

STATISTICAL ANALYSIS PLAN

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

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ABBREVIATIONS AND DEFINITIONS

BSA: Body surface area

CSC: Neoadjuvant Docetaxel+Oxaliplatin+S-1 (DOS) + Surgery + Adjuvant S-1 arm

ECOG PS: Eastern Cooperative Oncology Group Performance status

HR: Hazard ratio

IDMC: Independent data monitoring committee

ITT: Intention-to-treat

IWRS: Interactive web response system

KPS: Karnofsky Performance Score

MedDRA: the Medical Dictionary for Regulatory Activities Terminology

NA: Not applicable

NCI CTCAE: National cancer institute common terminology criteria for adverse events

OS: Overall Survival

PD: Progressive disease

PFS: Progression free survival

RECIST: Response Evaluation Criteria in Solid Tumors

SC: Surgery + Adjuvant S-1

SI units: International system of units

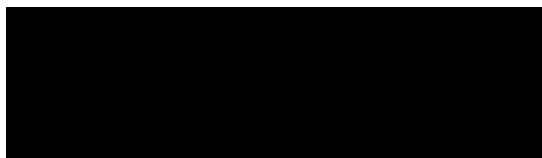
TEAE: Treatment emergent adverse event

WHO drug: World health organization drug

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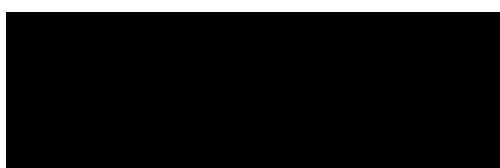
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1 OVERVIEW

The statistical analysis process to be performed in the clinical trial is based on the clinical trial protocol and this statistical analysis plan (SAP), and evaluates the demographic and medical information, as well as the efficacy and safety data. This SAP may be changed during the trial in order to reflect the changes in the clinical trial protocol and to accept unexpected problems in the study implementation and data affecting the planned analysis. These changes will be examined in the blinded state of the trial and data.

The statistical software, SAS (Version 9.4 or higher, SAS Institute, Cary, NC, USA) will be used for the statistical analysis.

1.1 OBJECTIVES

1.1.1 Primary Objectives

To compare a 3-year progression free survival (PFS) in patients with resectable advanced gastric cancer who are randomly assigned into either Neoadjuvant Docetaxel+Oxaliplatin+S-1 (DOS) + Surgery + Adjuvant S-1 (hereinafter, CSC arm) or Surgery + Adjuvant S-1 (hereinafter, SC arm).

1.1.2 Secondary Objectives

The following endpoints are evaluated and compared in the two treatment arms:

- Overall Survival (OS)
- Postoperative Pathological Stage
- R0 (Complete) Resection Rate

1.1.3 Safety

The following data are evaluated and compared in the two treatment arms:

- Adverse Event: Reported and evaluated according to NCI CTCAE v4.03
- Hematology, biochemistry, and urinalysis laboratory data
- Other safety test results

1.2 MODIFICATIONS FROM THE STATISTICAL SECTION IN THE PROTOCOL

NA

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2 INVESTIGATIONAL PLAN

2.1 STUDY DESIGN AND RANDOMIZATION

This study is a randomized (1:1), open-label, multicenter, comparative, phase III clinical trial, in which patients with resectable advanced gastric cancer are randomly assigned to either the CSC or SC arm.

Patients who signed the informed consent form and were randomly assigned are considered eligible to participate in this trial. Based on the clinical trial flowchart below, the trial is conducted as follows: CSC arm starts neoadjuvant chemotherapy within 7 days after randomization and undergoes surgery within 1 to 3 weeks after 3 cycles of investigational product dosing. SC arm undergoes surgery within 2 weeks after randomization. After the surgery, both arms are administered adjuvant chemotherapy for 8 cycles (approximately 1 year) within 3 to 6 weeks after the surgery and safety evaluation is carried out on day 30 after the final investigational product dosing and follow-up (every 3 months for the first 1 year and thereafter every 6 months by visiting the site; after disease progression, survival status is checked by telephone call or visit every 6 months for up to 5 years from enrollment). Subjects who have ended the study (End of Study) in a survival state can be further followed up for survival status by visits or phone calls, and the additionally collected information can be used only for exploratory evaluation. However, the entire follow-up shall end at the end of the study for subjects under follow-up (expected to be 5 years after the enrollment of the last subject).

The clinical trial data deadline shall be the date on which approximately 244 cases of disease progression or death have occurred or the median follow-up period has reached a minimum of three years.

Subjects are assigned with a treatment arm by the Interactive Web Response System (IWRS) according to a computer-generated randomization list. By having the site and TNM stage (T2/N+, T3-4/N+, and T4/N-) based on the AJCC 7th edition as the stratification factors, the subjects who met the inclusion/exclusion criteria will be randomly assigned to either the CSC or SC arm at a ratio of 1:1.

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◀ 수술후 보조항암화학요법 ▶ 수술 ◀ 수술후 보조항암화학요법 ▶

CSC 군 : DOS + 수술 + S-1

DOS 1 주기 → 중앙평가

R

SC 군 : 수술 + S-1

무진행 → DOS 2,3주기 → 수술후 중앙평가

진행 → 임상시험종료 의약품 투여 중단 후 추적관찰기

수술후 중앙평가

진행 → 임상시험종료 의약품 투여 중단 후 추적관찰기

무진행

수술

병기 재분류

근거리 절제

1년간 S-1

비근거리 절제

추적관찰 시행

임상시험종료 후 추적관찰기

시험종료 (EOS: 사망, 임상시험 마감)

종료진행 혹은 시험 종료까지
 수술일 기준으로 매 8개월마다 중앙평가
 수술일 기준으로 매 12개월마다 위임이지정경 검사

● 베이스라인
 -환자동의서
 무작위 배정 14일 이내:
 -선정/제외기준 확인
 -Lab
 -신체검진
 -ECG
 -연구학적 자료
 -약물/수술적/병용약물
 -총부 X선 검사
 -중앙평가

무작위 배정 3개월 이내:
 -위임이지정경 검사
 -조직검사결과

CSC = Chemotherapy + Surgery + Chemotherapy
 SC = Surgery + Chemotherapy
 DOS = 도세탁셀, 옥실리플라틴, S-1
 R = 무작위배정
 EOT = End of Treatment, 치료 종료
 EOS = End of Study, 시험 종료

The primary evaluation for efficacy is based on a 3-year progression free survival (PFS).

A 5% significance level for two-sided tests and a total of 7.5 years of follow-up period, including a recruitment period of 4.5 years, were assumed. This clinical trial is terminated if at least 244 events are observed at the time of the final analysis or at least 3 years in the median follow-up period. The duration of the study for a survival follow-up will be up to 5 years from randomization. However, subjects who have ended the study (End of Study) in a survival state can be further followed up for survival status by visits or phone calls

An interim analysis is performed during the 122 PFS events (50% information rate). O'Brien-Fleming alpha-spending function is used for the interim analysis of efficacy. Based on this suggestion, the required total number of events is 244, in addition to the interim analysis to be performed at the time of occurrence

KRBDM(BS)-SD-004-02

of 122 PFS events. In the interim analysis, the boundary of early termination of the trial with an overwhelming efficacy of CSC will be at a significance level of 0.0031.

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3 STATISTICAL AND ANALYTICAL PROCEDURES

3.1 ANALYSIS VARIABLES

3.1.1 Efficacy Variables

3.1.1.1 Primary Efficacy variable

The primary efficacy variable is the 3-year PFS rates, defined as the period from randomization date to progressive disease (PD) or proof of death.

PD is defined according to RECIST1.1 criteria as follows, and the time to progression is calculated based on the first date the progression is proven.

1. PD is determined based on the RECIST 1.1 criteria during the neoadjuvant chemotherapy period in the CSC arm. When PD is determined based on the sum of the diameters of target lesions, the determination date is defined as the final tumor assessment day for the target lesions, and the determination date of PD due to the clear progression of non-target lesions is defined as the corresponding tumor assessment day.
2. Regardless of radical resection, it is considered as PD when distant metastasis is observed during surgery or reported in the pathological examination. The date of operation is defined as progression confirmation day.
3. The case where cancer cells are visibly remaining in the resection margin during surgery but cannot be completely resected (R2) is considered PD, and the date of operation is defined as progression confirmation day.
4. The case where the remaining cancer cells in the resection margin are finally confirmed in the histological examination after surgery (R1) is considered as PD, and the date of operation is defined as progression confirmation day.
5. The case where there is a recurrent/distant metastasis found during follow-up after the R0 complete resection or a new lesion is found, it is defined as the first tumor assessment day.

If the condition does not meet the criteria for PD, censoring is carried out based on the earlier time point among the dates specified as follows :

1. The last day of evaluating the progression of tumor for the subjects whose follow-up has failed, or whose disease progression or death has not been confirmed until the end of the trial

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2. The last day of evaluating the progression of tumor if a second primary cancer is found that is different from gastric adenocarcinoma at any time during the trial
3. The last day of evaluating the progression of tumor if the patient receives treatment other than the scheduled treatment without the recurrence of tumor
4. Randomization date if no tumor assessment information is available after randomization
5. The deadline of the clinical trial

3.1.1.2 Secondary efficacy variables

The secondary efficacy variables include the overall survival (OS), postoperative pathological stage, and R0 resection rate.

The OS is defined as the period from the randomization date to the proof of death regardless of the cause. If death is not confirmed, the survival time is based on the earlier time point between the last known date of survival and the deadline of the clinical trial.

After surgery, the stage of disease and R0 resection rate are collected.

3.1.2 Safety Variables

Safety data include adverse events, hematological toxicity, clinical examination (e.g., physical examination, blood pressure, BSA, body weight, and ECOG PS), special tests (e.g., chest x-ray and ECG), and laboratory data.

3.1.2.1 Adverse Events

Toxicity profiles are determined based on NCI CTCAE v4.03 and collected at each visit after the baseline.

3.1.2.2 Laboratory Safety Variables

Hematology and blood chemistry data are 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

3.1.2.3 Creatinine clearance(Cockcroft-Gault Formula)

: Collected Only at Baseline and Neoadjuvant Chemotherapy Period Other Safety Variables

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3.1.2.4 Blood Pressure

The normal/abnormal status of the blood pressure is collected at each visit.

3.1.2.5 Other Safety Variables

General physical examinations are evaluated before and after the treatment.

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3.2 ANALYSIS POPULATIONS

3.2.1 Efficacy Populations

All efficacy analyses are performed on the FAS as a main analysis, while ITT and PP set are also analyzed in order to check the robustness of this trial.

3.2.1.1 *Intent -to-Treat (ITT) and Full Analysis Set Population*

Intent-to-treat (ITT) set includes all randomized subjects. That is, all subjects assigned to the treatment arms by randomization are included, regardless of whether the subject received the study drug or a study drug different from the one that was randomly assigned. The subjects included in the ITT group will be analyzed according to their randomized treatment arm.

Full analysis set (FAS) is defined as all randomized subjects who have met the inclusion/exclusion criteria, and those who have received at least one tumor assessment since the baseline visit. In addition, the CSC arm will include those who have received DOS investigational products at least once, while the SC arm will include the subjects who underwent surgery.

3.2.1.2 *Per-protocol Population*

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

- 1) The CSC arm will include the subjects who started postoperative adjuvant chemotherapy (S-1) as planned in this protocol after completing all three cycles of DOS treatment as neoadjuvant chemotherapy and undergoing surgery
- 2) The SC arm will include the subjects who started postoperative adjuvant chemotherapy (S-1) as planned in this protocol after undergoing surgery.

However, 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.

Critical Protocol Violation

- Inclusion/exclusion criteria violation
- Randomization Error: The case of assigning the patient into a treatment arm other than the one assigned by the IWRS (this is not the case of randomization stratification factor error)

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- Administration of contraindicated medications
- Cross-administration of the study drug
- Start of dosing before randomization
- Randomization before obtaining written consent
- Dose modification error or malpractice deviating 80% to 120% from the scheduled dose

3.2.2 Safety Population

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

3.3 STATISTICAL METHODS

Categorical data will be summarized in the table showing the frequencies and corresponding proportion for each treatment arm. Continuous data will be summarized for each treatment arm using number of subjects, mean, standard deviation, median (if applicable), and minimum and maximum. Descriptive analysis will be summarized for the description of pre-treatment characteristics for each treatment arm and total number of subjects.

A descriptive summary of the time-to-event data includes the Kaplan-Meier method, the median time to event, and its 95% confidence interval.

In general, all statistical tests will be performed at a two-sided significance level of 5% unless otherwise noted.

3.3.1 Demographics and Baseline Characteristics

The demographic characteristics, medical history, and diagnosis at baseline visit will be tabulated based on the ITT set. For continuous and qualitative variables, t-tests (or Wilcoxon rank sum tests) and chi-square tests (or Fisher's exact tests) will be used to compare the treatment arms. The statistical analysis for data at the baseline visit will be done entirely in an exploratory manner. When there is a difference between the two treatment arms ($p < 0.05$), additional analysis will be performed in order to determine how the imbalance of baseline visit data affected the primary efficacy endpoint.

The difference between the two treatment arms will be tested for the variables specified in 3.3.1.1 below.

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3.3.1.1 Variables Related to Demographics and Baseline Characteristics

Demographic Characteristics

Age is calculated in the unit of 'year' as follows, and the value of the decimal point is discarded:
Number of Months of (Date of Informed Consent Form – Date of Birth) / 12 **Gender** (Male/Female)

Tumor Assessment

Endoscopy Evaluation (Yes/No)

Site (gastroesophageal junction, body, pylorus, greater curvature, posterior wall, fundus, antrum, duodenum, lesser curvature, anterior wall, and others)

Histological Type (Adenocarcinoma, etc.)

Tumor staging (T4 N- / T2 N+ / T3-4 N+ / Others)

Physical Examination

Body Weight (kg)

Height (cm)

Systolic Blood Pressure (mmHg)

Diastolic Blood Pressure (mmHg)

ECOG Performance Status (0 1 / 2 / 3 / 4)

12-Lead ECG (Normal / Abnormal NCS / Abnormal CS)

Chest X-Ray (Normal / Abnormal NCS / Abnormal CS)

3.3.2 Discontinuations and Dropouts

The frequencies and percentages of the subjects who have completed the trial and those who have dropped out are presented. In case of a dropout, frequency analysis will be performed.

3.3.3 Extent of Exposure and Compliance

For the number of administered cycles, dosing period (week), accumulated dose (mg/m²), dose intensity (mg/m²/week), percentage of projected dose intensity (%), and average percentage of projected drug intensity (%), continuous variables will be summarized with descriptive statistics (e.g., number of subjects, mean, standard deviation, median, and minimum and maximum), and t-tests (or Wilcoxon rank sum tests) will be used to compare the treatment arms.

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The results will be summarized for the safety analysis set. The findings of the CSC arm will be presented by dividing them into neoadjuvant chemotherapy and postoperative adjuvant chemotherapy periods. The findings of the SC arm are presented for the postoperative adjuvant chemotherapy period.

3.3.3.1 Variables of Extent of Exposure and Compliance

Number of administered cycles :

The frequencies and percentages of the study drug administration cycles until the end of treatment are presented.

Dosing period (week) is calculated as follows:

For the neoadjuvant chemotherapy period,

(Final dosing date of docetaxel – Initial dosing date of docetaxel + 21) / 7

(Final dosing date of oxaliplatin – Initial dosing date of oxaliplatin + 21) / 7

(Preoperative final dosing date of S-1 – Initial dosing date of S-1 + 8 [since S-1 is administered for 14 days]) / 7

For postoperative adjuvant chemotherapy period,

(Final dosing date of S-1 – Postoperative final dosing date of S-1 + 15 [since S-1 is administered for 28 days]) / 7

Accumulated dose (mg/m²) is calculated by adding the total doses of all cycles where the study drug is administered.

Dose intensity (mg/m²/week) (%) is calculated as follows:

For each subject,
$$\frac{\sum_{i=1}^n \text{Total dose given at cycle } i / BSA_i}{\text{Total duration of dosing}}$$

Here, BSA_i is BSA at ith cycle, and n is the maximum number of cycles in which the subject underwent treatment.

Percentage of projected dose intensity (%) is calculated as follows:

Actual dose intensity for each patient / Projected dose intensity for the regimen

Here, projected dose intensity (mg/m²/week) is calculated as follows:

For the neoadjuvant chemotherapy period, (intended dose per cycle) / 3

For the postoperative adjuvant chemotherapy period, (intended dose per cycle) / 6

Average percentage of projected drug intensity for all drugs (%) is calculated as follows:

For the neoadjuvant chemotherapy period,

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$$(\text{Percentage of projected dose intensity of docetaxel} + \text{Percentage of projected dose intensity of oxaliplatin} + \text{Percentage of projected dose intensity of S1}) / 3$$

For the postoperative adjuvant chemotherapy period, the average percentage of projected drug intensity for S-1 is not calculated because there is only one drug used.

Dose Modification:

The frequency and percentage of the subjects with dose modification after the last visit are presented by treatment arm and by each cycle.

3.3.4 Concomitant Treatment

3.3.4.1 Prior and Concomitant Medication

As for the analysis by classification, concomitant medication is standardized with “Anatomical Category” and “Therapeutic Category” by using the latest version of the ATC code, while the number of subjects (%) and the number of events are presented for each treatment arm. A summary of the concomitant medications will be presented for the ITT analysis set. In addition, chi-square tests or Fisher's exact tests will be performed in order to find the difference between the arms in the proportion of subjects with concomitant medications.

Combination therapy is any type of treatment that lasts from three weeks before the screening to the investigational product dosing period, and one month after the final dosing date, or any treatment initiated after the first investigational product dosing.

3.3.4.2 Past and Current Medical History

Past/current comorbid diseases will be classified according to the continuity status collected in the case report form. The medical history selected as “ongoing” is considered as the current medical history.

All comorbid diseases will be standardized with “System Organ Class” and “Preferred Term” by using the latest version of MedDRA, and the number of subjects (%) and number of events will be presented for each arm. A summary of the past and current medical history will be presented for the ITT analysis set. In addition, chi-square tests or Fisher's exact tests will be conducted in order to find the difference between the arms in the proportion of subjects with past/current comorbid diseases.

3.3.5 Efficacy analyses

3.3.5.1 Primary efficacy analysis

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The primary efficacy analysis is used to compare the progression free survival (PFS). When $h_1(t)$ is the risk function of the CSC arm and $h_0(t)$ is the risk function of the SC arm, the null hypothesis and the alternative hypothesis in the main analysis are as follows. Therefore, this study intends to prove the superiority based on the comparison between the CSC and SC arms.

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

PFS is compared between the two treatment arms by using a stratified log-rank test by stratification factors (site and TNM stage [T2/N+, T3-4/N+, and T4/N-]) according to the specified at randomization at the overall significance level of 5%. Survival curves are estimated by using the Kaplan-Meier estimator. The median PFS time, 95% confidence interval, and 3-year PFS rate are presented for each treatment arm.

The final PFS analysis ends when at least 244 events are observed, or when the median follow-up period reaches at least three years. A single PFS interim analysis is planned to identify the efficacy upon the occurrence of approximately 122 PFS events (50% of entire events). The significance level of 0.049 will be used at the final analysis by using the O'Brien-Fleming alpha spending function and group sequential approach with the significance level of 5%. (Please see section 4 for details on the interim analysis.)

If the date of death, disease progression confirmation date, or the last follow-up date is unclear and no more information can be collected, i.e., 'month' or 'day' is not collected, the 'month' or 'day' will be considered as January or the 1st day for the analysis. If the date is entirely unclear, not partially, i.e., if the year, month, and day are unidentifiable, censoring will be performed at the last date among the dates collected. (If the last date is equal to or earlier than the randomization date, the randomization date will be used.)

The main analysis is performed for the FAS, and the ITT and PP set are also analyzed.

3.3.5.2 Secondary efficacy analyses

Overall survival (OS) is analyzed in the same way as PFS. The survival experience is compared between the two treatment arms with the stratified log-rank test by stratification factors (e.g., site and TNM stage [T2/N+, T3-4/N+, and T4/N-]) specified at the time of randomization at the overall significance level of 5%. Survival curves are estimated by using the Kaplan-Meier estimator. The median OS survival time and corresponding 95% confidence interval are presented for each treatment arm.

In addition, OS can be analyzed exploratorily by including data on survival status, additionally collected after the end of the study (End of Study), method of analysis is consistency with previous mentioned one. For the postoperative stage and R0 resection rate, frequencies and percentages are presented, and

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comparison is performed by using the Cochran-Mantel-Haenszel test stratified by stratification factors (site and TNM stage [T2/N+, T3-4/N+, and T4/N-]) specified at the time of randomization.

In case the postoperative stage and R0 resection are missing, the analysis will be based on the efficacy analysis set, and the subject whose data is missing when calculating the proportion will be excluded from the denominator.

The main analysis is performed for the FAS, and the ITT and PP set are also analyzed.

3.3.5.3 Additional efficacy analyses

For the CSC arm, the proportion and two-sided 95% confidence intervals of complete remission (CR), partial remission (PR), and stable disease (SD) are presented in the preoperative tumor assessment. The proportion is defined as the number of subjects who were assessed to have CR, PR, or SD, respectively, divided by the number of subjects with measurable lesions.

The mean, standard deviation, median, and minimum and maximum are used to analyze the time from the operation date to the start of the postoperative adjuvant chemotherapy. The differences between the two treatment arms are compared by using t-tests or Wilcoxon rank sum tests.

Additional efficacy analyses are performed on the FAS.

3.3.5.4 Subgroup Analysis

PFS, OS, and R0 resection rate are analyzed for the following subgroups. Subgroup analysis is done for the FAS.

- TNM Stage at Randomization: T2/N+ vs T3-4/N+ vs T4/N-
- Age: Below 65 years vs. 65 years or older
- Gender: Male vs. Female
- T Stage: T0 vs. T1 vs. T2 vs. T3 vs. T4
- N Stage: N0 vs. N1 vs. N2 vs. N3
- Histological Type: Intestinal vs. Diffuse vs. Mixed
- Postoperative Adjuvant Chemotherapy: Complete vs. Incomplete
- Response at CSC Arm: CR vs. Non-CR

For the PFS and OS, survival curves, median survival time, and 95% confidence interval using the Kaplan-Meier estimator are presented for each subgroup and each treatment arm. If the data meet the Cox proportional assumption, the hazard ratio and 95% confidence interval will be presented by using

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the Cox proportional hazard model stratified with the stratification factor (TNM stage [T2/N+, T3-4/N+, and T4/N-]) at the time of randomization.

The frequency and percentage of R0 resection are presented for each subgroup and each treatment arm.

Additional subgroup analysis can be performed for exploratory purposes in the future.

3.3.6 Safety Analyses

For the safety data analysis, adverse events, hematological toxicity, general physical examination, and laboratory data are described, and all safety analyses are performed in the safety set. For each safety variable, the pre-treatment level is defined as the last value or assessment value measured before the first treatment in the trial, and the final evaluation is based on the final value evaluated during the study drug dosing period.

3.3.6.1 Adverse Events

Adverse events are described by the total number of subjects who experienced toxicity or adverse events. In order to compare the safety of the two arms, the adverse events are summarized for each treatment arm, and the number of subjects (incidence rate) and the number of events are presented.

In the CSC arm, the adverse events reported during the preoperative DOS period are presented separately from the postoperative adverse events, and the postoperative adverse events will be compared by using the frequency analysis between the CSC and SC arms. In addition, adverse events in the whole period and postoperative adjuvant chemotherapy cycle 1 will also be summarized. Adverse events are divided into two types as follows according to the time of onset.

Pre-treatment adverse events are defined as adverse events that appear or worsen during the pre-treatment period.

Treatment emergent adverse events (TEAEs) are defined as adverse events that appear or worsen during the treatment period (up to 30 days after the last dose of the investigational product). However, if the subject is administered other anticancer drugs, in addition to the investigational product, during the treatment period, the adverse events after the administration of combined anticancer drugs will be excluded from the analysis.

For TEAEs, adverse drug reactions, serious adverse events, and CTCAE grade 3 or higher, the number of subjects who experienced the event, incidence rate (%), number of events, and 95% confidence interval of the incidence rate are presented. The statistical significance of the incidence rate between the

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treatment arms is examined by using chi-square tests or Fisher's exact tests. If the Fisher's exact test is performed for the comparison of the treatment arms, the 95% exact confidence interval for the incidence rate is presented.

If there are same adverse events with different CTCAE grade and causality, they will be considered as one case when calculating the number of subjects, and they will be treated as having the greatest CTCAE grade and causality. The total number of subjects in each treatment arm is used in calculating the incidence rate. In the calculation of the number of events, the above cases are considered as different adverse events.

All adverse events are classified with MedDRA and summarized with the grade determined by NCI CTCAE v4.03. At the time of the analysis, the latest version of MedDRA owned by Sanofi is used.

The number of subjects (incidence rate) and the number of events of the following adverse events are presented in the safety setg by system organ class (SOC) and preferred term (PT). However, 3) and 8) are presented in the list of subjects.

- 1) All adverse events and TEAEs that are likely to be related to the investigational products, which are classified by SOC in order of frequency
- 2) All TEAEs and TEAEs that are likely to be related to the investigational products, which are classified by SOC and by severity
- 3) Serious Adverse Events: All serious and possibly related serious TEAEs, which are classified by seriousness
- 4) Serious Adverse Events: All and possibly related TEAEs, which are classified by SOC
- 5) Death: All and possibly related TEAEs, which are classified by SOC
- 6) Study Discontinuation: All and possibly related TEAEs
- 7) Other Significant Adverse Events: All and possibly related TEAEs based on "other significant*" adverse event criteria
- 8) Discontinuation or Change of Treatment: All and possibly related TEAEs, which led to the discontinuation or change** of the investigational product dosing

* Other Significant: Defined as other medically important events in the seriousness criteria

** Action Taken: 2. Delayed, 3. Dose reduced, 4: Delayed and reduced, and 5: Interrupted.

3.3.6.2 Laboratory Safety Variables

If the laboratory test values are measured in unit other than the one recorded in the CRF, the unit should be converted according to the International System of Units (SI) given in the table in Appendix B.

Hematological toxicity is assessed based on the laboratory test results. Worst NCI CTCAE grades of leukopenia, neutropenia, thrombocytopenia, and anemia are calculated according to the NCI common terminology standards.

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Qualitative and quantitative results for hematological toxicity and biochemistry tests are summarized.

For the quantitative analysis, descriptive statistics (e.g., number of subjects, mean, standard deviation, median, and minimum and maximum) are presented for each cycle and changes before and after dosing by treatment arm. The pre-treatment level is defined as the last value or assessment value measured prior to the first treatment in the trial, and the final evaluation is based on the last value evaluated during the study drug dosing period.

For the qualitative data (worst NCI CTCAE grade or Normal [or NCS]/CS), the frequency is presented by treatment arm using the calculated worst NCI CTCAE grade or Normal (or NCS)/CS in a shift table for the change after the investigational product dosing compared to the baseline.

In addition, if the status was Normal/NCS at baseline, but showed a change into CS after the investigational product dosing, the results of each cycle of the subject are presented according to the time of measurement, and treatment information, subject identification number, gender, age, measurement time, measurement date, Lab item, baseline result, result of each time point, and information on normality are listed.

Hematological Test (Unit)

Haemoglobin (g/dL)

Hematocrit (%)

WBC ($\times 10^9/L$)

PMN (%)

LYM (%)

ANC ($\times 10^9/L$)

Platelet ($\times 10^9/L$)

PT (INR)

aPTT (sec)

Biochemistry Test (Unit)

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Sodium (mmol/L)

Potassium (mmol/L)

Calcium (mmol/L)

BUN (mg/dL)

Creatinine (mg/dL)

Total protein (g/dL)

Albumin (g/dL)

SGOT(AST) (U/L)

SGPT(ALT) (U/L)

Total bilirubin (mg/dL)

ALP (U/L)

Glucose (mg/dL) (fasting / non-fasting)

Creatinine clearance (mL/min)

3.3.6.3 Other Safety Variables

The descriptive statistics (e.g., number of subjects, mean, standard deviation, median, and minimum and maximum) of the physical examinations (e.g., body weight, blood pressure, and ECOG PS) are presented on a visit basis, and the changes before and after dosing are summarized. In addition, the frequencies of special tests (e.g., chest x-ray and ECG) are presented using Normal (or NCS)/CS in a shift table for the change after the investigational product dosing compared the baseline.

Weight (kg)

SBP (mmHg)

DBP (mmHg)

ECOG Performance Status (0 / 1 / 2 / 3 / 4)

Chest X-Ray (Normal / Abnormal, not clinically significant / Abnormal, clinically significant)

ECG (Normal / Abnormal, not clinically significant / Abnormal, clinically significant)

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3.4 DATA HANDLING CONVENTIONS

The rules for data processing are as follows.

3.4.1 Baseline Definitions

Overall, the baseline values of the analysis variables are defined as pre-treatment or preoperative last observation values.

3.4.2 Missing Data

3.4.2.1 Missing data of Efficacy Variable

Overall, no imputation method for missing data is used. The following are the basic methods for handling missing data.

- Categorical Data: When calculating the proportion for a categorical variable, the subjects whose data is missing in the calculation of the ratio are excluded from the denominator.
- Continuous Data: Observed data are based on the analysis and summary of continuous variables, and the number of subjects with missing data is presented.
- Time-to-Event Data: If there are missing data, the censoring rule shall be followed. The information on censoring is described in the analysis variable section.

3.4.2.2 Missing data of Safety Variable

In the safety data, if a subject has withdrawn prior to the end of the trial or has a missing data, the case is treated as missing without imputation.

3.4.3 Handling of Incomplete Data

If part of a day or month is missing from the start or end date of medical history, concomitant medication, adverse event, etc., and collected as unknown, the date is compared only to the unit collected without replacing the date. If the entire start date is missing, it is considered to be prior to the first dose of the investigational product, and if the end date is missing, it is considered to be ongoing or being administered.

However, if the date of death, disease progression confirmation date, which are related to the primary efficacy analysis, or last follow-up date, is unclear, and no further information can be collected, i.e., 'month' or 'day' is not collected, 'month' or 'day' is considered as January or the 1st day. If the entire date

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is unclear, not partially, i.e., if all the year, month, and day are unidentifiable, censoring is done at the last date collected. (If the last date is equal to or earlier than the randomization date, the randomization date is used.)

3.4.4 Character Values of Clinical Laboratory Evaluation

If any of the measurements, including inequality signs, of the clinical laboratory results are collected, the data are summarized by replacing as follows. When presenting a list of subjects, the recorded values in the case report form are presented.

- If the result is recorded as not less than or over (i.e., ≥ 100 or > 100), replace it with a minimum value (i.e., 100)
- If the result is recorded as not more than or below (i.e., ≤ 4 or < 4), replace it with a maximum value (i.e., 4)

3.4.5 Decimals

Descriptive statistics (e.g., mean, standard deviation, median, and minimum and maximum) for continuous data are presented to the second decimal place for the efficacy data and demographic information. Laboratory results are rounded to the significant digit, i.e., the digit below the maximum decimal point for each item. When presenting the ratio of categorical data, the values are presented to the second decimal place, and the p-value is summarized to the fourth decimal place. If the calculated p-value is below 0.0001, it will be presented as $< .0001$.

3.4.6 Pooling of Centers for Statistical Analyses

Not applicable

3.4.7 Statistical Technical Issues

Not applicable

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4 INTERIM ANALYSIS

The purpose of the interim analysis is to provide IDMC members with methodological theoretical rationale and decision rules for recommending the continuation of the trial as planned or early termination of the trial because the efficacy has already been proven based on the pre-described boundaries. Additional details will be described in the IDMC Charter.

A single interim analysis is planned, and IDMC members will review the primary efficacy and safety. An independent statistician will perform the analysis during the interim analysis, and the trial will not be interrupted. The interim analysis results are reported only to IDMC members during this trial. IDMC will regularly monitor the safety of the subjects who are exposed to the investigational products, while TEAE, hematological toxicity, and biochemical toxicity will be summarized by using descriptive statistics.

If the IDMC review result falls under any of the following, early termination of the trial will be considered:

Early Evidence of Superiority

In order to prevent the increase of type I error due to a single interim analysis, the O'Brien-Fleming alpha spending function is used.

An interim analysis is conducted at the time of occurrence of about 122 PFS events (50% information rate). If there is a significant difference in PFS between the two arms at the significance level of 0.0031, the trial will be discontinued, and a planned final analysis will be performed. Otherwise, follow-up is conducted until the total number of PFS events reaches 244 or more, and the final analysis for efficacy will be performed at the significance level of 0.049.

Problem with AEs

Discontinuation of the trial may be considered later if hematological or biochemical toxicity is more serious than anticipated.

Details about the interim analysis will be described in the other SAP for interim analysis.

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5 SOFTWARE DOCUMENTATION

For all result summaries and statistical analyses, SAS (version 9.4 or higher, SAS Institute, Cary, NC, USA) will be used.

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LIST OF APPENDICES

Appendix A: Summary of statistical analyses
Appendix B: Unit conversion table

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Guidance for Clinical Trial Sponsors-Establishment and Operation of Clinical Trial Data Monitoring Committees

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APPENDIX A: SUMMARY OF STATISTICAL ANALYSES

EFFICACY ANALYSIS:

	Analysis		Statistical	Supportive	Subgroup	Other
Endpoint	Population	Primary Analysis	Method	Analysis*	Analysis*	Analyses*
Primary Endpoint						
Progression free survival	FAS, ITT, PP	To compare progression free survival between two treatment arms	Stratified log-rank test, Kaplan-Meier Estimate	No	Yes, Subgroup: TNM stage, Age, Gender, T stage, N stage, Histological type, Adjuvant chemotherapy completion, Response(CSC arm only)	Yes, if possible, hazard ratio and 95% CI will be presented using Cox proportional hazard model
Secondary Endpoints						
Overall survival	FAS, ITT, PP	To compare overall survival between two treatment arms	Stratified log-rank test, Kaplan-Meier Estimate	No	Yes, Subgroup: TNM stage, Age, Gender, T stage, N stage, Histological type, Adjuvant chemotherapy completion, Response(CSC arm only)	Yes, if possible, hazard ratio and 95% CI will be presented using Cox proportional hazard model
R0 resection rate	FAS, ITT, PP	To compare R0 resection rate between two treatment arms	Cochran-Mantel-Haenszel test	No	Yes, Subgroup: TNM stage, Age, Gender, T stage, N	No

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Endpoint	Analysis		Statistical	Supportive	Subgroup	Other
	Population	Primary Analysis	Method	Analysis*	Analysis*	Analyses*
					stage, Histological type, Adjuvant chemotherapy completion, Response(CSC arm only)	
Pathological stage	FAS, ITT, PP	To compare pathological stage between two treatment arms	Cochran-Mantel-Haenszel test	No	No	No

SAFETY ANALYSES:

Endpoint	Analysis		Statistical	Robust	Subgroup	Other
	Populations	Primary Analysis	Method	Analysis*	Analysis*	Analyses*
Adverse Events	Safety	To compare adverse event rates between two treatment arms	Chi-square test or Fisher's exact test	No	No	No
Hematological toxicity	Safety	To compare hematological toxicity rates between two treatment arms	Chi-square test or Fisher's exact test	No	No	No

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APPENDIX B: UNIT CONVERSION TABLE

Variable	Sex	Unit	Conversion Factor	SI unit
Hemoglobin	Both	mg/dL	$\times 0.01$	g/L
Hemoglobin	Both	g/dL	$\times 10$	g/L
Hematocrit	Both	%	$\times 0.01$	L/L
WBC	Both	$\times 10^3/\text{mm}^3$	$\times 1.0$	$\times 10^9/\text{L}$
ANC	Both	$\times 10^3/\text{mm}^3$	$\times 1.0$	$\times 10^9/\text{L}$
Platelet	Both	$\times 10^3/\text{mm}^3$	$\times 1.0$	$\times 10^9/\text{L}$
Sodium	Both	mg/dL	NA	mmol/L
Potassium	Both	mg/dL	$\times 0.2558$	mmol/L
Potassium	Both	mEq/L	$\times 1.0$	mmol/L
Calcium	Both	mg/dL	$\times 0.250$	mmol/L
Calcium	Both	mEq/L	$\times 0.500$	mmol/L
Phosphorus	Both	mg/dL	$\times 0.3229$	mmol/L
Magnesium	Both	mg/dL	$\times 0.4114$	mmol/L
Magnesium	Both	mEq/L	$\times 0.500$	mmol/L
BUN	Both	mg/dL	$\times 0.357$	mmol/L
Creatinine	Both	mg/dL	$\times 76.25$	$\mu\text{mol/L}$

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Variable	Sex	Unit	Conversion Factor	SI unit
Total protein	Both	g/dL	× 10	g/L
Albumin	Both	mg/dL	× 0.01	g/L
Albumin	Both	g/dL	× 10	g/L
SGOT (AST)	Both	μkat/L	× 59.988	U/L
SGPT (ALT)	Both	μkat/L	× 59.988	U/L
Total bilirubin	Both	mg/dL	× 17.1	μmol/L
Total bilirubin	Both	mg/L	× 1.71	μmol/L
ALP	Both	μkat/L	× 0.01667	U/L
Glucose	Both	mg/dL	× 0.05551	mmol/L
Creatinine clearance	Both	NA	NA	mL/min

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