle 3; additional tumor assessment can be conducted at any time if disease progression is clinically suspected. Abdominal-pelvic CT at Baseline and after neo-adjuvant chemotherapy will be read by a central reviewer. If tumor progression is demonstrated, the subject will complete administration of the investigational product.
If tumor progression is demonstrated with tumor assessment during the neo-adjuvant chemotherapy period, it will be recorded in the Case Report Form, the investigational product treatment will be discontinued, and then (1) surgery or (2) other anticancer treatment not applicable to contents of this study will be instituted at the discretion of the investigator, among treatments established at the relevant site. In this case, the investigator should inform the patient of tumor progression, and the subject should voluntarily determine continuation or discontinuation of participation in this study.

Nevertheless, discontinuation of the investigational product administration does not mean discontinuation of participation in this study, and the further process will be implemented according to the follow-up plan in the protocol. In this study, discontinuation of study participation only refers to the case that the patient voluntarily withdraws consent on study participation.

8.3.2 Surgery

Subjects in the SC Arm will undergo surgery within 2 weeks after randomization. Subjects in the CSC Arm will complete the entire total 3 cycles of neo-adjuvant chemotherapy (3 weeks per cycle), and then will undergo surgery within 1~3 weeks.

Pre-operative assessment (within 14 days before surgery)
The following tests should be conducted within 14 days before surgery.

- Pre-operative clinical examination: ECOG PS, physical examination, blood pressure, body weight
- Concomitant medication
- All adverse events
- Clinical laboratory safety assessment:
  Hematology: Hemoglobin/Hematocrit, RBC, WBC, PMN, LYM, ANC, Platelet
  Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose.
  Coagulation test: PT (INR), aPTT (sec)
- 12-lead EGG
- Chest X-ray
- Other tests as clinically necessary

Surgery
The goal of the surgery is complete resection (R0). Tumor condition is explained according to the Residual Tumor (R) Classification:

- R0; No residual cancer (negative cross-section)
- R1; Microscopically observed residual cancer (positive cross-section)
- R2; Macroscopically observed residual cancer

While the surgery method would be determined at the discretion of the investigator, it is recommended to be based on the Surgical Manual presented in this study (Appendix 26.3).

Post-operative assessment

- Confirmation of the postoperative stage and the R0 resection rate: TNM pathological stage will be determined according to standardized histopathology and the AJCC 7th Edition.
- In case of postoperative histological finding of R1 or finding of R2 at the operating room, it is considered as the progressive disease, the case will be handled as the End-

of-Treatment (EOT), and then, the patient will receive standard treatment at each site and subsequently followed for survival/death status. However, in case of R1, one resurgery will be allowed for R0 resection, and depending on the resurgery result, the final resection (R status) will be determined.

- Post-operative adverse events: Post-operative adverse event is determined as an event that occurs within 30 days after surgery, and an adverse event that can develop as part of the surgical procedure will be reported only when considered by the investigator as an adverse event (for an intraoperative or postoperative adverse event, see Appendix 26.3 Surgical Manual presented in this study.)

8.3.3 Adjuvant chemotherapy; S-1

As the adjuvant chemotherapy, S-1 will be administered from 3-6 weeks by which the patient would have recovered from surgery, and total 8 cycles (for about 1 year) will be implemented with 6 weeks per cycle (4 weeks of S-1 administration, followed by 2 weeks of wash-out). During this period, subjects will visit the site every 6 weeks and get prescription of the investigational product (for the detailed administration method, see Section 9.2.).

In the SC Arm, if the TNM stage is confirmed by postoperative histology as one of T1/N0, T1/N1, or T2N0 according to the AJCC 7th Edition, the investigator should fully discuss and determine with the subject the subsequent treatment by necessarily including the following two items, and the subject can determine whether or not to administer S-1, the postoperative adjuvant anticancer treatment presented in this study.

1) There is no international treatment guideline established for postoperative adjuvant anticancer treatment at the relevant stage.
2) In this case, even if the patient does not receive adjuvant chemotherapy in this study, this does not represent discontinuation of participation in this study, and disease progression and survival follow-up will be performed as specified in the protocol.

Tests conducted during this period are as follows (within 7 days prior to start of each cycle).

- Clinical examination before start of each cycle: ECOG PS, physical examination, blood pressure, body weight
- Concomitant medication
- All adverse events
- Chest X-ray
- Clinical laboratory safety assessment:
  Hematology: Hemoglobin, WBC, ANC, Platelet count
  Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose.
- Tumor assessment: From the date of surgery, tumor assessment will be conducted with abdominal-pelvic CT every 6 months (±2 weeks) and gastroduodenoscopy every 12 months (±2 weeks) (see 2.2 Study flow chart). However, in case of clinically suspected progressive disease, additional evaluation can be performed irrespective of the relevant period
- Other tests as clinically necessary

8.4 End-of-Treatment (EOT)

The following tests should be conducted at least 30 days (+1 week) after the last dose of the investigational product.

- Clinical examination: ECOG PS, physical examination, blood pressure, body weight
- Concomitant medication
- All adverse events
- Clinical laboratory safety assessment:
  Hematology: Hemoglobin, WBC, ANC, Platelet count
  Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose.
- Other tests as clinically necessary

However, for a subject for whom treatment was discontinued prior to the investigational product administration or for whom treatment was discontinued after the investigational product administration due to the progressive disease, the study withdrawal date will be the day when treatment discontinuation was determined. In such cases, the End-of-Treatment (EOT) visit will be conducted, and the visit date, physical examination, and clinical laboratory tests will be implemented at the discretion of the investigator within the extent of checking the subject's safety, depending on the reason for study withdrawal.

8.5 Follow-up period after End-of-Treatment (EOT)

At the follow-up visit, the following assessment will be conducted every 3 months for the first year from the End-of-Treatment, and subsequently, every 6 months until the End-of-Study.

Follow-up every 3 months for the first year and subsequently every 6 months

- Clinical examination: ECOG PS, physical examination, blood pressure
- Adverse events: AEs ongoing at the completion of the investigational product administration and newly occurring AEs during follow-up and related with the investigational product will be recorded until recovery or stabilization of progression or initiation of additional anticancer treatment.
- Other tests as clinically necessary
- In case only survival/death status is checked, in-person visit or phone call follow-up every 6 months

*** Tumor assessment:** To be conducted with physical examination, abdominal-pelvic CT, or gastroduodenoscopy. Physical examination will be conducted every 3 months for the first year of the End-of-Treatment(EOT) and subsequently, every 6 months. The following tests will be scheduled **based on the date of surgery**, irrespective of the follow-up visit date; abdominal-pelvic CT will be conducted every 6 months (± 2 weeks), and gastroduodenoscopy will be conducted every 12 months (± 2 weeks).

Follow-up will continue after the End-of-Treatment until death or study closing date, whichever is earlier. In case only the survival/ death status is followed, if disease progression is confirmed or new anticancer treatment is initiated, withdrawal of the subject's consent on follow-up assessment will be included. The investigator should do one's best to follow the subject's disease progression and survival status.

8.6 End of Study

The following test will be conducted after the follow-up visit, or for subjects who have no further follow-up:

- Survival status check

8.7 Progression of disease

If any of the following criteria is met, it is defined as the progressive disease.

1. Determination as the progressive disease according to the RECIST 1.1
2. Finding of a distant metastasis or reporting of a distant metastasis from pathology, irrespective of intraoperative curative resection
3. Persistence of visually observed cancer cells at the resection margin during surgery that could not be further removed (R2)
4. Persistence of cancer cells at the resection margin from postoperative histology (R1)
5. Finding of a recurrence/distant metastasis during follow-up after R0 complete resection

For a subject determined to have disease progression, administration of the investigational product will be discontinued according to Section 11.1.1 Permanent treatment discontinuation criteria. Cases that are censored although not meeting the disease progression criteria are described in 12.3.2.1 Primary efficacy variable.

8.8 Treatment after the last administration of study drugs

Treatment after discontinuation of the investigational product administration is determined at the discretion of the investigator. If the subject or the investigator wants to discontinue the investigational product administration and change to other treatment without disease progression, the case will be censored, and unless the subject voluntarily withdraws consent on study participation, only survival status will be continuously followed according to the protocol.

9 Administration of the investigational product

9.1 Name and formulation

The investigational products (Docetaxel, Oxaliplatin, and S-1) are packaged, provided, and labeled by the sponsor. Contents in the label will follow domestic regulations and requirements.

Docetaxel
Brand name: Taxotere injection / Taxotere 1-vial injection, 20 mg and 80 mg concentrated solution

Oxaliplatin
Brand name: Eloxatin injection 5 mg/ml (Oxaliplatin), 50 mg and 100 mg ampoule, solid substance

S-1
Brand name: TS-1, 20 mg and 25 mg capsule

9.2 Preparation and administration

For Docetaxel, Oxaliplatin, and S-1, a Mosteller method is used for the BSA formula as follows: (height (cm) is rounded off to an integer and body weight (kg) is rounded to the first decimal point)

$BSA\ (m^2) = ([Height\ (cm) \times Weight\ (kg)]/\ 3600)^{1/2}$

Dose is determined based on the BSA measured at the start of each chemotherapy Cycle 1. However, if the BSA on Day 1 of each treatment cycle differs from the BSA at the initiation of Cycle 1 by ≥ +/-10%, the re-measured BSA will be used.

9.2.1 Docetaxel

One of the following 2 types of Docetaxel will be supplied to sites. One is a package (2 vials) in which the Docetaxel study drug and solvent are separately provided to be diluted and mixed at the site, and the other (1 vial) is a form that is previously diluted and mixed at the factory.

The package consisting of the study drug and solvent should be provided to subjects after the following process. If the vials were refrigerated, leave the required Taxotere® package at room temperature for 5 min. Hold the vial at an angle, take the entire content in the solvent vial with a syringe and a needle using an aseptic technique, and infuse solvent into the Taxotere® vial. Carefully invert this stock solution upside down for at least 45 sec, and necessarily allow to stand at ambient temperature for 5 min. This stock solution contains Docetaxel 10 mg/mL, and should be used immediately for preparation of the infusion fluid.

Several stock solution vials may be required to obtain the appropriate dose (mg) for the subject. This stock solution is infused into a 200 mL injection bag or an injection bottle containing 5% dextrose or 0.9% sodium chloride.

Docetaxel 50mg/m^2 is intravenously administered on Day 1 of each 3-week cycle over ≥1 hr. Rounding off of the calculated dose is determined at the discretion of the investigator at the site.

Pretreatment with Dexamethasone (8 mg) should be concurrently administered to prevent the hypersensitivity reaction and pulmonary/peripheral edema, and reduce and/or delay Docetaxel-related skin toxicity and fluid retention, as follows. Hypersensitivity reaction may develop irrespective of pretreatment.

Treatment of the hypersensitivity reaction to Docetaxel:

When infusing Docetaxel, it is necessarily infused using an instillation (dropping) method for the first 5 min. The administrator should stay beside the patient's bed, and while monitoring the patient's general conditions during the first dose, check the blood pressure and pulse, if possible. In case of an adverse event, emergency resuscitation should be performed immediately.

As the device and treatment for emergency resuscitation, antihistamine, corticosteroid, aminophyline, and epinephrine should be readily available beside the patient.

In case of the hypersensitivity reaction during Docetaxel administration, appropriate emergency treatment should be instituted depending on the symptom. For severity and corresponding treatment of the hypersensitivity reaction, see the following table.

Mild symptom: Local adverse events of pruritus, flushing, and rash	Reduce the infusion rate until the patient's condition is recovered. Stay available next to the patient. If the patient's condition recovers, infuse again at the initially planned rate. For subsequent cycles, infuse at the planned pretreatment and infusion rate.
Moderate symptom: Abnormal symptom not listed in mild or severe symptoms, generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure >80 mm Hg	Discontinue Docetaxel infusion. After intravenous infusion of Dexamethasone 10 mg, administer intravenous infusion of Diphenhydramine 50 mg. Infuse Docetaxel again after recovery of symptoms. For subsequent cycles, after the planned pretreatment and 1 hr before Docetaxel infusion 1 hr, administer intravenous infusion of Dexamethasone 10 mg, intravenous infusion of Diphenhydramine 50 mg, and then infuse Docetaxel.
Severe symptom: Bronchospasm, generalized urticaria, low blood pressure (systolic blood pressure <80mmHg), angioedema (periocular edema)	Discontinue Docetaxel infusion. Administer intravenous infusion of Dexamethasone 10 mg, followed by intravenous infusion of Diphenhydramine 50 mg. Infuse Epinephrine as necessary. After symptom recovery, infuse Docetaxel within 3 hr, or within 72 hr, administer intravenous infusion of Dexamethasone 10mg, intravenous infusion of Diphenhydramine 50 mg, and then infusion Docetaxel 1 hr later. For subsequent cycles, (1) in the evening of the Docetaxel infusion day, administer Dexamethasone 20 mg orally, (2) in the morning of the Docetaxel infusion day, administer Dexamethasone 20 mg orally 1 hr before, (3) in the morning of the Docetaxel infusion day, administer intravenous infusion of

	Diphenhydramine 50 mg 1 hr before, and then infuse Docetaxel. In case of recurrence of the severe symptom, the patient will be excluded from treatment.
Anaphylaxis (NCI CTCAE Grade 4)	Discontinue treatment.

◆ **Note**: Docetaxel is an anticancer agent, and as with other potential toxic chemicals, attention should be paid to handling and preparation of the Docetaxel solution. The investigator should wear gloves, and in case of skin contact with the Docetaxel concentrated stock solution or injection solution, should immediately wash thoroughly with soap and running water.

9.2.2 Oxaliplatin

Oxaliplatin is reconstituted with water for injection or 5% dextrose solution 10 mL (solid substance 50 mg) or 20 mL (solid substance 100 mg) to obtain the concentration of 5 mg/mL. Prepared solution is diluted with the final infusion solution, 5% dextrose fluid 200 mL or 250 mL, or 500 mL.

Oxaliplatin 100 mg/m^2 is administered with intravenous administration over ≥2 hr on Day 1 of every 3-week cycle. Rounding off of the calculated dose is determined at the discretion of the investigator at the site.

In case of extravasation, administration should be immediately discontinued, and after removing a needle, keep the injection site higher than the heart to minimize the extent of tissue damage.

In case of acute throat paresthesias during or after 2 hr instillation of Oxaliplatin during a treatment cycle, extend the next Oxaliplatin injection time to 6 hr. Patient should be carefully monitored for paresthesias during injection, and should be advised in advance to avoid cold stimulus.

◆ Note 1: Neurological toxicity - Neurological toxicity is classified into 2 types, i.e. acute paresthesias within several hours or days after treatment and accumulative sensory nerve damage occurring after several treatment cycles. The incidence of hypoesthesia in extremities and/or paresthesias after Oxaliplatin instillation is 85~90%. It may or may not be accompanied by convulsion, caused by coldness, and symptoms are resolved between two treatment cycles. The acute paresthesias syndrome of the throat has the incidence of 1~2%, occurs within several hours after administration, and is caused by coldness. Symptoms are characterized by subjective dysphagia and dyspnea. However, even though the objective evidence of dyspnea is not observed, and symptoms are resolved promptly without treatment. Oxygen may be supplied, depending on symptoms.
To prevent nausea and vomiting, antiemetics (example: 5-HT 3 antagonists) should be administered with Dexamethasone or Methylprednisolone. Antiemetic administration can be prescribed according to the practice at the relevant site.

◆ Note 2: Oxaliplatin becomes ineffective when it contacts 0.9% sodium chloride or other chlorine-containing infusion solution. Oxaliplatin should be administered alone at all times, and between administration of Oxaliplatin and another drug, the infusion line should be appropriately washed with 5% dextrose solution. Oxaliplatin should be never mixed with alkaline drugs or substances such as the 5-FU stock solution. In addition, an aluminum-containing product should never be used during Oxaliplatin administration. Needle or intravenous injection set with an aluminum part that may contact Oxaliplatin should never be used for preparation or mixing of this drug.

9.2.3 S-1

TS-1 20: FT (Tegafur), 20 mg
CDHP (Gimeracil), 5.8 mg
Oxo (Oteracil), 19.6 mg
TS-1 25: FT (Tegafur), 25 mg
CDHP (Gimeracil), 7.25 mg
Oxo (Oteracil), 24.5 mg

S-1, administered as pre- and adjuvant chemotherapy, is supplied as a soft capsule with 2 doses of 20 mg and 25 mg.

For administration as neo-adjuvant chemotherapy, S-1 40 mg/m^2 is orally administered for 14 continuous days (Day 1~14 of every 21-day cycle) twice daily, within 1 hr after a meal (breakfast and supper), followed by 1 week wash-out. For the S-1 dose calculated by BSA, see Table 1.

Table 1. Neo-adjuvant chemotherapy S-1 administration by BSA

Initial dose	**40 mg/m^2**	
BSA (m^2)	Calculated dose (mg)	Actual dose (mg)
≤1.11	≤ 44.4	40 (20,20)
1.12-1.17	44.8-46.8	45 (20,25)
1.18-1.42	47.2-56.8	50 (25,25)
1.43-1.57	57.2-62.8	60 (20,20,20)
1.58-1.67	63.2-66.8	65 (20,20,25)
1.68-1.82	67.2-72.8	70 (20,25,25)
1.83-1.92	73.2-76.8	75 (25,25,25)
≥ 1.93	≥ 77.2	80 (20,20,20,20)

For administration as adjuvant chemotherapy, a 6-week cycle is implemented consisting of 4 weeks of administration period and 2 weeks of wash-out. They are repeated for 8 cycles (for about 1 year). For the S-1 dose calculated by BSA, see Table 2. Even in case of S-1 dose reduction during neo-adjuvant chemotherapy, for the adjuvant chemotherapy, treatment will start at the protocol-specified dose, instead of the previously reduced dose.

Table 2. Adjuvant chemotherapy S-1 administration by BSA

Initial dose	**40 mg/m^2**	
BSA (m^2)	Calculated dose (mg)	Actual dose (mg)
≤ 1.24	≤ 49.6	40
1.25 - 1.49	50 – 59.6	50
≥ 1.5	≥ 60	60

9.3 Administration schedule

9.3.1 Neo-adjuvant chemotherapy (Neo DOS) - CSC Arm

Subjects randomized to the CSC Arm will receive the following treatment before surgery, within 7 days after randomization.

Day 1		Day 2-14	Day 15-21
Docetaxel 50 mg/m^2, intravenous administration for ≥1 hr	Oxaliplatin 100 mg/m^2, intravenous administration for ≥2 hr	S-1 (40 mg/m^2) Day 1-14, twice daily, oral administration within 1 hr after a meal (breakfast and supper) ⟷	Wash-out

On Day 1, **Docetaxel** 50 mg/m^2 will be intravenously administered for ≥1 hr and then **Oxaliplatin** 100 mg/m^2 will be intravenously administered for ≥2 hr. S-1 40 mg/m^2 will be orally administered twice daily for 14 days from Day 1 to Day 14, within 1 hr after a meal.

As the sequence of drug administration on Day 1 of each cycle, Docetaxel should be necessarily administered first, followed by Oxaliplatin.

◆ **Pretreatment**

Docetaxel

Premedication should be administered including a glucocortisteroid class drug, prior to Docetaxel administration. Premedication can be administered according to the practice at the relevant site, and examples are presented below.

- 8 mg Dexamethasone, oral administration in the evening before treatment (Day 0)
- 8 mg Dexamethasone, intravenous administration 30 min before Docetaxel infusion (Day 1)
- 8 mg Dexamethasone, oral administration in the evening (Day 1)
- 8 mg Dexamethasone, oral administration in the morning and the evening (Day 2)

Oxaliplatin

To prevent nausea and vomiting, antiemetics (e.g.: 5-HT 3 antagonists) should be administered with Dexamethasone or Methylprednisolone. Antiemetic administration can be prescribed according to the practice at the relevant site.

S-1

Pretreatment is not required.

◆ Use of recombinant granulocyte colony stimulating factors (G-CSFs): Use for prophylaxis or simple neutropenia is not recommend; it is recommended to follow the ASCO guideline [58].

◆ **Neo DOS schedule adjustment: Cycle delay and dose interruption**

One cycle consists of 3 weeks, and a total of 3 cycles will be performed. In case of unresolved toxicity, it is acceptable to delay administration for up to 3 weeks, and the new administration cycle cannot be initiated until the investigational product-related toxicity recovers to ≤ Grade 1 or Baseline or is stabilized (except for alopecia, skin hyperpigmentation, and nail ridging). In case of dose delay due to any one of the relevant drugs, the entire treatment cycle should be delayed.

If the neo-adjuvant chemotherapy exceeds 3 weeks per cycle or in case of dose adjustment, the next phase, i.e. surgical treatment can be selected for any reason, at the discretion of the investigator or at the request of the subject.

However, unless the investigational product discontinuation criteria are met, the maximum of 3 cycles should be all administered.

9.3.2 Adjuvant chemotherapy S-1

Adjuvant chemotherapy is administered from 3-6 weeks after surgery. One cycle consists of 6 weeks, and after 4 weeks of S-1 40 mg/m^2 twice daily oral administration, 2 weeks of wash-out will follow, and a total of 8 cycles will be implemented for about 1 year.

◆ **S-1 schedule adjustment: Cycle delay and dose interruption**

The investigational product should be administered for all 8 cycles, unless the administration discontinuation criteria are met.

In case of unresolved investigational product-related toxicity during the adjuvant chemotherapy period, it is acceptable to delay administration for up to 3 weeks, and the new administration cycle cannot be initiated until recovery to ≤ Grade 1 or Baseline or stabilization (except for alopecia, skin hyperpigmentation, and nail ridging). However, for Grade 2 neutropenia during adjuvant chemotherapy, S-1 can be administered after reducing dose as presented in Table 4, at the discretion of the investigator.

In case of dose delay for ≥ 3 weeks for the investigational product-related toxicity, adjuvant chemotherapy should be discontinued, and unless the subject withdraws consent on participation in this study, the study will continue, except for discontinuation of the relevant adjuvant chemotherapy.

9.3.3 Dose adjustment

Dose of the investigational product can be adjusted according to Table 3, based on the worst (nadir) grade of toxicity that occurred at any time during a cycle, and the reduced dose will be applied from the cycle with the event, and subsequent re-escalation will not be allowed.

Table 3. Dose adjustment: Based on the worst toxic response during a cycle

Toxicity	CTC grade	Dose reduction
Neutropenia	Grade 4 (ANC < 0.5/nL) persisting for	1) First occurrence (once) 75% of Docetaxel starting dose

	≥ 7 days	75% of Oxaliplatin starting dose 75% of S-1 starting dose 2) Second occurrence (twice) 50% of Docetaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose 3) Third occurrence (three times) Discontinuation of chemotherapy of this study
Febrile neutropenia	Grade 3 or Grade 4	
Thrombocytopenia	Grade 3 with bleeding (platelet <50 k/nL), or Grade 4	
Diarrhea, mucositis/ stomatitis and hand foot skin reaction	Grade 2	1) Second occurrence (twice) 75% of S-1 starting dose 2) Third occurrence (three times) 50% of S-1 starting dose 3) Fourth occurrence (four times) Discontinuation of chemotherapy of this study
	Grade 3	1) First occurrence (once) 75% of S-1 starting dose 2) Second occurrence (twice) 50% of S-1 starting dose 3)Third occurrence (three times) Discontinuation of chemotherapy of this study
	Grade 4	1) First occurrence (once) 50% of S-1 starting dose 2)Second occurrence (twice) Discontinuation of S-1 chemotherapy (Docetaxel and Oxaliplatin are continued)
Peripheral neuropathy (sensory anomaly, paresthesias)	Grade 2	1) First occurrence (once) 75% of Oxaliplatin starting dose 75% of Docetaxel starting dose 2) Second occurrence (twice) Discontinuation of chemotherapy of this study
	Grade 3/4	1) First occurrence (once) Discontinuation of chemotherapy of this study
Other non-hematological toxicity (other than nausea/vomiting and alopecia)	Grade 2	1) Second occurrence (twice) 75% of Docetaxel starting dose 75% of Oxaliplatin starting dose 75% of S-1 starting dose 2) Third occurrence (three times) 50% of Docetaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose 3) Fourth occurrence (four times) Discontinuation of chemotherapy of this study

	Grade 3	1) First occurrence (once) 75% of Docetaxel starting dose 75% of Oxaliplatin starting dose 75% of S-1 starting dose 2) Second occurrence (twice) 50% of Docetaxel starting dose 50% of Oxaliplatin starting dose 50% of S-1 starting dose 3) Third occurrence (three times) Discontinuation of chemotherapy of this study
	Grade 4	Discontinuation of chemotherapy of this study

For S-1, the reduced dose will be implemented according to the calculation method in Table 4

Table 4. S-1 dose reduction table (one dose)

Initial dose (mg)	75% (mg)	50% (mg)
40	25	20
45	25	20
50	40	25
60	45	25
65	45	25
70	50	25
75	50	40
80	60	40

9.4 Storage

All investigational products should be stored in a secure area.

Docetaxel

Vial should be stored at 2°C~25°C and protected from light. The expiry date is 24 months. While physicochemical test results indicate the stock solution is stable for 8 hr at 2°C~8°C or ambient temperature, the stock solution should be used immediately for preparation of the infusion solution. Infusion solution should be used within 4 hr at ambient temperature. As with any parenteral drug, the Docetaxel stock solution and the infusion solution should be visually inspected prior to use, and should be discarded if there is any precipitate.

Oxaliplatin

Store at 1℃~25℃.

Solution reconstituted from the original vial: Reconstituted solution should be diluted immediately.

Prepared infusion solution: Physicochemical safety was demonstrated to be maintained for 24 hr at 2°C~8°C. From a microbiological perspective, the prepared solution should be used immediately. Nevertheless, this is not applicable to the diluted solution prepared in a controlled environment where aseptic conditions are guaranteed. In case of not using the infusion solution

immediately, it is the responsibility of the user to store it. Storage period should not exceed 24 hr at 2°C~8°C or 6 hr at 20°C~25°C. Oxaliplatin is not sensitive to light.

S-1
The storage period should not exceed 30 months from the manufacturing date at 1°C~30°C.

9.5 Handling and Disposal

Subjects will not discard but return unused blisters remaining after administration.

All unused, partially used, or used investigational products will be checked for accurate accountability, signed by the investigator, and the returned to and destroyed by the sponsor.

The investigator (or clinical trial pharmacist) will complete a detailed administration log of the investigational product, and the investigator's Monitoring Team will co-sign the log.

The investigator will not destroy the investigational product without the sponsor's written approval.

All materials used for dilution and administration can be disposed according to the standard procedure at the relevant site.

9.6 Potential recall

The investigational product can be recalled if there is a potential quality defect. In this case, the investigator has the responsibility to promptly respond to the sponsor's request for the investigational product recall and elimination of the potential risk.

9.7 Combination therapy

Concomitant therapy refers to any type of treatment continued from 14 days before randomization, during the study administration period, and until 30 days after the last dose, or all treatment initiated since the first dose of the investigational product. Such treatment should be carefully and accurately documented in the Case Report Form and source data.

Any concomitant therapy during the study should be minimized to avoid the influence on results of this study. However, concomitant therapy can be implemented if determined by the investigator as not affecting the investigational product and necessary for the patient's welfare. In this case, it should be necessarily recorded in the Case Report Form.

It is recommended to use G-CSF according to the ASCO guideline[58].
Supportive treatment such as analgesics or blood products may be administered as necessary, based on a medical judgment.

The following concomitant therapy is not allowed during administration of the investigational product in this study.

- Other investigational product

- Administration of other types of anticancer agent including conventional therapy or herbal medicine and/or radiotherapy
- Drugs excluded due to possible drug-drug interactions with S-1 during the study drug administration period (Table 5)
- Treatment with warfarin or other coumarin class anticoagulants

Table 5. List of drugs that should be used with care or are prohibited due to potential drug-drug interactions with S-1

	Drug name
Prohibited from concurrent use	**Fluoropyrimidine anti-malignant tumor agent** Fluorouracil Tegafur, Uracil compound Tegafur Doxifluridine Capecitabine (Xeloda) Camofur
	Folinate, Tegafur, Uracil therapy (e.g., UZEL/UFT, etc.) **Levofolinate, Fluorouracil therapy** (e.g., Isovorin/5-FU, etc.)
	Fluoropyrimidine antifungal agent Flucytosine
Attention required for concurrent use	Phenytoin
	Warfarin potassium
	Other anti-malignant tumor agent, radiation, etc.

*TS-1® Capsule 20, 25, Insert Paper dated 25Apr2015; 3[59]

If use of prohibited concomitant medication or treatment is required for a subject, administration of the investigational product should be necessarily discontinued. Such cases should be necessarily reported as a reason for the investigational product discontinuation.

9.8 Investigational product accountability management and compliance

The investigator or the clinical trial pharmacist should check the inventory of all investigational product shipments, and confirm their receipt. The investigational product should be stored in a locked place with limited access, and stored and handled according to the manufacturer's guideline.
Administration of the investigational product is supervised by the investigator or the subinvestigator.
The investigational product dispensing personnel should appropriately document all investigational products. Not only the total number of vials or tablets administered or dispensed to a patient per cycle but also Lot No. should be recorded in the Case Report Form or the Investigational Product Accountability Log.
The person in charge of drug administration to a subject should accurately record the dosing date.

The study monitor should periodically check the quantity of the investigational product retained by the investigator or the clinical trial pharmacist to confirm the accountability records of all used investigational products. Unless there is a method approved by the sponsor, all unused investigational products and all drug containers should be returned to the sponsor. The sponsor should check the final report of the Investigational Product Accountability Log, and confirm retention in the Investigator Study File.

10 SAFETY OF SUBJECTS

10.1 Safety endpoints

In this study, clinical adverse events and data from conducted tests will be graded according to the NCI CTCAE v4.03.

The investigator will collect information on the following variables and record in the Case Report Form.

- Clinical examination including body weight, blood pressure, and ECOG PS
- Clinical laboratory data
  - Total blood count and clinical chemistry
  - Other tests as clinically necessary
- Adverse events and serious adverse events
- Concomitant medication and concomitant therapy
- Reasons for administration discontinuation and the last dose date
- Adverse events that occurred prior to initiation of the investigational product are summarized separately.
- For adverse events that occurred before and during administration, type, frequency, and cycle are assessed according to the Medical Dictionary for Regulatory Activities, and severity, seriousness and relationship, and abnormal levels of the conducted tests are evaluated according to the NCI CTCAE v4.03.

10.2 Safety guidelines

10.2.1 Physical examination

Physical examination includes the tests including but not limited to the followings.

- Blood pressure
- Height (Baseline only), body weight
- ECOG PS

In case of an abnormal finding or worsening from Baseline, it should be documented in the Adverse Event page of the Case Report Form. If such finding meets the serious adverse event criteria, the appropriate reporting procedure should be followed, as described in Section 10.5. Height is recorded at Baseline only. Body weight and ECOG PS are recorded prior to start of each administration cycle, and every 3 months or 6 months during follow-up until death or End-of-Study (EOS), whichever is earlier.

10.2.2 Clinical laboratory variables

Clinical laboratory tests are conducted at the clinical laboratory of each site. Baseline findings should be necessarily performed and recorded to determine eligibility for enrolment, and protocol-specified tests should be conducted and the results should be confirmed and documented prior to starting administration of the investigational product at each cycle.

Normal ranges of tests to be conducted at each site laboratory should be forwarded to the sponsor before starting this study. In case of abnormal and clinically significant findings based on these ranges, the relevant findings should be documented in the relevant section of the Case Report Form, and depending on the findings, a corresponding and appropriate medical action should be taken promptly. Data on test findings will be analyzed according to the Sanofi Test Result Data Processing and Reporting Guideline.

Note: In case it is necessary to make a decision on permanent discontinuation of the investigational product due to abnormal findings of laboratory or ECG parameters, re-measurement should be performed immediately to confirm the relevant test result, before determining permanent discontinuation of the investigational product.

10.3 Monitoring of adverse events

All adverse events will be managed and reported in compliance with applicable regulations, and included in the final result report.

10.4 Definition of adverse event (AE) and serious adverse event (SAE)

An **adverse event** is any untoward and unintended sign (e.g.: abnormal laboratory findings), symptom, or disease occurring in a subject who administered the investigational product and does not necessarily have a causal relationship with the relevant investigational product.

The protocol-specified efficacy endpoint is not considered an adverse event. However, this is not applicable in case the event is considered exceptional in the medical judgment of the investigator due to the course, severity, or other characteristics of the case.

For an intra-operative or postoperative adverse event, if the event can occur as part of the surgical procedure or represents a usual postoperative adverse event, it does not have to be collected, at the discretion of the investigator. However, all other adverse events (see Appendix 26.3 Surgical Manual Table 1) should be necessarily collected and reported according to the seriousness criteria.

A **serious adverse event** is an adverse event or adverse drug reaction at any dose of the investigational product that corresponds to one of the following:

1) Resulting in death or is life-threatening;

2) Requiring in-patient hospitalization or prolongation of existing hospitalization;

3) Resulting in persistent or significant disability of dysfunction;

4) Resulting in congenital anomaly or birth defect;

5) Important medical event: Medical and scientific judgment is required to determine necessity of expedited reporting for other cases such as a medical event that is not immediately life-threatening or does not result in death or hospitalization but may jeopardize the subject or requires intervention to prevent one of other outcomes defined above.

Such cases are usually considered serious.

Note: Examples of such events are allergic bronchospasm, blood dyscrasias, convulsion requiring intensive care at an emergency room or home, or ALT elevation ≥ 10xULN, development of drug dependence or drug abuse that is asymptomatic but not resulting in hospitalization.

Planned hospitalization for the surgery included in the process of this study is not considered a serious adverse event.

10.5 Investigator's responsibility on safety report

10.5.1 Adverse event (AE)

The safety observation period starts from the moment that a subject signs the Informed Consent Form for this study.

Adverse event that occurred while the subject was not being exposed to the investigational product is considered an adverse event only if it persisted until the initial dose of the investigational product or was serious, and should be recorded in the relevant page of the Case Report Form.

All adverse events that occurred from the initial dose of the investigational product to 30 days after the last dose should be recorded in the relevant page of the Case Report Form, irrespective of seriousness or the causal relationship with the investigational product.

For follow-up, see Section 10.5.3.

Adverse event symptoms should be grouped as one syndrome or diagnosis. The investigator should record the adverse event onset date, severity, action taken for the investigational product, treatment, results of additionally conducted tests, outcome, and his/her opinion on the causality with the investigational product in the relevant pages.
Abnormal blood pressure or ECG findings are recorded as an adverse event only when considered medically relevant, such as the followings:

- Symptomatic or requiring correctional treatment;
- Resulting in discontinuation/dose adjustment of the investigational product and/or satisfying the seriousness criteria.

Abnormal clinical laboratory findings are recorded as an adverse event if they result in discontinuation or dose adjustment of the investigational product and/or are considered clinically relevant.

10.5.2 Serious adverse event (SAE)

In case of a serious adverse event(SAE), the investigator should report as follows.

- Send the relevant Case Report Form page signed and dated to the Monitoring Team representative whose name, address, and fax number are specified in the protocol. It should be sent within 24 hr after the date that SAE was recognized.
  - Email: [redacted]
  - Fax: [redacted]
  - Attach a copy of all conducted tests and test dates. Care should be taken to ensure that the subject's identity is protected and the subject identification number is appropriately specified on the copy of all source documents provided to the sponsor (e.g.: de-identify the subject name). For laboratory results, the laboratory normal range should be included.
- Follow-up of all SAEs resulting in death or are life-threatening should be additionally provided within one week.

10.5.3 Follow-up

- The investigator should take all actions as medically appropriate to ensure safety of subjects. In particular, the investigator should follow all adverse events (e.g., clinical signs, test results) until the subject's condition recovers to the NCI CTCAE v4.03 ≤ Grade 1 or Baseline or is stabilized.
- In case of a serious adverse event, the subject should be followed until complete clinical recovery, and recovery of laboratory results to Baseline or stabilization of progression. This means that the subject may be followed until reaching these conditions even after the subject discontinues the study, and further investigations can take place at the request of Monitoring Team.
- For an adverse event occurring at any time after the investigational product discontinuation that is related with the investigational product or possibly caused by the investigational product at the discretion of the investigator, it should be recorded in the case report and reported to Monitoring Team if it is serious.

10.6 Pregnancy

Pregnancy is considered a serious adverse event only if it meets the seriousness criteria. However, even if it not meets the seriousness criteria, administration of the investigational product should be discontinued and the SAE Form and/or DEVP (Drug Exposure Via Parents) Form should be completed and submitted to the Monitoring Team representative whose name, address, and fax number are specified in the protocol (Email. [redacted] / Fax. [redacted]) or the sponsor within 24 hr (expedited reporting). The investigator should discuss with the subject about the pregnancy, necessarily explain risks involved in case the pregnancy is maintained and possible effects on the fetus, and immediately discontinue administration of the

investigational product, and implement follow-up as planned in this study.

This would remain effective until 90 days after completion of the investigational product administration, and the subject's pregnancy status monitoring and follow-up will be necessarily performed during this period.

For a male subject, if the partner gets pregnant, it should be reported to the investigator and the sponsor. Partner of the relevant subject should get medical consultation and be followed as described above.

10.7Overdose

Overdose of the investigational product is defined as administration of 30% or more from the planned dose in case of Docetaxel and Oxaliplatin, and administration of 30% or more from the allowed dose in case of S-1. Accidental or intentional overdose with symptoms of the investigational product should be reported to the sponsor within 24 hr (expedited reporting) regardless of seriousness criteria, and the circumstances of the overdose should be clearly recorded and the reason should be fully documented. In case of an asymptomatic case resulting from overdose, it should be recorded in a separate AE Form.

10.8Responsibility of sponsor

During the study, the sponsor will promptly report all SAEs that are suspected to be related with the investigational product and unexpected (i.e. SUSAR) to applicable relevant authorities, IRB/IEC, and the investigator.

In addition, the sponsor may promptly report all expected SAEs that are suspected to be related with the investigational product to relevant authorities according to applicable local regulations.

In this study, serious adverse events that are determined to be related with the underlying disease are considered unexpected only when they are deemed exceptional in light of the medical context according to the medical decision of the investigator, based on the course or severity or other characteristics of such events.

Adverse events other than the expected adverse events in the Investigator's Brochure and this protocol are considered unexpected adverse events.

The sponsor will report all safety information observed during the conduct of this study in the Clinical Study Report (CSR).

11 TEMPORARY OR PERMANENT DISCONTINUATION OF TREATMENT AND MANAGEMENT OF THE DISCONTINUATION

Administration of the investigational product should continue according to the protocol, if possible. In case of discontinuing administration of the investigational product, it should be

checked if it represents temporary interruption. Permanent administration discontinuation should be carefully considered, and should be necessarily recorded in the Case Report Form. In case of pregnancy, administration of the investigational product should be necessarily discontinued permanently.

11.1 Permanent discontinuation of treatment with study drug

11.1.1 Criteria for permanent discontinuation of treatment

In following cases, the subject's investigational product administration can be discontinued. However, unless the subject withdraws consent on participation in this study, assessment and follow-up planned in this study will be continuously performed:

- The subject may request for discontinuation of the investigational product administration at one's wish, at any time, irrespective of the reason. For a subject who is not capable of voluntary self-expression, administration of the study drug can be discontinued at the request of the subject's legally acceptable representative. "Legally acceptable representative" refers to an individual or legal or other entity authorized to provide consent on the subject's participation in study-related procedure on behalf of the subject according to applicable laws.
- Continuous administration of the investigational product may be harmful to the subject as follows, at the discretion of the investigator:

(Example)
- Disease progression defined in Section 8.7;
- Unacceptable adverse event not controlled with symptomatic treatment, dose delay, or dose adjustment that interferes with subsequent administration of the investigational product;
- Finding of a second primary cancer during the study, so that the study-specific treatment cannot be continued at the discretion of the investigator, and the subject agrees with this decision;

- Intercurrent disease that makes it impossible to administer the investigational product;
- Pregnancy;
- At the special request of the sponsor;
- Subject lost to follow-up.

For all cases, the reason and date of discontinuation should be documented in the Case Report Form and the subject's medical record. The subject should be followed to determine if the relevant reason represents an adverse event, and if it is an adverse event, it should be reported according to the adverse event reporting procedure.

11.1.2 Subject managemnet after permanent discontinuation of treatment

In case of permanent discontinuation of the investigational product administration, it should be recorded in the relevant page of the Case Report Form.

Then, the subject will have an End-of-Treatment (EOT) visit as described in the protocol and enter follow-up subsequently. For a subject who cannot make an in-person visit to the relevant site, the investigator should do one's best to contact the subject to identify the health condition of the relevant subject including survival status. And such attempts should be documented in the patient log (e.g., phone contact attempt date, registered mail receipt, etc.)

If the subject does not withdraw consent on follow-up of this study even after the End-of-Treatment (EOT), follow-up should be implemented as specified in the protocol.

Subject management

A subject may discontinue follow-up of this study according to one's voluntary decision at any time, for any reason. This is also possible at the discretion of the investigator.

- If follow-up is discontinued, this should be necessarily recorded in the relevant page of the protocol.
- .

It will be specified in the Statistical Analysis Plan (SAP) how to consider the primary efficacy endpoint of subjects who are lost to follow-up.

11.3 Results

A subject who discontinued treatment in this study cannot re-enter this study, and the selection and treatment number of such subject should not be reused. However, a subject may be re-selected in the study in exceptional cases that the subject has previously satisfied all inclusion/exclusion criteria at Baseline, was not randomized, and with the discussion of the investigator and the sponsor. Meanwhile, it will be determined whether the subject can be re-tested for Baseline by the discussion of the investigator and the sponsor.

11.4 Definition of source data

Source data include clinical results, observations, and all information included in the original and certified copy of other activities required for reconstruction and assessment of the study. Source data are in source documents. Source documents are original documents, data, and records related to the study (e.g.: hospital note, clinical and administrative chart, laboratory note, memo, subject diary or assessment checklist, pharmacy dispensing record, data recorded in an automated machine, printout or copy certified after accuracy and integrity check, microfiches, film negative, microfilm or magnetic media, X-ray, subject file, pharmacy record, laboratory record, Medical-Technical Department record). Source documents should be maintained to support information from the Case Report Form.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical and analysis plan

Section 12 of this protocol will serve as the basis of the Statistical Analysis Plan for this study. This plan can be revised during the course of the study to reflect protocol amendments, and to address unexpected problems to the study conduct and data that may affect the planned analysis. Such revisions will be reviewed with the study and data kept as blind, and the final plan will be issued prior to the database lock for the interim analysis.

12.2 Sample size

The primary assessment of efficacy is based on the 3-year Progression-Free Survival (PFS). Results from the following previous studies were used as reference for sample size calculation.

Reference	Treatment	3-year Relapse-Free Survival
N ENGL MED 2007;357:1810-20[16)]	Surgery+S-1	72%
ASCO 2008, Gastrointestinal Cancer Symposium, abstracts No.6, [18)]	Surgery+MFP or MF	60%, 50%
J Clin Oncol 26: 2008 (May 20 suppl; abstr LBA4511) [21)]	Surgery+iceMFP or MF	64%, 67%

In a prior study of the postoperative adjuvant anticancer treatment (S-1) in Japanese gastric cancer patients, the 3-year Relapse-Free Survival to recurrence or death was 72%, and in another study of the postoperative adjuvant anticancer treatment, it was approximately 50%~67%. A study of S-1 in Japanese patients showed a much superior 3-year RFS to other study results, and the 3-year RFS of other adjuvant chemotherapy was 60%. Given the difference with subjects of this study since all these studies were conducted by randomly assigning subjects who had tumor resection, the 3-year Progression-Free Survival (PFS) in the SC Arm was assumed as 60%, and the 3-year PFS in the CSC Arm was calculated by assuming a 10% improvement from this level.

Based on the assumption of the 3-year PFS of 70% in the CSC Arm and 60% in the SC Arm (i.e. HR=0.698), a total of 244 events and at least 238 subjects per group are required for comparison of PFS distribution between two groups with the 80% power. Given the dropout rate of 10%, a total of 530 subjects are required. This calculation was carried out by considering one interim analysis, using the group sequential approach with efficacy boundaries suggested by the O'Brien-Fleming alpha spending function. Two-sided 5% significance level and a total of 7.5 years of follow-up were assumed, including 4.5 years of enrollment period. This study is completed upon observation of at least the target number of 244 events at the final analysis or reaching the median follow-up of 3 years.

The software used for sample size calculation is nQuery Advisor 6.0, and the significance level for interim analysis and final analysis was calculated with PASS11.

12.3 Analysis variables

12.3.1 Demographic and baseline characteristics

Standard demographic characteristics and Baseline characteristics (age, sex, body weight, and height included), relevant medical history, cancer diagnosis, prior anticancer agent treatment, pre-existing signs and symptoms will be collected at Baseline.

Baseline efficacy variables and other prognostic variables such as tumor assessment will be also evaluated. At this time, Baseline is defined as the last level or assessment prior to administration of the first dose in the study.

12.3.2 Efficacy variables

12.3.2.1 Primary efficacy variable:

The primary efficacy variable is the 3-year Progression-Free Survival (3-year PFS) defined as the time from randomization to demonstration of progressive disease (PD) or death.
Progressive disease is defined as follows according to the RECIST1.1 Criteria and the time to progression is calculated until the first date of demonstration of progression.

1. In the CSC Arm, PD is determined according to the RECIST 1.1 Criteria during the neo-adjuvant chemotherapy period. In case of PD determination based on the sum of diameters of target lesions, the date of such determination is defined as the last tumor assessment date of target lesions; PD based on apparent progression of a non-target lesion is defined as the relevant tumor assessment date.
2. Irrespective of curative resection, if an intraoperative distant metastasis is observed or a distant metastasis is reported from pathology, it is considered PD, and the date of surgery is defined as the progression demonstration date.
3. If residual cancer cells were visually identified at the resection margin during surgery but could not be completely resected (R2), it is considered PD, and the date of surgery is defined as the progression demonstration date.
4. If residual cancer cells are finally confirmed at the resection margin during postoperative histology (R1), it is considered PD, and the date of surgery is defined as the progression demonstration date.
5. In case of finding a recurrence/distant metastasis or a new lesion during follow-up after R0 complete resection, it is defined as the first tumor assessment date when it was observed.

In case of not being applicable to disease progression, the study will be censored on the following date, whichever is the earliest.

1. For a subject lost to follow-up or disease progression or death is not confirmed until the End-of-Study, the last tumor progression status assessment date
2. In case of finding a second primary cancer other than gastric adenocarcinoma at any time during the study, the last tumor progression status assessment date
3. In case of receiving treatment other than the planned treatment without tumor recurrence, the last tumor progression status assessment date

4. In case of no tumor assessment after randomization, the randomization date

5. Study completion date

12.3.2.2 Secondary efficacy variables

Secondary efficacy variables are overall survival (OS), the postoperative stage, and the R0 resection rate.

OS is defined as the time from randomization to death for any cause. In case it is not clear whether the subject is dead or not, the survival period is calculated based on the last day that the subject is known to be alive or the study completion date, whichever is earlier.

Post-operative stage and the R0 resection rate will be collected.

12.3.3 Safety variables

The following safety data will be collected: adverse events, hematological toxicity, clinical examination (physical examination, blood pressure, BSA, body weight, ECOG PS), special tests (chest X-ray, ECG), and laboratory data

12.3.3.1 Adverse events

Toxicity profile will be determined based on the NCI CTCAE v4.03 and collected at each visit after Baseline.

12.3.3.2 Laboratory safety variables

Hematology and blood chemistry data will be collected at each visit during the treatment period.

- Hematology: Hemoglobin, WBC, ANC, Platelet count
- Blood chemistry: Sodium, Potassium, Calcium, BUN, Creatinine, Total protein, Albumin, SGOT (AST), SGPT (ALT), Total bilirubin, Alkaline phosphatase, Glucose
  * Creatinine clearance (using the Cockcroft-Gault calculation method): Collected at Baseline and during the neo-adjuvant chemotherapy period only

12.3.3.3 Blood pressure

Normal/abnormal result for blood pressure is collected at each visit.

12.3.3.4 Other safety variables

Routine physical examination is evaluated before and after administration.

12.4 Analysis sets

12.4.1 Efficacy set

Intent-to-treat (ITT) Set includes all randomized subjects.

Full Analysis Set (FAS) is defined as all randomized subjects who satisfied the inclusion/exclusion criteria and had at least one tumor assessment after the Baseline visit. While the CSC Arm includes subjects who administered at least one dose of the DOS investigational products, the SC Arm will include subjects who had surgery.

Per-Protocol (PP) Set includes all randomized subjects who have no major protocol deviation and satisfy the following conditions.

1) For the CSC Arm, subjects who completed the entire total 3 cycles of DOS administration as neo-adjuvant chemotherapy and then started adjuvant chemotherapy (S-1) according to this protocol

2) For the SC Arm, subjects who had surgery and then started adjuvant chemotherapy (S-1) according to this protocol

Note: Subjects who intended to receive postoperative S-1 adjuvant chemotherapy but did not start it at the discretion of the investigator based on consideration of the patient's medical condition such as toxicity will be included in the PP Set.

Serious protocol deviations will be specified in the Statistical Analysis Plan (SAP).

Main analysis will be conducted in the FAS and all efficacy analyses will be also conducted using the ITT Set and the PP Set to confirm robustness of this study.

12.4.2 Safety analysis set

Safety analysis set includes subjects who administered at least one dose of the investigational product. Medication compliance/administration and all clinical safety data will be summarized using the Safety analysis set. All analyses using this population will be based on the actually administered drug.

12.4.3 Characteristics of subjects

Subjects who entered Baseline are defined as all subjects who completed the Informed Consent Form and had assessment for enrollment eligibility criteria confirmation during the Baseline period.

Randomized subjects are defined as all subjects who satisfied the enrollment eligibility criteria and randomized to one of two treatment groups.

In addition, reasons for treatment discontinuation and study discontinuation will be presented for randomized subjects by treatment group.

12.5 Statistical method

Categorical data will be summarized in a table for frequency and the corresponding percentage by treatment group. Categorical data will be summarized by treatment group using frequency,

mean, standard deviation, median (if applicable), minimum, and maximum. Descriptive analysis will be summarized for Baseline characteristics by treatment group and overall.

Descriptive summary of the time to event data includes a Kaplan-Meier method, median time to event, and corresponding 95% confidence interval.

All statistical tests will be conducted at an overall two-sided significance level of 5%.

12.5.1 Demographic and baseline characteristics

Demographics, medical history, and diagnosis at the Baseline visit will be tabulated using the ITT Set. Continuous variables, i.e. age, body weight, and height, and qualitative variables, i.e. sex, medical history, anticancer agent treatment history, diagnosis, and underlying signs and symptoms will be summarized as appropriate for characteristics of each data as explained previously, and will be compared for the between-group difference.

12.5.2 Level of treatment exposure and drug compliance

Extent of exposure will be assessed using the Safety analysis set.

Number of treated subjects, number of administered cycles, dosing period (week), accumulated dose (mg/m^2), dose intensity (mg/m^2/week), and relative dose intensity (%) will be summarized by group.

Dose delay and dose reduction will be also analyzed.

S-1 compliance will be assessed based on the S-1 administration diary.

12.5.3 Analysis of efficacy variables

12.5.3.1 Analysis of the primary efficacy variable

The primary analysis will be conducted using the FAS as described in Section 12.4.1.

The efficacy analysis is to compare the Progression-Free Survival (PFS). If $h_1(t)$ is a risk function of the CSC Arm and $h_0(t)$ is a risk function of the SC Arm, the null and alternative hypotheses for the main analysis are as follows and therefore, this study aims to demonstrate superiority of the CSC Arm to the SC Arm.

$$H_0: \ h_0(t) = h_1(t) \quad vs \quad H_1: \ h_0(t) \neq h_1(t)$$

Progression-Free Survival is compared between two treatment groups using a log rank test stratified by stratification factors (site, TNM stage (T4/N-, T2/N+, T3-4/N+) according to the AJCC 7th Edition) specified at randomization at the overall 5% significance level. Survival curve is estimated using the Kaplan-Meier estimate. Median and the corresponding 95% confidence interval, and the 3-year Progression-Free Survival will be presented by treatment group.

The final PFS analysis is conducted upon observation of at least 244 events or reaching median follow-up of at least 3 years. One PFS interim analysis was planned for efficacy confirmation upon occurrence of approximately 122 PFS events (50% of all events). Using group sequential approach with the O'Brien-Fleming alpha spending function and the overall significance level of 5%, the significance level for the final analysis is 0.049 (for details of the interim analysis, see Section 12.6).
The analysis described above will be repeated for the PP Set defined in Section 12.4.1.

12.5.3.2 Analysis of secondary efficacy variables

Overall survival is analyzed in the same way as the PFS. At the overall 5% significance level, survival experiences are compared between two treatment groups using a log rank test stratified by stratification factors (site, TNM stage (T2/N+, T3-4/N+, T4/N-) according to the AJCC 7th Edition) specified at randomization. Survival curve is estimated using the Kaplan-Meier estimate. Median and the corresponding 95% confidence interval will be presented by treatment group.

For the postoperative stage and the R0 resection rate, frequency and percentage will be presented, and compared using a Cochran-Mantel-Haenszel test stratified by stratification factors (site, TNM stage (T2/N+, T3-4/N+, T4/N-) according to the AJCC 7th Edition) specified at randomization.
In case the postoperative stage and the R0 resection rate are missing, analysis will be conducted using the Efficacy Set, and subjects with missing data will be excluded from the denominator when calculating percentage.

12.5.3.3 Analysis of additional efficacy variables

Additional explorative analysis can be considered and will be fully presented in the SAP. For example, a Cox proportional hazard model can be used to investigate the effect of various prognostic factors on PFS and OS. Hazard ratio assessment and the corresponding 95% confidence interval can be presented using the Cox proportional hazard model stratified by the same stratification factors as used for the aforementioned log rank test, if data satisfy conditions for a Cox proportional hazard model.

12.5.4 Analysis of safety data

For analysis of safety data, adverse events, hematological toxicity, routine physical examination, and laboratory data will be described and analyzed using the Safety analysis set defined in Section 12.4.2. Safety data will be also summarized by cycle (if applicable). For each safety variable, Baseline will be defined as the last level or assessment measured prior to the first treatment in the study.

12.5.4.1 Analysis of adverse events

Adverse events will be described using the total number of subjects who experienced toxicity or an adverse event. For comparison of safety between two groups, adverse events will be summarized by treatment group, and the number and percentage of subjects with an adverse event will be presented. For the CSC Arm, adverse events reported during the pre-operative DOS period will be presented separately from postoperative adverse events, and adverse events reported postoperatively will be compared between the CSC Arm and the SC Arm using frequency analysis.

Baseline adverse event is defined as an adverse event that developed or worsened during Baseline.

Treatment-emergent adverse event (TEAE) is defined as an adverse event that developed or worsened during the treatment period (from the investigational product administration to 30 days after the last dose of the investigational product). However, in case a subject used an anticancer agent other than the investigational product during the treatment period, the adverse event after using concomitant medication will be excluded from analysis.

All adverse events will be classified using the MedDRA and summarized as grades determined according to the NCI CTCAE v4.03. MedDRA version retained by Sanofi at the time of analysis will be used. Severity of adverse events will be summarized as the highest grade experienced by the subject. For the following adverse events, frequency and percentage will be presented by System Organ Class and Preferred Term in the Safety analysis set.

- All adverse events classified by System Organ Class and TEAEs possibly related with the investigational product, in descending order of frequency
- All TEAEs and TEAEs possibly related with the investigational product by severity and System Organ Class
- Serious adverse events: All and possibly related serious TEAEs classified by seriousness criterion
- Serious adverse events: All and possibly related TEAEs classified by System Organ Class
- Death: All and possibly related TEAEs classified by System Organ Class
- Study discontinuation: All and possibly related TEAEs
- Other significant adverse events: All and possibly related TEAEs according to the “Other significant” adverse event criteria

12.5.4.2 Analysis of laboratory variables

Hematological toxicity will be assessed based on laboratory findings. Worst NCI CTCAE grade for leukocytopenia, neutropenia, thrombocytopenia, and anemia will be calculated according to the NCI Common Terminology Criteria.

Hematological toxicity will be summarized with quantitative and qualitative results. Qualitative data (worst NCI CTCAE grade) will be summarized by cycle and subject.

Biochemistry will be analyzed using the worst NCI CTCAE grade calculated from laboratory findings, if applicable (laboratory normal range, other).

12.5.4.3 Analysis of blood pressure variables

Change from Baseline in blood pressure will be descriptively analyzed.

12.5.4.4 Analysis of other safety variables

Descriptive statistics for clinical examination (physical examination, blood pressure, height, body weight, ECOG PS) and special tests (gastroduodenoscopy, laparoscopy) will be presented by visit, and change from Baseline will be summarized.

12.5.5 Analysis of pharmacokinetic and pharmacodynamic variables

There was no plan for pharmacokinetic and pharmacodynamic analysis.

12.5.6 Analysis of health economic variables

Health economic analysis was not conducted in this study.

12.6 Interim analysis

The objective of the interim analysis is to provide IDMC members with a methodological rationale and decision making rules for continuation of the study as planned or recommendation of early study discontinuation in case of demonstrating efficacy based on the previously described boundary area. Further details will be described in the IDMC Charter.

The interim analysis will be conducted upon occurrence of approximately 122 PFS events (50% information rate). O'Brien-Fleming α-spending function will be used for interim analysis of efficacy. Under this suggestion, a total of 244 events are required along with the interim analysis upon occurrence of approximately 122 PFS events. At the interim analysis, the boundary for early study discontinuation with the absolute efficacy of CSC would be the significance level of 0.0031.

13 ETHICS AND REGULATIONS

13.1 Ethical principles

This study will be conducted according to the principles set out at the 18th World Medical Association (Helsinki, 1964), all applicable revisions at World Medical Association meetings, and the International Conference on Harmonisation Good Clinical Practice Guideline (ICH GCP).

13.2 Laws and regulations

This study is conducted in compliance with all international laws and regulations, local laws and regulations in the country where the study is conducted, and applicable guidelines.

13.3 Informed consent

The investigator (according to applicable regulatory requirements) or a person designated by the investigator should fully inform a subject of all study-related aspects, including information on the Approval/Approval with Correction Letter (favorable opinion) of the IRB/IEC, under the responsibility of the investigator. All participants should receive as much information as possible on the study, in the language and terms they can understand.

Prior to the subject's study participation, the subject or subject's legally acceptable representative, and the person who conducted the informed consent process should sign the Informed Consent Form and other relevant documents according to local laws and regulation, and personally sign and date them. A copy of the signed and dated Informed Consent Form is provided to the subject.

The Informed Consent Form used by the investigator to obtain consent of the subject should be reviewed and approved by the sponsor before being submitted for approval/approval with correction of the relevant IRB/IEC.

13.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The investigator or the sponsor should submit the protocol to the relevant IRB/IEC and provide the Approval Letter/Approval with Correction Letter dated and signed by the Ethics Committee Chairperson to the sponsor.

The study (study number, protocol title, and version number), reviewed documents (e.g., protocol, Informed Consent Form, Investigator's Brochure, investigator's Curriculum Vitae), voting member list and qualification, and the review date should be clearly mentioned in the Approval Letter/Approval with Correction Letter of the relevant IRB/IEC.

The investigational product cannot be supplied to the site nor can the study be initiated before the sponsor receives the dated Approval Letter/Conditional Approval Letter.

During the study, all revisions or amendments of the protocol should be submitted to the IRB/IEC. In addition, any matter that may affect subject safety and continuous conduct of the

study, in particular, safety-related change should be reported during the course of the study. All revised Investigator's Brochures are to be submitted to the IRB/IEC.

If requested, a study progression report is to be submitted to the IRB/IEC every year, and summarized study results are to be submitted at study completion.

14 MONITORING

Responsibilities of i(s)

The investigator conducts the study according to this protocol, the International Conference on Harmonisation Good Clinical Practice Guideline (ICH GCP), and applicable laws regulation.

The investigator should comply with all protocol-required procedures and all study procedures provided by the sponsor (confidentiality principle included). The investigator should provide reliable data and all protocol-required information (using the Case Report Form (CRF), Discrepancy Report Form (DRF), or other applicable tool) according to the provided guideline in an accurate and legible manner, and allow the sponsor's representative to have direct access to source documents.

The investigator may designate other person according to the protocol if deemed appropriate as a subinvestigator to support the study conduct. All subinvestigators are to be designated in a timely manner and recorded in a list. The subinvestigator is under the supervision and responsibility of the investigator. The investigator is to provide the subinvestigator with the protocol and a copy of all necessary documents.

14.2 Responsibilities of sponsor

Sponsor of this study has the responsibility to take any reasonable action to guarantee appropriate conduct of and compliance with the protocol in relation to the ethical aspect and integrity and validity of Case Report Form entries to public health authorities. Therefore, the major responsibility of Monitoring Team is to support the investigator and the sponsor to maintain high ethical, scientific, technical, and legal standards in all aspects of the study.

Monitoring Team representative will periodically conduct site visits during the study via monitoring visits, letters, or phone calls to review the study progress status, compliance of the investigator and subjects with protocol requirements, and any emergent issue. During such monitoring visits, the following matters (not minor issues) will be closely examined with the investigator: Informed Consent Form, subject eligibility, subject enrollment and follow-up, serious adverse event recording and reporting, investigational product dispensing, subject's compliance with the protocol and investigational product treatment, investigational product accountability check, use of concomitant medication, and data quality level.

14.3 Source document requirements

According to the International Conference on Harmonisation Good Clinical Practice Guideline (ICH GCP), Monitoring Team should compare Case Report Form entries with source documents, except for source data that are to be directly recorded in the Case Report Form as specified previously. Informed Consent Form includes a statement that the subject allows the sponsor's formally designated representative, IRB/IEC, and relevant authorities to have direct access to source documents (e.g., subject's medical records, appointment table, original of laboratory test reports) that support the Case Report Form. All such people bound by professional confidentiality should maintain confidentiality of all personal or medical information according to the confidentiality principle.

Preparation of crf requests

It is the responsibility of the investigator to maintain the Case Report Form designed by Sanofi (according to the Sanofi guideline) to capture all observations and other clinical test-related data in an appropriate and accurate manner (depending on the used method). All Case Report Forms should be completed in a clear and legible manner to allow accurate data interpretation.

Corrected information should not obscure the original entry. The corrected information is to be recorded by an authorized person next to the previous entry, and the person who made the correction is to sign and date.

NCR Form is used for the Case Report Form, and an original and a copy will be collected by the monitor. The original form will be sent to Statistical Department for analysis and the first copy will be retained at Sanofi. The last and second copy should be maintained at the site.

14.5 Use of computer system

A computer system will be used to develop, correct, maintain, save, and, search a database of all data collected from this study.

15 ADMINISTRATIVE REGULATIONS

15.1 Curriculum Vitae

The original Curriculum Vitae reflecting the latest details of the career, qualification, and education of each investigator and subinvestigator should be provided to the sponsor prior to study initiation.

15.2 Record retention in study site(s)

The investigator should maintain all study records as confidential, and take action to prevent accidental or premature destruction of these documents.

Unless separately specified in the Investigator Agreement according to standards and/or laws of the relevant country, the investigator is recommended to retain study records for 15 years after study completion or discontinuation.

However, if a longer period is required by applicable regulations, it should be followed.

The investigator should inform the sponsor prior to destruction of key study documents after study completion or discontinuation.

In case further retention cannot be ensured due to the investigator's personal situation, the investigator should inform the sponsor and transfer relevant documents to a mutually agreed delegate.

16 CONFIDENTIALITY

All information disclosed or provided by the sponsor (or a company/site working on behalf of the sponsor) or generated during the study is confidential, including the protocol, Case Report Form, Investigator's Brochure, and results obtained during the course of the study. The investigator and all subinvestigators under the supervision of the investigator should agree to confidentiality and no disclosure of information to any other site without the sponsor's prior written approval.

However, it is clearly acceptable to submit this protocol and other necessary documents to the IRB/IEC, and IRB/IEC members are also bound by the same confidentiality obligation.

The subinvestigator has the same obligation as the investigator. The investigator should inform the subinvestigator of the confidentiality principle of the study.

The investigator and the subinvestigator should use such information only for the study purpose, but not for one's own or a third site's interests.

17 PROPERTY RIGHTS

Any information, document, and investigational product provided by the sponsor or its representative are the exclusive property of the sponsor.

The investigator should not mention the information or the investigational product associated with a patent or any other intellectual property.

In any form, any result, document, or details of intervention derived directly or indirectly from the study represent an exclusive property of the sponsor.

The sponsor can use or utilize all results at the sponsor's own discretion, without any restriction in the ownership (area, field, persistency). The sponsor shall not have any responsibility for other use of the patent, development, marketing, or study results.

18 DATA PROTECTION

Personal information of the subjects and the investigator that may be included in the sponsor's database will be handled according to applicable laws and regulations.

During retention and processing of personal information related to the investigator and/or the subject, the sponsor should take all appropriate actions to prevent and protect from unauthorized access to such data.

19 COMPENSATION INSURANCE

The sponsor ensures subscription to a liability insurance policy covering all studies supported by the sponsor. This insurance policy is to comply with laws and regulation of the relevant country. The obligation of the investigator and cooperators to maintain their own liability insurance policy cannot substitute the insurance taken out by the sponsor. In a country that requires such document, a copy of the insurance certificate is to be submitted to the IRB/IEC or relevant authorities.

20 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

To ensure compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements, the investigator should accept an audit by the sponsor or its representative and an inspection by applicable regulatory authorities.

The investigator should agree to allow an auditor/inspector bound by professional confidentiality to have direct access to study records for a review, and this would not result in disclosure of personal identity or personal medical information.

The investigator will do his/her best to support the audit and inspection by allowing access to any necessary facilities, data, and documents.

Upon being notified of the inspection from authorities, the investigator is to immediately inform the sponsor and authorize the sponsor to attend the inspection. Priority will be given to confidentiality of validated data and protection of subjects during implementation of such inspection.

The investigator should immediately inform the sponsor of all results and information raised from the inspection by regulatory authorities.

The investigator should take an appropriate action as requested by the sponsor to correct any problem found during the audit or inspection.

21 EARLY DISCONTINUATION OF THE STUDY OR EARLY TERMINATION OF A SITE

At the decision of the sponsor:

- In case of a suspected benefit/risk ratio from information on the product;
- In case the investigator has not enrolled any subject after a mutually agreed appropriate period, after having received all investigational products, methods, and information required for the study conduct from the sponsor;
- In case the study results do not appear scientifically reliable to the sponsor (for example, based on results of the planned futility analysis);
- In case the study objective is outdated or not relevant anymore;
- In case the investigator violated the basic responsibilities in this contract including but not limited to the protocol deviation, and the International Conference on Harmonisation Good Clinical Practice Guideline (ICH GCP);
- In case of recruiting the target number of subjects earlier than expected.

In any case, the sponsor will inform the investigator of such decision in writing.

At the decision of the investigator:
The investigator should inform the sponsor of the decision and the reason in writing (at least 30 days prior to discontinuation).
In any case (whether decided by the sponsor or the investigator), the relevant IRB/IEC and public health authorities will be informed.

22 RESULTS

The sponsor has the right to complete the Clinical Study Report (CSR).

The sponsor will transfer study results to the investigator after sufficiently analyzing data from all sites;

23 PUBLICATION AND RELEASE

The investigator has the obligation not to make any publication or presentation in relation to this study and/study results before getting the sponsor's written consent, and this is based on the understanding that the sponsor would not unduly postpone such approval.

Since this study is conducted in multiple sites, the sponsor agrees that the first presentation or publication of results of this study will be based on results obtained from all sites conducting this protocol to be in line with scientific standards. However, if multicenter publication is not implemented or there is no such plan within 12 months after completion of this study at all sites, the investigator has the right to independently publish or present results from this study according to the review procedure established herein. The investigator should provide a copy of all such presentations or publications derived from this study at least 45 (calendar) days, or a copy of an abstract at least 30 days prior to submission for such presentation or publication to the sponsor to get a review and opinions. In addition, at the request of the sponsor, submission for presentation or publication should be postponed for a limited period not exceeding 90 days for patent application or other action as determined appropriate for establishment and retention of the sponsor's property right.

The investigator should not use the name of the sponsor or its employee in an advertisement or promotion material or publication without getting the prior written approval of the sponsor. The sponsor shall not use the name of the investigator and/or co-investigator in an advertisement or promotion material or publication without getting the prior written approval of the investigator and/or co-investigator.

The sponsor has the right to publish results of this study at any time.

24 REVISION OF THE PROTOCOL

All appendices attached to and referenced in this document are treated as part of this protocol.

The investigator cannot violate the protocol or implement the protocol amendment before the sponsor's consent and documentation of the result of the IRB/IEC review and approval/approval with correction (favorable opinion) for the amendment, unless it is necessary to eliminate the immediate hazard to subjects or in case of an amendment involving only a logistical or administrative aspect of the study. Contents of all agreed amendments will be documented, the investigator and the sponsor will sign the written amendment version, and the signed amendment version will be filed with this protocol.

All protocol amendments require the Approval Letter/Conditional Approval Letter of IRB/IEC before implementation, unless there is a prioritized safety issue.

In some cases, it may be necessary to revise the Informed Consent Form due to amendment. The investigator should get written approval/conditional approval of IRB/IEC for the revised Informed Consent Form before implementing the amendment.

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26 APPENDICES

26.1 Creatinine Clearance Calculation Method
26.2 ECOG Performance Status
26.3 Surgical Manual (v3.0_20120206)
26.4 Participating Sites and Investigators
26.5 AJCC TNM Classification (7th Edition)

26.1 Creatinine Clearance Calculation Method

26.2 ECOG Performance Status

26.3 Surgical Manual (v3.0_20120206)

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Table 1) Postoperative complication reporting criteria

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26.4 Participating Sites and Investigators

26.5 AJCC TNM Classification (7th Edition)