Official Title: A Phase II, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) and Trastuzumab in Combination With Capecitabine and Oxaliplatin (Xelox) in Patients With HER2 Positive Locally Advanced Resectable Gastric Cancer of Adenocarcinoma of Gastroesophageal Junction (GEJ)

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE II, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) AND TRASTUZUMAB IN COMBINATION WITH CAPECITABINE AND OXALIPLATIN (XELOX) IN PATIENTS WITH HER2 POSITIVE LOCALLY ADVANCED RESECTABLE GASTRIC CANCER OR ADENOCARCINOMA OF GASTROESOPHAGEAL JUNCTION (GEJ)**

PROTOCOL NUMBER: ML42058

STUDY DRUG: Atezolizumab (RO5541267)
Trastuzumab (RO0452317)

VERSION NUMBER: 1.0

IND NUMBER: Not Applicable

EUDRACT NUMBER: Not Applicable

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: 13 MAR 2023

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

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Abbreviation

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
HR	Hazard Ratio
MedDRA	Medical Dictionary for Regulatory Affairs
NAST	Neoadjuvant Systemic Therapy
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

Abbreviation	Definition
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
SAS	Statistical Analysis System
SD	Stable Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

1. BACKGROUND

This Statistical Analysis Plan (SAP) is based on Protocol ML42058, “A Phase II, Randomized Study Of Atezolizumab (Anti-PD-L1 Antibody) and Trastuzumab in Combination with Capecitabine and Oxaliplatin (XELOX) in Patients with HER2 Positive Locally Advanced Resectable Gastric Cancer or Adenocarcinoma of Gastroesophageal Junction (GEJ)”. The background for the study can be found in the study protocol.

This SAP describes the statistical methods that will be used during the analysis for ML42058. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP has been developed using study protocol Amendment Version 6.0 dated on 21 Feb 2023. Any analyses that are beyond those outlined in the protocol are delineated in this document.

2. STUDY DESIGN

This is a phase II, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of perioperative trastuzumab+XELOX with / without atezolizumab in patients eligible for surgery with locally advanced HER2-positive gastric cancer or adenocarcinoma of GEJ. The study will enroll approximately 42 patients in China.

Patients who have histologically confirmed, HER2 positive, locally advanced (cT3/T4a/T4b or N+, M0, AJCC 8th edition) gastric cancer or adenocarcinoma of GEJ (Siewert I-III) are eligible. HER2 status of the primary gastric/GEJ tumor will be assessed in local laboratory and mandatory sent to the central laboratory for HER2 positivity confirmation. Patients without centrally confirmed HER2-positive result will be included in ITT analysis but not in PP analysis.

Eligible patients will be enrolled and 1:1 randomized to perioperative treatment with either trastuzumab plus atezolizumab with XELOX (Arm A) or trastuzumab alone with XELOX (Arm B).

Arm A: Atezolizumab plus Trastuzumab with XELOX
Patients randomized to treatment Arm A will receive atezolizumab + trastuzumab + XELOX for 3 treatment cycles prior to surgery, 3 weeks each cycle, as described below. Following surgery, patients will receive 5 further cycles of this regimen.

- Atezolizumab 1200mg IV day 1 every 3 weeks Q3W
- Trastuzumab 6 mg/kg IV day 1 (8 mg/kg as loading dose at 1st administration pre and post-operation) Q3W
- XELOX: Capecitabine 1000mg/m^2 PO bid, days 1-14 Q3W
  Oxaliplatin 130mg/m^2 IV day 1 Q3W

Arm B: Trastuzumab with XELOX
Patients randomized to treatment Arm B will receive trastuzumab + XELOX for 3 treatment cycles prior to surgery, 3 weeks each cycle, as described below. Following surgery, patients will receive 5 further cycles of this regimen.

• Trastuzumab 6 mg/kg IV day 1 (8 mg/kg as loading dose at 1st administration pre- and post-operation) Q3W
• XELOX: Capecitabine 1000mg/m^2 PO bid, days 1-14 Q3W
Oxaliplatin 130mg/m^2 IV day 1 Q3W

Surgery is recommended to be performed 3 to 6 weeks after the last dose of neoadjuvant study treatment. The first dose of postoperative treatment is recommended to initiate within 8 weeks after surgery. Surgical approaches will be tailored to the individual patient according to local standards with the goal of achieving R0 resection.

Note: there will be a Safety Run-in Phase comprising the first 10 patients enrolled into both arms who have completed neoadjuvant treatment and surgery. All available safety data (including perioperative morbidity and mortality) of the first 10 patients will be reviewed by the internal monitoring committee (IMC) for providing a recommendation whether to continue, modify or terminate the study.

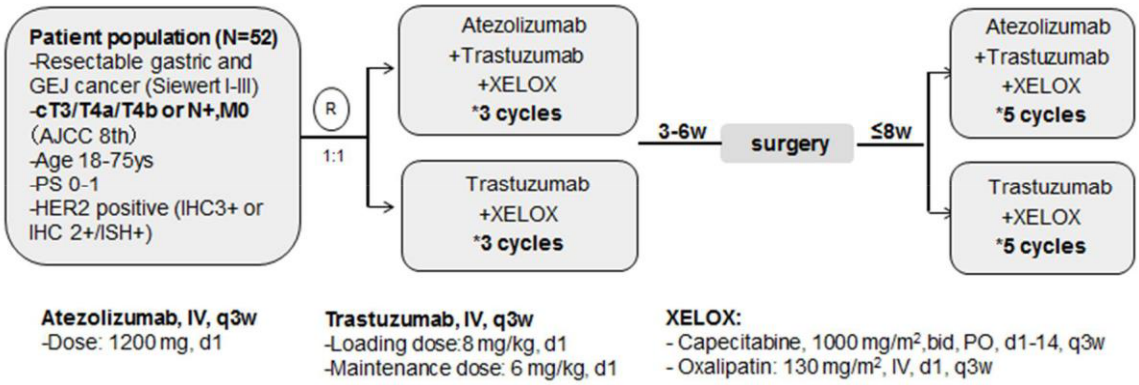
The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported. During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event electronic Case Report Form (eCRF) and in the patient's medical record to facilitate source data verification. Following completion of the treatment of the study, every effort should be made to follow up all patients for their disease and survival status until patient death or termination by the Sponsor, except withdrawing consent. Patients who discontinue neoadjuvant therapy early as a result of disease progression or who receives non-protocol therapy prior to surgery must be discontinued from all study treatment, and will be managed per local practice. These patients will remain on study for survival follow-up.

Patients who discontinue treatment for reasons other than disease progression (e.g.,toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Tumor specimens (by pre-operative biopsy and surgical resection) from eligible patients will be prospectively tested for biomarkers. ctDNA will also be collected for HER2 copy number monitoring. These samples will enable analysis of tumor tissue biomarkers related to clinical benefits.

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



AJCC= American Joint Committee on Cancer; GEJ = gastroesophageal junction ; d = day; IHC= immunohistochemistry; IV = intravenous; PO = per os; PS= Performance Status; Q3W= every 3 weeks

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURE

2.2.1 Primary Efficacy Endpoint

- Pathological complete regression (pCR) rate, defined as no evidence of vital residual tumor cells on hematoxylin and eosin evaluation of the complete resected gastric/GEJ specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST).

2.2.2 Secondary Efficacy Endpoints

- Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

- Disease-free survival (DFS), defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first.

- Overall survival (OS), defined as the time from randomization to death from any cause in all patients.

- Major pathologic response (MPR), defined as < 10% residual tumor per tumor bed based on evaluation of the resected primary esophagogastric specimen by a local pathologist.

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) during NAST, as determined by the investigator according to RECIST v1.1.

- R0 resection rate, defined as the proportion of patients with a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed and/or sampled regional lymph nodes based on evaluation by the local pathologist.

2.2.3 Exploratory Efficacy Endpoints

- HER2 copy number in ctDNA and HER2 status

- MMR status

- PD-L1 expression

- sTIL infiltration

2.2.4 Safety Endpoints

- Incidence, nature and severity of adverse events (AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).

- Changes from baseline in targeted vital signs and physical findings

- Changes from baseline in targeted clinical laboratory test results

2.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation of this study is based on the primary endpoint, the pCR rate. Assuming mean difference between two arms is 22% and pCR rate is 10% for control arm (arm B), sample size of 19 per each group could provide the precision (half width) of 90% CI of 0.21.

It is planned to recruit 42 patients (21 patients in each group) into this study assuming a 10% drop-out rate.

2.4 ANALYSIS TIMING

Not Applicable.

3. STUDY CONDUCT

3.1 RANDOMIZATION

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: atezolizumab plus trastuzumab with XELOX or trastuzumab with XELOX. Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

3.2 INDEPENDENT REVIEW FACILITY

Not Applicable.

3.3 DATA MONITORING

An internal Monitoring Committee (IMC) will evaluate all available safety data (including perioperative morbidity and mortality) of the first 10 patients during the study for providing a recommendation whether to continue, modify or terminate the study. The IMC is a Roche internal committee and consists of the statistician, safety scientist and representatives from clinical science.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

The operation of IMC will follow the IMC agreement.

4. STATISTICAL METHODS

The following represents an overview of the planned statistical analysis. If any additional exploratory analyses are found to be necessary, the analyses will be performed.

4.1 STATISTICAL CONSIDERATION

4.1.1 General Rule

Continuous variables: Descriptive statistics, including the n, mean, standard deviation, median, minimum, and maximum values will be provided for continuous variables. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean and median will be presented to one more decimal place than the raw data, standard deviation will be presented to two more decimal places than the raw data.

Categorical measurements will be described in number of patients for each item and percentage to the analysis set. Percentage will be rounded to one decimal place.

Time-to-event endpoints will be assessed with median survival time, lower quartile, upper quartile and its corresponding 95% CI using Kaplan-Meier method, these statistical will be presented to two decimal places. Besides, Kaplan-Meier product-limit plot will be produced.

Confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. For binomial variables, the normal approximation methods will be employed unless otherwise specified. The 95% CI will be presented to one more decimal place than the raw data.

P-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as "<0.0001."

Statistical programming and analyses will be conducted using SAS® Software (SAS Institute Inc., Cary, NC) Version 9.4 or higher.

4.1.2 Baseline Definition

The baseline value is defined as the last non-missing value prior to start of study drug.

4.1.3 Study Day

The randomization date is considered as Day 1, patients' time on study will be determined in study days. Study day is defined as follows:

Study Day = the current date – Day 1 + 1, if the current date ≥ date of Day 1;

Study Day = the current date – Day 1, if current date < date of Day 1.

4.1.4 Visit Window Definitions

In general, for by-visit summaries, data recorded at the nominal or observed visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the baseline value, or best/worst case value where required (e.g. shift tables).

For best/worst case (e.g. shift tables), all available measurements including retest values will be used.

Listings will include scheduled, unscheduled, retest and early discontinuation data

4.2 ANALYSIS POPULATIONS

4.2.1 Intention-to-treat Population

It is defined as all patients who were randomly assigned to a treatment, regardless of whether they had surgery. The ITT population will be used for efficacy analyses.

4.2.2 Per-protocol Population

It is defined as all patients who are centrally confirmed as HER2 positive and underwent resection. The PP population will used for sensitivity analysis of pCR. The PP population will be reviewed by sponsor in data review meeting.

4.2.3 Safety Population

It is defined as all randomized patients who received at least one dose of study treatment, with patients grouped according to treatment received. The safety population will be used for safety analyses.

4.3 ANALYSIS OF STUDY CONDUCT

Descriptive statistics will be used in evaluating the conduct of the study.

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study drug discontinuation will also be tabulated.

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm. All protocol deviations will be listed.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, min, and max for continuous variables and proportions for categorical variables, as appropriate. These analyses will be presented in ITT population, see details below:

Demographics and Baseline Characteristics:

- Age
- Sex (Female, Male)
- Ethnicity (Asian, Other, Unknown)
- Weight
- BMI
- Smoking history (Never, Current, Previous)
- Alcohol use history (Never, Current, Previous)

Baseline GC/ GEJ History and Baseline Disease Characteristics:

- Time from initial diagnosis to randomization
- Histology classification at initial diagnosis
- Lauren classification at initial diagnosis
- Differentiated degree at initial diagnosis
- Stage at initial diagnosis
- Primary tumor location
- Status of disease (locally recurrent disease, locally advanced unresectable disease, metastatic disease)
- Molecular Profile at Study Entry
    - HER2 (positive, negative, uncertain, not done)
    - IHC Score (0, 1+, 2+, 3+)
- Exploratory Analysis Variables
    - HER2 copy number in ctDNA
    - MMR status
    - PD-L1 expression
    - sTIL infiltration
- Current Stage (TNM and clinical stage)
- Baseline ECOG score
- Baseline tumor assessment
    - Target lesions (Yes, No)
    - Non-target lesions (Yes, No)
- Number of target lesions (1, 2, 3, 4, 5)
- Sum of the target lesion diameters

Demographics and baseline characteristics will also be listed for each patient.

4.4.2 Medical History

All reported medical history from eCRF page of Medical History will be coded with MedDRA 26.0 or the latest version before database lock. Number and percentage of patients with any medical related history will be summarized for the ITT by system organ class (SOC) and preferred term (PT). Autoimmune Diseases and other medical history will display separately.

All reported medical related history will be listed for ITT.

4.4.3 Concomitant Medication

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary March 1,2023 or the latest version before database lock. The number (percent) of patients who took concomitant medications will be summarized and listed by treatment, Anatomical Therapeutic Chemical (ATC) Level 2 Classification and WHO Drug preferred term.

Concomitant Medication contains any medication used by a patient in addition to protocol-mandated treatment from 7 days prior the initiation of study treatment until the treatment discontinuation visit or 30 days after the last study treatment (whichever occurs first).

All anti-cancer therapies will be summarized with patients for the ITT set. The number of patients with anti-cancer therapies will be summarized using descriptive statistics. Any anti-cancer therapies will also be listed.

For prior anti-cancer therapy, just number of patients is required to provide by category of prior therapy. For the post-study treatment anti-cancer therapy, it will be summarized in terms of therapy given, duration of subsequent therapies (based on start / stop dates).

4.5 EFFICACY ANALYSIS

4.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is Pathological complete regression (pCR) rate. It will be established following completion of neoadjuvant therapy and surgery. pCR status of surgery specimens will be analyzed by local pathologists at each site.

pCR rate will be analyzed in the intention-to-treat (ITT) population. Patients without surgery will be considered non-pCR. An estimate of the pCR rate and its 95% CI will be calculated for each treatment arm. The CIs for each treatment arm will be calculated with the Clopper-Pearson exact method. The difference in pCR rates will be provided with 90% CIs, using the normal approximation to the binomial distribution such as Miettinen-Nurminen method. P value of comparison between two arms will be calculated with Chi-square test.

It will be additionally assessed in a pre-specified sensitivity analysis in the per-protocol (PP) population.

4.5.2 Secondary Efficacy Endpoints

4.5.2.1 Event-Free Survival

Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

Date of progression will be determined based on the earliest of the dates of the component that triggered the progression. For example, for PD based on a new lesion, the PD date is the date of the first radiological assessment when the new lesion was detected. Regardless of radical resection, it is considered as PD when distant metastasis is observed during surgery or reported in the pathological examination (ypTNM stage-M M1). The date of operation is defined as progression confirmation day. 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.

Date of disease recurrence will be determined based on Disease Recurrence assessment form. Patients who have not experienced disease recurrence, progression or death at the time of analysis will be censored at the time of the last adequate tumor or recurrence assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization. The detail on programmatically determining events or censored times is described in Table 1.

Table 1

Situation	Situation -sub	Date of Event or Censor	Event / Censor
No post baseline tumor assessment available	a). no death reported within 2 scan intervals following the date of randomization	Date of Randomization	Censored
	b). death reported within 2 scan intervals following the date of randomization	Date of Death	Event
Tumor progression (PD) or disease	a). disease recurrence documented after 2 scan intervals following previous evaluable	Date of previous evaluable tumor or	Censored

Situation	Situation -sub	Date of Event or Censor	Event / Censor
recurrence with no new anti-cancer	tumor or disease recurrence assessment	disease recurrence assessment	
	b). PD or disease recurrence documented within 2 scan intervals following previous evaluable tumor assessment	Date of PD or disease recurrence	Event
No tumor PD and NO disease recurrence but Death reported	a). death reported after 2 scan intervals following last evaluable tumor or disease recurrence assessment	Date of last evaluable tumor or disease recurrence assessment before missing 2 scan intervals	Censored
	b). Death within 2 scan intervals following previous evaluable tumor or disease recurrence assessment	Date of Death	Event
No tumor progression and NO disease recurrence and no Death reported		Date of last evaluable tumor or disease recurrence assessment	Censored
new anti-cancer prior to PD or disease recurrence or Death		Date of last evaluable tumor or disease recurrence assessment before start of new anti-cancer	Censored

Patients will undergo tumor assessments at baseline, within 2 weeks before surgery, every 6 months after surgery in the first 3 years, and once a year until 5 years after surgery regardless of dose delays, until radiographic disease progression per RECIST v1.1. Therefore, in order to determine if a PD event occurred after 2 missed/non-

evaluable tumor assessment visits, the definition of 2 scan intervals (allowing for early and late visits) will be as follows:

- If the previous evaluable tumor assessment is less than 30 months after surgery, then 2 scan intervals equates to 12 months from the previous evaluable tumor assessment.

- If the previous evaluable tumor assessment is greater than or equal to 30 months after surgery and less than 48 months after surgery, then 2 scan intervals equates to 18 months from the previous evaluable tumor assessment.

- If the previous evaluable tumor assessment is greater than or equal 48 months after surgery, then 2 scan intervals equates to 24 months from the previous evaluable tumor assessment.

EFS in months is calculated as (first event date/censored date – date of randomization +1) / 30.4375.

The Kaplan-Meier estimates will be presented by each treatment arm including median time and its corresponding 95%CI if applicable. The 95%CI of median time will be calculated according to the Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982).

The estimated event-free survival rates at 6, 9 and 12 months will be estimated via the Kaplan-Meier method and displayed and repeated for every 6 months after if follow-up goes beyond 12 months. The corresponding 95% confidence interval (using the Greenwood formula method of Kalbfleisch and Prentice, 1980) for each estimated EFS rate will be presented. The Cox proportional hazards model will be used to estimate the hazard ratio between the two treatment arms and its 95% CI. The p-value of Log-rank test results will be provided. EFS will be presented graphically using Kaplan-Meier plots.

The median follow-up time for EFS and the corresponding 95% confidence interval (using the method of Brookmeyer and Crowley, 1982 with the log-log transformation) will also be summarized using the reverse KM method. The analysis involves the event and censoring rules to be switched (i.e. the patients with documented disease progression or death become ‘censored’, and the censored patients are treated as the ‘event’).

4.5.2.2 Disease-Free Survival (DFS)

Disease-free survival (DFS), defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first.

DFS in months is calculated as (first event date/censored date – date of surgery +1) / 30.4375

DFS will be analyzed in a similar manner as EFS.

4.5.2.3 Overall survival

OS is defined as the time from randomization to death from any cause.

Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization.

The last known alive date will be derived for patients known to be alive at the analysis cut-off date using the latest complete date among the following data:

- All assessment dates (e.g. vital signs assessment, performance status assessment, disease recurrence assessment and also assessment date in third-party data such as tumor imaging).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events dates
- Date last known alive collected on the eCRF page of 'Follow-up Visit'

OS in months is calculated as (date of death/last known to be alive – date of randomization +1) / 30.4375.

OS will be analyzed in a similar manner as EFS.

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided.

4.5.2.4 Major Pathologic Response

Major pathologic response (MPR), defined as < 10% residual tumor per tumor bed based on evaluation of the resected primary esophagogastric specimen by a local pathologist.

MPR will be analyzed in a similar manner as primary endpoint pCR.

4.5.2.5 Objective Response Rate

Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) during NAST, as determined by the investigator according to RECIST v1.1. Patients without any post-baseline tumor assessment, will be considered non-responders.

The Best Overall Response (BOR) is the best response recorded from the first dose date of study drug) until disease progression, death, or start of new anticancer therapy. Tumor scan assessments done after PD or after “new anti-cancer” treatment, but prior to PD, will not be considered in the evaluation of BOR. Confirmation of PR or CR is not required.

ORR will be analyzed in a similar manner as primary endpoint pCR.

4.5.2.6 R0 Resection Rate

R0 resection rate, defined as the proportion of patients with a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed and/or sampled regional lymph nodes based on evaluation by the local pathologist.

Patients who will not undergo surgery or will not have a resection will be considered as treatment failures (not having R0 resection). R0 resection rates will be analyzed in a similar manner as primary endpoint pCR

4.5.3 Exploratory Efficacy Endpoints

4.5.3.1 HER2 copy number in ctDNA

HER2 copy number in ctDNA will be displayed by visit and treatment group. HER2 status will be used for the efficacy endpoints.

4.5.3.2 MMR status

MMR status will be assessed centrally or locally using biopsy samples. Deficient MMR (dMMR) is defined by immunohistochemistry (IHC) as a loss of expression in $\geqslant$1 mismatch repair proteins (MLH1, PMS2, MSH2 or MSH6).

MMR results (dMMR yes or no) will be collected for analysis for the efficacy endpoints.

4.5.3.3 PD-L1 expression

Expression of PD-L1 will be assessed both in pre-treatment tumor biopsy and surgical resected samples by the IHC assay (PD-L1, 22C3; Agilent Technologies) in the central laboratory. Tumors will be considered PD-L1 positive if the combined positive score (number of PD-L1–positive cells [tumor cells, macrophages, lymphocytes] divided by the total number of tumor cells, multiplied by 100) is 1 or greater.

Analysis for the efficacy endpoints based on PD-L1 expression status (positive or negative) will be evaluated.

4.5.3.4 sTIL infiltration

sTIL signature will be assessed by multiplex immunohistochemistry staining on pretreatment tumor tissue by central pathologist. Briefly, 4-5 µm sections of FFPE will be applied with several antibodies to label different kinds of cells. TILs are reported for the

stromal compartment (% stromal TILs, sTIL) in all areas containing invasive tumor cells on the H&E slide containing the most invasive tumor.

4.5.4 Sensitivity Analysis

For the primary efficacy analysis, a sensitivity Analyses will be based on the per-protocol (PP) population.

4.6 SAFETY ANALYSIS

4.6.1 Exposure of Study Medication

The following data will be summarized by neoadjuvant and adjuvant period. A cycle is defined as 21 days = 3 weeks.

The following will be derived:

- Treatment duration (days) = (date of last study drug administration – date of first study drug administration + 21) for Atezolizumab, Trastuzumab and Oxaliplatin; while for Capecitabine, = (date of last study drug administration – date of first study drug administration + 8)

- Number of cycles= Treatment duration of study drug (days)/21

- Total actual dose received = sum of the total dose that a patient received during the study

- Dose intensity (dose unit per cycle) is calculated as follows:

  $=\frac{\sum_{i=1}^{n}(Total\ dose\ received\ at\ cycle\ i)}{Total\ duration\ of study\ drug\ (days)/21}$,for Atezolizumab

  $=\frac{\sum_{i=1}^{n}(Total\ dose\ received\ at\ cycle\ i/W_i)}{Total\ duration\ of study\ drug\ (days)/21}$,for Trastuzumab

  $=\frac{\sum_{i=1}^{n}(Total\ dose\ received\ at\ cycle\ i/BSA_i\ )}{Total\ duration\ of study\ drug\ (days)/21}$, for Oxaliplatin and Capecitabine

  Here, BSA_i is BSA at i^{th} cycle, W_i is $Weight$ at i^{th} cycle and n is the maximum number of cycles in which the subject underwent treatment.

- Planned dose intensity is the value specified in the protocol. For Atezolizumab 1200 mg per cycle, Capecitabine 28000mg/m^2 per cycle; Oxaliplatin 130mg/m^2 per cycle; Trastuzumab (8+6+6+8+6*(number of post-surgery cycle-1))/ (number of post-surgery cycle +3) mg/kg per cycle for overall;(8+6+6)/3 mg/kg per cycle for

neoadjuvant period, 8+6*(number of post-surgery cycle-1))/ (number of post-surgery cycle) mg/kg per cycle for adjuvant period;

- Relative dose intensity (%) = (Dose intensity / Planned dose intensity) × 100

The numbers of patients who experience any dose interruption, dose reduction, overdose, or dose discontinuation for any component of the study treatment and the reasons will be summarized by treatment arm.

4.6.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as all adverse events reported, or worsening of an existing condition, after initiation of study treatment, until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

An overall summary of TEAEs will be provided. The number and percentage of patients with the following will be summarized.

- Patients with at least one TEAE
- Patients with Infusion Related Reactions TEAE
- Patients with any study drug related TEAEs
- Patients with Atezolizumab only related TEAEs
- Patients with Trastuzumab only related TEAEs
- Patients with Capecitabine only related TEAEs
- Patients with Oxaliplatin only related TEAEs
- Patients with TEAEs of CTCAE Grade 3 or higher
- Patients with any study drug related TEAEs of CTCAE Grade 3 or higher
- Patients with Atezolizumab only related TEAEs of CTCAE Grade 3 or higher
- Patients with Trastuzumab only related TEAEs of CTCAE Grade 3 or higher
- Patients with Capecitabine only related TEAEs of CTCAE Grade 3 or higher
- Patients with Oxaliplatin only related TEAEs of CTCAE Grade 3 or higher
- Patients with serious TEAEs
- Patients with any study drug related TEAEs of SAE
- Patients with Atezolizumab only related TEAEs of SAE
- Patients with Trastuzumab only related TEAEs of SAE

- Patients with Capecitabine only related TEAEs of SAE
- Patients with Oxaliplatin only related TEAEs of SAE
- Patients with adverse events of special interest (AESI)
- Patients with any study drug related of AESI
- Patients with Atezolizumab only related of AESI
- Patients with Trastuzumab only related of AESI
- Patients with TEAEs leading to any study drug interruption
- Patients with TEAEs leading to Atezolizumab only interruption
- Patients with TEAEs leading to Trastuzumab only interruption
- Patients with TEAEs leading to Capecitabine only interruption
- Patients with TEAEs leading to Oxaliplatin only interruption
- Patients with TEAEs leading to any study drug reduction
- Patients with TEAEs leading to Atezolizumab only reduction
- Patients with TEAEs leading to Trastuzumab only reduction
- Patients with TEAEs leading to Capecitabine only reduction
- Patients with TEAEs leading to Oxaliplatin only reduction
- Patients with TEAEs leading to any study drug discontinuation
- Patients with TEAEs leading to Atezolizumab only discontinuation
- Patients with TEAEs leading to Trastuzumab only discontinuation
- Patients with TEAEs leading to Capecitabine only discontinuation
- Patients with TEAEs leading to Oxaliplatin only discontinuation
- Patients with TEAEs leading to death

All TEAEs will be coded using MedDRA 26.0 or the latest version before database lock and summarized by MedDRA SOC and PT. The severity of all TEAEs will be graded by the investigator using NCI CTCAE version 5.0. TEAEs starting after the first dose of study drug with a missing severity will be classified as 'missing'. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries. In determining maximum severity, response values will be ranked in order from minimum severity to maximum severity as Missing, Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5.

A summary table will present TEAEs, showing number of patients (%) for all grades (including missing grades) and grades $\geqslant$ 3 for each SOC/PT. This summary table will also be repeated for TEAEs related to study drug (Atezolizumab, Trastuzumab).

AE causality to the study medication is classified as “Yes”, “No” and “NA”. All AE causality will be grouped as “related” and “unrelated” in the analysis, in which AEs with causality of “Yes” or “NA” will be categorized to “Related” and “No” will be categorized to “Unrelated”.

Serious adverse events will be summarized by SOC and PT. This summary table will also be repeated for SAEs related to study drug (Atezolizumab, Trastuzumab).

Adverse events of special interest (AESIs) defined in Section 5.2.3 of the Protocol will be summarized by SOC and PT. This summary table will also be repeated for AESIs related to study drug (Atezolizumab, Trastuzumab).

Adverse events leading to any study drug discontinuation will be summarized by SOC and PT.

If any patients die during the study as recorded on the Death page of the eCRF, the information will be summarized in a table by primary reason for death and presented in a data listing. Adverse events leading to death will also be summarized by SOC and PT.

Non-serious adverse events with >=5% occurring rate will be summarized by SOC and PT.

Serious adverse events, fatal SAEs and SAEs related to study drug will be summarized by SOC and PT.

Adverse events with difference of at least 10% and serious adverse events with difference of at least 2% between treatment arms will be summarized by PT.

Listings to be provided are:

- All reported AEs
- Serious AEs
- AESIs
- TEAE leading to dose interruption, reduction or discontinuation
- Death

4.6.3 Laboratory Data

For laboratory tests covered by the NCI CTCAE version 5.0 the study team will grade laboratory data accordingly. For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher.

The following summaries will be provided for selected laboratory data. These summaries will be repeated for hematology, biochemistry and urinalysis:

- Shift from baseline to the worst on-treatment/follow-up value according to NCI CTCAE grading system for quantitative measurements, as well as for urinalysis categorical measurements. The percentage of patients shift from CTCAE grade 0-2 baseline to 3-4 post baseline will be summarized.
- For measurements that have an NCI CTCAE grading system, 'worst' will be defined as the maximum (i.e. most severe) Grade obtained during treatment; A special note: For laboratory tests that have CTCAE grades defined for both a lower and higher level of extremity, separate shift from baseline summaries will be presented for each extreme of abnormality, e.g. (i) Lymphocytes Absolute Count – Low and (ii) Lymphocytes Absolute Count – High.
- Listing of all clinically relevant laboratory data.

4.6.4 Vital Signs

Vital signs results are assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant. Shift from baseline to worst post-baseline/last observation value will be presented using number and percentage.

All vital signs assessments will be listed by patient, visit and vital sign parameters.

4.6.5 Physical Examination Finding

Physical examination results are assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant. Shift from baseline to worst post-baseline/last observation value will be presented using number and percentage.

Physical examination data will be presented in listing and all the abnormalities will be flagged.

4.6.6 ECG Results

At each visit, the ECG result is to be assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant. Shift from baseline to worst post-baseline/last observation value will be presented using number and percentage.

A listing of ECG result and parameters' values will be provided for each patient.

4.6.7 ECOG Performance Status

The number and percentage of patients in each category (0, 1, 2) of ECOG performance status will be listed by visit. In addition, ECOG performance status will be summarized in a shift table from baseline to worst post-baseline/last observation for the Safety Analysis Set.

ECOG Performance Status will be listed for each patient by visit.

4.6.8 Left Ventricular Ejection Fraction (LVEF)

Left Ventricular Ejection Fraction (LVEF) results and change from baseline will be summarized by visit. Shift table of LVEF from baseline to post-baseline/last observation according to abnormality assessed by investigators (normal, abnormal NCS and abnormal CS) will be presented.

A listing of all LVEF results will be provided by patient and visit.

4.7 MISSING DATA HANDLING

All analyses and descriptive summaries will be based on the observed data. Except for the data otherwise specified below, missing data will not be imputed. For the patient data listings, no imputation of incomplete data will be applied. The listings will present the incomplete data without any change.

4.7.1 Missing Dates in Initial Diagnosis

Missing or partial missing date of initial diagnosis will be imputed as below:

- If the year is missing (or completely missing), diagnosis dates will not be imputed.
- If both the day and the month are missing, July 1st of the year will be imputed as the diagnosis dates.
- If only the day of the month is missing, use the 15th of the month to impute the date of diagnosis.

The imputed diagnosis date will be compared with ICF date. The minimum of the (imputed diagnosis date, ICF date - 1) will be considered as the date of initial diagnosis.

4.7.2 Concomitant Medications

Start date of concomitant medications

- If only the day of the month is missing, use the first day of the month to replace the missing part.
- If both the day and month are missing, January 1st will be used to replace the missing part.
- If Day, Month and Year are all missing, use a date 7 days before the date of initial study treatment.

End date of concomitant medications

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and Year are all missing, assign ‘ongoing’ status to stop date

If the imputed concomitant end date is after the death date or the last known alive date, then the date of the death or last known alive will be imputed as the concomitant end date.

4.7.3 Adverse Events

Onset date of AE

If the AE onset date is completely missing, the AE start date will be imputed as the date of initial study treatment;

If the AE onset date is partial missing, then

- If both the year and month are available and the year and month are the corresponding year and month of the date of initial study treatment, then the AE onset date will be imputed as the date of initial study treatment;
- If both the year and month are available and the year or the month are not equal to the corresponding year and month of the initial study treatment, then the AE onset date will be imputed as the 1st date of the month;
- If only the year is available and the available year is the corresponding year of the date of initial study treatment, then the AE onset date will be imputed as the date of initial study treatment
- If only the year is available, and the available year is not equal to the corresponding year of the initial study treatment, then the AE onset date will be imputed as the January 1st of the year.

4.7.4 Last Known Alive Date

Partial missing last known alive date will be imputed as below:

- If both the day and the month are missing, January 1st of the year will be imputed.
- If only the day of the month is missing, use the 1st of the month to impute the last known alive date.

4.7.5 Missing Dates in Death

Missing or partial missing date of death will be imputed as below:

- If the year is missing (or completely missing), death dates will be imputed as the last known alive date + 1 day.
- If both the day and the month are missing, January 1st of the year will be imputed as the death dates.
- If only the day of the month is missing, use the 1st of the month to impute the date of death.

The imputed death date will be compared with the last known alive date (date of censoring for survival). The maximum of the (imputed death date, last known alive date + 1) will be considered as the date of death.

4.7.6 Missing Dates in Post-study Treatment Anti-cancer Therapy

- If only the day of the month is missing, the post-study treatment anti-cancer therapy will be assumed to start on the first day of given month if this day is later

than the last administration date of study drug. Otherwise the subsequent therapy will be assumed to start on the next day following the last administration date of study drug.

- If both the day and month are missing the post-study treatment anti-cancer therapy will be assumed to start on the first day of given year if this day is later than the last administration date of study drug. Otherwise the subsequent therapy will be assumed to start on the next day following the last administration date of study drug.

4.8 INTERIM ANALYSES

There will be no formal interim efficacy analysis for the primary endpoint of pCR, although data on efficacy may be provided to the IMC upon request in order to evaluate benefit-risk for patients. Interim analyses of EFS, DFS, and OS at the time of and/or after the primary analysis of pCR may be conducted as needed and/or requested by Health Authorities.

5. REFERENCES

1. ICH guidance for industry E9 Statistical Principles for Clinical Trials, 1998

2. ICH guidance for industry E3 Structure and Content of Clinical Study Reports, 1996

3. Brookmeyer, R., & Crowley, J. (1982). A Confidence Interval for the Median Survival Time. International Biometric Society, 29-41

4. Kalbfleisch, J. D., and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED STUDY OF ATEZOLIZUMAB(ANTI-PD-L1 ANTIBODY) AND TRASTUZUMAB IN COMBINATION WITH CAPECITABINE AND OXALIPLATIN (XELOX) IN PATIENTS WITH HER2 POSITIVE LOCALLY ADVANCED RESECTABLE GASTRIC CANCER OR ADENOCARCINOMA OF GASTROESOPHAGEAL JUNCTION(GEJ)**
PROTOCOL NUMBER:	ML42058
VERSION NUMBER:	3
Eudract Number:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Atezolizumab (RO5541267) Trastuzumab (RO0452317)
PHASE:	II
INDICATION:	Resectable, HER2 positive gastric cancer or adenocarcinoma of gastroesophageal junction
SPONSOR:	F. Hoffmann-La Roche Ltd
Primary Efficacy Objective	Corresponding Endpoint

• To evaluate the efficacy of study treatments on the basis of the endpoint: pathological complete regression (pCR) rate	• Pathological complete regression (pCR) rate pCR is defined as no evidence of vital residual tumor cells on hematoxylin and eosin evaluation of the complete resected gastric/gastroesophageal junction (GEJ) specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST) (i.e., ypT0N0 in the current AJCC staging system, 8th edition). pCR status of surgery specimens will be analyzed by local pathologists at each site according to the tumor regression grade (TRG) score of the 8th AJCC (See **Error! Reference source not found.**). pCR rate will be analyzed in the intention-to-treat (ITT) population, defined as all patients who were randomly assigned to a treatment, regardless of whether they had surgery. It will be additionally assessed in a pre-specified sensitivity analysis in the per-protocol (PP) population. This population is defined as all patients who are centrally confirmed as HER2 positive and underwent resection.

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of study treatments on the basis of the endpoints: event-free survival (EFS), disease-free survival (DFS), overall survival (OS), major pathologic response (MPR), objective response rate (ORR) and R0 resection rate	• Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. • Disease-free survival (DFS), defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first. • Overall survival (OS), defined as the time from randomization to death from any cause in all patients. • Major pathologic response (MPR), defined as < 10% residual tumor per tumor bed based on evaluation of the resected primary esophagogastric specimen by a local pathologist. • Objective response rate (ORR), defined as the proportion of patients with a complete response (CR)

	or partial response (PR) during NAST, as determined by the investigator according to RECIST v1.1. • R0 resection rate defined as the proportion of patients with a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed and/or sampled regional lymph nodes based on evaluation by the local pathologist.
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To monitor the effects of treatments by detecting HER2 copy number in circulating tumor DNA (ctDNA).	• HER2 copy number in circulating tumor DNA Blood samples are collected at several time points indicated in **Error! Reference source not found.**(ctDNA analysis,HER2 copy number) and circulating DNA is extracted for detecting HER2 copy number centrally using droplet digital PCR.
• To explore the effects of treatment on HER2 status by detecting HER2 expression in surgical resected samples.	• HER2 status in surgical resected samples HER2 will also be evaluated centrally using surgical resected samples to explore the effects of treatment on HER2 status.
• To evaluate measures of efficacy based upon mismatch repair (MMR) status, PD-L1 expression and stromal tumor-infiltrating lymphocytes (sTIL) infiltration.	• MMR status MMR is the repair of normal nucleotide sequences in DNA molecules containing mismatched bases. Deficient MMR (dMMR) is defined as a loss of expression in ⩾1 mismatch repair proteins (MLH1, PMS2, MSH2 or MSH6). MMR status will be assessed centrally or locally using biopsy samples by IHC. • PD-L1 expression Expression of PD-L1 will be assessed both in pre-treatment tumor biopsy and surgical resected samples by the immunohistochemistry assay (PD-L1, 22C3; Agilent Technologies) in the central laboratory. Tumors will be considered PD-L1 positive if the combined positive score (number of PD-L1–positive cells [tumor cells, macrophages, lymphocytes] divided by the total

	number of tumor cells, multiplied by 100) is 1 or greater. Subgroups based on PD-L1 expression status will be evaluated. • stromal tumor-infiltrating lymphocytes (sTIL) infiltration sTIL signature will be assessed by multiplex immunohistochemistry staining on pre-treatment tumor tissue by central pathologist. Briefly, 4-5 μm sections of FFPE will be applied with several antibodies *(FoxP3, CD56, CD4, CD3, CD8, HER2, CD68, CD163, IRF8, CD20)* to label different kinds of cells. TILs are reported for the stromal compartment (% stromal TILs, sTIL) in all areas containing invasive tumor cells on the H&E slide containing the most invasive tumor.
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety of study treatments	• Incidence, nature and severity of adverse events(AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0). • Changes from baseline in targeted vital signs and physical findings. • Changes from baseline in targeted clinical laboratory test results.

Study Design

Description of Study

This is a phase II, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of perioperative trastuzumab+XELOX with / without atezolizumab in patients eligible for surgery with locally advanced HER2-positive gastric cancer or adenocarcinoma of GEJ. The study will enroll approximately 42 patients in China.

Patients who have histologically confirmed, HER2 positive, locally advanced (cT3/T4a/T4b or N+, M0, AJCC 8th edition) gastric cancer or adenocarcinoma of GEJ (Siewert I-III) are eligible. HER2 status of the primary gastric/GEJ tumor will be assessed in local laboratory and mandatory sent to the central laboratory for HER2 positivity confirmation. Patients without centrally confirmed HER2-positive result will be included in ITT analysis but not in PP analysis.

Eligible patients will be enrolled and 1:1 randomized to perioperative treatment with either trastuzumab plus atezolizumab withXELOX (Arm A) or trastuzumab alone with XELOX (Arm B).

Arm A: Atezolizumab plus Trastuzumab with XELOX

Patients randomized to treatment Arm A will receive atezolizumab + trastuzumab + XELOX for 3 treatment cycles prior to surgery, 3 weeks each cycle, as described below. Following surgery, patients will receive 5 further cycles of this regimen.

- Atezolizumab 1200mg IV day 1 every 3 weeks Q3W
- Trastuzumab 6 mg/kg IV day 1 (8 mg/kg as loading dose at 1st administration pre- and post-operation) Q3W
- XELOX: Capecitabine 1000mg/m^2 PO bid, days 1-14 Q3W
  Oxaliplatin 130mg/m^2 IV day 1 Q3W

Arm B: Trastuzumab with XELOX

Patients randomized to treatment Arm B will receive trastuzumab + XELOX for 3 treatment cycles prior to surgery, 3 weeks each cycle, as described below. Following surgery, patients will receive 5 further cycles of this regimen.

- Trastuzumab 6 mg/kg IV day 1 (8 mg/kg as loading dose at 1st administration pre- and post-operation) Q3W
- XELOX: Capecitabine 1000mg/m^2 PO bid, days 1-14 Q3W
  Oxaliplatin 130mg/m^2 IV day 1 Q3W

Surgery is recommended to be performed 3 to 6 weeks after the last dose of neoadjuvant study treatment. The first dose of postoperative treatment is recommended to initiate within 8 weeks after surgery. Surgical approaches will be tailored to the individual patient according to local standards with the goal of achieving R0 resection.

Note: there will be a Safety Run-in Phase comprising the first 10 patients enrolled into both arms who have completed neoadjuvant treatment and surgery. All available safety data (including perioperative morbidity and mortality) of the first 10 patients will be reviewed by the internal monitoring committee (IMC) for providing a recommendation whether to continue, modify or terminate the study.

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported. During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event electronic Case Report Form (eCRF) and in the patient's medical record to facilitate source data verification. Following completion of the treatment of the study, every effort should be made to follow up all patients for their disease and survival status until patient death or termination by the Sponsor, except withdrawing ICF. Patients who

discontinue neoadjuvant therapy early as a result of disease progression or who receives non-protocol therapy prior to surgery must be discontinued from all study treatment, and will be managed per local practice. These patients will remain on study for survival follow-up.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Tumor specimens (by pre-operative biopsy and surgical resection) from eligible patients will be prospectively tested for biomarkers. ctDNA will also be collected for HER2 copy number monitoring. These samples will enable analysis of tumor tissue biomarkers related to clinical benefits.

Number of Patients

Approximately 42 patients will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Aged $\geq$ 18 and $\leq$ 75 years
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically confirmed (by enrolling center) gastric cancer or adenocarcinoma of GEJ (Siewert I-III)
5. HER2-positive status defined as either IHC score of 3+ or IHC 2+ (See **Error! Reference source not found.**) with amplification proven by in situ hybridization (ISH) as assessed by local review based on pretreatment endoscopic biopsies. ISH positivity is defined as a ratio of $\geq$ 2.0 for the number of HER2 gene copies to the number of signals for chromosome 17 copies (HER2/CEP17).
6. Clinical stage at presentation: cT3/T4a/T4b, or N+, M0 as determined by AJCC staging system, 8th edition
    a. An esophageal-gastro-duodenoscopy is mandatory
    b. Diagnostic laparoscopy and endoscopic ultrasonography are recommended

7. Avaliability of formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 12 biopsy tissue slides containing unstained, freshly cut, serial sections must be submitted for central assessment of HER2, PD-L1, MMR and sTIL signature.

    a. For MMR, there is no need to submit for central assessment if local lab is available.

8. Physical condition and organ function allowing to undergo appropriate surgical management

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

10. Baseline LVEF $\geq$ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans

11. Life expectancy $\geq$ 12 weeks

12. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment:

    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support

    b. Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)

    c. Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion

    d. Hemoglobin $\geq$ 90 g/L (9 g/dL). Patients may be transfused to meet this criterion

    e. AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN)

    f. Serum total bilirubin $\leq 1.5 \times$ ULN with the following exception:

        Patients with known Gilbert disease: serum total bilirubin level $\leq 3 \times$ ULN

    g. Serum creatinine $\leq 1.5 \times$ ULN or Creatinine clearance (CCr) $\geq$ 60mL/min (calculated using the Cockcroft-Gault formula):

$$\text{CCr (ml/min)} = \frac{(140\text{-age}) \times \text{Weight (kg)}}{72 \times \text{SCr (mg/dL)}} (\text{Female} \times 0.85)$$

$$\text{OR CCr (ml/min)} = \frac{(140\text{-age}) \times \text{Weight (kg)}}{0.818 \times \text{SCr (umol/L)}} (\text{Female} \times 0.85)$$

    h. Serum albumin $\geq$ 25 g/L (2.5 g/dL)

i. For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN

j. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR

13. For female patients of childbearing potential, agreement (by patient) to remain abstinent (refrain from heterosexual intercourse) or to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) during the treatment period and to continue its use for at least i) 5 months after the last dose of atezolizumab, ii) 7 months after the last dose of trastuzumab, or iii) 6 months after the last dose of capecitabine or oxaliplatin, whichever is longer.

    a. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (<12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)

    b. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices

    c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

14. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

    a. With female partners of childbearing potential or pregnant female partners, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least i) 7 months after the last dose of trastuzumab, ii) 3 months after the last dose of capecitabine, or iii) 6 months after the last dose of oxaliplatin, whichever is longer.. Men must refrain from donating sperm during this same period

    b. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Stage IV (metastatic) or unresectable gastric/GEJ cancer determined by investigators

2. Prior systemic therapy for treatment of gastric cancer

3. History of malignancy other than GC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

4. Cardiopulmonary dysfunction as defined by any of the following prior to randomization:

    b. History of congestive heart failure of any classification

    c. Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease

    d. High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 [Mobitz 2] or third degree AV-block])

    e. Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia

    f. Myocardial infarction within 12 months prior to randomization

    g. Uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg)

    h. Evidence of transmural infarction on ECG

    i. Requirement for oxygen therapy

5. Dyspnea at rest

6. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

a. Patients with a history of autoimmune-mediated hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

b. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

c. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

i. Rash must cover < 10% of body surface area

ii. Disease is well controlled at baseline and requires only low-potency topical corticosteroids

iii. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

7. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

    a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

8. Active tuberculosis

9. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study

10. Severe infections within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia

11. Treatment with therapeutic antibiotics within 2 weeks (IV antibiotics) or 5 days (oral antibiotics) prior to initiation of study treatment

    a. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

12. Prior allogeneic stem cell or solid organ transplantation

13. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

14. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab

15. Current treatment with anti-viral therapy for HBV

16. Positive test for HIV

17. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

    a. Patients with past HBV infection or resolved HBV infection (defined as having a negative HBsAg test or a positive antibody to hepatitis B core antigen [anti-HBc] antibody followed by a negative HBV-DNA test at screening) are eligible.

18. Patients with active hepatitis C

    a. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

19. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)

20. Treatment with any approved anti-cancer therapy, 5 half-lives prior to initiation of study treatment

21. Treatment with investigational therapy within 28 days prior to initiation of study treatment

22. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies

23. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment

24. Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α[TNF-α] agents) within 2 weeks prior to initiation of study treatment

a. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

25. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins

26. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

27. Known allergy or hypersensitivity to any component of trastuzumab, capecitabine or oxaliplatin formulations

28. Known dihydropyrimidine dehydrogenase (DPD) deficiency or history of severe and unexpected reactions to fluoropyrimidine therapy in patients selected to receive capecitabine

29. Have a significant impact on oral drug absorption factors, such as unable to swallow, chronic diarrhea and intestinal obstruction

30. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine in patients selected to receive capecitabine. Use of these drugs is not allowed within 4 weeks prior to study treatment that includes capecitabine

31. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within i) 5 months after the last dose of atezolizumab, ii) 7 months after the last dose of trastuzumab, or iii) 6 months after the last dose of capecitabine or oxaliplatin, whichever is longer

    a. Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur approximately 40 months after the last patient is enrolled (36 months after the last patient receives surgery).

In addition, the Sponsor may decide to terminate the study.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 52 months, assuming a recruitment period of approximately 12 months plus 40 months from the date of enrollment of the last patient.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal products (IMPs) for this study are atezolizumab and trastuzumab.

Atezolizumab (Tecentriq ®)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle for 3 cycles prior to surgery and 5 cycles after surgery.

Atezolizumab should be administered as the first infusion.

Treatment will continue as scheduled or until progression, recurrence of disease, or unmanageable toxicity, whichever occurs first.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see **Error! Reference source not found.**. Atezolizumab infusions will be administered per the instructions outlined in the protocol.

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in **Error! Reference source not found.**.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab interruption or discontinuation for patients who experience adverse events are provided in**Error! Reference source not found.**.

Trastuzumab (Herceptin ®)

Trastuzumab is given as an 8 mg/kg IV loading dose and then 6 mg/kg IV on Day 1 of a 21-day cycle for 3 cycles before surgery, and administration will continue after surgery. The first administration of trastuzumab after surgery should also be given at the loading dose of 8 mg/kg.

Trastuzumab should be administered after atezolizumab and prior to oxaliplatin.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be that measured on Cycle 1, Day 1. The amount of trastuzumab to be administered must be recalculated if the patient's body weight has changed by > 10% (increased or decreased) from the Cycle 1, Day 1 weight. The amount of trastuzumab administered is calculated according to the patient's actual body weight, with no upper limit.

The initial dose of trastuzumab will be administered over 90 (+/-10) minutes, and patients will be observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever or chills. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (+/-10) minutes, and patients will be observed for a further 30 minutes. All infusion-related symptoms must have resolved before chemotherapy is given or the patient is discharged.

Anti-emetic premedication and supportive care will be given according to local/international standards. For patients who have experienced mild, moderate or severe infusion reactions after the first administration of trastuzumab, trastuzumab therapy can be resumed. Subsequent trastuzumab infusion is generally well tolerated. Premedications of corticosteroids, antihistamine and antipyretics can be used before trastuzumab therapy at the discretion of investigators.

Patients can be administrated with premedication (e.g. phenothiazines, antihistaminics, or anticholinergic agents) to control nausea/vomiting per local practice standards.

Guidelines for trastuzumab interruption or discontinuation are provided in **Error! Reference source not found.**. No dose modification is allowed for trastuzumab. If the patient misses a dose of trastuzumab by one week or less, then the usual dose of trastuzumab (6 mg/kg) should be given as soon as possible (do not wait until the next planned cycle). Subsequent maintenance trastuzumab doses of 6 mg/kg are then given every 3 weeks, according to the previous schedule. If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab should be given (8 mg/kg over 90 minutes). In general, subsequent maintenance trastuzumab doses of 6 mg/kg are then given every 3 weeks, starting 3 weeks later.

The patients who are diagnosed to be recurrent must be discontinued the treatment with study drug. The treatment for recurrent is at the investigators' discretion but must be recorded in the CRFs.

Non-Investigational Medicinal Products

Chemotherapy

XELOX is the chemotherapy regimen used in this trial, which will be administered in the 3 cycles before surgery (neoadjuvant) and 5 cycles after surgery (adjuvant) as follows:

- Capecitabine 1000 mg/m^2 administered twice orally on days 1–14, repeated every 3 weeks(21[+/-*3*]days); The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15 of each cycle;

- Oxaliplatin 130mg/m^2 IV on day 1 of a 21-day cycle; infusion over 2 hours.

The dose of chemotherapy is calculated according to the patient's BSA. The BSA and the amount of drug administered must be recalculated if the patient's body weight has changed by > 10% (increased or decreased) from baseline. Recalculation of the amount of drug administered on the basis of smaller changes in body weight or BSA is at the investigators' discretion.

In case the oxaliplatin treatment should be discontinued due to its specific toxicity (such as neurotoxicity), then capecitabine can be continued alone for up to 8 cycles (including preoperative chemotherapy cycles). If capecitabine is discontinued, oxaliplatin won't be continued.

There is no mandatory delay between atezolizumab/trastuzumab and oxaliplatin, assuming the infusion is well tolerated. If local policy is to give the atezolizumab/ trastuzumab on day one and start the oxaliplatin the next day, (still within a 24 hour period), this is acceptable on an exceptional basis.

Error! Reference source not found. provides the dosage calculation of capecitabine. For the other information of dosage and administration of capecitabine and oxaliplatin, please refer to the local prescribing information.

Supportive medications

Supportive medications (anti-emetics, antihistamines, and analgesics) will be administered per local practice standards.

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating IRRs because of its potential for causing agranulocytosis.

Oxaliplatin can be administrated with premedication (e.g. phenothiazines, antihistaminics, or anticholinergic agents) at each cycle to control nausea/vomiting per local practice standards.

Patients who experience mild, moderate or severe infusion reactions on the first dose may be retreated with trastuzumab. Subsequent trastuzumab infusions are generally well tolerated.

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab infusions at the Investigator's discretion.Statistical Methods

Primary Analysis

The primary efficacy endpoint for this study is pCR rate. pCR is defined as no evidence of vital residual tumor cells on hematoxylin and eosin evaluation of the complete resected stomach/GEJ specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST) (i.e., ypT0N0 in the current AJCC staging system, 8th edition). The primary efficacy endpoint will be established following completion of neoadjuvant therapy and surgery.

pCR status of surgery specimens will be analyzed by local pathologists at each site.

This primary endpoint will be analyzed in the intention-to-treat (ITT) population, defined as all patients who were randomly assigned to a treatment arm, regardless of whether they had surgery. An estimate of the pCR rate and its 95% confidence Interval (CI) will be calculated for each treatment arm. The CIs for each treatment arm will be calculated with the Clopper-Pearson exact method. The difference in pCR rates will be provided with 90% CIs, using the normal approximation to the binomial distribution. P value of comparison between two arms will be calculated with Chi-square test.

Determination of Sample Size

The sample size calculation of this study is based on the primary endpoint, the pCR rate. Assuming mean difference between two arms is 22% and pCR rate is 10% for control arm (arm B), sample size of 19 per each group could provide the precision (half width) of 90%CI of 0.21.

It is planned to recruit 42 patients (21 patients in each group) into this study assuming a 10% drop-out rate.

Interim Analyses

There will be no formal interim efficacy analysis for the primary endpoint of pCR, although data on efficacy may be provided to the IMC upon request in order to evaluate benefit-risk for patients. Interim analyses of EFS, DFS, and OS at the time of and/or after the primary analysis of pCR may be conducted as needed and/or requested by Health Authorities.

Appendix 2
Schedule of Activities

	Screening phase		Treatment phase											Survival follow up Once every 6 months ±7 *days* in the first 3 years, followed by once a year ±7 *days* until 5 years after surgery
Cycle	before 1st dose administration		1	2	3	After C3	After surgery	4	5	6	7	8	Treatment discontinuation	
Days	-28 to -1	-7 to -1	Day 1	Day 1 ± 3	Day 1 ± 3	3 to 6 weeks after the last dose of C3 (D1~21± 3)	≤ 8 weeks after surgery (Day 1~56 ± 3)	Day 1 (± 3 days) of every 3 weeks					≤ 30 days of last administration	
HER2 testing [1]	X						X							
ICF	X													
Inclusion/exclusion criteria	X													
Demographic and Medical history	X													
Operability and Resectablity [2]	X					X								
Physical examination [3]	X		X	X	X	X		X	X	X	X	X	X	X[20]
Vital signs [4]		X	X	X	X	X	X	X	X	X	X	X	X	X[20]
ECG [5]	X		X	X	X	X		X	X	X	X	X	X	
ECOG PS	X		X	X	X	X		X	X	X	X	X	X	X[20]
Hematology [6]		X		X	X	X	X	X	X	X	X	X	X	

	Screening phase		Treatment phase											Survival follow up Once every 6 months ±7 *days* in the first 3 years, followed by once a year ±7 *days* until 5 years after surgery
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Days	-28 to -1	-7 to -1	Day 1	Day 1 ± 3	Day 1 ± 3	3 to 6 weeks after the last dose of C3 (D1~21± 3)	≤ 8 weeks after surgery (Day 1~56 ± 3)	Day 1 (± 3 days) of every 3 weeks					≤ 30 days of last administration	
Biochemistry [6]		X		X	X	X	X	X	X	X	X	X	X	
Coagulation (INR, aPTT)		X				X						X	X	
Urinalysis [6]		X		X	X	X	X	X	X	X	X	X	X	
TSH, free T3 (or total T3), free T4 [7]		X				X						X	X	
HIV test [8]	X													
HBV test [8]	X													
HCV test [8]	X													
Pregnancy test (if applicable) [9]		X												
Esophageal-gastro-duodenoscopy	X													X [20]
EUS / Laparascopy [10]	X													
LVEF assessment（*MUGA or ECHO*）[11]	X					X						X		X

	Screening phase		Treatment phase											Survival follow up Once every 6 months ±7 *days* in the first 3 years, followed by once a year ±7 *days* until 5 years after surgery
Cycle	before 1st dose administration		1	2	3	After C3	After surgery	4	5	6	7	8	Treatment discontinuation	
Days	-28 to -1	-7 to -1	Day 1	Day 1 ± 3	Day 1 ± 3	3 to 6 weeks after the last dose of C3 (D1~21± 3)	≤ 8 weeks after surgery (Day 1~56 ± 3)	Day 1 (± 3 days) of every 3 weeks					≤ 30 days of last administration	
Randomization			X											
Administration of study treatment[12]			X	X	X			X	X	X	X	X		
Tumor assessment [13]	X					X [14]							X [15]	X
Other biomarker (except HER2) [16]			X				X							
ctDNA analysis (HER2 copy number)			X			X	X			X			X	X [20]
Histopathological assessment							X[17]							
Adverse event [18]	X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy [19]	X		X	X	X	X	X	X	X	X	X	X	X	X

1. HER2 testing can use biopsy sample at baseline and surgery sample after surgery. Written consent must be obtained prior to performing any protocol-specified procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test.
2. Evaluation of surgical resectability by the investigator before registration, and including general operability within a multidisciplinary team before randomization and before surgery.
3. The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs. Directed Physical Exam will be performed by the investigator or qualified designee as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs. Height will be measured only at screening.
4. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment, and at time of study discontinuation.
5. Can have additional test if clinically necessary.
6. Laboratory assessments (hematology, biochemistry and Urinalysis) will be performed before randomization, before treatment (unless treatment is given within 7 days following screening assessments). Can have additional test if clinically necessary.
7. TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4.
8. At screening, HIV, HBV and HCV serology should be conducted in all of patients who have signed ICF. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment).
    - HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA
    - If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
    - HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA
    - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
9. For female patients who have childbearing potential. Serum pregnancy test should be done within 7 days before the first dose of study treatment and repeated at any time during the study if pregnancy is suspected. During the study treatment, if a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive serum test result.
10. Recommended, not mandatory.

11. LVEF will be measured using multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO), using the same technique throughout the study in an individual patient. Baseline LVEF assessments should be done within 28 days prior to the start of treatment. LVEF measurement should then be done every 12 weeks $\pm$*7days* (and more often if clinically indicated) during treatment and every 6 months $\pm$*7days* following discontinuation of treatment until 24 months from the last administration of trastuzumab.
12. Patients should receive their first dose of study drug on the day of randomization (no later than 3 days after randomization).
13. Tumor assessment should consist of CT and/or MRI and include chest, abdomen and pelvis as clinically indicated/determined by the investigators. For each patient, the same radiographic procedures and technique must be used throughout the study, and results must be reviewed by the investigator before dosing at the next cycle. Tumor response will be evaluated according to RECIST v1.1.
14. Tumor assessment and multi-disciplinary treatment (MDT) evaluation should be performed within 2 weeks before surgery.
15. Tumor assessment should performed every 6 months after surgery in the first 3 years, and once a year until 5 years after surgery. Additional assessment can be performed if signs or symptoms indicate a possible recurrence or development of a new gastric cancer.
16. Biomarker testing can use biopsy sample at screening and surgical sample at surgery. *MMR and sTIL testing use biopsy sample; PD-L1 testing use biopsy sample and surgical sample.*
17. Histopathological tumor regression should be analyzed by local pathologists at each site. Instruction manuals will be provided for all local laboratory assessments.
18. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events (SAEs) caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. SAEs and adverse events of special interest (AESIs) will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section **Error! Reference source not found.**).
19. Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment should be recorded from 7 days prior the initiation of study treatment until the treatment discontinuation visit.
20. If clinically necessary.