Clinical Study Protocol

Investigational Product	< Trastuzumab>
Amendment	<Ver. 2.0>
Amendment Date	03JUL2026

A Phase II, Single-Center Platform Trial of Neoadjuvant Trastuzumab Plus Durvalumab and FLOT Targeted Chemoimmunotherapy in Patients With Locally Advanced, Resectable HER2-Positive Gastric or Gastroesophageal Junction Cancer

Investigator-Sponsor / Principal Investigator: Professor Jeeyun Lee, MD

Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

The following amendments and administrative changes have been made to this protocol since its preparation.

Amendment Number	Amendment Date	:	
1.0	*27MAY2026*		
2.0	*03JUL2026*		

Protocol Synopsis

A Phase II, Single-Center Platform Trial of Neoadjuvant Trastuzumab Plus Durvalumab and FLOT Targeted Chemoimmunotherapy in Patients With Locally Advanced, Resectable HER2-Positive Gastric or Gastroesophageal Junction Cancer

Investigator and Study Site	
Study Site	Samsung Medical Center 81 Irwon-ro, Gangnam-gu, Seoul, Republic of Korea
Sponsor /Principal Investigator:	Jeeyun Lee, MD Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
Co-investigators	Seung Tae Kim, MD Sung Hee Lim, MD Minsuk Kwon, MD

Study Design	Interventional, Phase II, open-label study

Study Synopsis

Rationale
Perioperative regimens including neoadjuvant chemotherapy, or postoperative adjuvant chemotherapy alone, Perioperative regimens incorporating neoadjuvant chemotherapy, or adjuvant chemotherapy alone, are established standards of care for resectable gastric and gastroesophageal junction cancer (GC/GEJC). Currently recommended chemotherapy regimens have improved survival in this population (Al-Batran et al., 2016, 2017; Bang et al., 2012; Cunningham et al., 2006; Sasako et al., 2008, 2011; Smalley et al., 2012; Ychou et al., 2011). Nevertheless, recurrence rates within five years of surgery remain high, and five-year overall survival (OS) remains poor, particularly in Western populations. There is therefore a substantial unmet medical need for more effective treatments for resectable GC/GEJC worldwide. Gastric cancer (GC) is the fifth most commonly diagnosed malignancy, with more than one million new cases worldwide each year. Overexpression of human epidermal growth factor receptor 2 (HER2), reported in 4.4%–53.4% of patients across different studies, is a predictive biomarker of response to HER2-targeted therapy. Trastuzumab combined with cisplatin or oxaliplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil [5-FU]) is an approved anti-HER2 regimen for first-line treatment of HER2-positive gastric or gastroesophageal junction (GEJ) cancer [1]. In the Trastuzumab for Gastric Cancer (ToGA) trial, this combination improved median overall survival (OS) to 13.8 months, compared with 11.1 months with

chemotherapy alone.

Preclinical and clinical evidence indicates that trastuzumab modulates antitumor immunity through several mechanisms. It induces antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), enhances HER2 antigen presentation by dendritic cells, promotes CD8+ cytotoxic T-cell activation, and increases natural killer cell infiltration and MHC class I expression. The resulting release of interferon gamma (IFN-γ) can induce PD-L1 expression, providing a rationale for PD-1 pathway blockade to counteract an immunosuppressive tumor microenvironment.

Based on this mechanistic rationale, a single-center Phase II study at MSKCC (37 enrolled patients) reported an objective response rate (ORR) of 91%, including a complete response rate of 17%, and a six-month progression-free survival rate of 70% with trastuzumab, chemotherapy, and pembrolizumab. Grade 3–4 toxicities were predominantly chemotherapy-related anemia, elevated liver enzymes, diarrhea, and mucositis; immune-related colitis and hepatitis were also reported. {Janjigian, 2020 #8}

These findings led to the multinational randomized Phase III KEYNOTE-811 trial, which compared trastuzumab plus chemotherapy with or without pembrolizumab in 434 previously untreated patients with metastatic HER2-positive esophagogastric cancer. The pembrolizumab group achieved substantially higher ORR (74.4% vs 51.9%) and complete response rates (11.3% vs 3.1%), without a significant increase in toxicity. This combination was subsequently approved as first-line therapy for metastatic HER2-positive esophagogastric cancer {Janjigian, 2023 #10}.

In the treatment of locally advanced, resectable gastric cancer, MATTERHORN (NCT04592913) is a randomized, double-blind, placebo-controlled, multinational Phase III study evaluating perioperative durvalumab in patients with resectable stage II–IVA GC/GEJC. A total of 948 participants were randomized to receive two preoperative cycles of fixed-dose durvalumab 1,500 mg plus FLOT chemotherapy every four weeks or placebo plus FLOT, followed by up to 12 postoperative cycles

of durvalumab or placebo every four weeks (comprising two cycles with FLOT and ten additional cycles of durvalumab or placebo alone). Participants were enrolled at 176 centers in 20 countries across North and South America, Europe, and Asia. MATTERHORN met the prespecified statistical boundary for its key secondary endpoint of pathological complete response (pCR), assessed by central pathological review using the modified CAP Ryan tumor regression grading system. Preoperative durvalumab plus FLOT significantly improved the pCR rate compared with placebo plus FLOT: 19.2% (95% CI, 15.75–23.04) versus 7.2% (95% CI, 5.02–9.88), an absolute difference of 12.0 percentage points (odds ratio, 3.08; 95% CI, 2.03–4.67; p<0.001). Safety and tolerability were consistent with the known profiles of the combination, without reducing the proportion of patients undergoing surgery compared with chemotherapy alone (Janjigian et al., 2023). On this basis, the present study will assess whether adding trastuzumab to durvalumab plus FLOT is safe and effective as neoadjuvant therapy for patients with locally advanced, resectable HER2-positive esophagogastric cancer. This Phase II trial is designed to provide an initial assessment of the safety and efficacy of neoadjuvant trastuzumab combined with durvalumab and FLOT in patients with locally advanced, resectable HER2-positive gastric cancer.
Objectives and Endpoints

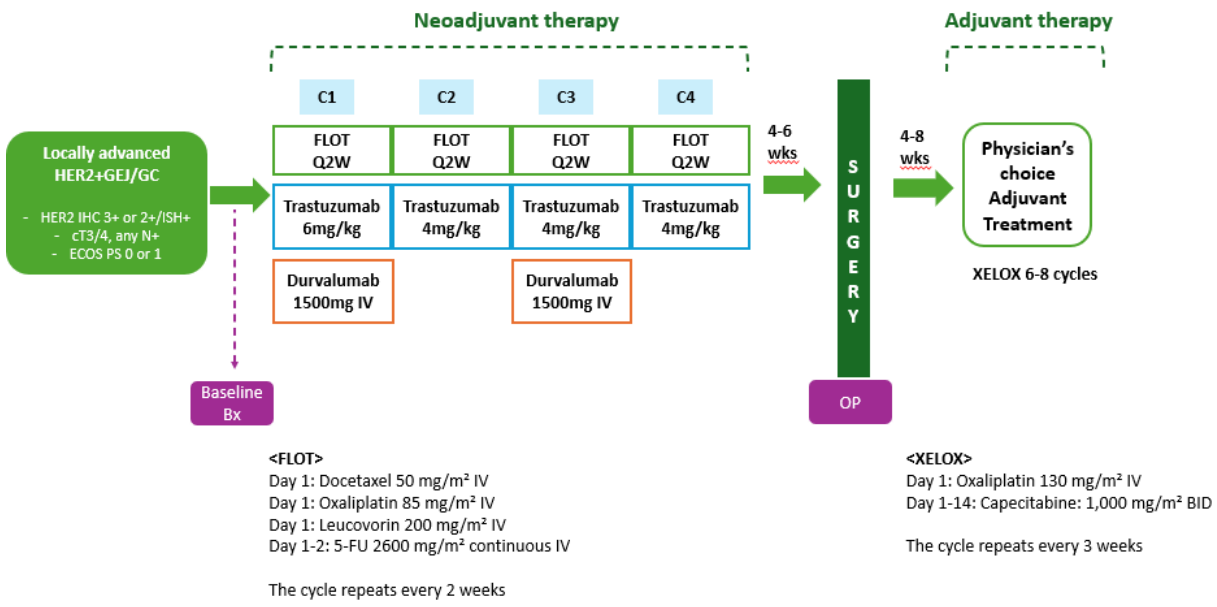
Primary Objectives:	**Endpoints:**
To evaluate safety and tolerability and efficacy based on pathological complete response (pCR) of FLOT plus trastuzumab and durvalumab administered as neoadjuvant chemotherapy	- Pathological complete response (pCR; ypT0N0) - Adverse events (AEs/SAEs)

Secondary Objectives:	**Endpoints:**
To evaluate secondary measures of clinical efficacy of the investigational regimen administered as neoadjuvant chemotherapy	- Complete (R0) resection rate (ypTxNxM0, excluding ypT0N0M0) - Overall survival (OS) - Event-free survival (EFS) - Duration of response - Objective response rate (ORR; during neoadjuvant therapy)
Planned Subgroup Analyses	- Whole-genome and RNA sequencing of baseline, on-study, and surgical specimens - Spatial transcriptomics (baseline and surgical specimens; CosMx) - Single-cell sequencing (tissue) - Proteomics

The pathological complete response (pCR) rate is defined as the proportion of patients with no residual viable tumor in the resected surgical specimen, as determined by pathological review. Additional secondary endpoints, including the rate of surgery, objective response rate (ORR), complete (R0) resection rate, event-free survival (EFS), and overall survival (OS) at 24 and 36 months, will be examined to further assess antitumor activity in each cohort.

Exploratory Objectives:	**Endpoints:**
Tumor Tissue 1. Tumor specimens (archival and/or fresh-frozen) from patients treated with durvalumab, trastuzumab, and FLOT will be collected for exploratory analyses of predictive markers of sensitivity or resistance to the combination. Specimens collected at progression will also be used to investigate potential mechanisms of acquired resistance. 2. Collect tumor genomic alterations in tissue and examine their associations with clinical outcomes.	**Tumor Tissue** Diagnostic and/or archival tumor specimens and newly obtained tumor biopsies (at baseline, during treatment, at surgery, and at progression) will be collected and stored for possible future exploratory research on factors that may influence response or resistance to durvalumab, trastuzumab, and FLOT. These specimens will undergo next-generation sequencing and single-cell RNA sequencing, as appropriate, as well as other exploratory protein-based analyses. Sequencing will be performed. Fresh baseline tissue is required. • Single-cell RNA sequencing and spatial transcriptomics to identify early response biomarkers and changes in the immune compartment •Subgroup analysis of HER2 mutations (HER2-mutant vs nonmutant tumors with the same IHC score) •Targeted quantitative and global semiquantitative protein-expression profiling by mass spectrometry to identify patterns associated with efficacy and/or acquired resistance across tumor types

	•Compare protein-expression changes between pretreatment and progression tumor specimens •Evaluate tumor morphology as a predictor of clinical outcomes Immune-cell profiling by fluorescent IHC and/or spatial transcriptomics using the most recent FFPE tissue
Plasma and PBMCs • Assess ctDNA tumor genomic alterations and correlate them with tissue alterations and clinical outcomes • Investigate whether ctDNA kinetics predict early recurrence and minimal residual disease	**Plasma and PBMCs** • Changes in ctDNA quantity, including but not limited to allelic frequency changes from baseline during treatment, as predictors of clinical outcomes
Explore pharmacodynamic biomarkers, such as immune gene expression or plasma cytokines	•Compare mutation profiles in pretreatment and on-treatment samples; evaluate detectable ctDNA as a marker of progression •Immune profiling of baseline tissue and blood (DNA/RNA) specimens and early-treatment samples Collect PBMCs for immune-cell analysis. Additional exploratory analyses may be conducted as new scientific knowledge emerges.
Study Design	



This Phase II study will assess the safety and efficacy of neoadjuvant trastuzumab plus durvalumab and FLOT targeted chemoimmunotherapy in patients with locally advanced HER2-positive gastric or gastroesophageal junction cancer. After enrollment, participants will receive treatment according to the procedures described below.

Neoadjuvant chemotherapy will begin after completion of screening. Participants will undergo resection surgery 4–6 weeks after the last neoadjuvant dose. Surgery more than six weeks after the last dose may be permitted following discussion with the investigator-sponsor.
Adjuvant chemotherapy will begin 4–8 weeks after surgery, depending on postoperative recovery.

Tumor assessments using modified RECIST 1.1 will be performed at screening (within 28 days before the first neoadjuvant dose), within 28 days after the last neoadjuvant dose, and after surgery (before the first adjuvant dose).
Subsequently, assessments will be performed every 12 weeks (±1 week) for the first year from the adjuvant baseline scan and every 24 weeks (±2 weeks) until progression or recurrence.

Imaging for modified RECIST 1.1 will consist of chest, abdominal, and pelvic CT or MRI and will be interpreted by the site investigator.

Treatment and Treatment Duration

Neoadjuvant treatment will begin on Cycle 1 Day 1 and be administered every two weeks for four cycles. After surgery, standard adjuvant XELOX chemotherapy will be administered for 6–8 cycles at the physician's discretion, as described below.

Study Duration

Approximately three years from IRB approval.
(Subject to change depending on enrollment rate.)

Sample Size

The target enrollment is 20 participants.

Investigational Products, Doses, and Administration

Neoadjuvant therapy starts on Cycle 1 Day 1 and comprises four cycles administered every two weeks.

Neoadjuvant Chemotherapy

- Cycle length: 2 weeks (14 days)
- Total duration: 4 cycles (8 weeks)
- Cycle n Day 1: trastuzumab 4 mg/kg IV Q2W (loading dose 6 mg/kg IV on C1D1)
: durvalumab 1,500 mg IV Q4W (administered only on C2D1 and C4D1)
: (FLOT) Docetaxel 50mg/m2 IV Q2W
Oxaliplatin 85mg/m2 IV Q2W
Leucovorin 200mg/m2 IV Q2W
5-FU 2600mg/m2 24hr CIV Q2W

After surgery, standard adjuvant XELOX will be given for 6–8 cycles at the treating physician's discretion.

Adjuvant Chemotherapy

- Cycle length: 3 weeks (21 days)

- Four cycles, with up to six cycles at investigator discretion (12–18 weeks in total)
- Day 1: oxaliplatin 130 mg/m² IV every 3 weeks (Q3W)
- Days 1–14: capecitabine 1,000 mg/m² orally twice daily every 3 weeks (Q3W)

Statistical Methods

The primary efficacy endpoint is the pathological complete response (pCR) rate. The null hypothesis (H0: p ≤15%) and alternative hypothesis (H1: p ≥40%) were assessed using a type I error of 0.05 and 80% power. The calculation required 19 evaluable participants. Allowing for a 5% dropout rate, the target enrollment was set at 20 participants.

Safety and toxicity as primary outcomes and secondary endpoints (overall response rate, R0 resection rate, overall survival [OS], Becker tumor regression grade [TRG1a/b], surgery-related morbidity and mortality, feasibility, and adverse events according to NCI CTCAE version 5.0) will be summarized descriptively. Time-to-event outcomes will be estimated using the Kaplan–Meier method. Calculations will use all available data. Missing time-to-event outcomes will be censored, and missing primary endpoint data will be treated as failures. Confidence intervals (CIs) for pathological response rates will be calculated using the Clopper–Pearson method. CIs will be calculated in Prism version 9.5.1; other endpoints will be analyzed using SAS version 9.4 or later (SAS Institute Inc.) or R version 3.6.1 or later (R Foundation for Statistical Computing).

Table of Contents

TITLE PAGE 1 ..... **1**

Protocol Synopsis 2 ..... **2**

Table of Contents 10 ..... **12**

List of Abbreviations and Definitions 14 ..... **16**

1. Introduction 15 ..... **18**

1.1 Background 15 ..... **18**

1.1.1 Gastric Cancer 15 18

1.1.2 Targeted Therapies for Gastric Cancer 15 19

1.1.3 Perioperative Therapy for Locally Advanced Gastric Cancer 16 20

1.1.4 Durvalumab 17 21

1.1.5 Durvalumab Plus FLOT for Gastric and Gastroesophageal Junction Cancer (Phase III MATTERHORN Study) 18 22

1.2 Rationale for Study Design and Dose Selection 19 ..... **23**

1.2.1 Rationale for Study Design 19 23

1.2.2 Mechanistic Rationale for Trastuzumab Plus Pembrolizumab 20 24

1.2.3 Unmet Need and Study Rationale in Locally Advanced HER2-Positive Gastric Cancer 21 25

1.3 Study Design 22 ..... **27**

1.4 Study Objectives 23 ..... **28**

2. Patient Selection, Enrollment, Restrictions, Discontinuation, and Withdrawal 25 ..... **31**

2.1 Inclusion Criteria 26 ..... **31**

2.2 Exclusion Criteria 27 ..... **33**

2.3 Withdrawal Criteria 31 ..... **38**

2.4 Study Discontinuation 32 ..... **38**

3. Study Plan and Procedures 33 ..... **39**

3.1 Enrollment and Screening 33 ..... **39**

3.2 Treatment Period 34 ..... **41**

3.3 Follow-up Period 36 ..... **44**

3.3.1 End-of-Treatment Visit 36 44

3.3.2 Follow-up Visit 37 44

3.3.3 Survival Follow-up 37 45

3.3.4 CT or MRI Imaging (Modified RECIST 1.1) 37 45

4. Study Assessments 40 ..... **48**

4.1 Efficacy Assessments 40 ..... **48**

4.2 Safety Assessments 41 ..... **50**

4.2.1 Clinical Laboratory Safety Assessments 41 50

5. Safety Reporting and Medical Management 44 ..... **52**

5.1 Definition of Adverse Events 44 ..... **52**

5.2 Recording of Adverse Events 44 .....

52
5.2.1 AE Collection Period 44 52
5.2.2 Follow-up of Unresolved AEs 44 52
5.2.3 AE Parameters 44 52
5.2.4 Causality Assessment 45 53
5.2.5 Disease Progression 45 53
5.2.6 Maternal Exposure 45 54
5.3 Reporting of Serious Adverse Events 46 ..... **54**
5.3.1 Definition of Serious Adverse Events 46 54
5.3.2 Adverse Events of Special Interest 47 56
5.4 Toxicity Management 50 ..... **59**
5.5 Concomitant Medications and Treatments 50 ..... **60**
6. Investigational Medicinal Products 53 ..... **63**
6.1 Product Identification 53 ..... **63**
6.2 Neoadjuvant Chemotherapy 53 ..... **63**
6.3 Adjuvant Chemotherapy 53 ..... **63**
6.4 Dose and Treatment Regimens 54 ..... **64**
7. Statistical Analysis 58 ..... **68**
7.1 Sample Size Estimation 58 ..... **68**
7.2 Definition of Analysis Sets 58 ..... **68**
7.2.1 Full Analysis Set 58 69

7.2.2 Safety Analysis Set 58 69
7.3 Outcome Measures for Analysis 58 ..... **69**
7.4 Statistical Analysis Methods 60 ..... **71**
8. Study and Data Management 60 ..... **71**
8.1 Site Staff Training 60 ..... **71**
8.2 Study Monitoring 60 ..... **72**
8.2.1 Study Document Retention 61 72
8.3 Study Timelines and Study Completion 61 ..... **72**
8.4 Data Management 61 ..... **72**
9. Ethical and Regulatory Requirements 61 ..... **72**
9.1 Ethical Study Conduct 61 ..... **72**
9.2 Protection of Participant Data 61 ..... **73**
9.3 Ethics 62 ..... **73**
9.4 Informed Consent 62 ..... **73**
9.5 Protocol and Informed Consent Amendments 62 ..... **74**
9.6 Audits and Inspections 62 ..... **74**
9.7 Biomarker Analysis 62 ..... **74**
9.8 Exploratory Biomarker Analysis 63 ..... **75**

9.9 Storage and Disposal 64 ..... **76**

10. References 65 ..... **77**

Appendix A. Additional Safety Information 68 ..... **81**

Appendix B. Guidance for Objective Tumor Response Assessments Using Modified RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) 70 ..... **84**

Appendix C. Examples of ECOG Performance Status 80 ..... **96**

Appendix D. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 81 ..... **97**

Appendix F. Definition of Women of Childbearing Potential and Acceptable Contraception 81 ..... **97**

List of Abbreviations and Definitions

The following abbreviations and special terms are used in this protocol.

Abbreviation or Special Term	Description	
AE	Adverse event	Adverse event
CRF	Case Report Form (paper)	Case report form (paper)
CSA	Clinical Study Agreement	Clinical study agreement
CSR	Clinical Study Report	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Event	Common Terminology Criteria for Adverse Events
DAE	Discontinuation of Investigational Product due to Adverse Event	Discontinuation of study drug due to an adverse event
DLT	Dose-limiting toxicity	Dose-limiting toxicity
DNA	Deoxyribonucleic acid	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)	Ethics Committee; synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice	Good Clinical Practice
ICH	International Conference on Harmonisation	International Council for Harmonisation
IP	Investigational Product	Investigational medicinal product
LSLV	Last Subject Last Visit	Last patient last visit
NCI	National Cancer Institute	National Cancer Institute
OAE	Other Significant Adverse Event	Other significant adverse event
PI	Principal Investigator	Principal investigator
PK	Pharmacokinetic	Pharmacokinetics

SAE	Serious adverse event	Serious adverse event

1. Introduction

1.1 Background

1.1.1 Gastric Cancer

Gastric cancer (GC) is the fourth most common cancer worldwide and the second leading cause of cancer-related death (Kamangar et al., 2006). More than 70% of cases occur in developing countries, and approximately half of the global burden occurs in East Asia, predominantly China. Although early diagnosis is more common in Asia than elsewhere, most patients present with disease that is not amenable to surgery. No single treatment has become the universally accepted standard; fluoropyrimidine- and platinum-based combinations, with or without a third agent (usually docetaxel or epirubicin), remain among the most widely used regimens worldwide.

However, nearly all patients with metastatic GC experience disease progression after first-line therapy (Takiuchi, 2011), and approximately 30%–50% of patients with advanced GC receive second-line treatment (Wesolowski et al., 2009). Most recently reported second-line chemotherapy studies have been small Phase II trials or retrospective studies, and randomized controlled evidence establishing a single standard second-line regimen has been limited. In routine practice, taxanes such as paclitaxel are frequently selected for second-line therapy, but their efficacy remains limited (Hironaka et al., 2006; Kodera et al., 2007; Bang et al., 2010).

Overexpression of human epidermal growth factor receptor 2 (HER2) in gastric cancer, reported in 4.4%–53.4% of patients across different studies, is a predictive biomarker for response to HER2-directed therapy.

Trastuzumab combined with cisplatin or oxaliplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil [5-FU]) is an approved anti-HER2 regimen for first-line treatment of gastric or gastroesophageal junction (GEJ) cancer. In the Trastuzumab for Gastric Cancer (ToGA) trial, this regimen improved median overall survival (OS) to 13.8 months, compared with 11.1 months with chemotherapy alone. No anti-HER2 therapy was approved for patients with HER2-overexpressing GC who progressed on first-line (1L) standard-of-care (SOC) trastuzumab plus chemotherapy at the time described in this protocol. Regardless of HER2 status, ramucirumab plus paclitaxel is a preferred second-line (2L) regimen for GC, with a

median OS of 9.6 months. Given the limited survival achieved with available treatments, effective and tolerable options are urgently needed for patients with HER2-overexpressing advanced or metastatic GC.

1.1.2 Targeted Therapies for Gastric Cancer

Emerging evidence suggests that targeted agents may provide clinical benefit in addition to standard cytotoxic regimens such as 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, S-1, and irinotecan. Approximately 20% of gastric cancers express ErbB2 (HER2) on the tumor cell surface (Bang et al., 2010). HER2 (ErbB2/neu), a member of the ErbB receptor tyrosine kinase family, is encoded by ERBB2 and promotes proliferation through downstream PI3K–AKT and MEK–ERK signaling pathways (R13-1023). No ligand has been identified for this receptor, which is activated through homodimerization or heterodimerization with other ErbB family members.

In the Trastuzumab for Gastric Cancer (ToGA) trial, this regimen improved median overall survival (OS) to 13.8 months, compared with 11.1 months with chemotherapy alone.

Ramucirumab plus paclitaxel is the preferred second-line (2L) treatment for gastric cancer regardless of HER2 status. Median overall survival with this combination was 9.6 months.

Since survival with current treatments remains limited, more effective and tolerable treatment options are needed for patients with advanced or metastatic HER2-overexpressing gastric cancer.

Recent evidence suggests that targeted therapies may benefit selected patients beyond standard cytotoxic regimens such as 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, S-1, and irinotecan. Approximately 20% of gastric cancers express ErbB2 (HER2) on the tumor cell surface (Bang et al., 2010), making HER2 an attractive therapeutic target. In a randomized trial of trastuzumab (Herceptin; Roche–Genentech) in patients with HER2-expressing tumors, trastuzumab extended survival by less than three months. Nevertheless, approximately 80% of patients are not eligible for trastuzumab, underscoring the need for additional targeted therapies.

Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody–drug conjugate (ADC) that has been approved for patients with unresectable or metastatic HER2-positive breast cancer following failure of at least two prior HER2-targeted regimens. It comprises a humanized

immunoglobulin G1 (IgG1) monoclonal antibody with the trastuzumab amino-acid sequence, conjugated through a cleavable peptide linker to deruxtecan (DXd, MAAA-1181a), a potent topoisomerase I inhibitor. After binding HER2 on tumor cells, T-DXd is internalized, the linker is cleaved, and the membrane-permeable topoisomerase I inhibitor is released to induce DNA damage and apoptosis. Phase I data from DS8201-A-J101 showed a promising safety profile and preliminary antitumor activity with T-DXd monotherapy in heavily pretreated patients with gastric cancer.

1.1.3 Perioperative Treatment of Locally Advanced Gastric Cancer

FLOT is a docetaxel-based four-drug regimen comprising 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel, and is among the most extensively studied treatments for locally advanced gastric and gastroesophageal junction (GEJ) cancer. It has been evaluated in metastatic, oligometastatic, elderly, and surgically resectable populations. The AIO FLOT4 Phase II/III study compared FLOT with epirubicin/cisplatin/5-fluorouracil (ECF) or epirubicin/cisplatin/capecitabine (ECX) in 716 patients with resectable gastric or GEJ adenocarcinoma; enrollment was completed in 2015.

The Phase II component of FLOT4, focused on pathological response, was published in The Lancet Oncology. FLOT yielded a higher pathological complete response (pCR) rate than ECF (20 of 128 patients [16%] vs 8 of 137 [6%]; p=0.02). The proportion achieving complete or near-complete pathological regression (TRG1a/b) was also higher with FLOT (47 of 128 [37%] vs 31 of 137 [23%]; p=0.02).

In the Phase III FLOT4 analysis (Al-Batran, Lancet Oncology 17:1697–1708), overall survival was better with FLOT than with ECF/ECX (HR, 0.77; 95% CI, 0.63–0.94; median OS, 50 months [38.33–not reached] vs 35 months [27.35–46.26]). FLOT also improved progression-free survival (median PFS, 30 vs 18 months; HR, 0.75 [0.62–0.91]; p=0.004). Postoperative complications occurred in 50% of the ECF/ECX group and 51% of the FLOT group. Thirty- and 90-day mortality rates were 3% and 8% with ECF/ECX, respectively, versus 2% and 5% with FLOT.

The relative benefit of FLOT was observed across subgroups, including older patients and those with signet-ring cell carcinoma. Numerically favorable hazard ratios were noted for Siewert type I esophageal cancer (HR, 0.60), Barrett-associated tumors (HR, 0.62), smaller

T1/T2 tumors (HR, 0.66), and node-negative disease (HR, 0.64). In multivariable analyses, favorable prognostic factors included FLOT treatment (HR, 0.75; p=0.006), a gastric primary site (HR, 0.74; p=0.005), and node-negative disease (HR, 0.72; p=0.022), with a trend for ECOG PS 0 (HR, 0.82; p=0.078). In a post hoc analysis excluding patients without R0 resection, PFS remained more favorable with FLOT (HR, 0.80; p=0.049). Most recurrences (87%) were systemic or combined systemic and locoregional; the most common recurrence sites were the peritoneum (31%), lymphatic system (26%), and liver (19%) (Al-Batran, Lancet 393:1948–1957).

1.1.4 Durvalumab

Durvalumab is a human immunoglobulin G1 kappa monoclonal antibody targeting human PD-L1. It is expressed in Chinese hamster ovary cells and has an approximate molecular weight of 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its interactions with PD-1 and CD80. The fragment crystallizable (Fc) region contains three mutations in the constant region of the IgG1 heavy chain that reduce binding to complement component C1q and Fc gamma receptors involved in antibody-dependent cellular cytotoxicity (ADCC; Oganesyan et al., 2008).

Durvalumab, an anti-PD-L1 antibody, has demonstrated the following activities:

• Durvalumab binds PD-L1 and blocks its interactions with PD-1 and CD80.

• Durvalumab can reverse PD-L1-mediated inhibition of human T-cell activation in vitro.

• Durvalumab inhibits tumor growth in xenograft models through T-cell-dependent mechanisms.

• In syngeneic tumor models, an anti-mouse PD-L1 surrogate antibody improved survival as monotherapy and induced complete tumor regression in more than 50% of treated mice when combined with chemotherapy.

• In the same study, mice receiving anti-mouse PD-L1 antibody remained completely tumor-free for three months after tumor implantation and exhibited long-term immunity on rechallenge.

• In a subsequent study in the same syngeneic model, anti-mouse PD-L1 antibody combined with anti-CTLA-4 antibody induced complete tumor regression in all treated mice.

Immune checkpoint inhibitors such as durvalumab and tremelimumab have provided early

evidence of activity in advanced gastric cancer. Study CD-ON-MEDI4736-1108 included a cohort receiving durvalumab monotherapy for gastroesophageal cancer (Segal et al., 2014). As of August 21, 2014, two responses (one complete response [CR] and one partial response [PR]) had occurred among 28 evaluable patients, with a 12-week disease control rate (DCR-12w) of 25%. A Phase II study of tremelimumab monotherapy as second-line treatment in gastroesophageal cancer (n=18) also showed activity (four cases of stable disease and one PR; Ralph et al., 2010).

1.1.5 Durvalumab Plus FLOT Chemotherapy in Gastric and Gastroesophageal Junction Cancer (Phase III MATTERHORN Study)

Cancer can be recognized by the immune system and, under certain circumstances, controlled or even eliminated by immune responses (Dunn et al., 2004; Hanahan and Weinberg, 2011). Many tumors exhibit increased PD-L1 expression. PD-1/PD-L1 signaling suppresses effector T-cell activity and enhances immunosuppressive regulatory T-cell function, thereby allowing tumors to evade immune surveillance. Monoclonal antibodies (mAbs) directed against this pathway can restore T-cell function and strengthen antitumor immunity. Their demonstrated activity and manageable safety profiles across tumor types have established them as important anticancer therapies (Lin et al., 2024; Sun et al., 2020; Yamaguchi et al., 2022).

Anti-PD-1/PD-L1 monoclonal antibodies, administered alone or with chemotherapy, have shown clinical benefit in GC/GEJC. They are now components of systemic treatment for unresectable locally advanced, recurrent, or metastatic disease and of adjuvant treatment after neoadjuvant chemoradiotherapy for resectable GEJC (NCCN Guidelines 2025a, 2025b; Lordick et al., 2022; Obermannová et al., 2022).

MATTERHORN (NCT04592913) is a randomized, double-blind, placebo-controlled, multinational Phase III trial of perioperative durvalumab in patients with resectable stage II–IVA GC/GEJC. A total of 948 patients were randomized to two preoperative cycles of fixed-dose durvalumab 1,500 mg plus FLOT or placebo plus FLOT, administered every four weeks, followed by up to 12 postoperative cycles of durvalumab or placebo every four weeks (two cycles combined with FLOT and ten additional cycles as monotherapy). Participants were enrolled at 176 centers in 20 countries across the Americas, Europe, and Asia. The study

crossed its prespecified statistical boundary for its key secondary endpoint of centrally assessed pCR using the modified CAP Ryan tumor regression grading system. The pCR rate was 19.2% (95% CI, 15.75–23.04) with durvalumab plus FLOT and 7.2% (95% CI, 5.02–9.88) with placebo plus FLOT, an absolute difference of 12.0 percentage points (odds ratio, 3.08; 95% CI, 2.03–4.67; p<0.001). The safety and tolerability profile was consistent with prior experience, and adding durvalumab did not reduce the proportion of patients able to undergo surgery (Janjigian et al., 2023).

1.2 Rationale for Study Design and Dose Selection

1.2.1 Rationale for Study Design

Perioperative treatment for locally advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma has evolved substantially. Surgery alone was initially standard, but high recurrence rates prompted adoption of anthracycline-based perioperative chemotherapy, such as ECF/ECX, particularly in Western countries. Large trials including MAGIC (Cunningham et al., N Engl J Med. 2006;355:11–20) and FNCLCC/FFCD (Ychou et al., J Clin Oncol. 2011) demonstrated improvements in overall and disease-free survival, establishing perioperative chemotherapy as a treatment standard.

In East Asia, postoperative adjuvant chemotherapy has generally been standard practice. However, treatment completion rates can be low because of patients' postoperative condition. This prompted increasing interest in neoadjuvant chemotherapy, which can be delivered before postoperative recovery becomes a barrier, improve R0 resection rates, and initiate systemic treatment earlier.

Subsequently, the four-drug docetaxel-based FLOT regimen demonstrated superior overall survival, progression-free survival, and pathological response compared with ECF/ECX and became a perioperative standard, particularly in Western practice (Al-Batran et al., Lancet. 2029;393:1948–1957). Benefits were consistent across subgroups, with toxicity and surgical complication rates comparable to prior regimens.

More recently, MATTERHORN, a Phase III trial, established the potential role of adding the

immune checkpoint inhibitor durvalumab to FLOT. In patients with resectable, locally advanced gastric or GEJ adenocarcinoma, durvalumab plus FLOT improved event-free survival, overall survival, and pathological response compared with FLOT alone. Benefit was maintained irrespective of PD-L1 expression, without a substantial increase in serious toxicity or delays in surgery or adjuvant treatment.

Thus, perioperative treatment for gastric and GEJ cancer has progressed from surgery alone to ECF/ECX-based chemotherapy, then to FLOT, and most recently to regimens combining chemotherapy with immune checkpoint inhibition. These advances represent an important step toward improved long-term survival in locally advanced disease.

MATTERHORN is a large, double-blind, multinational trial in which 948 patients with locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma were randomized to durvalumab plus FLOT (D+FLOT) or placebo plus FLOT. At an interim median follow-up of 31.5 months, D+FLOT significantly improved the key secondary endpoint of event-free survival (EFS; HR, 0.71; 95% CI, 0.58–0.86; p<0.001; median not reached vs 32.8 months; two-year EFS, 67.4% vs 58.5%). An improvement in overall survival (OS) was also reported at the final analysis (HR, 0.78; 95% CI, 0.63–0.96; p=0.021; Yelena Y. Janjigian, N Engl J Med. 2025). Improvements in EFS and OS were observed regardless of PD-L1 expression (TAP <1% or ≥1%). The ypN0 rate was higher with durvalumab (58.2% vs 44.8%), consistent with a greater pathological response. The pCR rate was 19.2% versus 7.2% (relative risk, 2.69; 95% CI, 1.86–3.90). Grade 3–4 adverse event rates were similar between groups, with no meaningful differences in delays to surgery or initiation of adjuvant chemotherapy.

In conclusion, MATTERHORN demonstrated that adding durvalumab to standard FLOT significantly improves overall survival, EFS, and pathological response in patients with resectable gastric or gastroesophageal junction adenocarcinoma, supporting this approach as an emerging standard of care.

1.2.2 Mechanistic Rationale for Trastuzumab Plus the Immune Checkpoint Inhibitor Pembrolizumab

Preclinical and clinical studies show that trastuzumab modulates antitumor immunity through several mechanisms. It induces antibody-dependent cellular cytotoxicity (ADCC) and

antibody-dependent cellular phagocytosis (ADCP), promotes dendritic cell presentation of HER2 antigens and CD8+ cytotoxic T-cell activation, and increases natural killer cell infiltration and MHC class I expression. Interferon gamma (IFN-γ) released during this process may induce PD-L1 expression, supporting PD-1 pathway blockade to overcome immune suppression (Janjigian et al., 2021). In a single-center Phase II study at MSKCC (37 enrolled patients), trastuzumab plus chemotherapy and pembrolizumab achieved an ORR of 91% (including 17% complete responses) and a six-month progression-free survival rate of 70%. Grade 3–4 events were mainly chemotherapy-associated anemia, elevated liver enzymes, diarrhea, and mucositis, while colitis and hepatitis were reported as immune-related toxicities.

These findings led to the multinational randomized Phase III KEYNOTE-811 study, comparing trastuzumab plus chemotherapy with or without pembrolizumab in 434 previously untreated patients with metastatic HER2-positive esophagogastric cancer. ORR (74.4% vs 51.9%) and complete response rate (11.3% vs 3.1%) were substantially higher in the pembrolizumab group without a significant increase in toxicity. The combination was subsequently approved as a first-line treatment for metastatic HER2-positive esophagogastric cancer.

1.2.3 Unmet Need and Rationale for This Study in Locally Advanced HER2-Positive Gastric Cancer

Although combining trastuzumab with immune checkpoint inhibitors has improved outcomes in advanced HER2-positive gastric cancer, patients with locally advanced HER2-positive disease are generally treated perioperatively with FLOT or durvalumab plus FLOT, similarly to patients with HER2-negative disease.

An unmet need therefore remains for safe and effective neoadjuvant options for locally advanced HER2-positive gastric cancer. Recent trials from Germany and China have investigated adding an immune checkpoint inhibitor and HER2-targeted therapy to perioperative treatment in locally advanced HER2-positive esophagogastric and GEJ adenocarcinoma. PHERFLOT was a single-arm Phase II trial in 31 patients combining pembrolizumab, trastuzumab, and FLOT perioperatively (Andreas Stein, Nature Medicine 2025). Thirty patients underwent surgery with R0 resection, and the pCR rate was 48.4%, substantially exceeding expectations. Including near-complete regression (TRG1b), the major

pathological response rate was 67.7%. Responses were most prominent in tumors with strong HER2 expression and higher PD-L1 CPS, but activity was also observed in IHC 2+/ISH-positive and T3/T4 disease. Grade ≥3 adverse events occurred in approximately 48.4% of patients, without treatment-related deaths. Diarrhea and neutropenia were among the major toxicities, and the regimen was considered generally manageable.

As follow-up is still interim, two-year disease-free survival data remain immature; however, the high pCR and R0 resection rates and manageable safety profile support evaluation in a larger randomized trial.

A randomized Phase II study in China evaluated atezolizumab plus trastuzumab and XELOX in 42 patients with locally advanced HER2-positive gastric or GEJ adenocarcinoma (Lin Shen, JAMA Oncology 2025). Patients received trastuzumab plus XELOX with or without atezolizumab. The pCR rate was higher in the atezolizumab group (38% vs 14%; difference, 23.8 percentage points), particularly among patients younger than 65 years, men, and patients with intestinal-type tumors by Lauren classification. Treatment-emergent adverse events occurred in all patients; grade ≥3 events were reported in 57% and 67% of the combination and control groups, respectively. Serious adverse events were somewhat more frequent with atezolizumab but were considered manageable.

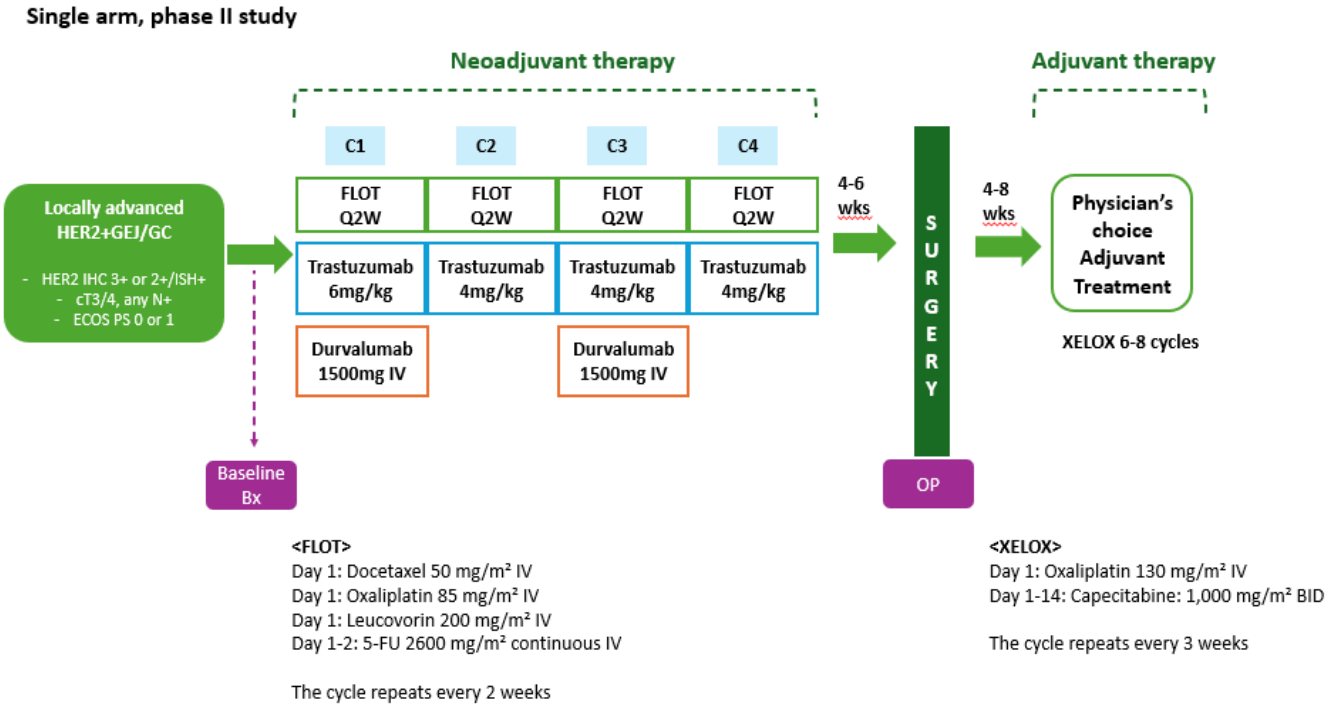
Interim survival endpoints have not yet been reached, but improvements in early tumor response measures such as pCR suggest potential clinical benefit.

Taken together, these studies suggest that adding immune checkpoint inhibition and HER2-directed therapy to perioperative chemotherapy may substantially improve pathological responses in locally advanced HER2-positive esophagogastric and GEJ adenocarcinoma. PHERFLOT added pembrolizumab and trastuzumab to FLOT, whereas the Chinese trial evaluated atezolizumab and trastuzumab with XELOX. Both reported favorable safety profiles and high pCR rates (approximately 40%–50%), supporting further development of perioperative chemoimmunotherapy. Long-term outcomes, including two-year disease-free survival, remain to be established. These early histological responses point toward a potential shift in treatment strategy, but longer follow-up and large randomized trials are needed.

On this basis, the present Phase II trial will provide an initial evaluation of the safety and

efficacy of neoadjuvant trastuzumab combined with durvalumab and FLOT in patients with locally advanced, resectable HER2-positive gastric or gastroesophageal junction cancer.

1.3 Study Design



Neoadjuvant chemotherapy will begin after completion of screening. Participants will undergo resection surgery 4–6 weeks after the last neoadjuvant dose. Surgery after six weeks may be permitted following consultation with the investigator-sponsor.
Adjuvant chemotherapy will start 4–8 weeks after surgery, depending on recovery.

Tumor assessments according to modified RECIST 1.1 will be performed at screening (within 28 days before the first dose), within 28 days after the final neoadjuvant dose, and after surgery but before initiation of adjuvant chemotherapy. Thereafter, scans will be performed every 12 weeks (±1 week) during the first year, measured from the adjuvant baseline scan, and every 24 weeks (±2 weeks) until progression or recurrence.

Modified RECIST 1.1 assessments will use CT or MRI of the chest, abdomen, and pelvis and will be interpreted by the site investigator.

Treatment Duration

Neoadjuvant treatment will begin on Cycle 1 Day 1 and comprise four cycles administered every two weeks. Following surgery, patients will receive 6–8 cycles of standard adjuvant XELOX at the treating physician's discretion, as detailed below.

Investigational Products, Doses, and Administration

Neoadjuvant therapy will start on Cycle 1 Day 1 and be given every two weeks for four cycles.

[Neoadjuvant Chemotherapy]
- Cycle length: 2 weeks (14 days)
- Total duration: 4 cycles (8 weeks)
- Cycle n Day 1: trastuzumab 4 mg/kg IV Q2W (6 mg/kg IV loading dose on C1D1)
: durvalumab 1,500 mg IV Q4W (administered on C2D1 and C4D1 only)
: (FLOT) Docetaxel 50mg/m2 IV Q2W
Oxaliplatin 85mg/m2 IV Q2W
Leucovorin 200mg/m2 IV Q2W
5-FU 2600mg/m2 24hr CIV Q2W

After surgery, standard adjuvant XELOX will be administered for 6–8 cycles at the physician's discretion.

[Adjuvant Chemotherapy]
- Cycle length: 3 weeks (21 days)
- Four cycles, up to six at investigator discretion (12–18 weeks in total)
- Day 1: oxaliplatin 130 mg/m² IV Q3W
- Days 1–14: capecitabine 1,000 mg/m² orally twice daily Q3W

1.4 Study Objectives

1.4.1 Primary Objective

Primary Objective:	**Endpoints:**
To evaluate safety and tolerability and efficacy based on pathological	- Pathological complete response (pCR; ypT0N0)

complete response (pCR) of neoadjuvant FLOT plus trastuzumab and durvalumab	- Adverse events (AEs/SAEs)

1.4.2 Secondary Objective

Secondary Objective:	**Endpoints:**
To evaluate secondary measures of clinical efficacy of the investigational neoadjuvant regimen	- Complete (R0) resection rate (ypTxNxM0 other than ypT0N0M0) - Overall survival (OS) - Event-free survival (EFS) - Duration of response - Objective response rate (ORR; during neoadjuvant therapy)
Planned Subgroup Analyses	- Whole-genome sequencing and RNA sequencing of baseline, on-treatment, and surgical specimens - Spatial transcriptomics (baseline and surgical specimens; CosMx) - Single-cell sequencing (tissue) - Proteomics

1.4.3 Exploratory Objectives

Exploratory Objectives:	**Endpoints:**

Tumor Tissue 1. Tumor specimens (archival and/or fresh-frozen) from patients treated with durvalumab, trastuzumab, and FLOT will be collected to investigate predictive markers of sensitivity or resistance and, where applicable, mechanisms of acquired resistance at progression.	**Tumor Tissue** Diagnostic and/or archival tumor specimens and new biopsies obtained at baseline, during treatment, at surgery, and at progression will be collected and stored for future exploratory research into factors affecting response or resistance to durvalumab, trastuzumab, and FLOT. Next-generation sequencing, single-cell RNA sequencing, and other protein-based exploratory analyses may be performed. Fresh baseline tissue is mandatory.
2. Collect tumor genomic alterations in tissue and correlate mutations with clinical outcomes.	• Single-cell RNA sequencing and spatial transcriptomics to identify early response biomarkers and changes in immune-cell populations •Subgroup analysis of HER2 mutations (HER2-mutant vs nonmutant tumors with equivalent HER2 IHC expression) •Quantitative targeted and global semiquantitative protein profiling by mass spectrometry to identify expression patterns associated with efficacy or acquired resistance across tumor types •Compare protein-expression changes in pretreatment and progression specimens

	•Assess tumor morphology as a predictor of outcome •Immune-cell profiling of the most recent FFPE specimen by fluorescence IHC and/or spatial transcriptomics
Plasma and PBMCs • Identify ctDNA genomic alterations and correlate them with tissue alterations and clinical outcomes • Examine whether ctDNA kinetics predict early recurrence and minimal residual disease	**Plasma and PBMCs** •Changes in ctDNA levels, including changes in variant allele frequency from baseline during treatment, as potential predictors of clinical outcomes

2. Patient Selection, Enrollment, Restrictions, Discontinuation, and Withdrawal

2.1 Inclusion Criteria

1. Written informed consent must be obtained before any study-specific procedure.
2. Patients must be at least 19 years old.
3. Body weight >30 kg.
4. Histologically documented adenocarcinoma of the stomach or gastroesophageal junction with available HER2 IHC results.
5. Confirmed HER2-positive disease (IHC 3+ or IHC 2+ and SISH-positive).
6. Locally advanced, resectable gastric or gastroesophageal junction cancer at the clinician's discretion (e.g., cT2 or higher or node-positive disease), without definite

distant organ metastasis and requiring perioperative therapy.

7. ECOG performance status 0–1 with no deterioration between screening and the first study dose.

8. LVEF ≥50% by echocardiography (ECHO) within 28 days before treatment.

9. Measurable target disease as assessed by the investigator using modified RECIST 1.1.

10. Adequate organ, bone marrow, hepatic, and renal function within 28 days before treatment.
    Note: Red blood cell or platelet transfusion and G-CSF administration are not permitted from 14 days before the bone marrow function assessment through C1D1.
    - Hemoglobin ≥9.0 g/dL (≥8.0 g/dL for the GC indication).
    - Platelet count ≥100 × 10^9/L.
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L.
    - Total bilirubin ≤1.5 × ULN (or <3 × ULN in documented Gilbert syndrome with unconjugated hyperbilirubinemia).
    - AST(SGOT)/ALT(SGPT) ≤ 3.0 x ULN
    - Serum albumin ≥2.5 g/dL.
    - Creatinine clearance (CrCl) ≥30 mL/min by Cockcroft–Gault using actual body weight.
    - INR, PT, or aPTT ≤1.5 × ULN.

11. Female patients must use highly effective contraception during the study and for 15 months after permanent discontinuation of the study medications, including each neoadjuvant and adjuvant agent. This period reflects the locally approved contraceptive period for oxaliplatin in women of childbearing potential and has been adopted as the overall requirement; any longer requirement in the most recent product labeling takes precedence. At screening, patients must provide evidence that they are not breastfeeding, have a negative pregnancy test, or are not of childbearing potential, according to one of the criteria below.
    - Postmenopause in women aged ≥50 years is defined as amenorrhea for

at least 12 months after cessation of all exogenous hormone therapy.

- Documented irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy (excluding tubal ligation).
- Amenorrhea for 12 months with serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol concentrations in the institution's postmenopausal reference ranges.

Further information is provided in Appendix F (Definitions and Acceptable Contraceptive Methods for Women of Childbearing Potential). Female participants must not breastfeed or donate or retrieve ova for 60 days after the final dose.

12. Nonsterilized male patients sexually active with a female partner of childbearing potential must use a condom together with spermicide from screening until 12 months after the final dose of investigational medicinal product. Complete heterosexual abstinence during treatment and drug elimination is an acceptable method only if consistent with the patient's usual lifestyle and maintained for the entire required period. Periodic or intermittent abstinence, the rhythm method, and withdrawal are not acceptable. Female partners are strongly encouraged to use at least one highly effective contraceptive method throughout this period. Male patients must not father a child, cryopreserve sperm, or donate sperm from enrollment until 12 months after the final dose. Any longer period specified in the current product labeling takes precedence.

2.2 Exclusion Criteria

1. Definite peritoneal metastasis (including malignant cells in peritoneal fluid) or distant metastatic disease.

2. Known dihydropyrimidine dehydrogenase (DPD) deficiency; DPD status will be determined in accordance with local or institutional requirements.

3. Uncontrolled intercurrent illness, including but not limited to ongoing or active infection, uncontrolled hypertension, clinically significant chronic gastrointestinal disease associated with diarrhea, or psychiatric illness or social circumstances that

could limit study compliance, materially increase the risk of adverse events, or impair the patient's ability to provide written informed consent.

4. Unresolved toxicity of Grade ≥2 from previous anticancer therapy according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, excluding vitiligo, alopecia, endocrine disorders controlled with hormone replacement, and asymptomatic laboratory abnormalities.

5. History of organ transplantation.

6. Active primary immunodeficiency or documented history thereof; active infectious disease.
   - Active or previously documented autoimmune or inflammatory disease at screening, including inflammatory bowel disease (IBD; e.g., Crohn disease, ulcerative colitis, or diverticulitis), systemic lupus erythematosus, sarcoidosis, tuberculosis, Wegener granulomatosis, myasthenia gravis, Graves disease, rheumatoid arthritis, hypophysitis, or uveitis. As appropriate for protocols involving known hepatotoxicity or related risks, consider histories of organ transplantation, glomerulonephritis, nephrotic syndrome, Fanconi syndrome, or renal tubular acidosis requiring immunosuppression within the two years before treatment. Exceptions are listed below.
   - Patients with vitiligo, alopecia, hypothyroidism stable on replacement therapy (e.g., following Hashimoto thyroiditis), or psoriasis not requiring systemic treatment; patients with celiac disease controlled by diet alone; and patients with no active disease for the preceding five years may be eligible after consultation with the principal investigator.
   - HBsAg carriers without active viral infection receiving entecavir prophylaxis may be eligible.

7. History of noninfectious ILD/pneumonitis requiring steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be excluded on screening imaging.

8. Active hepatitis B (positive hepatitis B surface antigen [HBsAg]) or active hepatitis C. Viral load testing is not mandatory for study eligibility. Patients with a history of or resolved HBV or HCV infection may be enrolled.

   Note: HBsAg-negative patients must have discontinued antiviral therapy for at least six months.

9. Patients with prior or resolved HBV infection are eligible only if all the following

criteria are met:

- Positive anti-HBc (IgG or total immunoglobulin).
- HBV DNA is undetectable.
- No evidence of cirrhosis or fibrosis on previous imaging or biopsy.
- No current or past HCV coinfection.
- Access to a local hepatitis B specialist during and after the study;

these patients require close monitoring for HBV reactivation.

Exclusion of all HBV-infected participants should be considered if control or combination study therapies with high risk of HBV reactivation are incompatible with antiviral medications.

10. Known positive testing for human immunodeficiency virus (HIV; HIV-1/2 antibodies) or active tuberculosis, established by clinical assessment that may include medical history, examination, radiographic findings, or local tuberculosis testing. Active or previously documented primary immunodeficiency at screening or poorly controlled HIV infection. Well-controlled HIV infection requires fulfillment of all the criteria below.
    - Undetectable viral RNA.
    - CD4+ count ≥350 cells/μL.
    - No AIDS-defining opportunistic infection during the preceding 12 months and a stable antiretroviral regimen for at least four weeks, with no further anticipated change in the number or type of antiretroviral agents.
    - For patients with HIV infection meeting these criteria, monitoring of viral RNA load and CD4+ counts is recommended. HIV testing should be performed where permitted by local regulations and the institutional IRB/IEC.

11. Patients meeting any of the following cardiac criteria:
    - Mean heart rate-corrected QT interval (QTc), calculated from ECG using Fridericia correction,

      QT interval (QTc) ≥470 ms.
    - Clinically significant abnormality of rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third-degree heart block,

second-degree heart block, or PR interval >250 ms).

- Any condition that increases the risk of QTc prolongation or arrhythmia, including heart failure, uncorrectable chronic hypokalemia, congenital long-QT syndrome, family history in a first-degree relative of long-QT syndrome or unexplained sudden death before age 40, or concomitant medications known to prolong the QT interval.
- Uncontrolled hypotension: systolic BP <90 mmHg and/or diastolic BP <60 mmHg, or Clinically significant orthostatic hypotension, including a 20-mmHg fall in blood pressure.
- Atrial fibrillation with resting ventricular rate >100 bpm on ECG.
- Symptomatic heart failure (NYHA class II–IV).
- Symptomatic congestive heart failure (NYHA class II–IV).
- Known reduction in LVEF to <50%.
- Previous or current cardiomyopathy of any cause.
- History of or current acute myocardial infarction within the past six months.
- Severe valvular heart disease.
- Uncontrolled angina (Canadian Cardiovascular Society class II–IV despite medical therapy).
- History of stroke or transient ischemic attack before screening.
- Acute coronary syndrome within six months before treatment initiation.

12. Pregnant or breastfeeding women, or patients of childbearing potential unwilling to use effective contraception from screening until 15 months (women) or 12 months (men) after the last dose of any component of trastuzumab, FLOT, durvalumab, or postoperative adjuvant XELOX (capecitabine/oxaliplatin), as specified in the eligibility criteria.

13. Known allergy or hypersensitivity to study medications or their excipients.

14. Serious current or prior chronic gastrointestinal disease associated with diarrhea (e.g., active inflammatory bowel disease) within 14 days before the first dose; active noninfectious skin disease requiring systemic therapy (including rash, urticaria, dermatitis, ulceration, or psoriasis of any grade); or active or previously documented

autoimmune or inflammatory disease requiring chronic steroids or other immunosuppressive therapy.

Exceptions to this criterion are as follows:

- Intranasal, inhaled, or topical steroids, or local steroid injections (e.g., intra-articular).
- Systemic corticosteroids at physiological doses equivalent to prednisone not exceeding 10 mg/day.
- Steroids as premedication for hypersensitivity/infusion reactions; live attenuated vaccination within 30 days before the first study dose.

15. Receipt of a live attenuated vaccine within 30 days before the first study intervention.
Note: Participants must not receive live vaccines during study intervention or within 30 days after the final dose.

16. Peripheral neuropathy of CTCAE Grade ≥2 at screening.

17. Hereditary disorders such as galactose intolerance, Lapp lactase deficiency, or glucose–galactose malabsorption.

Restrictions for Women of Childbearing Potential

Patients who are postmenopausal (e.g., amenorrhea for 12 months without another medical cause, with hormone levels as specified by local regulations) or permanently sterile following bilateral oophorectomy, bilateral salpingectomy, hysterectomy, and/or tubal ligation need not use contraception to be eligible.

All other patients are considered to be of childbearing potential and must use appropriate contraception throughout the study, from screening until the later of study completion or two weeks after the final dose of investigational medicinal product.

Women of childbearing potential must use, alone or in combination, highly effective contraception with a low failure rate when used consistently and correctly (less than 1% per year), such as an intrauterine device or intrauterine system, a double-barrier method, or male sterilization, in accordance with local requirements. A list of qualifying methods is

provided in the patient information sheet. A participant who becomes pregnant during the study must discontinue investigational medicinal product immediately. Pregnancy must be reported according to the procedures above.

2.3 Withdrawal Criteria

In all cases, the reason for withdrawal and the date must be recorded in the case report form and the patient's medical record. Wherever possible, all assessments scheduled for the final study visit should be completed for participants who received study treatment but did not complete the study according to the protocol.
Participants may be withdrawn from the study (including further IMP administration or study procedures) for any of the following reasons:

- At the participant's request.
- When, in the investigator's opinion, continued participation may compromise the participant's well-being.

Study medication may be discontinued in the following situations:

- Disease progression; continued study treatment beyond progression may be permitted if clinical benefit is evident.
- Unacceptable toxicity.

In all cases, the reason and date of discontinuation must be documented in the case report form and medical record. If feasible, assessments scheduled for the final study visit should be performed in every participant who received investigational medicinal product but did not complete the study according to the protocol.

2.4 Study Treatment Discontinuation

Study treatment may be permanently discontinued for the following reasons:

- Documented progressive disease (PD) by the site investigator according to modified RECIST 1.1.
- Unacceptable toxicity in the opinion of the patient or investigator.
- A delay of Day 1 dosing for 28 days or longer owing to a treatment-related adverse

event. Where a delay of 28 days or longer is due to another cause, treatment may continue if the patient is deriving clinical benefit.

- The investigator determines that continued dosing is not in the participant's best interest.
- Development of an exclusion criterion affecting participant safety, such as pregnancy or psychiatric illness.
- Refusal of further study treatment or withdrawal of consent; document the reason

for discontinuation in the medical record.

Lost to Follow-up

A participant will be considered lost to follow-up only when contact cannot be re-established before study completion and insufficient information is available to determine their status. Participants who decline further study participation, including telephone contact, should be documented as having withdrawn consent rather than being lost to follow-up. The investigator must document attempts to contact missing participants throughout the study. If contact is restored, the participant must no longer be classified as lost to follow-up and protocol-specified assessments should resume.

To support the primary PFS and OS analyses, survival status should be reconfirmed for all patients in the full analysis set and safety analysis set, including those who withdrew consent or were considered lost to follow-up.

- Lost to follow-up: site personnel should review hospital records, contact the patient's current treating physician, and consult publicly available death registries where permitted and available to establish current survival status and update the relevant CRF.
- If a participant has expressly withdrawn consent for processing of personal data, site staff may, where permitted by applicable local law, obtain survival information from publicly accessible death registries, if available, and update the relevant CRF.

3. Study Plan and Procedures

3.1 Enrollment and Screening Period

The following assessments and procedures must be completed within 28 days before the first study dose.

See below for details on assessments and their timing.

- Signed informed consent for the clinical study.
- Verification of inclusion/exclusion criteria.
- HER2 status confirmation (IHC 3+ or IHC 2+/SISH-positive).
- Age, sex, race, and ethnicity.
- Medical and surgical history.
- Current and previous medications, including prior anticancer treatment, if applicable.
- ECOG performance status.
- Vital signs (blood pressure, pulse, and temperature), physical examination, weight, and height (screening only).
- HBsAg, anti-HCV antibody, and HIV antigen (may be omitted in the absence of relevant history).
- Complete blood count, chemistry, coagulation studies, and urinalysis.
- CRP and thyroid function tests.
- Menopausal status; serum or urine pregnancy test for women of childbearing potential within 72 hours
  before neoadjuvant therapy, and subsequently before every second neoadjuvant cycle (every four weeks) and every adjuvant cycle (every three weeks).

ECG: At screening, once before adjuvant treatment, and at the end-of-treatment visit after chemotherapy (or upon PD during treatment); additional ECGs as clinically indicated.

- Echocardiography: At screening and thereafter as clinically indicated.
- Chest X-ray: At screening and thereafter as clinically indicated.
- Tumor assessments (CT/MRI scans of the abdomen, pelvis, or other clinically indicated areas) should ideally be performed as close as possible to treatment initiation. Scans obtained as part of routine care before informed consent may be used for study assessments if performed within the required window and in accordance with modified RECIST 1.1 imaging requirements.

- Concomitant medications and adverse events.
- Collection of a fresh tumor tissue specimen is mandatory. The specimen should be newly obtained from the patient before enrollment. Where tissue sampling is clinically infeasible, use of archival tissue obtained before enrollment is permissible.
- Additional blood sampling (mandatory): plasma (MRD), PBMCs, and gDNA (13 mL).

Any of the above tests performed within the screening window may be accepted even if obtained before informed consent, where permitted.

3.2 Treatment Period

In patients with locally advanced, resectable HER2-positive gastric or gastroesophageal junction cancer receiving preoperative FLOT, trastuzumab and durvalumab will be added to neoadjuvant chemotherapy.

Neoadjuvant Chemotherapy

Neoadjuvant treatment begins on Cycle 1 Day 1 and consists of four two-week cycles (trastuzumab plus FLOT four times, Q2W; durvalumab twice, Q4W). If radiographic progression according to modified RECIST 1.1 occurs during neoadjuvant therapy but does not preclude radical surgery, subsequent treatment may proceed at the discretion of the treating physician.

If progression renders surgery impossible or nonprotocol therapy is required as adjuvant chemotherapy, the investigational medicinal product (IMP) will be discontinued and the participant will enter follow-up.

Neoadjuvant treatment begins on Cycle 1 Day 1 and consists of four two-week cycles.

[Neoadjuvant Chemotherapy]
- Cycle length: 2 weeks (14 days)
- Total duration: 4 cycles (8 weeks)
- Cycle n Day 1: trastuzumab 4 mg/kg IV Q2W (6 mg/kg IV on C1D1)

: durvalumab 1,500 mg IV Q4W (on C2D1 and C4D1 only)

: (FLOT) Docetaxel 50mg/m2 IV Q2W
Oxaliplatin 85mg/m2 IV Q2W
Leucovorin 200mg/m2 IV Q2W
5-FU 2600mg/m2 24hr CIV Q2W

[Adjuvant Chemotherapy]
- Cycle length: 3 weeks (21 days)
- Four cycles, up to six at investigator discretion (12–18 weeks in total)
- Day 1: oxaliplatin 130 mg/m² IV Q3W
- Days 1–14: capecitabine 1,000 mg/m² orally twice daily Q3W

After surgery, participants will receive XELOX adjuvant chemotherapy every three weeks (Q3W), for four cycles (up to six at the investigator's discretion), with each cycle lasting 21 days. Adjuvant treatment may be discontinued earlier for unacceptable toxicity, withdrawal of consent, or other protocol-defined discontinuation criteria.

Participants with progression or recurrence during adjuvant chemotherapy must discontinue protocol treatment.
All participants discontinuing protocol treatment for any reason will enter follow-up.

Assessments during the study are as follows:

- Physical examination including ECOG performance status and vital signs at each visit.
- Clinical laboratory safety tests: hematology, coagulation, chemistry, etc. (see Section 4.2.1).
- Selected chemistry tests (see Section 4.2.1), coagulation studies, C-reactive protein (CRP), and urinalysis may be repeated after screening at the investigator's discretion if abnormalities are present. Thyroid function tests will be performed every two cycles during treatment with the immune checkpoint inhibitor durvalumab.
- ECG: At screening, once before adjuvant chemotherapy, at EOT after chemotherapy (or PD during treatment), and as clinically indicated.
- Echocardiography: At screening and subsequently at the investigator's discretion in the presence of abnormalities.

- Serum or urine pregnancy testing for women of childbearing potential will be performed within 72 hours before initiating neoadjuvant chemotherapy and before every second neoadjuvant cycle (every four weeks) thereafter. During adjuvant chemotherapy, testing will be performed before each three-week cycle.
- Adverse events.
- Tumor assessments by CT or MRI will be performed at screening, after neoadjuvant treatment (before surgery), and after surgery (before adjuvant chemotherapy). Based on the postoperative adjuvant baseline scan, imaging will be repeated every 12 weeks (±1 week) during the first year and every 24 weeks (±2 weeks) thereafter until objective progression or recurrence.
- Tumor tissue (mandatory/optional): mandatory at screening before neoadjuvant treatment and at surgery; at EOT in the event of PD.
- Research blood samples (mandatory):
  Screening: plasma (MRD), PBMCs, and gDNA (13 mL).
  Neoadjuvant C2D1: plasma (MRD) and PBMCs (10 mL).
  Adjuvant C1D1: plasma (MRD) (10 mL).
  Plasma MRD (10 mL) every six months thereafter.
  At EOT: 10 mL.

Tumor imaging should adhere as closely as possible to the assessment schedule. If an unscheduled scan is performed outside the ±1-week window and the patient has not progressed, every effort should be made to obtain the next scan at the planned visit. Patients will be assessed according to the study schedule until objective progression by modified RECIST 1.1 and thereafter followed for survival, irrespective of treatment discontinuation, delay, or protocol deviations, unless consent is withdrawn.

RECIST assessments will use CT or MRI of the chest, abdomen, and pelvis. Additional sites suspected of disease involvement should be imaged as appropriate. Radiological images obtained during the study must be collected and retained at the site as source documentation.

If interstitial lung disease (ILD) or pneumonitis is suspected, investigational treatment must be withheld pending evaluation, including high-resolution CT and pulmonary

specialist consultation, with infectious disease consultation where clinically indicated. If pregnancy is suspected during the study, testing must be repeated; a positive result requires immediate discontinuation of study treatment.

3.3 Follow-up Period

3.3.1 End-of-Treatment Visit

Study treatment must stop when a discontinuation criterion is met. Assessments at the visit are detailed in the Schedule of Activities.

Patients continuing study treatment despite objective radiological progression.

If objective radiological disease progression is identified under modified RECIST 1.1, study treatment should be discontinued unless, in the investigator's judgment, the patient continues to derive clinical benefit and meets no other discontinuation criterion. Subsequent treatment and follow-up for OS will be conducted according to the protocol. Safety assessments may be performed at scheduled visits unless more frequent evaluation is clinically indicated.

RECIST progression visit for patients who discontinued study treatment before progression.

Patients should continue to undergo modified RECIST 1.1 assessments until objective radiological progression. Patients who discontinue study treatment before progression should remain on the protocol-specified imaging schedule and attend the progression follow-up visit.

3.3.2 Follow-up Visit

Recurrence Follow-up

Recurrence follow-up will be conducted every 24 weeks (±2 weeks) after the treatment discontinuation visit. Ongoing adverse events and new events related to study treatment must be followed through the 90-day visit after the final dose. Concomitant medications will be collected only when related to recorded adverse events.

Discontinuation of Recurrence Follow-up

If recurrence is confirmed during follow-up, recurrence assessments will cease and survival follow-up will continue.

3.3.3 Survival Follow-up Visit

Survival assessments will be performed every eight weeks (±2 weeks) following objective disease progression. Survival data may be obtained directly from the patient, by telephone contact with family members, or from the current treating physician. Details of initial and subsequent anticancer treatments after discontinuation will be recorded. ECOG performance status should be collected where possible. Survival data will be collected until the final OS analysis or last follow-up date. Participants should also be contacted during the week following the data cutoff for the final survival analysis to maximize completeness of survival information.

If a patient expressly withdraws consent for processing personal data, no new information will be collected; previously collected data may be used for the planned study duration.

3.3.4 CT or MRI (Modified RECIST 1.1)

Assessments will use CT or MRI of the chest, abdomen, and pelvis and will be evaluated by the site investigator according to modified RECIST 1.1. Baseline imaging must cover all areas where the disease commonly metastasizes and any additional sites suggested by individual symptoms or signs. Other sites of suspected disease must be imaged as appropriate. The baseline scan must be obtained within 28 days before the first dose, ideally as close as possible to treatment initiation. Follow-up imaging will be performed at screening, after neoadjuvant treatment (before surgery), and after surgery (before adjuvant therapy). During the first year following the postoperative adjuvant baseline scan,

every 12 weeks (±1 week), followed by every 24 weeks (±2 weeks) until objective progression or recurrence.

Imaging will then be performed every 24 weeks (±2 weeks). If an unscheduled

assessment shows no progression, every effort should be made to perform the next assessment at the planned visit. Radiological images obtained during the trial must be retained as source documents at the site and made available to the investigator if required.

Ideally, scans obtained before informed consent as part of standard clinical care may be used for the trial, provided they fall within the specified window and meet the modified RECIST 1.1 requirements for CT or MRI.

Table 1. Study Procedures1

	Screening	Four Cycles of Neoadjuvant Chemotherapy				Preoperative	Surgery	Adjuvant Chemotherapy (Within 6–8 Weeks After Surgery)	Treatment Discontinuation	Recurrence Follow-up	Survival Assessment
Visit Schedule	-28 ~ Day – 1	C1D1	C2D1	C3D1	C4D1		Within 4–6 Weeks After Chemotherapy	CxD1	Within 30 Days After Chemotherapy	24 Weeks	8 Weeks
Visit Window	N/A	N/A	±3 Days	±3 Days	±3 Days	N/A	At the Investigator's Discretion According to Patient Condition	Each Cycle ±3 Days	N/A	±2 Weeks	±2 Weeks
Signed Informed Consent	√										
Inclusion / Exclusion Criteria	√										
HER2-Positive Test Result[1]	√										
Medical / Surgical History	√										
ECOG Performance Status	√	√	√	√	√			√	√	√	
Physical	√	√	√	√	√			√	√	√	

[1]HER2 positivity (HER2 IHC 3+ or HER2 IHC 2+/SISH-positive) must be confirmed at screening. Previous test results may be accepted even if obtained before informed consent.

Examination, Including Height and Weight[2]											
Vital Signs (BP, HR, Temperature)	√	√	√	√	√			√	√	√	
HBs Ag, Anti-HCV Antibody, HIV Ag[3]	√										
Hematology and Clinical Chemistry[4]	√	√	√	√	√			√	√	√	
Lipase and Amylase	√				√			√	√	√	
CCr[5]	√										
Thyroid Function Tests[6]	√	√		√		Thereafter, as clinically indicated.					
Urinalysis	√	Thereafter, as clinically indicated.									
Coagulation Tests	√	Thereafter, as clinically indicated.									
Pregnancy Test[7]	√	√		√				√			
ECG	√							√	√		
Echocardiography (ECHO)	√	Thereafter, as clinically indicated.									
Chest X-ray	√	Thereafter, as clinically indicated.									
Trastuzumab		√	√	√	√						
Durvalumab		√		√							

[2]Height is required at screening only.

[3]May be omitted if there is no relevant medical history.

[4]Perform according to Section 4.2.1, Clinical Laboratory Safety Assessments. At the investigator's discretion, some tests may be repeated after screening only if an abnormality is identified.

[5]Use the calculation method routinely employed at the institution.

[6]TSH should be assessed every two cycles (every four weeks) during neoadjuvant treatment with the immune checkpoint inhibitor durvalumab. Thereafter, testing may be performed at the investigator's discretion if abnormalities are present. If TSH is abnormal, free T3 and free T4 may also be measured.

[7]For women to whom pregnancy testing applies, a serum or urine test is required within 72 hours before C1D1, then every two cycles (every four weeks) during neoadjuvant therapy and before each cycle (every three weeks) of adjuvant XELOX.

FLOT Regimen		√	√	√	√						
Surgery							√				
Adjuvant Chemotherapy						Initiate 6–8 weeks after surgery according to local practice and the investigator-selected regimen.					
Modified RECIST Tumor Assessment[8]	√					√		√		√	√
Concomitant Medications	√	Collect and record throughout the study.									
Adverse Events	√	Collect and record throughout the study.									
Subsequent Anticancer Therapy										Collect when the information becomes available.	
Fresh Tumor Biopsy[9]	√ (Mandatory)						√ (Mandatory)		√ (Optional)		
Plasma (MRD) (Mandatory)	√			√				√		√	
PBMCs (Mandatory)	√			√							
gDNA (Mandatory)	√										

4. Study Assessments

4.1 Efficacy Assessments

This study will evaluate the efficacy of trastuzumab plus durvalumab and FLOT in patients with HER2-positive advanced gastric or gastroesophageal junction cancer.

Tumor assessment: Modified RECIST 1.1 criteria will be used to evaluate treatment response for PFS and ORR analyses. Modified RECIST 1.1 provides guidance on measurable and nonmeasurable disease, target and nontarget lesions, and objective response categories (complete response, partial response, stable disease, or progressive disease).

[8]Tumor assessments performed within 28 days before study treatment may be used as baseline assessments and need not be repeated before the first dose. Assessments using modified RECIST 1.1 will be performed at screening (within 28 days before the first dose of neoadjuvant therapy), after the final dose of neoadjuvant therapy (before surgery), and after surgery (before the first dose of adjuvant therapy). Thereafter, imaging will be performed every 12 weeks (±1 week) during the first year from the baseline scan for adjuvant therapy and every 24 weeks (±2 weeks) until progression or recurrence.

[9]Slides are acceptable only if a fresh biopsy cannot be obtained.

Chest, abdominal, and pelvic CT or MRI, using the same tumor assessment method as at baseline, must be used at each subsequent assessment.

Tumor assessments will be performed at screening, after neoadjuvant therapy (before surgery), and after surgery (before adjuvant therapy). Following the postoperative adjuvant baseline scan, assessments will occur every 12 weeks (±1 week) for the first year and every 24 weeks (±2 weeks) thereafter until objective progression or recurrence. Patients must continue to undergo imaging until objective progression under modified RECIST 1.1 even if they discontinue study treatment and/or receive subsequent anticancer therapy.

Objective tumor response will be categorized according to modified RECIST 1.1 as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Target-lesion (TL) progression is calculated relative to the lowest sum of lesion diameters recorded during the study. In the absence of progression, response (CR, PR, or SD) is calculated relative to baseline measurements before treatment.

For patients with only nonmeasurable disease at baseline, objective response will be categorized according to modified RECIST 1.1 as CR, PD, or non-CR/non-PD. If the investigator is uncertain whether progression has occurred, particularly in relation to nontarget lesions (NTLs) or a new lesion, treatment may continue until the next scheduled assessment or an earlier assessment if clinically indicated. If progression is confirmed on repeat imaging, the date of the first scan will be designated as the progression date. Other sites of suspected disease should be imaged as appropriate. If an unscheduled assessment shows no progression, every effort should be made to maintain the planned assessment schedule.

To constitute unequivocal progression of nontarget disease, there must be substantial overall worsening of the nontarget tumor burden sufficient to justify treatment discontinuation, even in the presence of SD or PD in target disease. A minor increase in the size of one or more nontarget lesions is generally insufficient to establish unequivocal progression.

Following progression, survival follow-up will continue as specified in the study schedule. Close adherence to the assessment schedule is important.

4.2 Safety Assessments

4.2.1 Clinical Laboratory Safety Assessments

Blood and urine specimens for chemistry, hematology, and urinalysis will be collected at scheduled time points and as clinically indicated.

Clinical laboratory safety assessments, including serum pregnancy tests, will be performed by an accredited laboratory according to local standard procedures. Sample tube types and volumes may vary with the laboratory methods and site practice. Pregnancy testing may be performed on site using a validated urine or serum assay. Clinically significant abnormal laboratory findings should be repeated promptly.

Laboratory parameters are listed in Table 2 (hematology), Table 3 (chemistry), Table 4 (urinalysis), and Table 5 (coagulation).

The following laboratory parameters will be measured:

Table 2. Hematology Laboratory Assessments

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white blood cell count
Mean corpuscular hemoglobin concentration	

Table 3. Clinical Chemistry (Serum or Plasma)

Albumin	Glucose
Alkaline phosphatase (ALP)[a]	Lactate dehydrogenase (LDH)[c]
Alanine aminotransferase (ALT)[a]	Magnesium[c]
Aspartate aminotransferase (AST)[a]	Potassium

Lipase[b]	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine[d]	Urea or blood urea nitrogen (per local practice)
Gamma-glutamyl transferase[c]	Uric acid
Amylase[b]	Quantitative CRP[c]
TSH [e]	Free T4 and free T3[e] (only if TSH is abnormal)

a. ALT, AST, alkaline phosphatase, and total bilirubin must be assessed concurrently. If total bilirubin is ≥2 × the upper limit of normal (ULN), in the absence of Gilbert syndrome, direct and indirect bilirubin fractions must be measured.

b. Both amylase and lipase should preferably be assessed.

c. After screening, testing may be repeated at the investigator's discretion if abnormal.

d. Creatinine clearance will be calculated using Cockcroft–Gault with actual body weight.

e. Free T3 or T4 will be measured only for abnormal TSH or suspected endocrine adverse events.

Table 4. Urinalysis[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

a. Assessed at screening and thereafter as clinically indicated.

Table 5. Coagulation Tests[a]

APTT	INR

a. Assessed at screening and thereafter as clinically indicated.

5. Safety Reporting and Medical Management

5.1 Definition of Adverse Events

An adverse event (AE) is the occurrence of an undesirable medical condition, or worsening of a pre-existing medical condition, during or after exposure to a medicinal product, regardless of whether it is considered causally related to that product. An undesirable condition may be a symptom (e.g., nausea or chest pain), sign (e.g., tachycardia or hepatomegaly), or abnormal investigation (e.g., laboratory or ECG finding). During a clinical trial, an AE may arise at any time, including run-in or washout periods, even if study treatment has not been administered.

The term AE encompasses both serious and nonserious adverse events.

5.2 Recording of Adverse Events

5.2.1 AE Collection Period

AEs will be collected from the time informed consent is signed throughout treatment and the 90-day follow-up period. All ongoing and new AEs identified during the 30-day period after the last dose will be followed until resolution. Following the interim analysis, all ongoing AEs will remain open and be followed until resolution. Serious adverse events (SAEs) will be recorded from the time of informed consent.

5.2.2 Follow-up of Unresolved AEs

Any SAE or nonserious AE ongoing at the 30-day follow-up visit must be followed until resolution unless the investigator considers resolution unlikely or the patient becomes unavailable for follow-up.

5.2.3 AE Parameters

The following information must be collected for each AE:

AE (verbatim term)

AE start and stop dates

Changes in severity

Changes in CTCAE grade

Seriousness of the AE

Investigator-assessed causality to the IMP (Yes/No)

Action taken with the IMP

Participant withdrawal due to the AE (Yes/No)

Outcome

The following additional information must be collected for SAEs:

Date the AE met SAE criteria

Date the investigator became aware of the SAE

Seriousness criterion

Date of hospital admission

Date of discharge

Presumed cause of death

Date of death

Whether an autopsy was performed

Causality to study procedures

AE narrative

5.2.4 Causality Assessment

The investigator will assess the causal relationship of each AE to study treatment by answering Yes or No to the question: "Is there a reasonable possibility that the adverse event was caused by the study drug?"

For SAEs, causal relationships to other medications and study procedures will also be assessed. An SAE considered potentially related to a study procedure should have causality recorded as Yes.

5.2.5 Disease Progression

Disease progression may be considered deterioration of the condition under investigation, including increased severity or worsening signs and symptoms of the malignancy. New metastases or progression of existing metastases from the primary cancer under study should be recorded as disease progression rather than as an AE. Events clearly attributable to disease progression should not be reported as AEs.

5.2.6 Maternal Exposure

If a participant becomes pregnant during the study, study treatment must be discontinued immediately.

All pregnancy outcomes from the first dose until 15 months after the last dose must be followed and documented.

Pregnancy itself is not considered an AE unless study treatment is suspected to interfere with contraceptive effectiveness.

Congenital anomalies, birth defects, and spontaneous abortions must be reported and managed as SAEs. An uncomplicated elective termination of pregnancy should not be classified as an AE. Pregnancy outcomes, including miscarriage, elective termination, ectopic pregnancy, normal delivery, and congenital anomalies, must be followed and documented even if the patient withdraws from the study.

5.3 Reporting of Serious Adverse Events

All SAEs must be reported to the principal investigator immediately and no later than 72 hours after the investigator becomes aware of the event, regardless of causality to study treatment or procedures. All SAEs must be recorded in the CRF and reported in accordance with IRB requirements.

The investigator-sponsor and investigator are responsible for:

- Meeting regulatory and IRB/IEC safety reporting requirements in the country where the study is conducted, including periodic reports;
  Safety reporting requirements;
- Promptly notifying regulators, IRB/IEC, and investigators of new or unexpected safety issues.

5.3.1 Definition of Serious Adverse Events

An SAE is any adverse event occurring at any dose of an investigational medicinal product during any study period (screening, run-in, treatment, washout, or follow-up) that meets one or more of the following criteria.

Any of the following:

- Results in death
- Is immediately life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect in a participant's offspring
- Is an important medical event that may jeopardize the patient or require intervention to prevent one of the above outcomes.
- Medical or scientific judgment must be applied in determining whether expedited reporting is warranted. Examples of medically important events include intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions without hospitalization, and the development of drug dependence or drug abuse.

An SAE beginning or worsening after the on-treatment period will be summarized if considered related to study treatment.

All suspected interstitial lung disease (ILD)/pneumonitis cases, serious or nonserious, must be reported within 24 hours (see the adjudication site manual for case definitions).

Hepatic events meeting potential Hy's law criteria, defined as ALT or AST ≥3 × ULN together with total bilirubin ≥2 × ULN, may arise simultaneously or at separate time points during the study, whether serious or nonserious.

All accidental or intentional overdoses, defined as administration of an excessive dose of the product, are considered medically important. A clinically important overdose includes any overdose causing a serious or nonserious AE or, even in the absence of an AE, considered by the investigator to pose an actual or potential clinical risk to the participant.

Overdose is always considered serious under this protocol because it meets the medically important event criterion. An overdose may or may not be accompanied by an AE, which may itself be serious or nonserious. Details, including the dose administered, clinical course, associated AEs, and outcome, must be documented in narrative form in the CRF.

Progression or worsening of the underlying cancer must not be recorded as an AE on the AE CRF; death from disease progression must be recorded on the death CRF.
If worsening laboratory values or vital signs are associated with clinical symptoms or signs, the clinical manifestation should be reported as the AE, and the laboratory or vital-sign abnormality should be recorded as supporting information. Whenever possible, use clinical diagnoses rather than laboratory terms (e.g., anemia rather than low hemoglobin). A clinically meaningful decline in left ventricular ejection fraction (LVEF), measured by MUGA or echocardiography, associated with left ventricular dysfunction must be verified and included in the AE report. Clinically relevant worsening of a nonrequired parameter without symptoms should also be reported as an AE.

5.3.2 Adverse Events of Special Interest

In view of known study-drug risks and class effects of trastuzumab-related agents, the following events are designated as adverse events of special interest (AESIs) and will be collected and evaluated with particular attention.

5.3.2.1 Agent-Specific Events

- Durvalumab

Durvalumab-associated AESIs include events potentially related to inflammatory or immune-mediated mechanisms that may require more frequent monitoring and/or treatment with corticosteroids, immunosuppressants, or hormone replacement. Such events are closely monitored in studies of durvalumab monotherapy and combination therapy.
An immune-mediated adverse event (imAE) is an AESI temporally associated with drug exposure, consistent with an immune-mediated mechanism, and without a clearly identified alternative etiology. Serological, immunological, or histopathological (biopsy) evidence should be obtained when needed to support the diagnosis. Appropriate efforts should be made to exclude neoplastic, infectious, metabolic, toxic, and other possible causes.
AESIs/imAEs observed with anti-PD-L1/PD-1 agents such as durvalumab include:

- Pneumonitis
- Hepatitis

• Diarrhea/colitis
• Hypophysitis/hypopituitarism
• Type 1 diabetes mellitus
• Nephritis
• Rash/dermatitis
• Myocarditis
• Myositis/polymyositis
• Pancreatitis

Rare or less frequent imAEs include neuromuscular toxicities such as myasthenia gravis and Guillain–Barré syndrome.

Other rare or less frequent inflammatory events of potentially immune-mediated origin include, but are not limited to:

• Pericarditis
• Sarcoidosis
• Uveitis
• Other ocular, cutaneous, hematological, and rheumatological events; vasculitis; aseptic meningitis; and noninfectious encephalitis.

Events involving inflammatory or immune-mediated mechanisms can occur in almost any organ system. Infusion-related reactions and hypersensitivity/anaphylactic reactions, although mediated by different pharmacological mechanisms, are also considered AESIs.

- Trastuzumab (Sampenet)

- Cardiotoxicity
- Congestive heart failure
- Left ventricular dysfunction
- Reduced left ventricular ejection fraction (LVEF)
- Cardiomyopathy
- clinically significant arrhythmia
- Infusion-related reactions (IRRs)

- Reactions during or after infusion, including fever, chills, hypotension, and dyspnea
- May include cytokine release syndrome
- Hypersensitivity / Anaphylaxis
- Grade ≥2 allergic reaction
- Anaphylaxis
- Angioedema
- Pulmonary Toxicity
- Interstitial lung disease (ILD)
- Pneumonitis
- Noninfectious pulmonary infiltrates
- Acute respiratory distress syndrome (ARDS)
- Severe Hematologic Toxicity (With Combination Chemotherapy)
- febrile neutropenia
- Grade 4 neutropenia
- Hematologic toxicity associated with severe infection
- Embryofetal Toxicity
- Exposure during pregnancy
- Fetal abnormalities or pregnancy complications

5.3.2.2 AESI Collection Period

AESIs will be collected from first study-drug administration through 30 days after the final dose.

Immune-mediated adverse events and cardiotoxicity may be followed longer at the investigator's discretion because of possible delayed onset.

5.3.2.3 AESI Assessment

The following information will be assessed for each AESI:

- Severity according to CTCAE v5.0
- Start and end dates
- Causality to study treatment

- Whether the event is serious
- Action taken
- Recovery status
- Recurrence following rechallenge

5.3.2.4 AESI Monitoring Plan

Cardiotoxicity

- Baseline ECG and echocardiography
- LVEF assessment every 12 weeks thereafter
- Troponin and BNP/NT-proBNP as clinically indicated

Immune-mediated Adverse Events

- Periodic liver, renal, and thyroid function assessments
- Additional immune-toxicity evaluation if new symptoms occur

Hematologic Toxicity

- Complete blood count before each cycle
- Immediate evaluation and management of febrile neutropenia

Pulmonary Toxicity

- Chest CT and oxygen saturation assessment for new respiratory symptoms

5.3.2.5 AESI Reporting

AESIs qualifying as SAEs will be reported promptly in accordance with applicable regulations and institutional procedures.

Suspected unexpected serious adverse reactions (SUSARs) will be reported as required by regulators.

Investigators will determine whether to continue, reduce, interrupt, or discontinue study treatment following an AESI.

5.4 Toxicity Management

Dose reductions and/or treatment delays are planned for severe hematological or nonhematological toxicities during study therapy. Dose modification should be guided by the organ system exhibiting the greatest toxicity. Toxicities will be graded using CTCAE v5.0.

If a participant experiences multiple toxicities and the recommendations conflict, the most conservative dose-modification approach should be followed. Doses reduced for toxicity must never be re-escalated. All toxicities, except Grade 2 neuropathy, must resolve to at least Grade 1 before retreatment. Missed doses within a cycle must not be replaced.

5.5 Concomitant Medications and Treatments

5.5.1 Permitted

Concomitant Medications

Table 6.2.1

Supportive Medication / Drug Class:	**Use:**
Concomitant medications or treatments considered necessary for appropriate prophylaxis or supportive care (e.g., acetaminophen or diphenhydramine), except for those explicitly listed as prohibited above.	Administer as prescribed by the investigator.
Optimal supportive care, including antibiotics, nutritional support, correction of metabolic disturbances, symptom control, and pain management (including palliative radiotherapy for nontarget lesions)	Use in all participants as needed.
Inactivated viruses, including those in inactivated influenza vaccines	Permitted

5.5.2 Prohibited

Concomitant Medications

Before administering study treatment, investigators must review concomitant medications for potential drug interactions. Particular care should be taken to avoid live vaccines, potent CYP3A4 inhibitors or inducers, strong immunosuppressive agents, and drugs affecting

fluoropyrimidine metabolism.

Investigators should assess each participant's clinical condition, laboratory findings, and adverse events in light of potentially increased toxicity from concomitant medications and may reduce, temporarily interrupt, or permanently discontinue study treatment as clinically indicated.

Category	Contraindicated or Cautionary Drug	Relevant Study Agent	Rationale / Risk	Recommended Action
Live Vaccines	Yellow fever, MMR, varicella, intranasal influenza vaccines, etc.	Durvalumab	Increased risk of severe infection during immune modulation	No live vaccines during the study
High-Dose Systemic Immunosuppressants	Prednisone >10 mg/day equivalent, tacrolimus, cyclosporine, etc.	Durvalumab	Possible reduction in immunotherapy efficacy and increased infection risk	Use the lowest necessary dose; consider exclusion if sustained use is required
Potent CYP3A4 Inhibitors	Clarithromycin, itraconazole, voriconazole, ketoconazole, etc.	Docetaxel	Increased docetaxel exposure with possible myelosuppression and toxicity	Avoid concomitant use or intensify toxicity monitoring
Potent CYP3A4 Inducers	Rifampin, phenytoin, carbamazepine, etc.	Docetaxel	Potential reduction in docetaxel efficacy	Avoid concomitant use whenever possible
QT-Prolonging Drugs	Amiodarone, certain quinolones and macrolides, etc.	5-FU	Possible increased risk of arrhythmia or QT prolongation	Consider ECG monitoring
Cardiotoxic Drugs	Anthracyclines (e.g., doxorubicin)	Sampenet (trastuzumab)	Increased risk of heart failure and reduced LVEF	Enhance cardiac monitoring if used concomitantly
Neurotoxic Drugs	Vincristine, high-dose	Oxaliplatin	Increased risk of	Consider

	paclitaxel, etc.		cumulative neurotoxicity	symptom-guided dose reduction or discontinuation
Nephrotoxic Drugs	Aminoglycosides, amphotericin B, repeated contrast media exposure, etc.	Oxaliplatin / 5-FU	Possible increased toxicity with deterioration of renal function	Monitor renal function and maintain hydration
Anticoagulants	Warfarin, etc.	5-FU	Potential INR fluctuations and bleeding risk	Frequent INR monitoring
DPD-Inhibiting Drugs	brivudine, sorivudine	5-FU	Risk of fatal fluoropyrimidine toxicity	Strictly contraindicated
Other Fluoropyrimidine-Containing Agents	Preparations containing capecitabine or tegafur	5-FU	Overlapping toxicity	Do not use together
Drugs That May Exacerbate Immune Toxicity	TNF-α inhibitors and other immunomodulators	Durvalumab	Altered immune responses and increased infection risk	Consult an appropriate specialist if needed
Excessive Alcohol Intake	Alcohol consumption	Entire FLOT Regimen	Possible exacerbation of hepatotoxicity and myelosuppression	Advise restriction
Pregnancy-Related Medication Risks	Use during pregnancy	All Study Regimens	Risk of embryofetal toxicity	Avoid pregnancy and use contraception
Other Anticancer Therapies (Including Immunochemotherapy)	Any chemotherapy or immunochemotherapy not specified in this protocol	All Study Regimens	Potential confounding of study results and inability to assess safety	Concomitant use prohibited
Radiotherapy	Tumor-directed radiotherapy	All Study Regimens	Potential confounding of study results	Concomitant use prohibited (palliative radiation to an isolated

				symptomatic lesion or the brain may be allowed at investigator discretion)

6. Investigational Medicinal Products

6.1 Product Identification

Patients will receive treatment as scheduled unless a protocol-defined discontinuation criterion occurs.

Trastuzumab will be supplied by Boryung Pharmaceutical, while other agents will be prescribed through standard processes.

Active Ingredient	Generic Name	Manufacturer
Trastuzumab	**Sampenet Injection**	**Boryung Pharmaceutical**

6.2 Neoadjuvant Chemotherapy

Administer trastuzumab, followed by durvalumab and then FLOT on Day 1.

- Cycle length: 2 weeks (14 days)
- Four cycles over 8 weeks
- Cycle n Day 1: trastuzumab 4 mg/kg IV Q2W (6 mg/kg IV on C1D1)

: durvalumab 1,500 mg IV Q4W (on C2D1 and C4D1 only)

: (FLOT) Docetaxel 50mg/m2 IV Q2W
Oxaliplatin 85mg/m2 IV Q2W
Leucovorin 200mg/m2 IV Q2W
5-FU 2600mg/m2 24hr CIV Q2W

6.3 Adjuvant Chemotherapy

Participants undergoing curative (R0) resection will receive postoperative adjuvant XELOX;

otherwise, standard-of-care (SOC) therapy will be given.

Participants must recover adequately before starting adjuvant chemotherapy.
Tumor imaging must be completed before initiation of postoperative adjuvant chemotherapy.

- Cycle length: 3 weeks (21 days)

- Four cycles, up to six at investigator discretion (12–18 weeks in total)
- Day 1: oxaliplatin 130 mg/m² IV Q3W
- Days 1–14: capecitabine 1,000 mg/m² orally twice daily Q3W

6.4 Dose and Treatment Regimens

Dose reductions of durvalumab and trastuzumab are not permitted.
FLOT dose reductions are at the treating physician's discretion.

The investigator will determine whether study medication should be interrupted, discontinued, or restarted based on AE severity, duration, recovery, risk of recurrence, and the participant's overall clinical condition.
Corticosteroids or other immunosuppressive therapy may be given for immune-mediated AEs when indicated.
FLOT dose reductions may follow institutional standard practice or investigator judgment.
Consider permanent discontinuation for recurrent toxicity or delayed recovery.

[Management of Adverse Events With Postoperative Adjuvant XELOX (Capecitabine/Oxaliplatin)]
The following guidance applies to postoperative adjuvant XELOX. If this protocol conflicts with the approved Korean prescribing information for an agent, the prescribing information takes precedence.
Hematologic toxicity: For CTCAE Grade ≥3 neutropenia, thrombocytopenia, or other hematologic toxicity, treatment should be withheld until recovery to Grade ≤1 or baseline, then resumed with a stepwise dose reduction. Further reduction is indicated for febrile

neutropenia or recurrent toxicity. The affected agent should be discontinued if toxicity recurs despite reduction or recovery is delayed.
Peripheral neuropathy (oxaliplatin): Reduce the oxaliplatin dose for persistent Grade 2 sensory symptoms or symptoms interfering with function. Discontinue oxaliplatin for Grade ≥3 neuropathy or function-limiting symptoms. Capecitabine may continue if tolerated.
Hand–foot syndrome (palmar–plantar erythrodysesthesia; capecitabine): For Grade 2 toxicity, withhold capecitabine until recovery to Grade ≤1, then resume at a reduced dose. For Grade 3 toxicity, resume at a reduced dose after recovery; discontinue if it recurs.
Diarrhea: Withhold treatment for Grade ≥2 diarrhea until recovery and provide supportive measures, including antidiarrheal therapy. Resume at a reduced dose after recovery. For Grade 3–4 diarrhea or associated dehydration, consider hospitalization and intravenous fluids; reduce or discontinue treatment if recurrent.
Mucositis/stomatitis: For CTCAE Grade ≥2, withhold capecitabine until recovery to Grade ≤1, then resume at a reduced dose; consider discontinuation for severe or recurrent toxicity.
Other nonhematologic toxicity: In general, withhold treatment for Grade ≥3 toxicity until recovery to Grade ≤1 or baseline, then resume at a reduced dose. Discontinue the causative drug if toxicity recurs after dose reduction or recovery is delayed. A reduced dose must not be re-escalated.

For management of durvalumab-related immune-mediated events—including nephritis, rash/dermatitis, infusion reactions, myasthenia gravis, encephalitis, Guillain–Barré syndrome, uveitis, and transverse myelitis—the approved Korean prescribing information takes precedence if it conflicts with the guidance in this protocol.
The table below provides general recommendations for dose modification in response to AEs/AESIs.

Adverse Event / AESI	Grade / Clinical Situation	Durvalumab	Sampenet (Trastuzumab Biosimilar)	FLOT	Criteria for Retreatment
Infusion-related reaction (IRR)	Grade 1	Continue at a reduced infusion rate	Continue at a reduced infusion rate	Not applicable	Continue when

					symptoms resolve
	Grade 2	Interrupt; may resume after symptom resolution	Interrupt temporarily; may resume	Withhold if necessary	Resume after recovery to Grade ≤1
	Grade 3	Discontinue; carefully consider rechallenge	Consider discontinuation	Withhold	Following investigator risk–benefit assessment
	Grade 4 or anaphylaxis	Permanently discontinue	Permanently discontinue	Discontinue	Rechallenge prohibited
Cardiotoxicity	Asymptomatic decline in LVEF	Consider continuing or withholding	Temporarily interrupt	May continue	May resume after LVEF recovery
Symptomatic CHF / myocarditis		Consider permanent discontinuation	Consider permanent discontinuation	Discontinue if necessary	At investigator discretion after clinical recovery
Immune-Mediated Pneumonitis (ILD/Pneumonitis)	Grade 1	Consider withholding or close monitoring	May continue	May continue	May resume when stable
	Grade 2	Temporarily interrupt and initiate steroids	Withhold if necessary	Withhold if necessary	After recovery to Grade ≤1 and steroid taper
	Grade 3~4	Permanently discontinue	Consider discontinuation	Consider discontinuation	Rechallenge not recommended
Immune-Mediated Hepatitis	AST/ALT >3 × ULN or elevated bilirubin	Temporarily interrupt	May continue	Reduce dose or withhold if necessary	May resume after laboratory recovery

	Grade 3~4 hepatotoxicity	Consider permanent discontinuation	Discontinue if necessary	Consider discontinuation	At investigator discretion after adequate recovery
Diarrhea / Colitis	Grade 1	Symptomatic management	May continue	May continue	Continue if symptoms are controlled
	Grade 2	Consider temporary interruption	May continue	Reduce dose if necessary	After recovery to Grade ≤1
	Grade 3~4 colitis	Consider permanent discontinuation	May continue	Consider discontinuation	Exercise caution with rechallenge
Hematologic Toxicity	Grade 3 neutropenia	May continue	May continue	cycle delay	Resume after ANC recovery
	Febrile neutropenia	May continue	May continue	Consider withholding and dose reduction	May resume at reduced dose after recovery
	Recurrent Grade 4 neutropenia	May continue	May continue	Consider dose reduction or discontinuation	At investigator discretion
Peripheral Neuropathy	Persistent Grade 2	May continue	May continue	Consider reducing oxaliplatin	Continue after symptom improvement
	Grade 3~4	May continue	May continue	Consider discontinuing oxaliplatin	May partly resume after recovery to Grade ≤1
Mucositis / Stomatitis	Grade 2	May continue	May continue	Consider 5-FU dose reduction	After recovery to Grade ≤1

	Grade 3~4	May continue	May continue	Withhold or reduce dose	Resume after recovery
Renal Dysfunction	Increased creatinine, Grade ≥2	Consider withholding	May continue	Consider withholding oxaliplatin/5-FU	Resume after recovery
Endocrine irAEs	Manageable thyroid dysfunction, etc.	May continue with hormone replacement	May continue	May continue	Continue when clinically stable
	Severe adrenal crisis, etc.	Temporarily interrupt or discontinue	May continue	May continue	Reassess after stabilization
Cutaneous Toxicity	Grade 1~2 rash	May continue	May continue	May continue	Symptomatic treatment
	Grade 3	Consider withholding	May continue	Reduce dose if necessary	Resume after recovery
SJS/TEN		Permanently discontinue	Consider permanent discontinuation	Consider permanent discontinuation	Rechallenge prohibited
Pregnancy	Confirmed pregnancy	Discontinue immediately	Discontinue immediately	Discontinue immediately	Do not restart

All agents will be prepared and handled in accordance with the product labeling and institutional standard procedures.

7. Statistical Analysis

7.1 Sample Size Estimation

This is a single-arm Phase II study using Simon's two-stage design to collect preliminary efficacy and safety data for neoadjuvant chemotherapy in 20 patients with locally advanced HER2-positive gastric or gastroesophageal junction cancer considered unsuitable for curative resection. It is a noncomparative study intended to be conducted in multiple cohorts over several years. The protocol may be amended in response to emerging safety concerns.

7.2 Definition of Analysis Sets

7.2.1 Full Analysis Set

The full analysis set (FAS) includes all participants who receive at least one dose of investigational product.
Patients will be categorized according to the planned treatment combination. The full analysis set (FAS) will be used for all raw-data listings and, unless otherwise specified, will be the default analysis population.

7.2.2 Safety Analysis Set

The safety analysis set (SAS) includes all participants who receive at least one dose of investigational product.

7.3 Outcome Measures for Analysis

All outcome measures will be specified in the statistical analysis plan.
The primary objective of this study is safety, assessed by changes in adverse events.
The pCR rate is defined as the proportion of patients with no viable tumor remaining in the resected specimen and
will be assessed by pathological review of surgical specimens.
Secondary outcomes include the surgery rate, ORR during neoadjuvant therapy, complete (R0) resection rate, EFS, and OS at 24 and 36 months.
Additional secondary endpoints, including OS, will be evaluated to further characterize antitumor activity in each cohort. ORR is defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) according to modified RECIST 1.1, as assessed by the local investigator.

- The response-evaluable set will be used for analysis; patients will be assessed according to the assigned study intervention.

- Data collected from the first dose until progression or the last evaluable assessment without progression will contribute to ORR evaluation regardless of treatment discontinuation. Patients who discontinue treatment without response or progression and subsequently respond to another anticancer treatment will not count as responders for ORR.

• The measure of interest is the estimated ORR.

• Duration of response, based on investigator-assessed modified RECIST 1.1, is defined as the time from the first documented response (subsequently confirmed) to the first documented disease progression as assessed locally or death in the absence of progression.

• Event-free survival (EFS) is defined as the time from randomization/enrollment until any of the following, assessed locally by modified RECIST 1.1 and/or pathology in accordance with BICR assessment: (1) progression that prevents surgery or requires nonprotocol treatment; (2) locoregional or distant recurrence or disease progression; or (3) death from any cause.

• The analysis will include participants in the full analysis set. Participants will be analyzed according to assigned study intervention regardless of treatment discontinuation, other anticancer therapy, or clinical progression before progression under modified RECIST 1.1. However, when progression or death occurs immediately after two consecutive missed visits, the participant will be censored at the last evaluable assessment before those missed visits.

• Measures of interest are median EFS and EFS landmark estimates at 24 and 36 months after first dosing.

• Measures of interest are median OS and OS rates at 24 and 36 months.

• Overall survival (OS) is defined as the time from study intervention initiation to death from any cause.

• R0 resection is defined as complete resection with microscopically negative margins and no gross or microscopic tumor remaining at the primary tumor site. R1 resection indicates removal of all gross disease but microscopic tumor involvement at a resection margin.

• The analysis will include participants in the FAS.

Participants will be analyzed by their assigned study intervention regardless of discontinuation or subsequent anticancer therapy.

7.4 Statistical Analysis Methods

Descriptive statistics will be presented for all variables. Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized as frequencies and percentages. Unless otherwise specified, percentages will be calculated using the relevant overall population as the denominator.
Baseline is the last assessment before the first dose for each variable, except efficacy variables. All collected data will be listed.
Safety data will be summarized and analyzed in the safety population.
Statistical results will be presented with 95% confidence intervals and two-sided p values. No adjustment for multiple comparisons is planned.
Overall survival is defined as the time from initiation of study intervention to death from any cause. Participants in the FAS will be included, with analysis by assigned study intervention irrespective of treatment discontinuation or subsequent anticancer therapy. Those not known to have died by the analysis cutoff will be censored at the last documented date on which they were known to be alive.
Survival status will be updated during the week after the data cutoff (DCO). Patients confirmed alive or with deaths occurring after the DCO will be censored at the cutoff date.
Analysis Methods
OS will be summarized as appropriate using the number of patients, deaths, median, quartiles, survival proportions at 24 and 36 months, corresponding 95% CIs, and Kaplan–Meier curves. The analysis will be based on the FAS.

8. Study and Data Management

8.1 Site Staff Training

Before the first patient is enrolled, a representative of the investigator-sponsor will review and discuss the protocol and relevant documents with site staff and train staff on study-

specific procedures and associated systems.
The investigator will ensure appropriate training for all site staff and communicate new study-related information to relevant personnel.
The investigator will maintain records of all study personnel, including medical, nursing, and other staff.

8.2 Study Monitoring

The investigator-sponsor will perform study monitoring and may delegate these activities, while retaining ultimate responsibility for delegated duties. The monitoring plan will describe procedures, including the monitoring methods to be used.

8.2.1 Study Document Retention

The investigator will comply with the principles set out in the clinical study agreement (CSA).

8.3 Study Timelines and Completion

The study completion date is defined as the date of final data analysis, at which point the clinical database will close to new data.
may be.

8.4 Data Management

Site personnel will be responsible for data management. Data obtained from third-party sources will be reconciled against the clinical study data. Adverse events and medical/surgical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Data queries will be raised for inconsistent, implausible, or missing information.

9. Ethical and Regulatory Requirements

9.1 Ethical Study Conduct

This clinical study will be conducted in accordance with ethical principles originating from the Declaration of Helsinki; International Council for Harmonisation (ICH) Good Clinical

Practice (GCP); applicable regulatory requirements; and ethical requirements concerning human participants and biological specimens.

9.2 Protection of Participant Data

The investigator-sponsor will assign each participant a unique identification code.
Participants must be informed that study-related data will be used in accordance with local data protection laws, and the extent of disclosure and use must be explained in the informed consent form (ICF).
The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, Korean GCP, and applicable regulations. Before any patient is enrolled, the final protocol, including the final written informed consent form, must receive written approval or a favorable opinion from the IRB. The principal investigator is responsible for notifying the IRB of protocol amendments and obtaining approval as required locally.

9.3 Ethics

The ethics committee (EC) must approve the final protocol, the final informed consent form (ICF), including consent for biomarker and/or pharmacogenetic specimens, and all other written information or materials provided to patients.
The investigator will ensure that these documents are distributed to the relevant EC and site personnel.
Each principal investigator will provide the EC/IRB with reports of serious and unexpected adverse drug reactions observed in other studies of the investigational drug.

9.4 Informed Consent

Each site's principal investigator will:
Before study participation, patients must sign and date the informed consent forms for the main study and any optional components. One signed, dated original will be provided to the patient, and a second original will be retained at the site. The investigator-sponsor must ensure that consent is freely given and that patients understand their right to withdraw from optional biomarker or pharmacogenetic research at any time. Repeat biopsy is mandatory or optional as specified, except where medically infeasible at the physician's discretion.

9.5 Protocol and Informed Consent Amendments

Material protocol changes will be documented in a protocol amendment and, where necessary, a revised protocol version.
Amendments must be approved by the relevant EC, and where required by national regulators, before implementation. Local requirements for amended protocols must be followed.

9.6 Audits and Inspections

Audits and inspections systematically and independently examine study-related activities and documentation to determine whether study activities were performed and data were recorded, analyzed, and reported accurately in accordance with the protocol, GCP, ICH guidance, and applicable regulatory requirements.

9.7 Biomarker Analysis

Blood-based biomarker analyses will be performed to investigate biological changes associated with study treatment and their potential predictive or prognostic value. These analyses include plasma minimal residual disease (MRD) testing using circulating tumor DNA (ctDNA), peripheral blood mononuclear cell (PBMC) analyses, and genomic DNA (gDNA) analyses.

Plasma MRD (ctDNA) Analysis
Minimal residual disease (MRD) will be assessed using circulating tumor DNA (ctDNA) isolated from plasma.
MRD analysis may be used to:
Assess treatment response
Detect molecular recurrence
Assess changes in tumor burden
Analyze somatic mutation profiles
Explore prognostic biomarkers
Next-generation sequencing (NGS) or an equivalently validated platform may be used. The analytical panel and cutoffs will follow separate laboratory standard operating procedures

(SOPs).

PBMC Analysis

PBMCs will be isolated by Ficoll density-gradient centrifugation or an equivalent method.
Isolated PBMCs may be used for:
Immune-cell subset analysis
T-cell activation marker assessment
Exploratory cytokine analyses
Assessment of immune response changes
Flow cytometry
Exploratory RNA/DNA analyses
PBMCs may be stored in liquid nitrogen or at ≤− 70°C under appropriate cryopreservation conditions until analysis.

gDNA Analysis

Genomic DNA (gDNA) will be extracted from whole blood or buffy coat.
gDNA analysis may include:
Analysis of germline genetic variation
Exploration of genetic determinants of drug response
Pharmacogenetic analyses
exploratory pharmacogenomic analysis
Genetic analyses will be conducted only within the scope of this study. Individual genetic testing results will not routinely be returned to participants.

9.8 Exploratory Biomarker Analysis

Planned genomic analyses include cell-free DNA, whole-exome sequencing, and RNA sequencing. Remaining tissue will be stored for 15 years after study completion and may be used for subsequent biomarker profiling for research purposes. Exploratory analyses may include, but are not limited to, cell-free DNA, whole-exome sequencing, whole-genome

sequencing, RNA sequencing, and ex vivo patient-derived cells. Single-cell sequencing and multiplex immunohistochemistry may also be performed.

9.9 Storage and Disposal

Results from specimens collected for this study will be used only for the purposes of the study. Neither specimens nor results will be sold, lent, or donated to an independent third party for other purposes. Following protocol-specified testing, specimens will be stored or disposed of in accordance with applicable law and institutional requirements. With separate patient consent, specimens may be used for additional research or stored for the period authorized after study completion; specimens will be destroyed upon withdrawal of consent. Except as required by law, patient names or information identifying patients as study participants will not be disclosed without written authorization. When the consented storage period ends, human biological materials will be disposed of in accordance with Article 13 of the Waste Control Act and applicable standards.

10. References

Al-Batran et al 2016

Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J et al Histopathological regression after Neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or Capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016 Dec;17(12):1697-1708.

Al-Batran et al 2017

Al-Batran SE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial.
JAMA Oncol. 2017 Sep 1;3(9):1237-1244.

Bang et al 2010

Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97.

Bang et al 2012

Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW et al. Adjuvant Capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012 Jan 28;379(9813):315-21.

Cunningham et al 2006

Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11-20.

Doi et al 2017

Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, et al. Safety, pharmacokinetics, and antitumour activity of Trastuzumab deruxtecan (DS-8201), a HER2- targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro- oesophageal tumours: a Phase 1 dose-escalation study. Lancet Oncol. 2017;18(11):1512-22.

Dovedi et al 2021

Dovedi SJ, Elder MJ, Yang C, Sitnikova SI, Irving L, Hansen A et al. Design and Efficacy of a Monovalent Bispecific PD-1/CTLA4 Antibody That Enhances CTLA4 Blockade on PD-1+ Activated T Cells. Cancer Discov. 2021;11(5):1100-17.

Eric et al 2023

Eric C. Maria B, Elizabeth S, Ian C, Hae P, Salvatoer S et al. Trastuzumab Deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a Trastuzumab-containing regimen(DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study Lancet Oncol. 2023 Jul;24(7):744-756

Janjigian et al 2020

Janjigian YY, Maron SB, Chatila WK, Millang B, Chavan SS, Alterman C, et al. First-line pembrolizumab and Trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. The Lancet Oncology. 2020;21(6):821-31.

Kohei et al 2020

Kohei S, Yung B, Satoru I, Naotoshi S, Min R, Daisuke S et al. Trastuzumab Deruxtecan in previously treated HER2-positive Gastric Cancer. N Engl J Med. 2020; 382(25):2419-2430

Li et al 2020

Li B, Michelini F, Misale S, Cocco E, Baldino L, Scaltriti M, et al. HER2-Mediated Internalization of Cytotoxic Agents in ERBB2 Amplified or Mutant Lung Cancers. Cancer Discov (2020) 10 (5): 674–687.

Modi et al 2022

Modi S, Jacot W, Yamashita T, Sohn J, Vidal M. et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 387;1, 2022

Sasako et al 2008

Sasako M. Surgery and adjuvant chemotherapy. Int J Clin Oncol. 2008 Jun;13(3):193-5. doi:

10.1007/s10147-008-0791-1. Epub 2008 Jun 14. PMID: 18553226.

Sasako et al 2011

Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T et al. Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011 Nov 20;29(33):4387-93.

Satoh et al 2014

Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN-a randomized, phase III study. J Clin Oncol. 2014;32(19):2039-49.

Shitara et al 2020

Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. New England Journal of Medicine.2020;382(25):2419-30

Smalley et al 2012

Smalley S., Benedetti J., Haller D., Hundahl S., Estes N., Ajani J et al. (2012) Updated analysis of SWOG-directed Intergroup Study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 30: 2327–2333.

Wilke et al 2014

Wilke H, Muro K, Van Cutsem E, Oh S-C, Bodoky G, Shimada Y et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. The Lancet Oncology. 2014;15(11):1224-35.

Yamaguchi et al 2020

Yamaguchi K on behalf of the DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan (T-DXd; DS-8201) in patients with HER2–low advanced gastric or gastroesophageal junction
(GEJ) adenocarcinoma: results of the exploratory cohorts in the Phase 2 multicenter, open-label DESTINY-Gastric01 study. Poster presented at the 2020 ESMO Congress.

Yamaguchi et al 2023

Yamaguchi K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Shitara K, et al. Trastuzumab Deruxtecan in

Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial. J Clin Oncol. 2023 Feb 1; 41(4): 816–825.

Ychou et al 2011

Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011 May 1;29(13):1715-21.

Zhang et al 2015, Fu et al 2020

Zhang YH, Tian M, Tang MX, Liu ZZ, Liao AH. Recent insight into the role of the PD-1/PD- L1 pathway in feto-maternal tolerance and pregnancy. Am J Reprod Immunol. 2015;74(3):201- 8

Appendix A. Additional Safety Information

Additional Guidance on the Definition of Serious Adverse Events (SAEs): Life-threatening

"Life-threatening" means that the participant was at immediate risk of death from the AE as it occurred.

Life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event or in which continued use of the product might have resulted in death. It does not refer to an event that might have caused death if it had occurred in a more severe form (e.g., hepatitis that resolved without liver failure).

Hospitalization

Outpatient treatment in an emergency department does not, in itself, constitute an SAE, although the underlying reason for treatment (e.g., bronchospasm or laryngeal edema) may qualify. Hospital admission or surgery planned before or during the study for a condition existing before enrollment is not considered an AE unless that condition worsens unexpectedly during the trial.

Important Medical Events or Medical Interventions

Medical and scientific judgment should be exercised in determining whether an important medical event is serious when it does not immediately threaten life or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or require intervention to prevent one of these outcomes. Such events should generally be considered serious.

Discontinuation of a suspected medicinal product alone does not establish that an event is medically important; medical judgment is required.

Guidance on Assessment of Causality

When determining whether there is a "reasonable possibility" that an AE was

caused by a drug, consider the following factors:

Temporal relationship and exposure to the suspected drug. Did the participant actually receive the suspected drug? Did the AE occur within a reasonable time after administration?

Consistency with the known drug profile: Is the AE consistent with prior pharmacological or toxicological knowledge of the suspected drug or other agents in the same pharmacological class? Could the AE be anticipated from the agent's pharmacological properties?

Dechallenge. Did the AE resolve or improve following discontinuation or dose reduction of the suspected drug?

Absence of alternative causes. Can the AE be reasonably explained by an underlying disease, another medication, or other host or environmental factors?

Rechallenge. If the suspected drug was withdrawn and subsequently reintroduced,

did the AE recur? Laboratory testing. Did any specific laboratory test, if performed,

support a causal relationship?

A "reasonable possibility" may be considered present if one or more of these factors apply to the AE.

Conversely, when none of the preceding criteria applies, or when drug exposure and timing are compatible but the dechallenge is negative or equivocal or there is a more plausible alternative cause, a reasonable possibility of causal relationship may not exist.

In difficult cases, additional factors may be

considered: Is the event a recognized

feature of overdose? Is there a known

mechanism?

Ambiguous cases should be considered to have a reasonable possibility of causal relationship unless further evidence excludes it. Worsening of the underlying malignancy as a consequence of lack of efficacy should be classified as not reasonably related.

Appendix B. Guidelines for Objective Tumor Response Assessment Using Modified RECIST Version 1.1 (Response Evaluation Criteria in Solid Tumors)

1. Introduction

This appendix describes the implementation of modified RECIST 1.1 (Eisenhauer et al., 2009) for investigator-based assessment of tumor burden, including the protocol-specific requirements for this study.

2. Definitions of Measurable and Nonmeasurable Disease, Target Lesions, and Nontarget Lesions

Patients enrolled in this study should have at least one lesion, measurable and/or nonmeasurable, that can be reliably assessed by imaging (CT/MRI) at baseline and follow-up visits.

Measurable disease: A previously nonirradiated lesion that can be accurately measured by CT or MRI at baseline, has a longest diameter of ≥10 mm (except lymph nodes, which must have a short axis ≥15 mm), and is suitable for reproducible repeated measurement.

Nonmeasurable disease: All other lesions, including small lesions (longest diameter <10 mm at baseline or pathological lymph nodes with short axis ≥10 mm but <15 mm). Truly nonmeasurable lesions include bone lesions, leptomeningeal disease, GEJ masses, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses or organomegaly detected on physical examination that cannot be measured by CT or MRI.

Previously irradiated lesions**;

skin lesions assessed by clinical

examination

Brain metastases

* Nodes with a short axis of less than 10 mm are considered nonpathological and should not be recorded or followed as nontarget lesions.

**Local postradiation changes can affect lesion size. Therefore, previously irradiated lesions are not considered measurable and must be selected as nontarget lesions (NTLs) at baseline and followed as part of the NTL assessment.

Special cases: Lytic bone lesions or mixed lytic–blastic lesions with an identifiable soft-tissue component may be considered measurable when that component meets the measurability criteria. Blastic bone lesions are nonmeasurable. Cystic metastases may be considered measurable if they meet radiological size criteria; however, noncystic lesions should be preferentially selected as target lesions when present in the same patient.

Target lesions: At baseline, up to five measurable lesions representative of all involved sites (no more than two per organ) that are suitable for accurate, reproducible measurement should be identified as target lesions (TLs).

Nontarget lesions: All other lesions or sites of disease not designated as target lesions (TLs) must be identified as nontarget lesions (NTLs) at baseline.

3. Assessment Methods

The same assessment method and technique should be used to characterize each lesion identified and documented at baseline and during follow-up visits.

Modified RECIST Version 1.1

The assessment methods are summarized below. Methods excluded from tumor assessment in this study are highlighted, with supporting rationale provided.

Summary of Assessment Methods

Target Lesions	Nontarget Lesions	New Lesions
CT (preferred) MRI	CT (preferred) MRI Clinical Examination Radiography, Chest X-ray	CT (preferred) MRI Clinical Examination Radiography, Chest X-ray Ultrasonography Bone Scan

CT = computed tomography; PET/CT = positron emission tomography/computed tomography; MRI = magnetic resonance imaging.

3.1 CT and MRI

CT and MRI are generally considered the most reproducible and appropriate imaging methods for measuring target lesions (TLs), assessing nontarget lesions (NTLs), and identifying new lesions. CT of the chest, abdomen, and pelvis is recommended for baseline and follow-up assessments, preferably with intravenous contrast. MRI should be used when CT is unavailable or medically contraindicated and is the preferred modality for assessing brain lesions.

3.2 Clinical Examination

Physical examination will not be used to measure TLs in this study. A clinically detected lesion may be selected as a TL if adequately assessed by CT or MRI. Physical examination may be used to assess NTLs and identify new lesions.

3.3 Radiography

3.3.1 Chest X-ray

Because TLs will be assessed using CT or MRI, chest radiographs will not be used for TL measurements. Chest radiography may be used to assess NTLs or detect new lesions.

3.3.2 Plain Radiography

In this study, plain radiography may be used to assess bone nontarget lesions and identify the presence of new bone lesions.

3.4 Ultrasonography

Ultrasound will not be used to assess TLs or NTLs because it is operator-dependent, subjective, and insufficiently reproducible for accurate tumor measurement. Ultrasound may be used to identify suspected new lesions, but findings prompted by new clinical symptoms should be confirmed by CT or MRI.

3.5 Endoscopy and Laparoscopy

Endoscopy and laparoscopy are not used for tumor assessment in this study because they have not been validated for this purpose.

3.6 Tumor Markers

Tumor markers will not be used for tumor response assessment according to modified RECIST Version 1.1 in this study.

3.7 Cytology and Histology

Histology will not be used for tumor response assessment under modified RECIST 1.1. If measurable disease meets response or stable disease criteria but a new or worsening effusion appears during treatment, cytological confirmation may be necessary to determine whether the effusion is neoplastic. Cytology may distinguish progressive disease from treatment-related effusion in this setting.

3.8 Radionuclide Bone Scan

Bone lesions identified on radionuclide bone scans at baseline and confirmed by baseline CT, MRI, or radiography should be recorded as NTLs and followed by the same method. During this study, radionuclide bone scanning may be used at follow-up to assess for new bone

lesions. A new focus of increased tracer uptake on a postbaseline bone scan may be recorded as a new lesion if absent at baseline and considered by the investigator to represent a clinically meaningful new site of malignant disease and true progression. Equivocal findings should be confirmed using CT, MRI, or radiography.

3.9 FDG-PET Scan

As FDG-PET assessment is not part of the RECIST framework, FDG-PET scans will not be used for tumor response assessment in this study.

4. Tumor Response Assessment

4.1 Assessment Schedule

Baseline imaging should cover all sites to which the disease is known to metastasize and other regions indicated by patient-specific signs and symptoms. It should be performed within 28 days before the first dose. Follow-up assessments will

occur at screening (before neoadjuvant treatment), after neoadjuvant therapy (before surgery), and after surgery (before adjuvant therapy), then every 12 weeks (±1 week) for the first year from the postoperative adjuvant baseline scan and every 24 weeks (±2 weeks) thereafter until objective progression or recurrence.

Other sites of suspected new disease should also be imaged as appropriate during follow-up.

If an unscheduled assessment shows no progression, every effort should be made to return to the planned visit schedule. Adherence to a common assessment schedule helps minimize bias arising from differences in imaging frequency between patients.

4.2 Target Lesions (TLs)

4.2.1 Documentation of Target Lesions

At baseline, up to five measurable lesions representing all involved sites, with no more than two lesions per organ (including lymph nodes), should be designated as TLs. Selection should consider lesion size (longest diameter for nonnodal lesions and short axis for lymph nodes) and the ability to repeat measurements reliably. When the largest lesion cannot be measured reproducibly, the next largest suitable lesion may be selected. The anatomical location and longest diameter of each nonnodal TL, or short-axis diameter of each nodal TL, must be documented in millimeters. The sum of TL diameters at baseline will be recorded as the baseline sum of diameters; the corresponding sum at each follow-up will also be calculated and documented.

Special Cases:

For TLs measurable in two or three dimensions, always record the longest diameter. For pathological lymph nodes, record the short-axis diameter. When CT/MRI slice thickness exceeds 5 mm, the minimum measurable lesion size at baseline should be at least twice the slice thickness. Record a diameter of 0 mm if a lesion disappears completely. If a TL divides into two or more components, record the sum of the component diameters. If two or more TLs merge, record the diameter of the confluent lesion for one TL and 0 mm for the others. If a TL remains visible but too small to measure, assign a default of 5 mm; if an accurate measurement below 5 mm can be obtained, record the actual value.

When a TL is faintly visible but too small for reliable measurement, assign 5 mm by default; record a lower value if accurately measurable. If a TL is too large to measure precisely, provide an estimated lesion size. Where feasible, continue to record TL dimensions after local intervention (e.g., radiotherapy, embolization, or surgery).

4.2.2 Assessment of Target Lesions

This section defines the criteria used to determine objective tumor response at each visit for TLs.

Table 4.2.2 Assessment of Target Lesions

Complete Response (CR)	Disappearance of all target lesions after baseline. Any pathological lymph node selected as a target lesion must have a reduction in short axis to less than 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of TL diameters, taking the baseline sum of diameters as reference.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	Progressive disease in target lesions requires at least a 20% increase in the sum of diameters relative to the smallest recorded sum during the study (including baseline if it is the smallest). In addition to this relative increase, the sum must also demonstrate the following: an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only if the target lesion was not assessed or could not be assessed at this visit, or if an intervention was performed on a lesion. Note: if the sum of diameters meets the criteria for progressive disease, the lesion cannot be categorized as a target-lesion response.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; NA = not applicable (only when no TLs/NTLs were present at baseline).

4.3 Assessment of Nontarget Lesions (NTLs)

All other lesions or disease sites not selected as TLs at baseline must be designated as NTLs. Measurements are not required, but their status should be followed at subsequent visits. At each visit, the investigator must record an overall NTL response.

This section defines the criteria for determining and documenting the overall NTL response at each site assessment.

Table 4.3.1 Assessment of Nontarget Lesions

Complete Response (CR)	Disappearance of all nontarget lesions after baseline. All lymph nodes must be nonpathological in size (short axis <10 mm).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progression (PD)	Unequivocal progression of existing nontarget lesions. Unequivocal progression may result from marked progression in one lesion or several lesions. In all cases, progression must be clinically meaningful enough that a physician would consider changing or discontinuing treatment.
Not Evaluable (NE)	Appropriate only when one or more nontarget lesions were not assessed and, in the investigator's judgment, an overall nontarget-lesion assessment cannot be made at this visit. Note: For participants with no target lesions at baseline, NE is appropriate if any nontarget lesion was not assessed at this visit and the criteria for progression have not been met.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; NA = not applicable (only when no TLs/NTLs were present at baseline).

4.4 New Lesions

Details of new lesions, including the assessment date, must be recorded. The presence of one or more new lesions constitutes progression. Lesions detected at follow-up in anatomical locations not imaged at baseline are considered new lesions and indicate

progression. A new lesion must be unequivocal and not attributable to differences in imaging technique, a change in modality, or a nonmalignant finding. If a suspected new lesion is equivocal, for example because of its small size, treatment and imaging should continue until its presence is confirmed. If confirmed on repeat imaging, the date of the initial scan should be assigned as the progression date.

4.5 Symptomatic Deterioration

Symptomatic deterioration is not an objective response category; it is a potential reason for discontinuing study treatment. Patients who discontinue treatment because of symptomatic deterioration without objective evidence of progression should, where feasible, continue tumor assessments until objective progression is documented.

4.6 Assessment of Overall Response at Each Visit

Overall visit response is determined using the algorithm presented in Table 4.6.

Table 4.6 Overall Visit Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	None	CR
CR	NA	None	CR
NA	CR	None	CR
CR	Non-CR/Non-PD	None	PR
CR	NE	None	PR
PR	Non-PD or NE	None	PR
SD	Non-PD or NE	None	SD
NA	Non-CR/Non-PD	None	SD (Non-CR/Non-PD)
NE	Non-PD or NE	None	NE
NA	NE	None	NE
PD	Any	Present or Absent	PD
Any	PD	Present or Absent	PD
Any	Any	Present	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease;

NE = not evaluable; NA = not applicable (only when no TLs/NTLs were present at baseline).

5. Radiologic Imaging Specifications

The following recommendations are intended for clinical trial use. Standardized CT and MRI acquisition protocols support comparability within and between trials regardless of the imaging site.

5.1 CT Scans

CT scans of the chest, abdomen, and pelvis must provide contiguous coverage of the relevant anatomical regions. The most important acquisition parameters for optimal tumor assessment under modified RECIST 1.1 are anatomical coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomical coverage:

For most solid tumors, optimal imaging coverage includes the chest, abdomen, and pelvis. It should encompass known common sites of metastasis and other regions suggested by individual signs or symptoms. Because lesions later detected outside the baseline imaging field may be considered new progressive disease, imaging coverage must be planned carefully and maintained consistently at baseline and follow-up to support reproducible tumor measurement and detection of new disease.

b. Intravenous contrast administration:

Optimal visualization and measurement of solid-tumor metastases require consistent administration of intravenous contrast, including dose, infusion rate, and timing. Most abdominal imaging should be obtained during the portal venous phase at approximately the same postinjection interval for each examination. An appropriate contrast agent and dose must be selected to ensure consistent enhancement of metastatic lesions. Use of the same technique at baseline and follow-up is particularly important. For patients who develop a contraindication to contrast after baseline contrast-enhanced CT, the choice between noncontrast CT and MRI (with or without

enhancement) should depend on tumor type and anatomical location and should preserve comparability with previous scans wherever possible. Individual cases should be discussed with a radiologist to determine whether modalities are interchangeable or, if not, whether subsequent assessments should be deemed nonevaluable. Care is needed because measured lesion dimensions and interpretation of nontarget disease or new lesions may change with the modality. Oral contrast is recommended where helpful for delineating and distinguishing abdominal structures.

If iodinated contrast is contraindicated at baseline or at any point during the study, the preferred approach is noncontrast CT of the chest and contrast-enhanced MRI of the abdomen and pelvis. If MRI is unavailable, noncontrast CT of the chest, abdomen, and pelvis may be used. MRI is preferred for assessment of brain metastases.

c. Slice thickness and reconstruction interval:

CT scans should preferably be acquired as contiguous 5-mm slices, which are assumed in the RECIST measurability recommendations. Exceptionally, a site may obtain medically acceptable scans with a slice thickness >5 mm; in that event, the minimum measurable lesion dimension at baseline should be at least twice the baseline slice thickness. Appropriate window settings must be reviewed, particularly lung and soft-tissue windows in chest imaging. TLs should be measured with the same window setting throughout repeated assessments. All images obtained at each examination, rather than a selection of images showing apparent lesions, should be included in the review.

5.2 MRI Scans

MRI provides excellent contrast and spatial and temporal resolution, but acquisition variables can substantially affect image quality, lesion conspicuity, and measurement. Availability also differs across sites. The same modality used at baseline should be retained for follow-up, with lesions assessed using the same pulse sequences. In general, axial abdominal and pelvic MRI should include T1- and T2-weighted sequences with gadolinium enhancement as

appropriate. Field of view, matrix, number of excitations, phase-encoding steps, fat suppression, and rapid sequences should be optimized for the body region and scanner. Detailed pulse-sequence specifications for every scanner and disease are beyond the scope of this appendix. Ideally, the same scanner type and closely matched acquisition protocols should be used at follow-up. Breath-hold techniques should be used for body MRI where feasible. For these reasons, CT remains the preferred imaging technique.

Appendix C. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status

0	Fully active; able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair throughout the day.
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Appendix D. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0

NCI CTCAE version 5.0 is available at

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.ht

m.

Spiral-bound copies of NCI CTCAE version 5.0 were obtained from CTEP/DCT/NCI and retained for AE grading by site trial staff, nursing and medical personnel, and the investigator-sponsor's clinical and data management teams.

Specific questions regarding the Common Toxicity Criteria

(CTC) should be directed to ncictephelp@ctep.nci.nih.gov.

Appendix F. Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

Definition of Women of Childbearing Potential

Woman of Childbearing Potential:

A premenopausal woman who has experienced menarche, has not been permanently or surgically sterilized, and is capable of becoming pregnant.

Woman Not of Childbearing Potential:

Women who are permanently or surgically sterile or postmenopausal (see definitions below): Permanent sterilization includes hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy, but not bilateral tubal ligation. Although tubal ligation is a highly effective contraceptive method, it does not

completely eliminate the possibility of pregnancy (ligation occludes the fallopian tubes without surgically removing them).

- Women who have undergone tubal ligation must be treated as women of childbearing potential for the purposes of this study (e.g., pregnancy testing must be performed as required by the protocol).
- A woman with amenorrhea lasting more than 12 months without another medical cause is considered postmenopausal. The following age-specific criteria apply:
    a. Women under 50 years are considered postmenopausal if amenorrhea persists for at least 12 months after cessation of exogenous hormonal therapy and LH and FSH levels are within the postmenopausal range.
    b. Women aged 50 years or older are considered postmenopausal if amenorrhea persists for at least 12 months after cessation of all exogenous hormonal therapy.

Acceptable Contraceptive Methods:

A highly effective contraceptive method is defined in Note 3 of ICH Guidance M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) as a method with a low failure rate (e.g., <1% per year) when used consistently and correctly.
Women should be stable on their selected contraceptive method for at least two weeks before study enrollment. Examples of generic and trade names of contraceptives are provided. As brand names may differ, investigators must verify the generic components of all contraceptive products to ensure their suitability.

Acceptable contraceptive methods are as follows:

- Complete sexual abstinence (abstinence must be maintained throughout the study and follow-up periods).
- Vasectomized partner combined with use of a male condom (abstinence must be maintained throughout the study and follow-up periods).

- Tubal ligation combined with use of a male condom.
- Copper-banded intrauterine device (IUD) combined with use of a male condom.
- Levonorgestrel-releasing intrauterine system (IUS; e.g., Mirena®) combined with use of a male condom.
- Medroxyprogesterone injection (e.g., Depo-Provera®) combined with use of a male condom.
- Etonogestrel implant (e.g., Implanon® or Norplant®) combined with use of a male condom.
- Standard-dose or low-dose combined oral contraceptive pill combined with use of a male condom.
- Norelgestromin/ethinylestradiol transdermal patch (e.g., Ortho Evra®) combined with use of a male condom.
- Ethinylestradiol/etonogestrel vaginal ring (e.g., NuvaRing®) combined with use of a male condom.
- A progestogen-only oral contraceptive containing desogestrel (with Cerazette® identified as the only highly effective progestogen-only formulation) used together with a male condom.

Recommended Evaluation of Elevated ALT During Immune Checkpoint Inhibitor Treatment in Clinical Trials[a]

Recommended Evaluation	**Alternative Causes of Abnormal Liver Tests**
Initial Evaluation	
Comprehensive history of symptoms, preexisting conditions, concomitant medications, dietary and nutritional supplements, strenuous exercise or muscle injury, alcohol intake, and illicit substance use.	Systemic infection/sepsis; ischemic/congestive hepatic injury; gallstone disease; alcohol-related liver disease; muscle injury/rhabdomyolysis; acetaminophen toxicity; drug-induced liver injury (DILI) from other medications, herbs, or dietary supplements.
Serum CK	Muscle injury/rhabdomyolysis[b]

Anti-HAV IgM	Acute HAV infection
HBsAg • Anti-HBc IgG, IgM; HBV DNA	Acute hepatitis B; exacerbation of chronic hepatitis B
Anti-HCV • HCV RNA(PCR)	Acute hepatitis C Exacerbation of chronic hepatitis C[c]
Anti-HEV (IgG, IgM); HEV RNA[d]	Acute hepatitis E
ANA, ASMA • Quantitative immunoglobulins (IgG, IgM, IgA)	Autoimmune hepatitis[e]
Hepatobiliary imaging (ultrasonography, CT, MRI, MRCP)[f]	Biliary disorders; pancreatitis; gallstones; portal/hepatic vein thrombosis; liver metastases
Additional Evaluation	
Serologic testing for EBV, CMV, and HSV. • Acute- and convalescent-phase serology may be required. • EBV DNA, CMV DNA, and HSV DNA by PCR; liver biopsy may be needed to establish HSV infection.	Hepatic injury caused by CMV, EBV, or HSV
Further Testing	
Anti-LKM-1	Autoimmune hepatitis
Serum ethanol • Urine ethyl glucuronide and ethyl sulfate[h]; serum phosphatidylethanol[i]	Alcohol-related liver disease
Serum acetaminophen level; acetaminophen protein adducts	Acetaminophen toxicity
Blood pressure, pulse, electrocardiogram, echocardiography, and cardiology consultation	Ischemic or congestive hepatic injury
Urine toxicology screen	Cocaine, amphetamines, opioids, and other illicit drug-induced hepatotoxicity
Anti-HDV	Hepatitis D
Blood or urine culture	Systemic infection; sepsis
Serum ceruloplasmin; serum copper	Wilson disease

Slit-lamp examination for Kayser–Fleischer rings; genetic testing	

[a] The extent and type of diagnostic workup may vary according to the patient's history, severity of liver injury, underlying conditions, and geographic setting.

[b] Serum AST is generally, but not invariably, higher than ALT.

[c] Acute hepatitis C may be anti-HCV negative but HCV RNA positive.

[d] If anti-HEV IgM is positive, consider confirmatory HEV RNA testing by nested PCR.

[e] Liver biopsy may be necessary to confirm the diagnosis of autoimmune hepatitis.

[f] Magnetic resonance cholangiopancreatography may be recommended for cholestatic liver injury.

[g] Based on clinical history and judgment.

[h] Alcohol consumption within the previous 3–5 days.

[i] Alcohol consumption within the previous 3 weeks.

Note: Adapted from: ALT = alanine aminotransferase; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; CMV = cytomegalovirus; CK = creatine kinase; CT = computed tomography; DILI = drug-induced liver injury; DNA = deoxyribonucleic acid; EBV = Epstein–Barr virus; EtOH = ethyl alcohol; HAV = hepatitis A virus; HBc = hepatitis B core antigen; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LKM1 = liver–kidney microsomal antibody type 1; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; RNA = ribonucleic acid.

Other Immune-Mediated Reactions

Severity Grade of Event (see the applicable NCI CTCAE version specified in the protocol for definitions of CTC grade/severity)	**Dose Modification**	**Toxicity Management**

All Grades	Note: Although inflammatory or immune-mediated events can occur in almost any organ system, some are not specifically covered by this guidance (e.g., immune thrombocytopenia, hemolytic anemia, uveitis, or vasculitis).	For immune-mediated events not listed under "Specific Immune-Mediated Reactions," contact the study physician. Conduct a thorough assessment, including consultation with appropriate specialists, to exclude other etiologies (e.g., disease progression, concomitant medications, or infection), consistent with local standards of care. as clinically indicated.
Grade 1	No dose modification is required.	Monitor as clinically indicated.
Grade 2	Withhold the study drug/study regimen until resolution to Grade 1 or lower or to baseline. If toxicity worsens, manage as Grade 3 or 4. Treatment may be resumed if the event has stabilized at Grade 1 or lower after completion of steroid tapering. Consider permanent discontinuation of study drug or therapy in Grade 2 cases associated with substantial morbidity or mortality risk that do not improve promptly to Grade 1 after systemic	**For Grades 2, 3, and 4, manage according to institutional standards, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO).** Follow the applicable recommendations.

	corticosteroid treatment and complete tapering.	
Grade 3	Permanently discontinue the study drug/study regimen.	
Grade 4	Permanently discontinue the study drug/study regimen.	

Note: If applicable to an early-phase study, the following statement may be added: "Discuss all Grade ≥2 events with the study physician."
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute.

Infusion-Related Reactions

Severity Grade of Event (see the applicable NCI CTCAE version specified in the study protocol)	**Dose Modification**	**Toxicity Management**
All Grades	**General Guidance**	**At the investigator's discretion, manage according to institutional standards for all grades and monitor patients for signs and symptoms of** Manage according to standard practice. Infusion-related reactions (e.g., fever and/or rigors, flushing and/or pruritus, changes in

		heart rate or blood pressure, dyspnea or chest discomfort, or rash) and anaphylaxis (e.g., systemic reactions, including urticaria, angioedema, wheezing, hypotension, or tachycardia.
Grades 1–2	**For Grade 1, the infusion rate of the study drug/study regimen** may be reduced by 50% or the infusion temporarily interrupted until the event resolves. **For Grade 2, the infusion rate of the study drug/study regimen** may be reduced by 50% or the infusion temporarily interrupted until the event resolves. Subsequent infusions may be administered at 50% of the initial infusion rate.	**For Grade 1 or 2 reactions, acetaminophen and/or an antihistamine may be given according to institutional standards at the investigator's discretion.** Consider premedication before subsequent doses in accordance with institutional standards. Steroids should not be used routinely as premedication for infusion-related reactions of Grade 2 or lower.
Grades 3–4	**For Grade 3 or 4 reactions, permanently discontinue the study drug/study regimen.**	**For Grade 3 or 4 reactions, manage severe infusion-related reactions according to institutional**

		standards (e.g., intramuscular epinephrine followed by intravenous diphenhydramine and famotidine, and intravenous glucocorticoids).

CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; IV = intravenous; NCI = National Cancer Institute.

Non–Immune-Mediated Reactions

Adverse Event Severity Grade (see the applicable NCI CTCAE version specified in the protocol for definitions of CTC grade/severity)	**Dose Modification**	**Toxicity Management**
All Grades	Note: No dose adjustment is needed for AEs considered unrelated to study treatment (e.g., events attributable to underlying disease) or laboratory abnormalities considered not clinically significant. No dose modification is required.	Treat according to institutional standards of care.
Grade 1	No dose modification is required.	Treat according to institutional standards of care.

Grade 2	Withhold the study drug/study regimen until resolution to Grade 1 or lower or to baseline.	Treat according to institutional standards of care.
Grade 3	Withhold the study drug/study regimen until resolution to Grade 1 or lower or to baseline. If the event improves to Grade 2 or lower within 7 days or Resume study drug or study therapy for AEs that resolve to Grade ≤1 or baseline within 14 days. Otherwise, discontinue study drug or therapy. Permanent discontinuation may be considered at the investigator's discretion. the study drug/study regimen may be permanently discontinued at the investigator's discretion.	Treat according to institutional standards of care.
Grade 4	Discontinue the study drug/study regimen. (For Grade 4 laboratory abnormalities, the decision to discontinue should be based on associated clinical signs/symptoms and the investigator's clinical judgment .)	Treat according to institutional standards of care.

Note: If applicable to an early-phase study, the following statement may be added: "Discuss adverse events of Grade ≥2 with the study physician."

AE = adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.