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)

Study protocol

Version 7.0

Version date: Jan 2024

PROTOCOL

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:	7
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Atezolizumab (RO5541267) Trastuzumab (RO0452317)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
7	**See electronic date stamp on title page**
6	21-Feb-2023
5	10-Aug-2022 (internal drop)
4	24 Feb 2022.
3	10 Feb 2021
2	17 June 2020
1	29 April 2020

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol ML42058, Version 7.0, has been amended to align the adverse event management guidelines for atezolizumab with the Atezolizumab Investigator's Brochure, Version 20. Substantive changes to the protocol, along with a rationale for each change, are summarized below.
To align with the Atezolizumab IB, Version 20, the following changes have been made:

- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.3).
- The risks and adverse event management guidelines have been updated to align with the Atezolizumab IB, Version 20 (Appendix 8).
- The risk description in the adverse event management guidelines have been updated to align with the Atezolizumab IB, Version 20 (Appendix 8).

Additional minor changes have been made to improve clarity and consistency.Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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)**
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I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

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:	7
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

Objectives and Endpoints

This study will 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. Specific objectives and corresponding endpoints for the study are outlined below.

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 Appendix 2). 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 Appendix 1(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 ⌈m sections of FFPE will be applied with several antibodies (FoxP3, CD56, CD4, CD3, CD8, HER2, CD68, CD163, IRF8, CD20, PD-1, PD-L1) 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 subjects for their disease and survival status until subject 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 ε 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 Appendix 3) 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 ε 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 16 available and of good quality biopsy tissue slides containing unstained, freshly cut, serial sections must be submitted for central assessment of HER2, PD-L1, MMR and sTIL signature. Agree to provide blood samples after enrollment.

    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 ε 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans

11. Life expectancy ε 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) ε 1.5 · 10^9/L (1500/⌈L) without granulocyte colony-stimulating factor support

    b. Lymphocyte count ε 0.5 · 10^9/L (500/⌈L)

    c. Platelet count ε 100 · 10^9/L (100,000/⌈L) without transfusion

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

    e. AST, ALT, and alkaline phosphatase (ALP) δ 2.5 · upper limit of normal (ULN)

    f. Serum total bilirubin δ 1.5 · ULN with the following exception:

        Patients with known Gilbert disease: serum total bilirubin level δ 3 · ULN

    g. Serum creatinine δ 1 · ULN or Creatinine clearance (CCr) ε 60mL/min (calculated using the Cockcroft-Gault formula):

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

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

    h. Serum albumin ε 30 g/L (3.0 g/dL)

i. For patients not receiving therapeutic anticoagulation: INR or aPTT δ 1.5 · 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

<u>Exclusion Criteria</u>

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:

a. History of congestive heart failure of any classification

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

c. 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])

d. Significant symptoms (Grade ε 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia

e. Myocardial infarction within 12 months prior to randomization

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

g. Evidence of transmural infarction on ECG

h. 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 Appendix 11 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

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, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-〈[TNF-〈] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

    – Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

    – Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

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 unless 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 Appendix 5. 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 Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab interruption or discontinuation for patients who experience adverse events are provided in Appendix 6.

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 initial 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. Weight at the time the dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to trastuzumab dose modification requirements. 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 Appendix 7. 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.

Appendix 8 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.

LIST OF ABBREVIATIONS AND DEFINITIONs OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	antibody to hepatitis B core antigen
ANC	Absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AV-block	Atrioventricular-block
BFI	Brief Fatigue Inventory
bid	bis in die
CCr	Creatinine clearance
COVID-19	Coronavirus 2019
CR	complete response
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DFS	disease-free survival
DLT	dose-limiting toxicities
dMMR	Deficient mismatch repair
DPD	dihydropyrimidine dehydrogenase
EC	Ethics Committee
ECF	epirubicin, cisplatin and 5-fluorouracil
ECHO	echocardiogram
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	Event-free survival
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin-embedded
GC	gastric cancer
GEJ	gastroesophageal junction
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen

HCV	hepatitis C virus
H&E	Hematoxylin-eosin
HER2	human epidermal growth factor receptor 2
HGRAC	Human Genetic Resources Administration Office of China
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IMC	internal monitoring committee
IMP	investigational medicinal product
INR	International Normalized Ratio
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intention-to-treat
IV	intravenous
LAGC	Locally advanced gastric cancer
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MDT	muti-disciplinary treatment
MMR	mismatch repair
MPR	Major pathologic response
MRI	Magnetic Resonance Imaging
MUGA	multiple-gated acquisition
NACT	Neoadjuvant chemotherapy
NAST	neoadjuvant systemic therapy
NCCN	National Cancer Comprehensive Network
NCI CTCAE v{XX}.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version {XX}.0
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
pCR	Pathological complete regression
PD	Progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PO	per os

PP	per-protocol
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCLC	small cell lung cancer
SITC	Society for Immunotherapy for Cancer
sTIL	stromal tumor-infiltrating lymphocytes
TNF-α	anti-tumor necrosis factor-α
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
XELOX	capecitabine plus oxaliplatin

1. BACKGROUND

1.1 BACKGROUND ON LOCALLY ADVANCED GASTRIC CANCER (LAGC)

With an estimated over one million new cases in 2018, gastric cancer (GC) ranks the 5th most common malignancy and the 3rd leading cause of cancer-related mortality worldwide (Bray et al., 2018). While the prevalence of GC is known to be higher in East Asian countries than Western countries, histological types of GC are similar between Asian and Western countries and the most common type is adenocarcinoma. China has the largest number of GC patients in the world, accounting for 42.6% and 45.0% of the global GC incidence and mortality (Ferlay et al., 2015). It is estimated that there are 679.1 thousands newly diagnosed cases and 498.0 thousands deaths of GC in 2015 (Ferlay et al., 2015), both ranking the 2nd place of all cancer types.

At present, radical resection is still the only possible cure method for gastric cancer. In Japan and Korea, mass screening programs to detect early-stage disease and operative technique improvement with meticulous regional lymph node dissection, patients' survival has been much improved. In contrast, early diagnosis rate of GC is rather low due to difficulties of disease screening in China. Therefore, more than half of Chinese GC patients have already been in locally advanced stage at presentation (Zhang et al., 2012). Even for patients with localized resectable gastric cancer, the prognosis is poor with 5-year overall survival (OS) rate ranging from 18% to 53% (Shu et al., 2017). Postoperative adjuvant chemotherapy for GC is intended to prevent disease relapse due to a residual microtumor after radical resection. The phase III ACTS-GC trial conducted in Japan tested S-1 (an oral fluoropyrimidine) as adjuvant chemotherapy in patients with stage II or III gastric cancer who had undergone D2 lymphadenectomy (Sakuramoto et al., 2007). The 3-year overall survival (OS) rate of S-1 treatment group was 80.1%, while that of the surgery only group was 70.1% (HR=0.68, 95%CI 0.52-0.87; P=0.003)

(Sakuramoto et al., 2007). CLASSIC study [7] is another phase III randomized controlled trial undertaken in 37 centres in South Korea and China (including Taiwan). It investigated the effect on disease-free survival of adjuvant chemotherapy with capecitabine plus oxaliplatin (XELOX) after D2 gastrectomy compared with D2 gastrectomy only in patients with stage II–IIIB (AJCC 6.0th edition) GC (Bang et al., 2012). The 3-year disease-free survival (DFS) was 74% (95% CI 69–79) in the XELOX group and 59% (95% CI 53–64) in the surgery only group (HR=0.56, 95% CI 0.44-0.72; P<0.0001) (Bang et al., 2012). In Japan, D2 gastrectomy plus adjuvant chemotherapy (ACT) using S-1 is the standard treatment for [6]; whereas in some others, like China, the standard is D2 gastrectomy with postoperative capecitabine plus oxaliplatin (CapeOX) (Wang et al., 2019). However, even with current ACT, the long-term survival for GC patients is not satisfactory, further development of treatment strategy and novel drugs is in urgent need.

1.2 NEOADJUVANT OR PERIOPERATIVE CHEMOTHERAPY FOR LAGC

Neoadjuvant chemotherapy (NACT) or perioperative chemotherapy are proposed as another approach to improve the outcomes, which can increase R0 resection rate by shrinking tumor size. Moreover, potential prognosis-related factors like micrometastases can be better addressed by chemotherapy prior to surgery. Neoadjuvant treatment has gradually become a standard of care for locally advanced, resectable GC and adenocarcinoma of the GEJ.

The MAGIC and FLOT studies have shown a possible survival benefit due to preoperative treatment (Cunningham et al., 2006; Al-Batran et al., 2017). However, the best and personalized regimen of NACT remains to be determined.

Definitive support for the favorable effect of perioperative chemotherapy in gastric, esophageal, and gastroesophageal junction (GEJ) adenocarcinoma was provided by the MAGIC study (Cunningham et al., 2006). The study observed a 5-year survival benefit for perioperative chemotherapy in patients with gastric and GEJ cancer. In the MAGIC-trial (Cunningham et al. 2006), patients with clinical stage II or III GC (75%) or adenocarcinoma of the gastroesophageal junction (GEJ) (25%) were either treated with three cycles of epirubicin, cisplatin and 5-fluorouracil (ECF) pre- and post-surgery or with surgery alone (Cunningham et al., 2006). Patients in the chemotherapy arm had a clinically relevant and statistically significant improvement of PFS and OS in comparison to patients without chemotherapy (Cunningham et al., 2006). Benefit in 5-year survival was 13% (5-year OS, 36% with perioperative chemotherapy versus 23% with surgery alone). Patients treated with chemotherapy had smaller primaries and a favorable pathological tumor stage. No differences were seen between the two treatment groups regarding surgical mortality and morbidity, and hospitalization time (Cunningham et al., 2006). A third trial (French ACCORD/FFCD 9703), including predominantly GEJ cancers (GEJ, 76%; stomach, 24%) showed similar results. In the FFCD trial, patients received 2-3 cycles of cisplatin/5-FU, followed by surgery, or surgery alone. After surgery, patients in the chemotherapy arm who responded to the preoperative therapy received additional cycles of chemotherapy. Treatment with neoadjuvant or perioperative chemotherapy resulted in significantly improved rates of margin-free resection (R0) and prolonged relapse-free and overall survival. The survival benefit at five years was 14% (Ychou et al., 2011). In the most recent AIO-FLOT4 phase III trial, which was presented at ASCO 2017, 716 patients with gastric (44%) or adenocarcinoma of the GEJ (56%) were randomized to receive either perioperative ECF/ECX or FLOT (a docetaxel-based triple combination consisting of 5-FU, leucovorin, oxaliplatin and docetaxel) (Al-Batran et

al., 2017). FLOT improved PFS and OS (5-year OS rate, 45% vs. 36%) compared to ECF or ECX. No increase in mortality or perioperative complications was observed (Al-Batran et al., 2017). It is important to note that neither study found that preoperative chemotherapy increased morbidity or mortality over surgery alone.However, despite these advances, the outcome of patients with advanced gastric or GEJ cancer remains unsatisfactory. Considerable investigation is still required to improve perioperative protocols and their efficacy.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Tecentriq®, RO5541267) is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab has been approved for the treatment of urothelial carcinoma, non small cell lung cancer (NSCLC), small cell lung cancer (SCLC) ,triple-negative breast cancer, hepatocellular carcinoma, melanoma, and *alveolar soft part sarcoma*.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.4 BACKGROUND ON TRASTUZUMAB

Trastuzumab (Herceptin®, RO0452317) is a recombinant, humanized, anti-$p185^{HER2}$ monoclonal antibody that binds specifically and with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 (HER2). Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo.

Trastuzumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Trastuzumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Trastuzumab has been approved for the treatment of HER2-overexpressing metastatic breast cancer, HER2-overexpressing operable early breast cancer, and HER2-overexpressing metastatic gastric cancer.

Refer to the Trastuzumab Investigator's Brochure for details on nonclinical and clinical studies.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

HER2 dysregulation is associated with tumorigenesis and poor outcomes of gastric/GEJ cancer. In China, approximately 12.0% of patients with gastric and GEJ cancer are HER-2 positive (Huang et al., 2013).

Trastuzumab, a monoclonal antibody that acts against HER2, which is an effective and well-tolerated treatment for HER2-positive GC and GEJ cancer. The NEOHX study, a Spanish, multicenter, open-label phase II study, evaluated the efficacy and toxicity profile of perioperative treatment with trastuzumab in combination with XELOX (capecitabine and oxaliplatin) in patients with HER2-positive resectable stomach or esophagogastric junction adenocarcinoma (Rivera et al., 2013). The data shows promising activity of the regimen (trastuzumab plus XELOX) with pCR of 8%, 18-month DFS of 71% (95% CI: 53-83%),2-year DFS of 60% (Rivera et al., 2013). The update result of NEOHX study shows in 31 patients who received surgery 9.6% had a pCR and benefit in 5-year survival was 58% (Rivera et al, 2021). The HerFLOT study showed a pCR of 21% in patients with HER2-positive advanced gastric or GEJ cancer who received XELOX and trastuzumab as perioperative treatment (Available online:http://www.clinicaltrials.gov/ct2/show/NCT01472029?term = NCT01472029&rank = 1). In addition, two phase II trials, both performed specifically in Asiatic population, have reported a favourable toxic profile and high efficacy of XELOX–trastuzumab (Ryu et al., 2015; Gong et al., 2016). In the ad-hoc analysis of the phase III Trastuzumab for Gastric Cancer (ToGA) study, trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone was evaluated as first-line therapy in patients with locally advanced or metastatic HER2-positive adenocarcinoma of the stomach including the gastroesophageal junction. The patients received trastuzumab achieved the greatest OS benefit compared with those received chemotherapy alone (16.0 vs. 11.8 months). The most common adverse events in both groups were nausea (trastuzumab plus chemotherapy, 197 [67%] vs. chemotherapy alone, 184 [63%]), vomiting (147 [50%] vs. 134 [46%]), and neutropenia (157 [53%] vs. 165 [57%]). Rates of overall grade 3 or 4 adverse events (201 [68%] vs. 198 [68%]) and cardiac adverse events (17 [6%] vs. 18 [6%]) did not differ between groups (Bang et al., 2010). These data have shown the high efficacy and tolerance of XELOX–trastuzumab in GC patients.

At present, immune checkpoint inhibitors, especially immune-combination therapies have resulted in a significant survival benefit in patients with advanced malignancies. Lots of evidence has shown that targeting the PD-1/PD-L1 pathway prolongs the survival in patients with different types of cancer, including NSCLC, gastric, bladder, and skin cancer. Pre-clinical research indicated synergetic effect on tumor reduction when combining anti-HER2 and anti-PD-1 (Müller et al., 2015). Moreover, 2019 ASCO GI reported a phase II single-arm study (NCT02954536) investigating the activity and tolerability of pembrolizumab and trastuzumab plus XELOX in treatment-naïve metastatic GC, showing ORR and DCR as 87% and 100% respectively (Janjigian et al., 2019). Recently, 2022 ASCO GI reported the latest result of one single-arm, phase II study (NCT03950271) which showed neoadjuvant combination of SHR1210 (PD-1 inhibitor), transtuzumab and XELOX is a safe and efficacious treatment option. Among sixteen patients who experienced D2 resection, 5 (31.3%) achieved pCR (Li et al, 2022). These primary data suggest a role for immune regulation of response to targeted and

chemotherapy, which support the combination strategy of anti-HER2 and anti-PD-1 plus XELOX to be investigated in more settings for HER2-positive GC patients.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, GC, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

Regarding perioperative chemotherapy for LAGC, no consensus on standard regimen exists so far. In the current study, XELOX is chosen as chemotherapy backbone regarding its recommendation in adjuvant (1A) and palliative (2B for HER2 positive) settings in CSCO guideline and also wide use in Chinese GC patients.

Based on the considerations mentioned above, this study is designed to investigate the potential of atezolizumab plus trastuzumab in combination with XELOX in HER2-positive LAGC Chinese patients. We aim to explore the efficacy and safety of the regimen in this special GC population, and hopefully provide valuable data for further research.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment. In addition, the safety of the regimen of trastuzumab plus XELOX is acceptable and manageable, which has been proved in the previous studies (Bang et al., 2010; Rivera et al., 2013).

This trial will enroll patients with HER2 positive GC or adenocarcinoma of gastroesophageal junction. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with trastuzumab and XELOX is expected to be acceptable in this setting.

In the setting of the coronavirus 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD 1/PD L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS CoV-2 infection is altered by cancer immunotherapy.

Severe SARS CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN) (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute severe acute respiratory syndrome corona virus 2 (SARS CoV-2) infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS CoV-2related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID 19 Vaccination Advisory Committee, COVID 19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID 19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID 19 vaccination include the following: the risk of SARS CoV 2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS CoV 2 infection, underlying disease, and the severity of COVID 19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID 19 vaccines. When administered, COVID 19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID 19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab when given in combination with trastuzumab+XELOX (Arm A: atezolizumab+trastuzumab with XELOX) compared with trastuzumab+XELOX (Arm B: trastuzumab with XELOX) in patients eligible for surgery with locally advanced HER2 positive gastric cancer or adenocarcinoma of gastroesophageal junction. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., trastuzumab+XELOX with / without atezolizumab).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of study treatments on the basis of the following endpoint:

- 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/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 Appendix 2). 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.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objectives for this study will be analyzed in ITT population, including:

- 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.

2.1.3 Exploratory Efficacy Objective

The following exploratory analyses are currently planned, but may be adapted taking into account new research data and approval of Human Genetic Resources Administration Office of China (HGRAC):

- To monitor the effects of treatments by detecting HER2 copy number in circulating tumor DNA (ctDNA). Blood samples are collected at several time points indicated in Appendix 1 (ctDNA analysis,HER2 copy number) and circulating DNA is extracted for detecting HER2 copy number centrally using droplet digital polymerase chain reaction (PCR).
- To explore the effects of treatment on HER2 status. HER2 will 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 will be assessed centrally or locally using biopsy samples. Deficient MMR (dMMR) is defined by immunohistochemistry (IHC) as a loss of expression in ≥1 mismatch repair proteins (MLH1, PMS2, MSH2 or MSH6). MMR results will be collected for subgroup analysis.

  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. Subgroups based on PD-L1 expression status will be evaluated.

sTIL signature will be assessed by multiplex immunohistochemistry staining on pre-treatment tumor tissue by central pathologist. Briefly, 4-5 ⌈m sections of FFPE will be applied with several antibodies (FoxP3, CD56, CD4, CD3, CD8, HER2, CD68, CD163, IRF8, CD20, PD-1, PD-L1) 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.

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of study treatments on the basis of the following 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.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of 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.

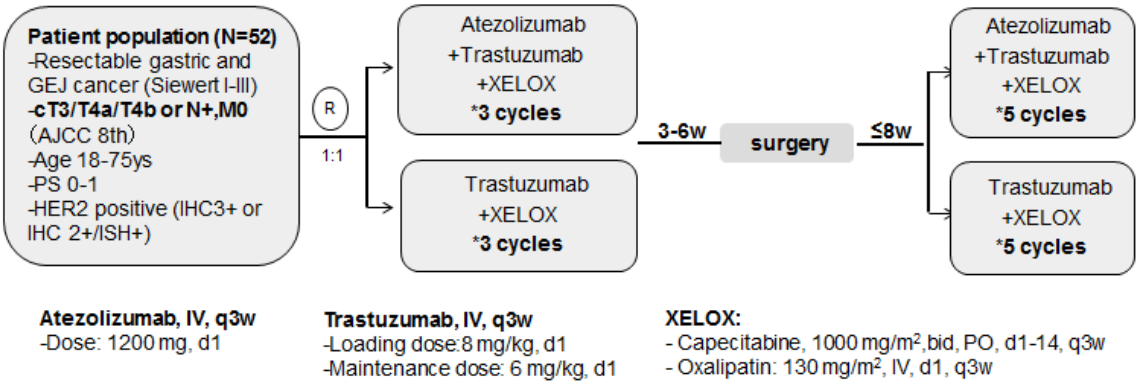
The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered 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 subjects for their disease and survival status until subject 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. A schedule of activities is provided in Appendix 1.

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

3.1.2 Internal Monitoring Committee

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.

3.2 End of Study and Length 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.

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.

3.3 Rationale for Study Design

3.3.1 Rationale for Atezolizumab and Trastuzumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq→ U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities (DLTs) were observed at

any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data. In the study PCD4989g, patients receiving 10 to 20 mg/kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 μg/mL (Deng et al. 2016) . Treatment with atezolizumab at a fixed dose of 1200 mg Q3W as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types and hematologic malignancies (including pediatric-type tumors), across lines of therapy, and across PD-L1 expression subgroups. The safety data indicate that atezolizumab is well tolerated and the observed AEs are consistent with the known mechanism of action of atezolizumab or the underlying disease. Please refer to the Atezolizumab Investigator's Brochure for details.

Trastuzumab will be administered at an 8 mg/kg IV loading dose and then 6 mg/kg IV on Day 1 of a 21-day cycle, which is the approved dosage for HER2+ advanced GC. In Study BO27798 (HELOISE), 16/28 HER2+ advanced GC patients received trastuzumab at an 8 mg/kg IV loading dose and then 6 mg/kg IV on Day 1 of a 21-day cycle had serum trastuzumab concentrations of ≥12 μg/mL at Cycle 2 Day 21. Median OS was 12.5 months, and median PFS was 5.7 months. No new safety signals was detected. Please refer to the Trastuzumab Investigator's Brochure for details.

3.3.2 Rationale for Patient Population

This study will enroll patients eligible for surgery with locally advanced HER2-positive GC or adenocarcinoma of GEJ.

In China, more than 80% of gastric cancer patients are already in advanced stages at the time of diagnosis (Wang et al., 2019). Patients with advanced disease (locally advanced or metastatic) have a somber prognosis. For LAGC, the overall 5-year survival rate in China is only 18-70% (Wang et al., 2016), and the HER2+ subgroup is much worse.

However, there are no standard perioperative/neoadjuvant regimens for the HER2+ GC population yet. In the previous perioperative trials, the efficacy for LAGC is unsatisfying, especially in the HER2+ LAGC patients. Thus, this study plans to recuit patients eligible for surgery with locally advanced HER2-positive GC or adenocarcinoma of GEJ to receive perioperative trastuzumab+XELOX with / without atezolizumab, which is expected to provide efficacy and safety data for further research.

3.3.3 Rationale for Open-Label Study

An open-label study design was chosen for this trial for a number of reasons. Given the known toxicities associated with atezolizumab, patients assigned to atezolizumab-containing arms, as well as physicians, may be capable of identifying treatment assignment in a blinded study. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require all patients to continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. This could then delay subsequent treatment with approved therapies in patients assigned to the control arm, as well as increase the complexity of treatment decisions.

The strategy and timing for final analysis of the primary endpoint, including censoring rules and methods for handling missing data, have been prespecified in the protocol.

3.3.4 Rationale for pathological complete regression (pCR) rate as Primary Endpoint

In this study, the primary efficacy endpoint will be local pathologists-assessed pCR.

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).

pCR is considered as a surrogate endpoint index to predict EFS, DFS and OS, and it is often used as the primary efficacy endpoint in clinical trials of neoadjuvant therapy (Homann et al., 2012; Issa et al., 2012). Furthermore, the whole trial period can be shorten, and sample size can be decreased if pCR used as the primary efficacy endpoint. As a result, pCR is used as the primary endpoint in this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 42 patients eligible for surgery with locally advanced HER2-positive gastric cancer or adenocarcinoma of GEJ will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Aged ε 18 and ≤ 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 Appendix 3) 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 ε 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 16 available and of good quality biopsy tissue slides containing unstained, freshly cut, serial sections must be submitted for central

assesment of HER2, PD-L1, MMR and sTIL signature. Agree to provide blood samples after enrollment.

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 left ventricular ejection fraction (LVEF) ε 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans

11. Life expectancy ε 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) ε 1.5 · 10^9/L (1500/$\lceil$L) without granulocyte colony-stimulating factor support
    b. Lymphocyte count ε 0.5 · 10^9/L (500/$\lceil$L)
    c. Platelet count ε 100 · 10^9/L (100,000/$\lceil$L) without transfusion
    d. Hemoglobin ε 90 g/L (9 g/dL). Patients may be transfused to meet this criterion
    e. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) δ 2.5 · upper limit of normal (ULN)
    f. Serum total bilirubin δ 1.5 · ULN with the following exception:

       Patients with known Gilbert disease: serum total bilirubin level δ3 · ULN

    g. Serum creatinine δ 1 · ULN or Creatinine clearance (CCr) ε 60mL/min (calculated using the Cockcroft-Gault formula):

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

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

    h. Serum albumin ε 30 g/L (3.0 g/dL)
    i. For patients not receiving therapeutic anticoagulation: INR or aPTT δ 1.5 · 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

4.1.2 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:

a. History of congestive heart failure of any classification

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

c. 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])

d. Significant symptoms (Grade ε 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia

e. Myocardial infarction within 12 months prior to randomization

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

g. Evidence of transmural infarction on electrocardiograph (ECG)

h. 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 Appendix 11 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 computed tomography (CT) scan
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 hepatitis B virus (HBV)
16. Positive test for human immunodeficiency virus (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 hepatitis C virus (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, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α[TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

    – Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study .

    – Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

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.

4.2 METHOD OF TREATMENT ASSIGNMENT

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.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab and trastuzumab

Atezolizumab will be supplied by the Sponsor as sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution. Atezolizumab is formulated in histidine acetate buffered at pH 5.8 containing sucrose and polysorbate 20. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. For intravenous administration, atezolizumab will be administered in IV infusion bags containing 0.9% sodium chloride (NaCl) and infusion lines equipped with 0.2 or 0.22 µm in-line filters.

Trastuzumab will be supplied by the Sponsor as a lyophilized formulation in multi-dose (440 mg) vial. Trastuzumab is formulated in histidine/histidine-HCl monohydrate (buffer), α,α-trehalose dihydrate (tonicity adjuster), and polysorbate 20 (stabilizer/emulsifier). Following reconstitution in bacteriostatic water for injection for the multi-dose preparation, trastuzumab is further diluted in 250 mL 0.9% sodium chloride solution for administration.

Please refer to the pharmacy manual for details of atezolizumab and trastuzumab formulation, packaging, and handling.

4.3.1.2 Chemotherapy

XELOX (capecitabine and oxaliplatin) is the chemotherapy regimen used in this trial.

Capecitabine will be supplied by the Sponsor as biconvex, oblong film-coated tablets for oral administration. Each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium,

hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate, and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides..

Oxaliplatin will be supplied by the Sponsor as lyophilized lump or powder in a glass vial which contains 50 mg of oxaliplatin lyophilized lump or powder. Excipients contain lactose hydrate and water for injection. For intravenous administration, oxaliplatin should be dissolved in 5% glucose solution 250ml to 500ml (for a concentration of 0.2mg/ml or above). The vial is intended for single use only.

For information on the formulation, packaging, and handling of capecitabine and oxaliplatin, refer to the local prescribing information for the chemotherapy regimen.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

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

Any dose modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 6, Appendix 7 and Appendix 9.

4.3.2.1 Atezolizumab and Trastuzumab

Atezolizumab

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 unless 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 Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab interruption or discontinuation for patients who experience adverse events are provided in Appendix 6.

Trastuzumab

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 initial 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. Weight at the time the dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to trastuzumab dose modification requirements. 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. Patients can be administrated with premedication (e.g. phenothiazines, antihistaminics, or anticholinergic agents) to control nausea/vomiting per local practice standards.

Guidelines for treatment interruption or discontinuation for trastuzumab are provided in the Appendix 7. No dose modifications are 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 study treatment. The treatment for recurrent is at the investigators' discretion but must be recorded in the eCRFs.

4.3.2.2 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.

Capecitabine shall be orally taken within 30 minutes after the meal (breakfast or dinner), bid, taking tablets with 200 ml water (juice is not allowed).

Capecitabine dose is the combined dose of 500mg tablets. Total dose in each day is divided into two times to take with approximately 12 hours of interval. Two doses shall be separated in order to take a whole tablet. Appendix 8 provides the dosage calculation of capecitabine.

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

Oxaliplatin should not be mixed with any other solutions (especially 5-fluorouracil, alkaline solutions, tromethamine or folic acid drugs containing tromethamine), or administered simultaneously with them through the same vein. The infusion pipeline should be flushed after oxaliplatin infusion.

It needs to be noted that patients should avoid cold exposure during oxaliplatin administration or for several hours after administration, and avoid eating raw/cold food or/and cold drinks.

The dose of chemotherapy is calculated according to the patient's body surface area (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.

Guidelines for dosage modification and treatment interruption or discontinuation for capecitabine and oxaliplatin are provided in Appendix 9.

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.

4.3.3 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.

4.3.4 Investigational Medicinal Product Accountability

All IMPs (i.e. atezolizumab and trastuzumab) required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Used IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. Unused IMPs will be returned to the Sponsor. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Surgery

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

White blood cell count should be above $3.5 \cdot 10^9$/L, platelet more than $100 \cdot 10^9$/L, drug treatment-related adverse reactions have been recovered to meet surgical requirements (according to guidelines). The surgical procedure will be carried out according to the CSCO clinical guidelines for the diagnosis and treatment of gastric cancer 2019 (Wang et al., 2019).

Surgery will be under general anesthesia supported by epidural anesthesia. Open surgery is considered to be the standard approach. Laparoscopic and robotic-assisted surgery is allowed only after discussion with the principal investigator if the surgical team has significant expertise in the minimally invasive approach with morbidity, mortality, and oncologic results that are comparable to the open approach. Trial laparoscopy may be considered by the surgical team to have an initial assessment of the extent and resectability of the tumor and evidence of distant metastases.

Please refer to the surgical guidelines for more details.

4.3.5.1 Resection

A sufficient distance between tumor bed and longitudinal resection margin should be ensured. The proximal and distal margins of resection will be based on the location of the tumor. The recommendations for an adequate distance of resection margin for Borrmann I–II gastric cancers are to be ≥ 3 cm, and for Borrmann III–IV it should be ≥ 5 cm. If the tumor has invaded the esophagus or pylorus, a resection margin of 5 cm is not obligatory only when R0 resection can be assured and the frozen pathological examinations of the resection margins are negative.

For EGJ adenocarcinoma which has invaded < 3 cm into the esophagus or the body of the stomach, non-endoscopic surgery is recommended.

4.3.5.2 Lymphadenectomy

The extent of the lymphadenectomy depends on the type of resection. D2 lymph node dissection is the standard recommendation for resectable gastric cancer classified as being cT1N+ and cT2-4N-/+. It is recommended that ≥ 16 lymph nodes should be pathologically examined to ensure accurate staging and prognostication. The lymph node dissection should follow the recommendations of the CSCO clinical guidelines for the diagnosis and treatment of gastric cancer 2019 (Wang et al., 2019).

The extent of resection and lymphadenectomy will be documented on the eCRF.

4.4 CONCOMITANT THERAPY

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 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 such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. New cancer treatment should be recorded in survival follow up phase.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza , COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

For atezolizumab, premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator (see Section 4.3.3).

Oxaliplatin can be administrated with premedication (e.g. phenothiazines, antihistaminics, or anticholinergic agents) at each cycle to control nausea/vomiting per local practice standards (see Section 4.3.3).

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.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and ®$_2$-adrenergic agonists; see Appendix 8).

In addition, a primary prophylaxis with G-CSF is not required, although permitted after balancing benefits and risks in the individual patient by the investigator. Upon occurrence of complicated neutropenia (e.g. either febrile neutropenia or infection during neutropenia), therapeutic and prophylactic actions according to local standards (e.g. administration of antibiotics and growth factors) should be applied. In order to avoid treatment delays, secondary prophylaxis with G-CSF will be required for all subsequent cycles if one of the following criteria is applicable:

- Occurrence of febrile neutropenia or infection in neutropenia at any time or
- Occurrence of grade 4 (NCI CTCAE v5.0) neutropenia or
- Delay of one therapy cycle due to leucopenia or neutropenia by more than 3 days

Anemia and thrombocytopenia should be managed according to local standards.

4.4.2 Cautionary Therapy

- Systemic corticosteroids and TNF-⟨ inhibitors: Systemic corticosteroids and TNF-⟨ inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-⟨ inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-⟨ inhibitors may be administered at the discretion of the investigator.
- Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).
- Herbal therapies: concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.
- Anticoagulants: patients treated with capecitabine should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. The use of low molecular weight heparin instead of coumarin is strongly recommended, but at the discretion of the Investigator.
- Phenytoin: patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.
- Care needs to be taken if a patient is taking both capecitabine and cimetidine.
- Interactions between capecitabine and drugs known to be metabolized by cytochrome p-450 2C9 have not been formally investigated. Thus, using of these drugs concomitantly with capecitabine should be cautious.
- Leucovorin has an effect on the pharmacodynamics of capecitabine and may increase the toxicity of capecitabine.

- Anthracyclines should be avoided whenever possible within 7 months of trastuzumab withdrawal.When anthracyclines are needed, the patient's heart function should be closely monitored.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- The antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine, are prohibited within 4 weeks prior to initiation of capecitabine treatment and during capecitabine treatment.
- Treatment with therapeutic antibiotics is prohibited within 2 weeks (IV antibiotics) or 5 days (oral antibiotics) prior to initiation of study treatment. Treatment with prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) is permitted.
- Drugs with potential nephrotoxicity should be avoided during treatment with chemotherapy.
- Allopurinol: interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

4.5 Study Assessments

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patients who fail their first screening for study eligibility may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. All re-screening requests should be discussed with the Medical Monitor or designee.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight should be measured and recorded in the eCRF.

Limited, symptom-directed physical examinations should be performed by the investigator or qualified designee at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusion as outlined in Table 2. In addition,

vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 2 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated
Trastuzumab	• Within 60 minutes prior to the trastuzumab infusion • At least 30 minutes from the end of the infusion	• Within 60 minutes prior to the trastuzumab infusion • At least 30 minutes from the end of the infusion
Oxaliplatin	• Within 60 minutes prior to the oxaliplatin infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the oxaliplatin infusion • Record patient's vital signs during or after the infusion if clinically indicated.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, within 2 weeks **(+7 days)** before surgery, every 6 months until 3 years after surgery regardless of dose delays, until radiographic disease progression or recurrence per RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression 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. Additional assessment can be performed by the investigator as clinically indicated. If signs or symptoms indicate a possible disease progression or recurrence, they need to be confirmed by the investigator after an integrated assessment of radiographic, pathologic (if available) and/or biochemical examinations. In that case, the time of progression or recurrence should be based on the time of first documented signs or symptoms. Abnormal laboratory test results alone should not be used as a criterion to determine progression or recurrence.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis as clinically indicated/determined by the investigators. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal

clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation, and results must be reviewed by the investigator before dosing at the next cycle. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Objective response during NAST at a single timepoint will be determined according to RECIST v1.1 (see Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR, and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (FT3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as FT4)
- HIV serology
- HBV serology: HBsAg, total HbcAb; 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; 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.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test 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 period, If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (ε12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes,

and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be **mandatory**:

- Pretreatment endoscopic biopsy sample obtained at baseline and surgery sample obtained after surgery for determination of HER2 status
- A formalin-fixed paraffin-embedded (FFPE) biopsy specimen in a paraffin block (preferred) or a minimum of 4 biopsy tissue slides containing unstained, freshly cut, serial sections must be submitted for central confirmation of HER2 positivity. A prespecified sensitivity analysis will be conducted in the centrally confirmed HER2 positive population.
- A formalin-fixed paraffin-embedded (FFPE) surgery specimen in a paraffin block (preferred) or a minimum of 4 surgery tissue slides containing unstained, freshly cut, serial sections must be submitted for central determination of HER2 status.
- Pretreatment endoscopic biopsy sample obtained at baseline and surgery sample obtained after surgery for exploratory research on PD-L1 expression.
- A formalin-fixed paraffin-embedded (FFPE) surgery/biopsy specimen in a paraffin block (preferred) or a minimum of 4 slides (2 biopsy and 2 surgery respectively) containing unstained, freshly cut, serial sections must be submitted for central evaluation of PD-L1 expression.
- Pretreatment endoscopic biopsy sample obtained at baseline for exploratory research on MMR status and sTIL signature.
- A formalin-fixed paraffin-embedded (FFPE) biopsy specimen in a paraffin block (preferred) or a minimum of 6 slides containing unstained, freshly cut, serial sections must be evaluated centrally/locally for MMR status.
- A formalin-fixed paraffin-embedded (FFPE) biopsy specimen in a paraffin block (preferred) or a minimum of 4 slides containing unstained, freshly cut, serial sections must be submitted for central evaluation of sTIL signature.
- Surgery sample (i.e. the complete resected stomach/GEJ specimen and regional lymph nodes) obtained after surgery for the primary endpoint pCR evaluation by local pathologists at each site.
- Blood samples collected at several time points (i.e. Day 1of Cycle 1, Day 1-35 after the last dose of Cycle 3, Day 1-56 after surgery, Day 1 of Cycle 6, treatment discontinuation visit, and during survival follow-up if clinically necessary) for exploratory research on HER2 copy number in circulating tumor DNA.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The leftover biological samples will be returned to the site as per the site requirement or destroyed when the final Clinical Study Report has been completed, with the following exception:

- Blood and tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law or HGRAC. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Evaluation of left ventricular ejection fraction

LVEF will be measured using MUGA scan or 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 (and more often if clinically indicated) during treatment and at most every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.

4.5.8 Electrocardiograms

An ECG is required at screening, before the treatment of each cycle and surgery, and at the time of treatment discontinuation. An ECG may be conducted if clinically necessary at any time after the initiation of the study treatment. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.9 Esophageal-gastro-duodenoscopy

An esophageal-gastro-duodenoscopy is mandatory at screening to confirm clinical stage.

4.5.10 Histopathological assessment

Histopathological tumor regression should be analyzed by local pathologists at each site after surgery according to AJCC staging system, 8th edition. Appendix 2 provides the tumor regression grade (TRG) score of the 8th AJCC.

4.5.11 Optional Procedure

Diagnostic laparoscopy and endoscopic ultrasonography are recommended to confirm clinical stage of indication at screening. Although they are optional procedures, the investigator should recommend the patients to complete them.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab+trastuzumab+XELOX or trastuzumab+XELOX) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)
- Radiographic disease progression or recurrence per RECIST v1.1 or symptomatic deterioration attributed to disease progression.
- Any event that meets stopping criteria defined in Appendix 6, Appendix 7 and Appendix 9

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit δ30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately once every 6 months in the first 3 years, followed by once a year until 5 years after surgery or until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.1.1 Handling Disease Progression Prior To Surgery

Progressive disease prior to surgery occurs when patients experience a progression of the primary tumor (as assessed by endoscopy for example) or develop metastases prior to surgery. Investigators will stop the study treatment for these patients. If surgical intervention is still reasonable (investigator decision), patients may proceed to surgery and the related information will be documented in the eCRF. After surgery, patients will be removed from the study treatment and will enter the survival follow-up phase. If surgery is not possible or not recommended, patients will be removed from the study treatment and enter the survival follow-up phase. The investigator will define the subsequent therapy for this patient according to local clinical practice. All related data will be collected in the eCRF and follow-up will be performed for OS assessment.

4.6.1.2 Handling Inoperability Defined During Surgery and R1/2 Resection

If metastatic disease is diagnosed during surgery (e.g. liver metastases or peritoneal carcinomatosis), resection can be performed if considered possible and reasonable by investigator. Patients found to be non-resectable during surgery as well as patients receiving palliative resection only will be removed from the study treatment. The investigator will define the subsequent therapy for these patients according to local clinical practice. After surgery, study treatment can be continued only if the investigator determines that the benefits outweigh the risks of continuing treatment for patients. All related data will be collected in the eCRF and survival follow-up will be performed. Any subsequent anti-tumor therapy should be documented in the eCRF.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab, trastuzumab, capecitabine and oxaliplatin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5 and 5.1.6.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab, trastuzumab, capecitabine and oxaliplatin will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 6, Appendix 7 and Appendix 9. Refer to Sections 5.2 5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Severe SARS CoV 2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-© (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS CoV 2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per

investigator judgment. If a diagnosis of SARS CoV 2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, pericardial disorders, myocarditis, and nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Trastuzumab

Trastuzumab has been associated with risks such as the following: infusion/ARRs and hypersensitivity, cardiac dysfunction, pulmonary adverse drug reactions, neutropenia/febrile neutropenia. Refer to Sections 5 and 6 of the trastuzumab Investigator's Brochure for a detailed description of anticipated safety risks for trastuzumab.

5.1.3 Risks Associated with Capecitabine

Capecitabine has been associated with risks such as the following: diarrhea, dehydration, hand-foot-syndrome, neutropenia/febrile neutropenia, leukopenia, thrombocytopenia, anemia and hyperbilirubinemia. Refer to the local prescribing informaion of capecitabine for a detailed description of anticipated safety risks for capecitabine.

5.1.4 Risks Associated with Oxaliplatin

Oxaliplatin has been associated with risks such as the following: anaphylactic/anaphylactoid reactions, peripheral sensory neuropathy, acute neurosensory symptoms, pulmonary fibrosis and hematological toxicity. Refer to the local prescribing informaion of oxaliplatin for a detailed description of anticipated safety risks for oxaliplatin.

5.1.5 Risks Associated with Combination Use of Atezolizumab, Trastuzumab and XELOX

The risk of overlapping toxicities between atezolizumab, trastuzumab and XELOX is anticipated to be controllable. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g. cardiac dysfunction, hypothyroidism, hyperthyroidism and neuropathy) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with trastuzumab and oxaliplatin could be exacerbated by the immunostimulatory activity of atezolizumab. On the basis of the frequency of adverse events associated with either atezolizumab, trastuzumab or

capecitabine, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, traszumab and capecitabine: cardiovascular, gastrointestinal (particularly diarrhea), renal, and hematologic toxicity.

Toxicities should initially be managed according to the recommendations in Appendix 6, Appendix 7 and Appendix 9 with dose holds and modifications (if applicable) applied to the component of the study treatment judged to be the primary cause. If individual component causality for the toxicity cannot be adequately determined, then the most conservative management recommendation should be applied.

5.1.6 Risk Associated with Surgery

In this study, the included patients will undergo the gastrectomy, therefore, the risk associated with surgery exists, such as the risk of anesthesia, bleeding and weakened the digestive function of the stomach.

Prior to the surgery, the laboratory tests are required to conducted, and drug treatment-related adverse reactions have been recovered to meet surgical requirements (according to guidelines). The surgical procedure will be carried out according to the CSCO clinical guidelines for the diagnosis and treatment of gastric cancer 2019 (Wang et al., 2019).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the International Council for Harmonisation (ICH) guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions (IRR), cytokine-release syndrome (CRS), Hemophagocytic lymphohistiocytosis (HLH), and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Congestive Heart Failure
- Myelitis
- Facial paresis

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, 5.6 and 5.7.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events 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, 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.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. Avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should

be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). In recognition of the challenges in clinically distinguishing between these two events, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 6.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see

Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: Certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5·ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\cdot$ULN) in combination with either an elevated total bilirubin ($>2\cdot$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\cdot$ULN in combination with total bilirubin $>2\cdot$ULN
- Treatment-emergent ALT or AST $>3\cdot$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of GC or adenocarcinoma of GEJ should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of gastric cancer or adenocarcinoma of GEJ

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose, or Medication Error

Overdose (accidental or intentional) and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab and trastuzumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab and trastuzumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

All these special situations associated with atezolizumab and trastuzumab regardless of whether they result in an adverse event and AEs associated with special situations should be reported to the Sponsor within 30 calendar days.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for site location

Medical Monitor (Roche):	[redacted]
Telephone No.:	/
Mobile Telephone No.:	[redacted]
Medical Monitor (CRO):	[redacted]
Telephone No.:	/
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab, 7 months after the last dose of trastuzumab, or 6 months after the last dose of capecitabine or oxaliplatin, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of trastuzumab, 3 months after the last dose of capecitabine, or 6 months after the last dose of oxaliplatin, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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 eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for all of serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/ Special Situation Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Trastuzumab Investigator's Brochure
- Prescribing Information of Capecitabine
- Prescribing Information of Oxaliplatin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

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.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, self reported race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of study treatments on the basis of the following endpoint:

- 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 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.

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. 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. 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. This population is defined as all patients who are centrally confirmed as HER2 positive and underwent resection.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study will be analyzed in ITT population, including: event-free survival (EFS), disease-free survival (DFS), overall survival (OS), major pathologic response (MPR), objective response rate (ORR) and R0 resection rate.

6.4.2.1 Event-Free Survival (EFS)

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.

Patients who have not experienced disease recurrence, progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

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).

6.4.2.2 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 will be analyzed in a similar manner as EFS.

6.4.2.3 Overall Survival (OS)

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

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 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).

6.4.2.4 Major Pathologic Response (MPR)

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.

6.4.2.5 Objective Response Rate (ORR)

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.

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

6.4.2.6 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.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are planned to include HER2 copy number in ctDNA, MMR status, PD-L1 expression and sTIL infiltration.

Descriptive statistics will be provided for each exploratory efficacy endpoint. Subgroup analysis based on these exploratory endpoints will be conducted if applicable.

More details about exploratory efficacy endpoints analyses will be specified in the SAP finalized before database lock.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by Preferred Term (PT), System Organ Class (SOC), and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.7 INTERIM ANALYSIS

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.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written Investigational New Drug (IND) safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 10-12 sites in China will participate to randomize approximately 42 patients.

Central facilities will be used for certain study assessments throughout the study (e.g., biomarker analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
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 3 years after surgery or until death
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	D1~35 ± 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				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	

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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													

Appendix 1: Schedule of Activities

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LVEF assessment（MUGA or ECHO）[11]	X					X						X[11]		X
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	

Appendix 1: 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 3 years after surgery or until death
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	D1~35 ± 3	**≤ 8 weeks after surgery** (Day 1~56 ± 3)	Day 1 (± 3 days) of every 3 weeks					**≤ 30 days of last administration**	
Surgery						X [21]								

1. HER2 testing can use biopsy sample at baseline and surgery sample after surgery. 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. Local HER2 testing is conducted at screening phase, biopsy sample collection at C1D1 and surgery sample after surgery are sent to central lab for status confirmation.
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. If screening laboratory assessments were performed within 7 days prior to the first dose of study treatment of Cycle 1, they do not have to be repeated. Laboratory assessments should be completed within 3 days prior to dosing at each subsequent treatment visit. 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; 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; 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±7days (and more often if clinically indicated) during treatment (including the recovery period of less than or equal to 8 weeks after surgery, and it is possible to test for LVEF before C8.) and at most every 6 months (+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(+7 days) before surgery.
15. Tumor assessment should performed every 6 months±7days until 3 years after surgery. Additional assessment can be performed if signs or symptoms indicate a possible recurrence or development of a new gastric cancer. During treatment phase, the visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.
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 5.6).
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 or 30 days after the last study treatment (whichever occurs first). New cancer treatment should be recorded in survival follow up phase.
20. If clinically necessary.
21. Surgery is recommended to be performed 3 to 6 weeks after the last dose of neoadjuvant study treatment, after completing other "C3 After" visit procedures.

Appendix 2
The tumor regression grade (TRG) score of the 8th American Joint Committee on Cancer (AJCC)

Tumor regression grade	Definition
TRG 0 Complete regression	No viable cancer cells
TRG 1 Near complete regression	Single or small groups of tumor cells
TRG 2 Moderate regression	Residual cancer outgrown by fibrosis
TRG 3 Minimal/absent regression	Minimal or no tumor cells killed

Note:
1. The tumor regression grade (TRG) score is limited to the assessment of the primary tumor after chemoradiotherapy.
2. Tumor cells refer to living cells, excluding degenerative cells and necrosis cells; Mucous lakes without cellular components cannot be assessed as residual tumor.

Appendix 3
Evaluation and scoring criteria for HER2 immunohistochemical staining of gastric cancer

In this study, the evaluation and scoring criteria for HER2 immunohistochemical staining of specimens should as per Table 1.

For surgical specimens whose staining intensity is equivalent to the IHC 3+ level, but the proportion of positive cells is less than 10%, it is recommended to replace a paraffin block with more intestinal type components for retest. If it is still short of IHC 3 + scoring criteria after retest, the specimen is still scored according to the grading standard as recommended by the guidelines (Guidelines for the detection of HER2 in gastric cancer, 2016), but the particularity of the case must be noted in the report (such as: less than 10% of the tumor cells are positive and HER2 IHC 3 +) , and discussion is suggested by multidisciplinary therapy (MDT) group for gastric cancer, FISH test may be conducted if necessary.

Table 1 Evaluation and scoring criteria for HER2 immunohistochemical staining of gastric cancer

Specimen type		Score	Evaluation of HER2 overexpression
Surgical specimen	**Biopsy specimen**		
No reaction or membrane staining in <10% of tumor cells	No staining in any tumor cell	0	Negative
Faint or dim membrane staning in ≥10% of tumor cells; staining in only part of the cells	Faint or dim membrane staning in tumor cell clusters (regardless of the percentage of stained tumor cells in the whole tissue)	1+	Negative
Weak to moderate staining of basolateral membrane, lateral membrane or complete membrane in≥10% of tumor cells	Weak to moderate staining of basolateral membrane, lateral membrane or complete membrane in tumor cell clusters (regardless of the percentage of stained tumor cells in the whole tissue, but staining in at least 5 tumor cell clusters)	2+	Uncertain

Appendix 3: Evaluation and scoring criteria for HER2 immunohistochemical staining of gastric cancer

Specimen type		Score	Evaluation of HER2 overexpression
Surgical specimen	**Biopsy specimen**		
Strong staining of basolateral membrane, lateral membrane or complete membrane in≥10% of tumor cells	Strong staining of basolateral membrane, lateral membrane or complete membrane in tumor cell clusters (regardless of the percentage of stained tumor cells in the whole tissue, but staining in at least 5 tumor cell clusters)	3+	Positive

Note: The cytoplasmic and nuclear staining of tumor tissues are non-specific staining, and the interpretation of the results should avoid the edge of the cancerous tissue and poor tissue treatment or morphology (such as obvious extrusion).

REFERENCE

The expert group for guidelines for the detection of HER2 in gastric cancer 2016. Guidelines for the detection of HER2 in gastric cancer. Chin J Pathol 2016;45:528-532.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval δ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ε 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be δ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis ε 10 mm but $<$ 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ε10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is δ5 mm. When CT scans have slice thickness of $>$5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation .

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological

nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ε15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\cdot$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ε10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the electronic Case Report Form (eCRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of $<$10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present

and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

Response Criteria

Criteria for Target Lesions

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ε 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting

lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 and Table 2.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228 47.

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 6
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in subsequent subsections.

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.

- Consider withholding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.

- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.

- Withhold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2 mg/kg/day oral prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.

- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone replacement therapy.

The investigator should consider the benefit risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's benefit risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ε1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening, cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist. ● For Grade 1 pneumonitis, consider withholding atezolizumab. ● *Consider resuming on radiographic evidence of improvement*.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. ● Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c],[d] ● For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c, d] ● Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. ● Bronchoscopy or BAL with or without transbronchial biopsy is recommended. ● Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. ◦ If strong clinical suspicion for immune-mediated colitis, initiate empiric IV corticosteroids while waiting for definitive diagnosis.. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. Ifevent does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. TSHand free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
hypothyroidism Grade 1	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely .
hypothyroidism Grade 2	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
hypothyroidism Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely . • Refer patient to endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]
hyperthyroidism Grade 1	**TSH ε0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
hyperthyroidism Grade 2	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
hyperthyroidism Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer patient to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging;

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging;

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin*, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on immune-mediated pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, *a TTE for evaluation of left ventricular injection fraction and global longitudinal strain*, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Immune-Mediated pericardial disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on immune-mediated myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (e.g., metastatic disease), cancer treatment (e.g., chest radiotherapy), cardiac injury (e.g., injury due to myocardial infarction or iatrogenesis), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, *TTE*, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grades 2-4 or Immune-mediated pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone for 3-5 days and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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, *anti-pyretic* medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported

with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and *interferon*-© (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ◦ For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.

Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or venturi-mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [f] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. e • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [f] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (v5.0) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ε 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at δ 6 L/min, and high flow is defined as oxygen delivered at $>$ 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate) .Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit risk ratio.
g. Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase >1.5 2.0 ·ULN:** ● Continue atezolizumab. ● Monitor amylase and lipase weekly. ● For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0 5.0 ·ULN:** ● Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to GI specialist. ● Monitor amylase and lipase every other day. ● If no improvement, consider treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] ● For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε1 month to the equivalent of δ10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε 1 month to the equivalent of δ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1 2 mg/kg/day if event does not improve within 48 72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Stevens Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens Johnson syndrome or toxic epidermal necrolysis ● Withhold atezolizumab for suspected Stevens Johnson syndrome or toxic epidermal necrolysis. ● Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant), and, if indicated, biopsy. ● Follow the applicable treatment and management guidelines above. ● If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε1 month to the equivalent of δ10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in Table 10, with specific guidelines for myelitis provided in Table 11.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	● Continue atezolizumab. ● Investigate etiology. ● Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Investigate etiology and refer patient to neurologist. ● Initiate treatment as per institutional guidelines. ● For general immune-mediated neuropathy: -If event resolves to Grade 1 or better, resume atezolizumab. [b] -If event does not resolve to Grade 1 or better while withholding

	atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For facial paresis: - *Initial observation OR initiate prednisone 1-2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain*. - If event resolves fully, resume atezolizumab. [b] - If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist • Initiate treatment as per institutional guidelines *and proceed as per Guillain-Barré syndrome management.*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1 2 mg/kg/day oral or IV prednisone. • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider IV methylprednisone 1 g/day for 3 5 days and consider other immunosuppressive agent.*

IVIG: intravenous immunoglobulin.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε1 month to the equivalent of δ10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.

Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.

Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor.
	• *Initiate non-opioid treatment (e.g., pregabalin, gabapentin, duloxetine) for pain.*
	• *Hospitalize patient.*
	  ○ *Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone.*
	  ○ *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines.*
	• Refer patient to a neurologist.
	•

IVIG: intravenous immunoglobulin.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Immune-mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε 1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε1 month to the equivalent of δ10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase*/creatine phosphokinase* increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis *(see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Immune-mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 14 Management Guidelines for Immune-mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ε1 month.

IVIG: intravenous immunoglobulin.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of δ10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ε1 month to the equivalent of δ10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ε38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)

  - Platelet count $< 100 \cdot 10^9$/L (100,000/⌈L)
  - ANC $< 1.0 \cdot 10^9$/L (1000/⌈L)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\varepsilon 2$ standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over $\varepsilon 1$ month.

HLH = hemophagocytic lymphohistiocytosis

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Appendix 7
Risks Associated with Trastuzumab and Guidelines for Management of Adverse Events Associated with Trastuzumab

General considerations

There are no dose adjustments of trastuzumab foreseen for toxicity. If a patient cannot tolerate trastuzumab infusions, trastuzumab treatment will be stopped completely.

To ensure continuity of study treatment, patients had to restart trastuzumab within 3 cycles (≤ 63 days after Day 1 of the previous cycle). If trastuzumab is delayed by more than 2 cycles, the patient will be **permanently discontinued from trastuzumab treatment**, unless the investigator considers that the benefit outweighs the risk to the patient.

During neo-adjuvant treatment: If any of the individual study drugs must be delayed for a day or more, generally all agents should be delayed in the same timeframe.

During adjuvant treatment: if this is considered to be in the patient's best interest by the investigator, in patients in whom resolution of a chemotherapy-induced AE seems unlikely within one week, administration of trastuzumab, alone or in combination with atezolizumab according to the treatment arm but without chemotherapy at the scheduled date is possible. In this case, if the patient has been treated with the antibodies but without chemotherapy for one cycle, the next treatment cycle of antibodies in combination with chemotherapy may be given only three weeks later according to the treatment regimen.

Infusion-Related Reactions

Patients who experience a life-threatening infusion reaction to the first dose of trastuzumab (e.g. tachypnoea, bronchospasm, hypotension, hypoxia) should immediately discontinue trastuzumab and be given appropriate therapy. They will not be re-challenged and will be taken off trastuzumab.

Patients who experience severe or moderate infusion reactions should be managed by:

– slowing or stopping the trastuzumab infusion

– supportive care with oxygen, beta agonists, antihistamines, corticosteroids as appropriate at the Investigator's discretion.

Patients who experience mild or moderate infusion symptoms may be treated with antipyretics and antihistamines.

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.

Cardiotoxicity

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline- (doxorubicin or epirubicin) containing chemotherapy. This may be moderate to severe and has been associated with death. In

addition, caution should be exercised in treating patients with increased cardiac risk (e.g., hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age). Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin IV treatment. Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction.

If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

All candidates for treatment with trastuzumab, should undergo cardiac assessment according to the protocol requirements including history, physical examination and cardiac assessment (ECG and echocardiogram or MUGA scan). A careful risk-benefit assessment should be made before deciding to treat with trastuzumab.

In this study, all patients must have a baseline LVEF value ε 55%, and LVEF is to be monitored every 12 weeks during antibody treatment and at most every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. To ensure patient safety, if an investigator assesses that an AE may be related to cardiac dysfunction, an additional LVEF measurement should be performed, as well as other appropriate procedures such as chest X-ray, and the scheduled cardiac toxicity assessments will continue unchanged.

If symptomatic Left ventricular systolic dysfunction (LVSD) is confirmed by a cardiologist's evaluation in any patient, **trastuzumab should be permanently discontinued**, and the patient should be discontinued from study treatment on account of unacceptable toxicity. Symptomatic LVSD should be treated and monitored according to standard medical practice.

At the present time, there are inadequate data available to assess the prognostic significance of clinically asymptomatic decreases in LVEF values. However, If LVEF drops 10 ejection points from baseline and to below 50%, Herceptin should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or clinically significant CHF has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen. The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with standard medications for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker and a β-

blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued with Herceptin without additional clinical cardiac events.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, Herceptin treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Herceptin after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a high body mass index (BMI > 25 kg/m^2).

Treatment with chemotherapy should be continued if considered in the patient's best interest as considered by the investigator. All such patients should be referred for assessment and follow up by a cardiologist.

Appendix 8

Capecitabine Dose Calculation

For a starting dose of capecitabine 1000 mg/m^2, the following tables describe the calculation of standard and reduced doses according to body surface area: the following tables apply to 500 mg tablet only, where 100% dose level is twice-daily 1000 mg/m^2 (total daily dose of 2000 mg/m^2).

100% Dose Level Twice Daily 1000 mg/m^2/dose		Number of 500 mg Tablets to be Taken	
Surface Area (m^2)	Average Dose per Administration (mg)	In the Morning	In the Evening
≤1.15	1000	2	2
1.16-1.40	1250	2	3
1.41-1.65	1500	3	3
1.66-1.90	1750	3	4
≥1.91	2000	4	4

75% Dose Level		Number of 500 mg Tablets to be Taken	
Surface Area (m^2)	Average Dose per Administration (mg)	In the Morning	In the Evening
≤1.15	750	1	2
1.16-1.40	1000	2	2
1.41-1.90	1250	2	3
≥1.91	1500	3	3

50% Dose Level		Number of 500 mg Tablets to be Taken	
Surface Area (m^2)	Average Dose per Administration (mg)	In the Morning	In the Evening
≤1.15	500	1	1
1.16-1.90	750	1	2
≥1.91	1000	2	2

Appendix 9

Dose Modifications for Chemotherapy Treatment for Specific Toxicities

General considerations

Capecitabine dosing interruptions are regarded as lost treatment days, and missed doses should not be replaced.

Capecitabine dose reductions for a given patient are permanent reductions for that patient.

If capecitabine must be permanently discontinued due to capecitabine-specific toxicity, oxaliplatin should also be permanently discontinued. Thus, patients may not continue on oxaliplatin monotherapy alone. During preoperative treatment, these patients need to proceed to surgery as rapidly as possible after recovery from toxicity.

If oxaplatin must be discontinued due to oxaliplatin-specific toxicity, capecitabine can be continued. If capecitabine is discontinued, oxaliplatin won't be continued.

During neo-adjuvant treatment: If any of the individual study drugs must be delayed for a day or more, generally all agents should be delayed in the same timeframe. If a patient requires a dose delay of chemotherapy for $>$ 3 weeks due to toxicity, chemotherapy will be definitively discontinued for neoadjuvant treatment for unacceptable toxicity. These patients should proceed to surgery as soon as possible after recovery from toxicity, to avoid a risk of tumor progression due to administration of insufficient chemotherapy doses before surgery.

During adjuvant treatment: if this is considered to be in the patient's best interest by the investigator, in patients in whom resolution of a chemotherapy-induced AE seems unlikely within one week, administration of trastuzumab, alone or in combination with atezolizumab according to the treatment arm but without chemotherapy at the scheduled date is possible. In this case, if the patient has been treated with the antibodies but without chemotherapy for one cycle, the next treatment cycle of antibodies in combination with chemotherapy may be given only three weeks later according to the treatment regimen.

General considerations for dose modification

The latest body weight is used to calculate body surface area for chemotherapy doses. If the body weight change is > 10%, the body surface area needs to be recalculated. Chemotherapy doses should not be modified for any body weight change of ≤ 10%.

Hematologic toxicity

Capecitabine is not expected to worsen, nor to unduly prolong episodes of neutropenia. Administration of capecitabine should be interrupted if grade 3 or 4 neutropenia develops. In case of fever or infection with neutropenia, the patients should be instructed to stop taking capecitabine immediately. When the ANC has recovered to ε $1.5 \cdot 10^9$/L and the fever or infection has resolved, patients may re-start treatment with a dose reduction according to the following guidelines:

Table 15 Dose modifications for FEBRILE NEUTROPENIA occurring anytime during treatment with capecitabine and oxaliplatin

	Grade 3 ANC < 1.0 x 10^9/L with a single temperature ≥ 38.3°C or persistent temperature ≥ 38°C for one hour	Grade 4 life threatening and need emergency treatment
1st occurrence	Capecitabine 75% of original dose, and oxaliplatin 85 mg/m^2	Stop treatment permanently unless it is in the best interest of the patient to treat with capecitabine at 50% of original dose, and oxaliplatin 85 mg/m^2
2nd occurrence	Stop treatment permanently unless it is in the best interest of the patient to treat with capecitabine at 50% of original dose, and oxaliplatin 85 mg/m^2.	Stop treatment permanently.

Table 16 Dose modifications for AFEBRILE NEUTROPENIA occurring anytime during treatment with capecitabine and oxaliplatin

	Grade 2 1.0 ≤ ANC < 1.5 x10^9/L	Grade 3 0.5 ≤ ANC< 1.0 x10^9/L	Grade 4 ANC < 0.5 x10^9/L
Laboratory values before the beginning of the chemotherapy cycle: delay chemotherapy until ANC 1.5 x10^9/L, platelet 75 x10^9/L, and non-hematologic toxicity is restored to baseline or ≤ grade 1, followed by chemotherapy at the following dose:			
1st occurrence	No dose adjustment	Capecitabine 75% of original dose, and oxaliplatin 100 mg/m^2.	Capecitabine 50% of original dose, and oxaliplatin 85 mg/m^2.
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose, oxaliplatin 85 mg/m^2.	Stop treatment permanently.
3rd occurrence	No dose adjustment	Stop treatment permanently unless it is in the best interest of the patient to treat with capecitabine monotherapy at 75% of original dose.	Not applicable.

Table 17 Dose modifications for thrombocytopenia occurring anytime during treatment with capecitabine and oxaliplatin

Thrombocytopenia	Platelets ≥ 50 to <75 x 10^9/L	Platelets ≥ 25 to <50 x 10^9/L	Platelets < 25 x 10^9/L
Laboratory values before the beginning of the chemotherapy cycle: delay chemotherapy until ANC 1.5 x10^9/L, platelet 75 x10^9/L, and non-hematologic toxicity is restored to baseline or ≤ grade 1, followed by chemotherapy at the following dose:			
1st occurrence	Oxaliplatin 100 mg/m^2, and no dose adjustment for capecitabine	Capecitabine 75% of original dose, and oxaliplatin 100 mg/m^2.	Capecitabine 50% of original dose, and oxaliplatin 85 mg/m^2.
2nd occurrence	Oxaliplatin 100 mg/m^2, and no dose adjustment for capecitabine	Capecitabine 75% of original dose, and oxaliplatin 85 mg/m^2.	Stop treatment permanently unless it is in the best interest of the patient to treat with capecitabine monotherapy at 50% of original dose.
3rd occurrence	Oxaliplatin 85 mg/m^2, and no dose adjustment for capecitabine	Capecitabine 50% of original dose, and oxaliplatin 85 mg/m^2.	Stop treatment permanently.

No dose modifications or interruptions will be required for anaemia (non-haemolytic) as it can be satisfactorily managed by transfusions.

Please note: the aforementioned rules for dose modifications are based on the blood counts before each treatment cycle. Blood counts during treatment cycles are not mandatory. However, if – according to institutional guidelines or other clinical reasons – the investigator decides to perform additional blood counts during the treatment cycle, and hematologic grade 3 or 4 toxicity (neutropenia or thrombopenia) or other non-hematological toxicities greater than grade I are diagnosed, treatment with capecitabine should be interrupted until recovery to grade 0 or 1. The indication to reduce the dose of capecitabine in subsequent treatment cycles should be decided by the investigator.

Non-hematologic toxicity

In general, dose modifications for capecitabine-associated, non-hematological toxicities should be conducted according to Table 18.

If Grade 2, 3, or 4 non-hematologic toxicity occurs (except for toxicity related solely to oxaliplatin), capecitabine dosing should be interrupted immediately and the instructions shown in Table 18 (below) should be followed.

The recommendations in this section apply to toxicities typically considered to be related to capecitabine treatment (e.g., neurotoxicity or ototoxicity does not require capecitabine dose modification).

Capecitabine dosing interruptions are regarded as lost treatment days, and missed doses should not be replaced.

Capecitabine dose reductions for a given patient are permanent reductions for that patient.

Table 18 Dose modification for capecitabine for non-hematologic toxicities

	Grade 2	Grade 3	Grade 4
1st occurrence	Interrupt treatment until resolved to Grade δ 1, then resume at 100% of original dose with prophylaxis if possible	Interrupt treatment until resolved to Grade δ 1, then resume at 75% of original dose with prophylaxis if possible	Permanently discontinue capecitabine or re-treat at 50% of original dose after discussion with study medical monitors
2nd occurrence of same toxicity	Interrupt treatment until resolved to Grade δ 1, then resume at 75% of original dose	Interrupt treatment until resolved to Grade δ 1, then resume at 50% of original dose	Permanently discontinue capecitabine
3rd occurrence of same toxicity	Interrupt treatment until resolved to Grade δ 1, then resume at 50% of original dose	Permanently discontinue capecitabine	/
4th occurrence of same toxicity	Permanently discontinue capecitabine	/	/

Grade 2 or 3 Palmar–plantar dysesthesia (Hand–Foot Syndrome)
Manage toxicity according to Table 18. Treat symptomatically (use of emollients is recommended) according to local standards.

Grade 2 or 3 diarrhea
Capecitabine can induce diarrhea, which can be severe. In general, diarrhea should be managed according to grade. Infectious diarrhea should be ruled out, and patients should be carefully monitored. If they become dehydrated, they should be given fluid and electrolyte replacement. Anti-diarrhea treatments (e.g.loperamide) should be initiated as medically appropriate and as early as possible.

In case of grade 2 or 3 diarrhea, capecitabine should be stopped and symptomatic treatment with loperamide should be started. Restart at 100% of previous dose if considered adequately controlled within 2 days of initiation of treatment. If control takes longer, then the dose should be modified according to Table 18. Any diarrhea of $>$ 2 days duration requires medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of dihydropyrimidine dehydrogenase deficiency. Capecitabine cannot be restarted until the diarrhea has resolved to Grade 0 or 1, with the last loperamide dose given at least 24 hours beforehand.

If the AE recurs despite prophylaxis, dose modifications should be followed as outlined in Table 18. If a patient experiences recurrent Grade 2 toxicity at the end of the 2-week

treatment period (Days 11-14), which resolves to Grade 0 or 1 within the scheduled treatment rest period (Days 15–21), dosing may continue at the same dose.

Grade 2 or 3 nausea or vomiting, or both
Nausea can be related to both – oxaliplatin and capecitabine. In case of nausea, which might as well be related to oxaliplatin, optimal anti-emetic treatment for oxaliplatin should be given. If furthermore necessary, a dose reduction to 75% of the dose of oxaliplatin may be considered by the investigator, in addition to the dose reduction for capecitabine.

Patients must be supplied with antiemetics at home (the choice of medications is at the discretion of the investigator, and should correspond to relevant guidelines) if nausea or vomiting occurs. Additional prophylactic treatment should be initiated if nausea or vomiting is not adequately controlled. If the AE recurs despite prophylaxis, then dose modifications should be made according to Table 18.

Grade 2 or 3 stomatitis
Stomatitis can be caused by oxaliplatin or capecitabine. In case of stomatitis, investigator should identify the causality, and the drug considered to be related with stomatitis should be immediately interrupted until the event resolves or decreases in intensity to Grade 1. Treat symptomatically.

Neurotoxicity
If patients occurrs neurotoxicity attributable to oxaliplatin, dose modifications should be followed as outlined in Table 19.

Table 19 Dose adjustment in case of oxaliplatin-related neurotoxicity

Neurotoxicity	Duration of neurotoxicity		
	≤ 7 days	>7 and < 14 days	present between cycles
Cold-induced dysaesthesia	no change	no change	no change
Paraesthesia	no change	no change	reduction to 75%
Paraesthesia with pain	no change	reduction to 75%	stop oxaliplatin* continue capecitabine
Paraesthesia with functional impairment	no change	reduction to 50%	stop oxaliplatin* continue capecitabine

* Usually, discontinuation will be permanently. Nevertheless, administration of oxaliplatin can be resumed (e.g. after complete recovery from the related symptoms) if the investigator decides that this is in the best interest of the patient and if he/she does not expect the toxicity to reoccur.

Other toxicities
If the calculated creatinine clearance (CCr) decreases to 30 mL/min, capecitabine and oxaliplatin should be permanently discontinued. An appropriate workup to identify - and if possible treat - the causes of the deterioration of renal function as decided by the investigator is necessary.

In case of Grade 2 cardiac toxicity attributable to capecitabine, capecitabine should be permanently discontinued.

For a first occurrence of a Grade 4 toxicity, please contact the study medical monitor to assess the possibility of continuing treatment at reduced dose (50% of original dose).

In the presence of unexplained respiratory symptoms, such as dry cough without sputum, dyspnea, alveolar rales, or radiographic evidence of lung infiltration, the use of oxaliplatin should be discontinued until further pulmonary examination confirms that the possibility of interstitial pneumonia has been ruled out.

If it is not certain that abnormalities in liver function test results or portal hypertension are caused by liver metastasis, the possibility of rare hepatic vascular abnormalities caused by oxaliplatin should be considered.

Appendix 10

ECOG Performance Status as developed by the Eastern Cooperative Oncology Group (Oken et al. 1982)

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix 11
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or lifethreatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

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