CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Study to Evaluate the Safety and Tolerability of Andecaliximab (GS-5745) as Monotherapy and in Combination with Anti-Cancer Agents in Japanese Subjects with Gastric or Gastroesophageal Junction Adenocarcinoma	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
Clinical Trials.gov Identifier:	02862535	
Indication:	Gastric Adenocarcinoma	
Protocol ID:	GS-US-296-1884	
Gilead Clinical Program Manager:	Name: Telephone: Email:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Email:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	5 February 2016 13 May 2016 15 November 2016 14 July 2017

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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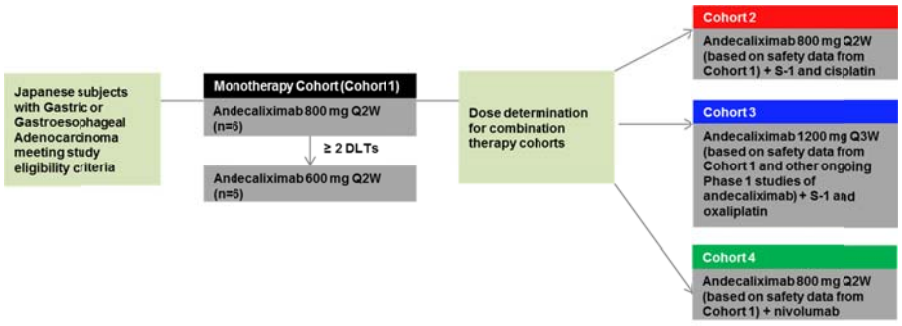
Study Title:	A Phase 1b Study to Evaluate the Safety and Tolerability of Andecaliximab (GS-5745) as Monotherapy and in Combination with Anti-Cancer Agents in Japanese Subjects with Gastric or Gastroesophageal Junction Adenocarcinoma
Clinical Trials.gov Identifier:	02862535
Study Centers Planned:	Approximately 4 centers in Japan
Objectives:	The primary objective of this study is: • To characterize the safety and tolerability of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with inoperable advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma The secondary objectives of this study are: • To characterize the pharmacokinetics (PK) of andecaliximab • To evaluate the formation of anti-andecaliximab antibodies The exploratory objectives of this study are: [redacted]
Study Design:	This is a Phase 1b, open-label, multicenter study to evaluate the safety and tolerability of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with inoperable advanced or recurrent gastric or GEJ adenocarcinoma.

The study will comprise 4 cohorts, 1 monotherapy cohort and 3 combination therapy cohorts.

- Cohort 1 is andecaliximab monotherapy
- Cohort 2 is combination therapy of andecaliximab with S-1 and cisplatin (SP)
- Cohort 3 is combination therapy of andecaliximab with S-1 and oxaliplatin (SOX)
- Cohort 4 is combination therapy of andecaliximab with nivolumab

Study Schema



Abbreviations: DLT = dose limiting toxicity; Q2W = every 2 weeks; Q3W = every 3 weeks

Cohort 1: Andecaliximab Monotherapy

Up to 6 Japanese subjects with inoperable advanced or recurrent gastric or GEJ tumors will be enrolled to receive andecaliximab 800 mg via intravenous (IV) infusion over approximately 30 (± 5) minutes every two weeks (Q2W) until disease progression.

The dose limiting toxicity (DLT) assessment window is 28 days. The safety and tolerability of the 800 mg dose will be assessed after all 6 subjects have been followed for at least 28 days after the first infusion of andecaliximab. If 2 or more subjects within the cohort of 6 subjects experience DLTs during the first 28 days of andecaliximab dosing, up to 6 additional subjects will be enrolled at a reduced dose of 600 mg Q2W. If a subject is withdrawn from the study for any reason other than a DLT prior to completion of the DLT assessment window, a replacement subject will be enrolled. If 2 additional DLTs occur at 600 mg, andecaliximab will be considered unsafe and will be discontinued.

A DLT is a toxicity defined below, considered possibly related to andecaliximab, occurring during the DLT assessment window (Day 1 through Day 28).

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) for > 7 days, or febrile neutropenia (per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 definition) regardless of duration.
- Primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is not permitted during the first cycle of study treatment. G-CSF may be used at any time at the discretion of the investigator in response to treatment emergent neutropenia. Subjects who develop Grade 4 neutropenia related to andecaliximab will be considered a DLT (subjects may receive G-CSF at the discretion of the investigator in response to treatment emergent neutropenia).
- Grade 4 thrombocytopenia, Grade 3 thrombocytopenia associated with bleeding, or Grade 3 or 4 thrombocytopenia requiring platelet transfusion
- Grade 3 or 4 non-hematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care)
- Non-hematologic toxicity of ≥ Grade 2 (at any time during treatment) that, in the judgment of the investigator and the medical monitor, is dose-limiting
- Treatment delay of > 14 days due to unresolved toxicity

For certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion between the investigator, medical monitor, and the sponsor may take place to determine if this adverse event (AE) should be assessed as a DLT necessitating dose reduction.

After all 6 subjects in Cohort 1 have completed the 28-day DLT assessment window and 0 or 1 out of 6 subjects experienced DLTs, an internal safety review team (SRT) will conduct a review of the safety and PK data from all subjects prior to proceeding with the combination therapy cohorts to evaluate andecaliximab with other anti-cancer agents.

The SRT completed their review of all available clinical safety and PK data for 6 DLT-evaluable subjects in Cohort 1 on 11 May 2017 and determined the dose for the combination therapy cohorts (Cohorts 2 and 4) to be 800 mg andecaliximab Q2W. See Section 1.3 for rationale of dose selection for Cohort 3 (1200 mg andecaliximab Q3W). The internal SRT consisted of Gilead study team members including the Medical Monitor, representatives from Clinical Operations, Drug Safety and Public Heath (DSPH), and Biostatistics.

Cohorts 2, 3, and 4: Andecaliximab Combination Therapy Cohorts

Japanese subjects with inoperable advanced or recurrent gastric or GEJ tumors will be enrolled in each combination therapy cohort to receive andecaliximab in combination with anti-cancer agents. Dosage and frequency of treatment in these cohorts will be as follows:

- Cohort 2: Combination therapy andecaliximab and SP
  - Andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression. The dose is based on safety data from Cohort 1. Andecaliximab treatment will be administered in 28-day cycles.
  - S-1 administered orally twice daily: dosage and regimen will be based on subject condition, investigator discretion, institutional practice and/or the in-country label
  - Cisplatin administered by IV infusion on Day 8 of every 5 weeks: dosage and regimen will be based on subject condition, investigator discretion, institutional practice and/or the in-country label
  - Up to 6 subjects will be enrolled in this cohort
- Cohort 3: Combination therapy andecaliximab and SOX
  - Andecaliximab 1200 mg via IV infusion over approximately 30 (± 5) minutes every 3 weeks (Q3W) until disease progression. The dose is based on safety data from Cohort 1 and other ongoing phase 1 studies of andecaliximab. Andecaliximab treatment will be administered in 21-day cycles.
  - S-1 administered orally twice daily at 80 mg/day for body surface area (BSA) $< 1.25m^2$, 100 mg/day for BSA ≥ 1.25 to $< 1.5m^2$, and 120 mg/day for BSA $\geq 1.5m^2$ for the first 14 days of the 21-day cycle
  - Oxaliplatin administered by IV infusion at 100 mg/m^2 over 2 hours on Day 1 of each 21-day cycle
  - Up to 10 subjects will be enrolled in this cohort
- Cohort 4: Combination therapy andecaliximab and nivolumab
  - Andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression. The dose is based on safety data from Cohort 1. Andecaliximab treatment will be administered in 28-day cycles.

— Nivolumab 3 mg/kg Q2W via IV infusion over 60 (± 5) minutes following the completion of andecaliximab administration. Dose is adjusted if the weight changes more than 10% from the baseline dosing weight.

— Up to 10 subjects will be enrolled in this cohort

For Cohorts 1, 2, and 4, computed tomography (CT) or magnetic resonance imaging (MRI) scans will be performed every 8 weeks to evaluate response to treatment by RECIST v1.1. For Cohort 4, response to treatment will also be evaluated using immune related response criteria recommendations {Wolchok 2009}.

For Cohort 3, CT or MRI scans will be performed every 9 weeks to evaluate response to treatment by RECIST v1.1.

The cohort dose levels for andecaliximab and associated combination anti-cancer agents are summarized below:

Cohort	Number of Subjects	Andecaliximab Dose	Andecaliximab Dosing Interval	Combination Anti-Cancer Agent(s)
1	6 to 12	800 mg or 600 mg	Q2W	N/A
2	Up to 6	800 mg	Q2W	SP
3	Up to 10	1200 mg	Q3W	SOX
4	Up to 10	800 mg	Q2W	Nivolumab

Abbreviations: SOX = S-1 and oxaliplatin; SP = S-1 and cisplatin; Q2W = every 2 weeks; Q3W = every 3 weeks

Number of Subjects Planned: Up to 38 subjects

Target Population: Japanese subjects ≥ 20 years of age with histologically confirmed inoperable advanced or recurrent gastric or GEJ adenocarcinoma

Duration of Treatment: For Cohorts 1, 2, and 4, each cycle will be 28 days and will continue in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

For Cohort 3, each cycle will be 21 days, to align with the SOX dosing schedule, and will continue in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 20 years of age

2) Subjects must have been born in Japan and must not have lived outside of Japan for a period >1 year in the 5 years prior to Day 1

3) Subjects must be able to trace their maternal and paternal ancestry of parents and grandparents as ethnically Japanese

4) Histologically confirmed inoperable advanced gastric adenocarcinoma (including adenocarcinoma of the GEJ) or relapsed gastric adenocarcinoma

5) Cohorts 1 (andecaliximab monotherapy), 2 (combination therapy andecaliximab and SP) and 3 (combination therapy andecaliximab and SOX): Human Epidermal Growth Factor Receptor 2 (HER2)-negative tumor (primary tumor or metastatic lesion). Enrollment in Cohort 4 (combination therapy andecaliximab and nivolumab) is not restricted by HER2 status (subjects with HER2-positive, HER2-negative, or unknown HER2 status are eligible).

6) Cohort 1 (andecaliximab monotherapy): Prior antitumor therapy or cytotoxic chemotherapy is acceptable. Subjects who are not eligible to receive standard treatments should enroll on the study. All acute toxic effects of any prior antitumor therapy must be resolved to Grade ≤ 1 (or baseline) before the start of andecaliximab dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).

7) Cohorts 2 (combination therapy andecaliximab and SP) and 3 (combination therapy andecaliximab and SOX): Prior antitumor therapy or cytotoxic chemotherapy for metastatic disease is **not** acceptable. Subjects must be chemo-naive in the metastatic setting. Subjects who relapse during adjuvant chemotherapy or within 180 days after adjuvant chemotherapy for their gastric cancer should not be enrolled.

8) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

9) Life expectancy of > 3 months in the opinion of the investigator

10) Adequate baseline organ function (within 28 days prior to Day 1) as shown in the following table:

Organ System	Parameter	Required Value
Hematopoietic	ANC	$\geq 1.5 \times 10^9$/L
	Platelets	$\geq 100 \times 10^9$/L
	Hemoglobin	Cohorts 1-3: ≥ 8.0 g/dL (not RBC transfusion dependent)
Hepatic	Serum total or conjugated bilirubin	≤ 1.5 x ULN
	Serum AST and ALT	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
Renal	Serum Creatinine	Cohort 1: ≤ 1.5 x ULN Cohorts 2 and 3: ≤ 1.0 x ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; RBC = red blood cell; ULN = upper limit of normal

11) Coagulation: International Normalized Ratio (INR) ≤ 1.5 (unless receiving anticoagulation therapy). Subjects on full-dose oral anticoagulation must be on a stable dose (minimum duration 14 days). If receiving warfarin, the subject must have an INR ≤ 3.0 and no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug). Subjects on low molecular weight heparin will be allowed.

12) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s) (See Appendix 9)

13) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of andecaliximab, throughout the study treatment period, and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s), and to refrain from sperm donation from the start of andecaliximab, throughout the study treatment period, and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s) (See Appendix 9)

14) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

15) Evidence of a personally signed informed consent form

16) In addition to the applicable criteria above, subjects in Cohort 4 (combination therapy andecaliximab and nivolumab) must meet *all* of the following inclusion criteria to be eligible for participation in this study:

a) Measureable gastric or GEJ adenocarcinoma according to RECIST v1.1

b) Subject must have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease. All toxicities attributed to prior anti-cancer therapy other than alopecia or fatigue must have resolved to Grade ≤ 1 (NCI CTCAE Version 4) or baseline

c) Adequate baseline organ function (within 28 days prior to Day 1) as shown in the following table:

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	≥ 9.0 g/dL
Hepatic	Serum total or conjugated bilirubin	≤ 1.5 x ULN
	Serum AST and ALT	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
Renal	Creatinine Clearance	Creatinine clearance (CLcr) ≥ 60 mL/min, estimated based on the Cockroft-Gault formula or measured based on 24 hour urine collection or other reliable method

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CLcr = creatinine clearance; RBC = red blood cell; ULN = upper limit of normal

d) Subjects not receiving anticoagulant medication must have an activated partial thromboplastin (aPTT) ≤ 1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the aPTT is within therapeutic limits (according to the medical standard in the institution) and the subject has been on stable dose of anticoagulants for at least 1 week at the time of enrollment

e) Thyroid function tests (thyroid-stimulating hormone (TSH), T3, free T4) should be within normal limits. Subjects with underlying thyroid disease are eligible if they are receiving appropriate medication and are clinically stable.

Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria will not be enrolled in this study:

1) History or evidence of a clinically significant disorder, condition, or disease that, in the opinion of the investigator and medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion
2) Pregnant or lactating. Enrollment of lactating females after discontinuation of breastfeeding is not acceptable.
3) Subjects with known central nervous system (CNS) metastases, unless metastases are treated and stable and the subject does not require systemic steroids
4) Radiotherapy within 28 days of Day 1; subjects given palliative radiotherapy to peripheral sites (eg, bone metastasis) may enter the study before 28 days have elapsed if subject has recovered from any acute reversible effects
5) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of Day 1
6) History of major surgery within 28 days of Day 1
7) Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics
8) Cohort 1 (andecaliximab monotherapy): Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of Day 1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{½}$ > 10 days)
9) Clinically significant bleeding within 28 days of Day 1
10) Subjects known to be positive for human immunodeficiency virus (HIV), hepatitis C infection (per local standard diagnostic criteria), or acute or chronic hepatitis B infection (per local standard diagnostic criteria)
11) Known hypersensitivity to any of the study drugs or components or to Chinese hamster ovary cell products or to recombinant human or humanized antibodies

12) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; asymptomatic prostate cancer without known metastatic disease, with no requirement for therapy or requiring only hormonal therapy, and with normal prostate-specific antigen for ≥ 1 year prior to Day 1; adequately treated Stage 1 or 2 cancer currently in complete remission; or any other cancer that has been in complete remission for ≥ 5 years

13) Known alcohol or drug abuse or any other medical or psychiatric condition which contraindicates participation in the study

14) Subject is expected to require any form of systemic or localized antineoplastic therapy while on study

15) In addition to the applicable criteria above, subjects in Cohort 4 (combination therapy andecaliximab and nivolumab) who meet *any* of the following exclusion criteria will not be enrolled in this study:

    a) Subjects who have received only neoadjuvant or adjuvant therapy for gastric adenocarcinoma

    b) Chronic daily treatment with oral corticosteroids (dose of > 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of Day 1. Inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed.

    c) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of Day 1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{½}$ > 10 days)

    d) Prior treatment with anti-CTLA-4 agents (eg, ipilimumab), anti-PD-1 or anti-PD-L1 agents (eg, pembrolizumab, nivolumab, atezolizumab), anti-PD-L2 agents, anti-MMP agents, or other immunomodulatory therapies

    e) Prior therapy with anti-tumor vaccines or other immuno-modulatory antitumor agents

    f) Current or history of pneumonitis or interstitial lung disease

    g) Active known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

    h) History of bone marrow, stem cell, or allogeneic organ transplantation

Study Procedures:

Screening:

Screening will commence with obtaining the subject's signed informed consent, and will occur up to 28 days prior to the first dosing of andecaliximab on Day 1. Screening procedures will include the following: medical history review, physical exam (PE), vital signs, 12-lead electrocardiogram (ECG), ECOG Performance Status, prior/concomitant medication review, blood collection for pregnancy test (females), urinalysis, chemistry, hematology, coagulation, thyroid function tests (for Cohort 4 only: combination therapy andecaliximab and nivolumab), biomarkers, AE assessment, pre-treatment fresh biopsy collection, and CT or MRI (scans obtained as part of standard medical practice up to 28 days prior to Day 1 are acceptable). Baseline tumor lesions will be measured and characterized prior to Day 1 to assess subject disease status prior to beginning treatment.

Treatment: Cohort 1: Andecaliximab Monotherapy

Treatment will occur over cycles comprised of 28 days. Subjects who meet eligibility will undergo CT or MRI scans every 8 weeks. Beginning with Day 1 of Cycle 1, subjects will receive andecaliximab 800 mg by IV infusion over approximately 30 minutes Q2W for a total of 2 infusions per cycle (Day 1 and Day 15 of each 28-day cycle). Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, ECG, collection of blood samples, urine pregnancy, urinalysis, and assessment of AEs at the protocol specified time points.

The DLT assessment window is 28 days. The safety and tolerability of the 800 mg dose will be assessed after all 6 subjects have been followed for at least 28 days after the first infusion of andecaliximab. If 2 or more subjects within the cohort of 6 subjects experience DLTs during the first 28 days of andecaliximab dosing, 6 additional subjects will be enrolled at a reduced dose of 600 mg Q2W. If 2 additional DLTs occur at 600 mg, andecaliximab will be considered unsafe and will be discontinued. Therefore, a total of up to 12 subjects may be enrolled in Cohort 1.

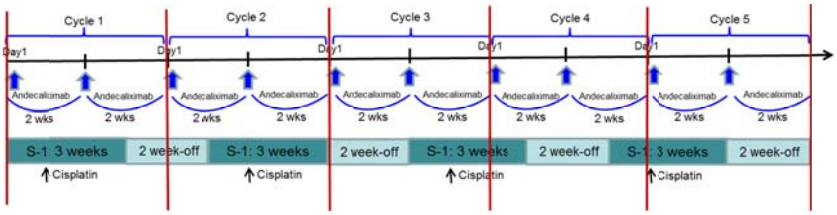
Once all subjects in Cohort 1 have completed the 28-day DLT assessment window and 1 or 0 out of 6 subjects experienced DLTs, an internal SRT will conduct a review of the safety and PK data from all subjects prior to proceeding with the combination therapy cohorts to evaluate andecaliximab with other anti-cancer agents.

The SRT completed their review of all available clinical safety and PK data for 6 DLT-evaluable subjects in Cohort 1 on 11 May 2017 and determined the dose for the combination therapy cohorts (Cohorts 2 and 4) to be 800 mg andecaliximab Q2W. See Section 1.3 for rationale of

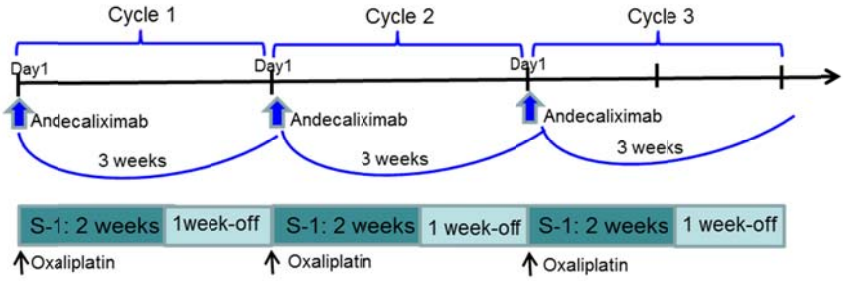
dose selection for Cohort 3 (1200 mg andecaliximab Q3W). The internal SRT consisted of Gilead study team members including the Medical Monitor, representatives from Clinical Operations, Drug Safety and Public Heath (DSPH), and Biostatistics.

Treatment: Cohorts 2, 3, and 4: Andecaliximab Combination Therapy Cohorts

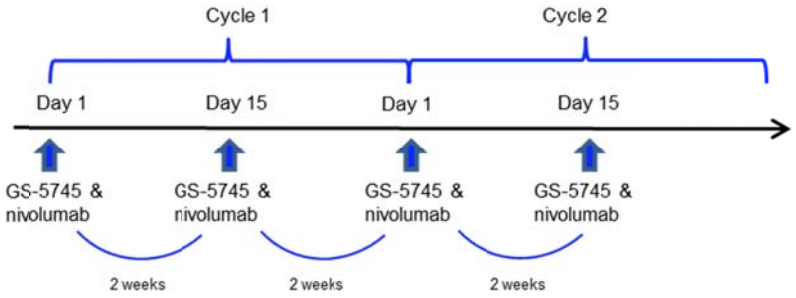
- Cohort 2: combination therapy andecaliximab and SP:
  - Treatment will be administered in 28-day cycles. Subjects who meet eligibility will undergo CT or MRI scans every 8 weeks. Beginning with Day 1 of Cycle 1, subjects will receive andecaliximab 800 mg by IV infusion over approximately 30 (± 5) minutes Q2W, for a total of 2 infusions per cycle (Day 1 and Day 15 of each 28-day cycle).
  - Subjects will also receive S-1 orally twice daily and cisplatin administered by IV infusion on Day 8 of every 5 weeks. The dosage and regimen of chemotherapy will be based on subject condition, investigator discretion, institutional practice and/or the in-country label (see below for the proposed regimen).



- Cohort 3: combination therapy andecaliximab and SOX:
  - Treatment will be administered in 21-day cycles. Subjects who meet eligibility will undergo CT or MRI scans every 9 weeks. Beginning with Day 1 of Cycle 1, subjects will receive andecaliximab 1200 mg via IV infusion over approximately 30 (± 5) minutes Q3W, for a total of 1 infusion per cycle (Day 1 of each 21-day cycle).
  - S-1 administered orally twice daily at 80 mg/day for BSA $< 1.25m^2$, 100 mg/day for BSA ≥ 1.25 to $< 1.5m^2$, and 120 mg/day for BSA $\geq 1.5m^2$ for the first 14 days of the 21-day cycle (see below for regimen)
  - Oxaliplatin administered by IV infusion at 100 mg/m^2 over 2 hours on Day 1 of each 21-day cycle (see below for regimen)



- Cohort 4: combination therapy andecaliximab and nivolumab:
  - Treatment will be administered in 28-day cycles. Subjects who meet eligibility will undergo CT or MRI scans every 8 weeks. Beginning with Day 1 of Cycle 1, subjects will receive andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W, for a total of 2 infusions per cycle (Day 1 and Day 15 of each 28-day cycle) (see below for regimen).
  - Nivolumab 3 mg/kg Q2W via IV infusion over 60 (± 5) minutes following the completion of andecaliximab administration for a total of 2 infusions per cycle (Day 1 and Day 15 of each 28-day cycle, see below for regimen). Dose is adjusted if the weight changes more than 10% from the baseline dosing weight.



Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, ECG, collection of blood samples, urine pregnancy, urinalysis, and assessment of AEs at the protocol specified time points.

Continuation of Treatment:

A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving treatment until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5. If corresponding anti-cancer agent treatment is permanently discontinued (SP, SOX, or nivolumab), andecaliximab must be discontinued. If andecaliximab is discontinued for reasons other than disease progression, subjects may continue to receive corresponding anti-cancer agent treatment (SP, SOX, or nivolumab) until disease progression.

	CT or MRI for assessment of tumor status will be conducted every 8 weeks for Cohorts 1, 2, and 4, and every 9 weeks for Cohort 3. However, tumor response may be assessed prior to the specified every 8- or 9-week time point if clinically indicated.
Test Product, Dose, and Mode of Administration:	Andecaliximab is formulated as a sterile, aqueous buffered solution and is stored at 2 to 8° C in single-use 10 ml vials containing 400 mg andecaliximab at a concentration of 40 mg/ml. Subjects will be administered 800 mg or 600 mg andecaliximab via IV infusion over approximately 30 minutes Q2W or 1200 mg andecaliximab via IV infusion over approximately 30 minutes Q3W.
Criteria for Evaluation:	All subjects who meet eligibility criteria, have signed a consent form, and have begun treatment, will be evaluated for response.
Safety	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital sign measurements, and by the incidence of AEs.
Pharmacokinetics/ Pharmacodynamics	Plasma drug concentrations CCI [redacted] will be analyzed.
Efficacy	The exploratory efficacy endpoints will include: [redacted]

Statistical Methods: Appropriate data analysis sets will be defined.

The Safety Analysis Set is defined as all subjects who receive at least 1 infusion at any dose of andecaliximab.

The Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set is defined as all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Subject characteristics and study results will be described and summarized by treatment dose level/cohort for the relevant analysis sets. Descriptive statistics including sample size, mean, median, standard deviation, and ranges will be summarized for continuous variables, and categorical variables will be summarized using frequency counts and percentages.

The Safety Analysis Set will be used for both the safety and efficacy analyses. Andecaliximab plasma concentrations and parameters will be described and summarized using the PK Analysis Set.

Sample size

The sample size of 6 subjects in Cohort 1 (andecaliximab monotherapy) allows a relatively high probability (> 65%) to observe 2 or more subjects with DLT when the true underlying probability of DLT is greater than 33.3% at current dose level.

Up to 6 subjects will be enrolled in Cohort 1 to receive 800 mg andecaliximab Q2W, and based on safety assessments, an additional 6 subjects may be enrolled in Cohort 1 to receive 600mg andecaliximab Q2W prior to proceeding with the combination therapy cohorts. Based on the dose level selected by Cohort 1, up to 6 subjects will be enrolled in Cohort 2 (combination therapy andecaliximab and SP), and up to 10 subjects will be enrolled in Cohorts 3 (combination therapy andecaliximab and SOX) and 4 (combination therapy andecaliximab and nivolumab), respectively.

Therefore, up to 38 subjects will be enrolled in the study.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AB0041	murine anti-human MMP9 monoclonal antibody
AB0046	murine anti-human MMP9 monoclonal antibody
ADR	adverse drug reaction
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUCinf	area under the concentration versus time curve extrapolated to infinite time, calculated as AUC0-last + (Clast/λz)
AUClast	area under the concentration versus time curve to the last measurable concentration
BSA	body surface area
BUN	blood urea nitrogen
CA 19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
CDDP	cisplatin
CDHP	5 chloro-2,4-dihydroxyphridine
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLcr	creatinine clearance
Clast	last observed quantifiable drug concentration
Cmax	the maximum observed drug concentration
CNS	central nervous system
ConMed	concomitant medication
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocytes
DCR	disease control rate
dL	deciliter
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihyropyrimidine dehydrogenase
DSPH	Drug Safety and Public Health

ECG	electrocardiogram
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOS	end-of-study
EOT	end of treatment
eSAE	electronic serious adverse event reporting system
EU	European Union
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
g	gram
GCP	Good Clinical Practice (Guidelines)
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
β-HCG	beta human chorionic gonadotropin
HCl	hydrochloric acid
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HLGT	high-level group term
HLT	high-level term
HR	hazard ratio
hsCRP	high sensitivity c-reactive protein
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IFNγ	interferon gamma
IHC	immunohistochemistry
IL1β	interleukin-1β
IL-8	interleukin-8
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
irRECIST	immune-related response evaluation criteria in solid tumors

ISH	in-situ hybridization
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
JCOG	Japanese Clinical Oncology Group
Kg	kilogram
KM	Kaplan-Meier methods
L	liter
LAM	lactational amenorrhea method
LLT	lower-level term
LTFU	long term follow-up
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-FU, leucovorin, and oxaliplatin
mg	milligram
min	minute
mL	millileter
mm	millimeter
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MSS	musculoskeletal syndrome
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer cell
NOAEL	no-observed adverse effect levels
NN	non-CR/non-PD
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time

Q2W	every two weeks
Q3W	every three weeks
QA	quality assurance
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SOX	S-1 plus oxaliplatin
SP	S-1 plus cisplatin
SPIRITS	S-1 plus cisplatin vs S-1 in first line treatment of advanced gastric cancer trial
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
t½	half life
TAN	tumor-associated neutrophils
TAM	tumor-associated macrophages
TIMP	tissue inhibitors of metalloproteinases
Tlast	time (observed time point) of Clast
Tmax	time (observed time point) of Cmax
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of the normal range
US	United States
V	distribution volume
VEGF	vasoactive endothelial growth factor
WBC	white blood cell count
Zn	zinc
λz	terminal elimination rate constant; estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug

1. INTRODUCTION

1.1. Background

Matrix metalloproteinases (MMPs) comprise a family of at least 23 Zn2+-dependent proteases which are primarily involved in the degradation and remodeling of the extracellular matrix (ECM) and basement membranes in many normal as well as pathologic biological processes. They are typically grouped based on their structure or their primary substrates and include the gelatinases, collagenases, stromelysins, matrilysins, an elastase, and membrane-type MMP, a group of cell surface tethered proteases {Hu 2007, Mott 2004}. The gelatinases comprise of MMP2 and MMP9, sometimes referred to as type IV collagenases, which are named for their ability to degrade type IV collagen and gelatin, a denatured form of collagen {Chen 2002, Kridel 2001}. The contrasting roles of MMP9 and MMP2 have been revealed in a variety of studies which support a more ubiquitous expression pattern and associated role for MMP2 in normal tissue homeostasis, as compared to disease-induced and pathology-associated expression and activity of MMP9 {Agrawal 2006, Castaneda 2005, Dubois 1999, Garg 2009, Hu 2007, Itoh 2002, Li 2009, Miyazaki 2011, Naito 2005, Santana 2006}. Additional substrates have been identified for MMP9, and the active enzyme can release cytokines, growth factors, and bioactive fragments which in turn modulate inflammation, neovascularization, and matrix remodeling {Hijova 2005}. MMP9 is an inducible MMP that is secreted as a zymogen and activated in a "cysteine switch" mechanism by the cleavage of the peptidoglycan binding domain {Van Wart 1990}. While activation of MMP9 appears to be carried out by other MMPs, the protease's activity is also regulated by the binding of tissue inhibitors of metalloproteinases (TIMPs), primarily by TIMP1 {Imai 1995, Olson 1997, Vempati 2007}. Elevated MMP9 expression in diseased tissue and plasma is associated with several human diseases. The health and largely normal development of the MMP9 knockout mouse has enabled evaluation in a variety of disease models, and these data support a significant role for MMP9 in a variety of inflammatory, fibrotic, and oncologic processes {Dubois 1999, Hu 2007, Itoh 2002, Itoh 1999, Opdenakker 2003}.

More recent studies in the MMP field have revealed diversity in the functional roles of MMPs in disease and normal homeostasis, suggesting a therapeutic opportunity for selective inhibitors. Despite their structural similarities, expression analysis in human disease and data from knockout mice reveal contrasting roles for MMP9 and MMP2 regulation and activity in normal homeostasis and in disease. MMP9 expression is restricted to limited cell types in healthy tissues whereas MMP2 is found to be more constitutively expressed {Hu 2007}. The disease-associated induction and functions of MMP9 render it an attractive therapeutic target. MMP9 expression is elevated in a wide array of tumor types and high MMP9 levels are correlated with poor prognosis in many cancers including gastric cancer {Egeblad 2002, Roy 2009}. MMP9, which is produced by tumor cells as well as by stromal inflammatory cells such as tumor-associated neutrophils (TANs) and macrophages (TAMs) and myeloid-derived suppressor cells (MDSC), has roles in primary tumor growth, metastasis, angiogenesis and tumor-associated immune suppression {Condeelis 2006}. MMP9 expression by these cell types in the context of the tumor microenvironment is also associated with local protumorigenic immune dysregulation.

MMP9-mediated cleavage potentiates the activity of various cytokines such as IL-8 and IL1β and these liberated or activated signaling molecules are then able to promote primary tumor cell growth both directly and indirectly, in addition to promoting ongoing recruitment of suppressive myeloid infiltrating cells {Kessenbrock 2010, Perng 2011, Van den Steen 2000}. The activation of TGFβ from its latent complex by MMP9 could promote further immune suppression and polarization {Dayer 2015, Ge 2006, Jenkins 2008, Wang 2011, Yu 2000}}. Similarly, the cleavage of MICA and ULBPs, ligands for natural killer (NK) cell recognition of tumor cells via NKG2D, can blunt local anti-tumor innate immune responses {Baragano Raneros 2014, Fiore 2002, Peng 2014, Shiraishi 2016, Sun 2011}. MMP9 degrades CXCL9, CXCL10 and CXCL11, 3 ligands for CXCR3 {Cox 2008, Liao 1995, Van den Steen 2003}. This chemokine plays a critical role in the trafficking of Th1 and CD8+ T cells to peripheral sites of Th1-type inflammation and the establishment on Th1 amplification loop mediated by IFNγ and the IFNγ-inducible CXCR3 ligands{Chheda 2016, Mikucki 2015}. MMP9 activity in the tumor microenvironment could thus result in ineffective trafficking of these tumoricidal effector T cells.

Consistent with these published studies, independent analyses at Gilead indicate that MMP9 expression is highly prevalent in gastric cancer, with widespread heterogeneous positivity observed for inflammatory infiltrate and tumor epithelia, as well as subpopulations of other cell types. While MMP9 expression in rodent tumor models is more limited than observed in the human disease, inhibition of tumor growth is observed using murine surrogate antibodies of andecaliximab (GS-5745). In an orthotopic xenograft model or colorectal cancer, treatment of established tumors with anti-MMP9 antibodies targeting the tumor epithelial (human) or stromal (murine) compartments resulted in consistent and significant inhibition of tumor growth across different studies, indicating that both tumor- and stroma-derived MMP9 contributed to tumor growth. Inhibition of tumor growth in this model was associated with reductions in metastasis, vascular endothelial growth factor (VEGF) levels, and tumor-associated fibrillar collagen.

Additional studies in an established orthotopic, syngeneic model of lung tumorigenesis (using Lewis lung carcinoma lines) demonstrated benefit with murine surrogate AB0046 with respect to survival, tumor volume, and altered inflammatory infiltrate. In a rodent NeuT (ERBB2)-driven orthotopic model of breast cancer, which is resistant to programmed cell death protein 1/ programmed death ligand 1 (PD1/PDL1) checkpoint blockade, MMP9 expression was observed in infiltrating myeloid cells. Treatment of established tumors resulted in significant efficacy with respect to tumor volume and transcript and pathway analysis indicated favorable changes in the tumor inflammatory profile, with activation of cytotoxic anti-tumor T-cell activity. Inhibition of MMP9 resulted in reductions in regulatory T cells and M2-polarized, immune suppressive macrophages in the tumor microenvironment. Immunophenotyping of tumor-associated T cells by flow cytometry showed that anti-MMP9 and anti-PDL1 co-treatment increased total T cells (CD3), CD8, and CD4 T cells, and activated effector T cells. T cell checkpoint inhibitors, such as antibodies targeting PD1 and PDL1, have demonstrated substantial and sustained anti-tumor responses consistent with the restoration of anti-tumor T-cell responses, however, their activity is limited to a subset of patients in many tumor types, and a desmoplastic tumor microenvironment, immune suppression by infiltrating myeloid cells, and deficient trafficking of effector T cells have all been suggested as contributing factors {Gajewski 2010, Gajewski 2013, Hegde 2016}.

Inhibition of MMP9 thus offers the potential, in combination, for enhancement of anti-tumor activity.

1.1.1. Gastric Adenocarcinoma

Adenocarcinoma of the stomach is the most common gastrointestinal cancer in the world and the third leading cause of cancer death worldwide {Ferlay 2013}. While the incidence of gastric adenocarcinoma has declined in the United States, gastric cancer remains quite frequent in certain minority populations and it is still the second most common cause of cancer death worldwide. Additionally, the disease continues to be common in Asian countries where nearly 60% of new cases occur {Crew 2006}. Many important differences have been observed in gastric cancer presentation and anatomic location and patient receipt of multi-modality therapy and surgery between Asian countries and the West. When considering disease presentation and location (proximal, body, antrum, pylorus), for example, Asian patients are more likely to be younger at initial diagnosis and have a higher proportion of distal gastric cancers {Gill 2003, Theuer 2000}. Furthermore, Asians were more likely to have localized disease and undergo curative surgery {Kim 2010}. Asians are less likely to have inadequate lymphadenectomy compared to whites {Al-Refaie 2010}. There have been some additional factors such as differences in tumor biology {Theuer 2006, Theuer 2002, Theuer 2000}, and infectious etiologies such as *Helicobacter pylori (H.pylori)* {Fock 2010} that may influence some of these disparities to variable extents.

McCulloch et al {McCulloch 1997, McCulloch 1995} showed that the oncogenes c-erbB2 and TP53 were expressed in similar ways in gastric cancer from Japanese and British patients. However, Theuer et al {Theuer 2002} showed a higher frequency of microsatellite stability in gastric cancer from Japanese compared to American patients. Theuer et al also showed that normal E-cadherin expression was more common in Japanese intestinal type gastric cancer whereas c-erbB2 expression was higher in American gastric cancer patients. This may be important because abnormal E-cadherin expression is associated with adverse features in gastric cancer such as loss of cell–cell adhesion {Becker 1994, Wang 2014b}, and increased c-erbB2 expression may be associated with depth of invasion and metastasis {Mizutani 1993}.

H. pylori infection affects 50% of the world wide population {Marshall 1984}. It has been implicated in the role of chronic gastritis and peptic ulcer disease {Plummer 2004, Wang 2014a}, and the association between *H. pylori* and gastric cancer is also well accepted {American Cancer Society 2005, National Comprehensive Cancer Network (NCCN) 2015, Wang 2014a}. Epidemiologic studies estimate that the risk of gastric cancer in *H. pylori* infected individuals is increased by 20 fold {Brenner 2004}. In general, *H. pylori* seroprevalence is higher in Asians {Fock 2010}. The higher rates of gastric cancer in Asia may occur from a complex interaction between many host factors, environmental factors, and *H. pylori* infection {Fock 2010}.

Surgically curable early gastric cancers are usually asymptomatic and only infrequently detected outside the realm of a screening program (in countries which have a very high incidence of gastric cancer, such as Japan, Venezuela, and Chile). The common presenting symptoms and diagnostic approaches to gastric cancer include weight loss (usually results from insufficient

caloric intake rather than increased catabolism) and may be attributable to anorexia, nausea, abdominal pain, early satiety, and/or dysphagia. Abdominal pain is often present which tends to be epigastric, vague and mild early in the disease but more severe and constant as the disease progresses. Dysphagia is a common presenting symptom in patients with cancers arising in the proximal stomach or at the esophagogastric junction. Patients may also present with nausea or early satiety from the tumor mass or in cases of an aggressive form of diffuse-type gastric cancer called linitis plastica, from poor distensibility of the stomach. They may also present with a gastric outlet obstruction from an advanced distal tumor.

The platinum-fluoropyrimidine doublet is the major back bone of most regimens in Western countries and in East Asia. S-1 is an oral fluoropyrimidine combining tegafur – a prodrug of 5-FU, 5 chloro-2, 4-dihydroxypyridine (CDHP) a reversible inhibitor of dihyropyrimidine dehydrogenase (DPD), and potassium oxonate, an antidiarrheal agent protective against 5-FU gastrointestinal toxicity in a molar ratio of 1:0.4:1. In a landmark Japanese study done by the Japanese Clinical Oncology Group (JCOG) 9912, S-1 was found to be non-inferior to 5-FU alone and irinotecan/cisplatin {Boku 2009}. Given the ease of oral dosing, without compromise in efficacy or excessive toxicity, S-1 was adopted as the standard treatment for metastatic gastric cancer in Japan.

The SPIRITS (S-1 plus cisplatin (SP) vs S-1 in first line treatment of advanced gastric cancer) trial showed that SP resulted in a significantly longer median survival and progression free survival (PFS) compared to S-1 alone {Koizumi 2008}. Both regimens were well tolerated although patients assigned to combination treatment experienced increased Grade 3 and 4 events including neutropenia (40% vs 11%), anemia (26% vs 4), nausea (11% VS 1%) and anorexia (30% vs 6%) {Koizumi 2008}. Based on the SPIRITS trial, the SP doublet remains the standard chemotherapy regimen for advanced gastric cancer in Japan, replacing 5-FU/cisplatin.

{Yamada 2015} compared SP and S-1 plus oxaliplatin (SOX) as first line therapy for advanced gastric cancer. The PFS of SOX was non-inferior to SP in PFS [median, 5.5 versus 5.4 months; hazard ratio (HR) 1.004, 95% confidence interval (CI) 0.840–1.199] while the median overall survival (OS) was 14.1 and 13.1 months, respectively (HR 0.958 with 95% CI 0.803–1.142). In the intention to treat (ITT) population, the HRs in PFS and OS were 0.979 (95% CI 0.821–1.167) and 0.934 (95% CI 0.786–1.108), respectively. Additionally, SOX demonstrated a more favorable safety profile.

Finally, {Kang 2017} demonstrated improved efficacy of nivolumab monotherapy compared to placebo as salvage treatment for patients who have received at least 2 lines of treatment for advanced gastric/gastroesophageal junction (GEJ) adenocarcinoma. The median OS was 5.32 months in the nivolumab arm versus 4.14 months in the placebo arm (HR, 0.63; 95%, CI, 0.50-0.78; p,0.0001) while the median PFS was 1.61 months versus 1.45 months for the nivolumab and placebo arms, respectively (HR, 0.60; 95% CI, 0.49-0.75; p,0.0001).

1.1.2. MMP9 Expression in Oncology

MMP9 is expressed heterogeneously by tumor epithelia as well as infiltrating myeloid cells including myeloid suppressor cells and tumor-associated macrophages and neutrophils, as well as components of fibroblastic stroma, and tumor-associated endothelial cells. Expression of

MMP9 by tumor epithelia in particular has been implicated in many pro-tumorigenic processes and is associated either with loss of tumor suppressor or gain of oncogenic activity, as a temporal response to either changes in local tumor environment, or during processes such as invasion and proliferation. MMP9 expression by tumor-associated macrophages, neutrophils, myeloid-derived suppressor cells and other cell types in the tumor microenvironment is also associated with local pro-tumorigenic immunomodulation and angiogenesis {Farina 2014}. In gastric tumors, MMP9 expression is consistently observed, often in several compartments including tumor epithelia, inflammatory infiltrate and stromal compartments.

1.2. Andecaliximab

1.2.1. General Information

Andecaliximab is a recombinant chimeric IgG_4 monoclonal antibody {Marshall 2015}. It has been engineered to remove T-cell epitopes in an effort to reduce the risk of immunogenicity {Baker 2010, Perry 2008}. Andecaliximab binds with high affinity to human MMP9, but not to other human MMPs. Andecaliximab was derived from the murine anti-human MMP9 monoclonal antibody, AB0041, and shares the same binding characteristics. Andecaliximab and AB0041 cross-react with and inhibit rat and cynomolgus monkey MMP9 but not murine MMP9. AB0046, which cross-reacts with and inhibits murine MMP9, was generated via immunization in MMP9 knockout mice. Epitope mapping analysis revealed that AB0046 binds a similar region in murine MMP9 to that bound by andecaliximab and AB0041 on human MMP9.

For further information on andecaliximab, refer to the current investigator's brochure (IB) for andecaliximab.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Pharmacology

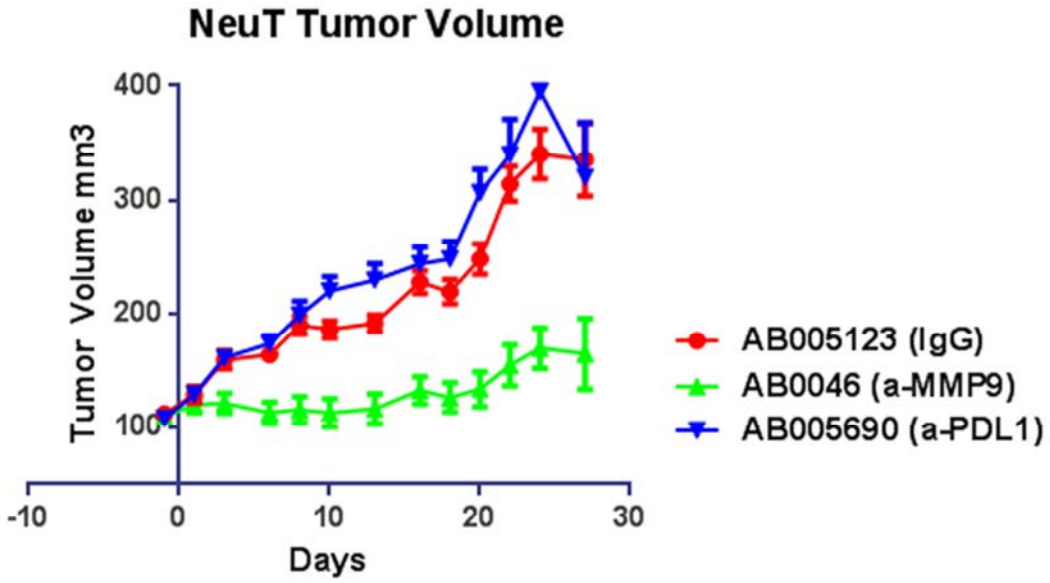
The therapeutic potential of inhibitory antibodies targeting MMP9 was evaluated in orthotopic xenograft and syngeneic models of tumorigenesis. Treatment of established tumors generated orthotopically using the HCT116 colorectal cell line with anti-MMP9 antibodies targeting the tumor epithelial (human) or stromal (murine) compartments resulted in consistent and significant inhibition of tumor growth across different studies, indicating that both tumor- and stroma-derived MMP9 contributed to tumor growth. Inhibition of tumor growth in this model was associated with reductions in metastasis, vascular endothelial growth factor (VEGF) levels, and tumor-associated fibrillar collagen. In an aggressive, disseminated, xenograft pancreatic cancer model (AsPC-1), selective inhibition of MMP9 prolonged survival in combination with either gemcitabine/abraxane or 5-fluorouracil. Additional studies in an established orthotopic, syngeneic model of lung tumorigenesis (using Lewis lung carcinoma lines) demonstrated benefit with murine surrogate AB0046 with respect to survival, tumor volume, and altered inflammatory infiltrate. In a rodent NeuT (ERBB2)-driven orthotopic model of breast cancer (adapted genetically engineered model implanted in the mammary fat pad), MMP9 expression was observed in infiltrating myeloid cells only. As shown below, this model is refractory to PD1/PDL1 checkpoint blockade. Inhibition of MMP9 using AB0046 resulted in significant

efficacy with respect to tumor volume (Figure 1-1), and transcript and pathway analysis indicated favorable changes in the tumor inflammatory profile, toward a Th1 response, consistent with activation of cytotoxic anti-tumor T-cell activity {Juric 2017}. The NeuT model was utilized as a PD1 axis checkpoint-resistant model to explore the effect on combination with anti-MMP9. Pharmacodynamic analyses were performed after 7 days of treatment of established tumors to ensure that tumors matched in mean volume across all groups. Immunophenotyping of tumor-associated T cells by flow cytometry showed that anti-MMP9 and anti-PDL1 co-treatment increased total T cells (CD3), CD8 and CD4 T cells, and activated effector T cells, while inhibition of MMP9 resulted in a decrease in regulatory T cells (Treg, with the effect maintained in combination) (Figure 1-2). In a separate study, inhibition of MMP9 resulted in significant decreases in both recruited and resident M2 polarized, immune-suppressive macrophages. These observations are consistent with the reported role of MMP9 activity in the tumor microenvironment in promoting immune-suppression via recruitment and activation of infiltrating myeloid cells, M2 macrophages, N2 neutrophils, and regulatory T cells, which both promote tumor growth and suppress anti-tumor T cells. In addition, studies in vitro revealed that cleavage of CXCR3 effector T-cell ligands CXCL9, 10 and 11 using activated MMP9 resulted in reduced migration of activated human primary T cells in chemotaxis assays, in a dose-dependent manner, for all 3 chemokines. These data suggest that inhibition of MMP9 could promote improved trafficking of effector T cells into the tumor microenvironment.

The major dose limiting toxicity (DLT) observed in clinical studies with pan-MMP inhibitors, such as marimastat, was musculoskeletal syndrome (MSS) consisting of tendonitis manifested by joint stiffness, edema, reduced mobility, and skin discoloration. A study to evaluate the potential of an anti-MMP9 antibody to induce MSS was conducted in Lewis rats. Unlike the pan-MMP inhibitor, marimastat, AB0041 did not induce any evidence of MSS or other toxicities in this Lewis rat MSS model.

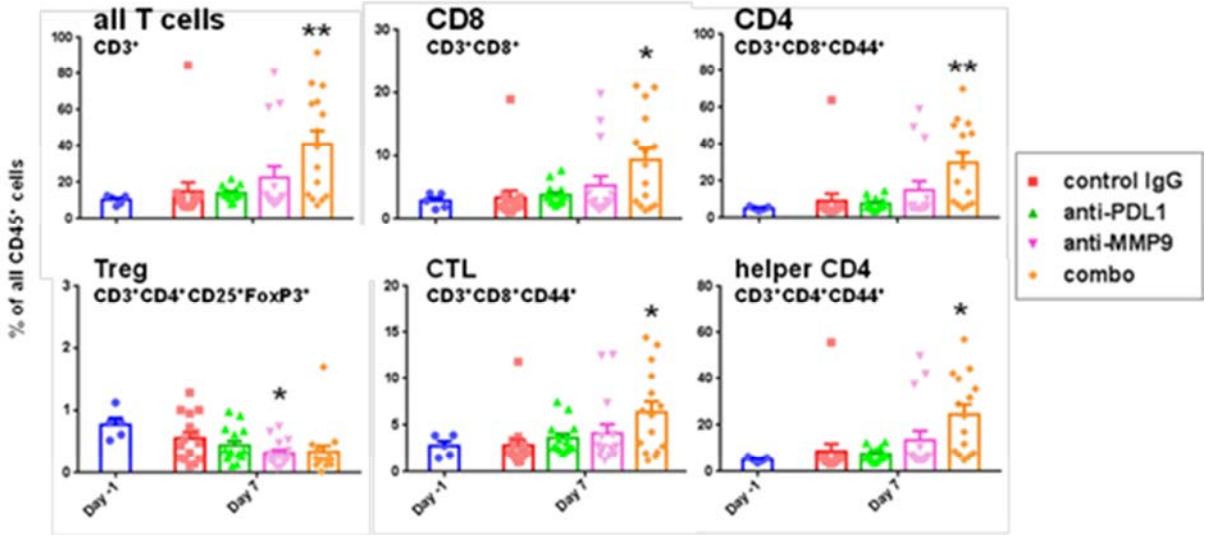
Further details on non-clinical pharmacology are available in the andecaliximab IB.

Figure 1-1. Inhibition of MMP9 in the NeuT Model of Breast Cancer



Inhibition of MMP9 in the NeuT model of breast cancer results in significant inhibition of tumor growth, whereas an anti-PDL1 antibody is ineffective, presumably due to the immunosuppressive effects of infiltrating myeloid cells in this model.

Figure 1-2. Combination Therapy of Anti-MMP9 and Anti-PDL1 Promotes an Increase in T Cells, Helper T cells, and Cytotoxic T Lymphocytes (CTL) in Tumors



Immunophenotyping of whole tumors from 7 day pharmacodynamics study in NeuT model from animals treated with control IgG, anti-MMP9, anti-PDL1, or a combination of anti-MMP9 and anti-PDL1 ("combo"). CTL: cytotoxic T lymphocytes.

1.2.2.2. Toxicology

The toxicological profile of andecaliximab has been evaluated in a human tissue cross-reactivity study, 4-week repeat dose intravenous (IV) toxicity studies with 4-week recovery in rat and monkey, and 26-week repeat-dose toxicity studies with 12-week recovery in rats and monkeys. Reproductive toxicity has been assessed following IV administration in rat and rabbit embryo fetal developmental toxicity studies and a rat fertility study.

There was no specific andecaliximab staining observed in normal human tissues. Findings associated with andecaliximab IV treatment in the 4-week repeat-dose toxicity studies were limited to nonadverse reversible physeal hypertrophy in rats and reversible increased adrenal gland weight in female monkeys at all doses, which was associated with slight hypertrophy of the zona fasciculata in a single 100-mg/kg/dose female monkey. Physeal hypertrophy findings associated with andecaliximab in the 4-week rat study are likely directly attributable to inhibition of MMP9, as similar findings were observed in MMP9 null mice {Vu 1998} and in children with mutations in MMP9 and MMP13 {Lausch 2009}. In MMP9 null mice, the hypertrophic cartilage zone was lengthened with ectopic ossification that resolved with subsequent remodeling producing normal-appearing bone by 8 weeks of age. In children, mutations in MMP9 and MMP13 are associated with metaphyseal anadysplasia syndrome {Lausch 2009}. Mutations in MMP9 result in a milder form of skeletal dysplasia characterized by transient bowing of the legs early in childhood due to metaphyseal irregularities that spontaneously regresses in late childhood. In the 26-week studies, there were no findings of toxicological concern in rats or cynomolgus monkeys following weekly IV or subcutaneous (SC) administration of andecaliximab at doses up to 100 mg/kg/dose and 150 mg/kg/dose, respectively. The lack of physeal hypertrophy observed in the rat 26-week study is presumably due to the reversible nature of this finding as longitudinal bone growth and growth plate closure slows/completes. There were no adverse injection site reactions observed in the 26-week studies, and no adverse findings in the local tolerability study. The no observed adverse effect level (NOAEL) in the rat and monkey 26-week studies was 100 mg/kg/dose (IV) and 150 mg/kg/dose (SC), the highest doses evaluated by each route of administration in each study. At doses of andecaliximab up to 100 mg/kg/dose IV, data indicate no test article-related maternal or fetal effects in rats and rabbits, and no test article-related effects on male or female fertility in rats.

Further details on toxicology are available in the andecaliximab IB.

1.2.3. Clinical Trials of Andecaliximab

Andecaliximab is currently being developed for the treatment of various solid tumors. Details of the clinical studies in these diseases can be found in the IB.

Study GS US-296-0101 is a Phase 1, open-label, sequential dose-escalation, and expansion study to evaluate safety, pharmacokinetics (PK), and pharmacodynamics of andecaliximab following multiple IV administrations of andecaliximab alone (at 200, 600, and 1800 mg every 2 weeks (Q2W)) or in combination with chemotherapy (at 800 mg Q2W or 1200 mg every 3 weeks (Q3W)) in subjects with advanced solid tumors. The study is active at centers in the United States.

Study GS-US-296-2013 is a phase 2, open-label, randomized study evaluating the efficacy, safety, PK, and pharmacodynamics of andecaliximab (800 mg every two weeks (Q2W)) and nivolumab (3 mg/kg Q2W) or nivolumab (3 mg/kg Q2W) alone in patients with unresectable or recurrent gastric or GEJ adenocarcinoma. The study is active at centers in the United States, Europe, and Australia.

Study GS-US-296-1080 is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of andecaliximab in combination with mFOLFOX6 as first line treatment in subjects with advanced gastric or GEJ adenocarcinoma. Andecaliximab 800 mg Q2W in combination with mFOLFOX6 is being evaluated globally at centers in the United States, Europe, Latin America, and Australia.

As of 31 August 2016, efficacy data is available from 40 subjects with advanced gastric/GEJ adenocarcinoma enrolled on Study GS-US-296-0101 treated with andecaliximab 800 mg IV Q2W and mFOLFOX6. The investigator assessed objective response rate (ORR) for all 40 subjects was 47.5% (90% CI, 33.8-61.5) with 3 (7.5%) CRs and 16 (40%) PRs. The duration of response was 8.4 months for all patients and 9.5 months for treatment-naïve patients. PFS was 7.8 (90% CI, 5.5-13) months in all patients and 10.7 (90% CI, 5.5-18) months in treatment-naïve patients {Shah 2017}.

1.3. Rationale for This Study

Andecaliximab was first evaluated in subjects with cancer in the Phase 1 Study GS-US-296-0101. That study was divided into 2 parts: a monotherapy dose finding stage enrolling subjects with advanced solid tumors who had failed or were intolerant to standard therapy or for whom no standard therapy was available and a combination stage evaluating the safety and efficacy of andecaliximab at the dose determined from the monotherapy stage with available chemotherapies in subjects with advanced pancreatic, non-small cell lung cancer (NSCLC), human epidermal growth factor 2 (HER2) negative gastric/GEJ adenocarcinoma, colorectal, and breast cancer.

Results from non-Japanese subjects with HER2 negative advanced gastric/GEJ adenocarcinoma treated with andecaliximab 800 mg IV Q2W and mFOLFOX6 in the Phase 1 Study GS-US-296-0101 demonstrated anti-tumor efficacy with an acceptable toxicity profile {Shah 2017}.

To enable clinical investigation of andecaliximab in Japan, Gilead is evaluating the safety and PK profile of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with advanced gastric/GEJ adenocarcinoma.

Rationale for Andecaliximab Dose Levels in Japanese Subjects

The first dose level of andecaliximab monotherapy in this study will be 800 mg IV Q2W. This dose was selected based on data from the dose-finding phase of the GS-US-296-0101 study. No DLTs were observed at andecaliximab doses up to 1800 mg IV Q2W. Based on safety and PK data from the dose finding phase of Study GS-US-296-0101, andecaliximab 800 mg IV Q2W was selected for the combination phase of the study for subjects with advanced gastric/GEJ

adenocarcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma and breast cancer. Data from these cohorts suggested andecaliximab 800 mg IV Q2W in combination with other anti-cancer agents was well tolerated and no new safety signal was identified compared to historic data from similar populations. Clinically relevant differences in andecaliximab PK between Japanese and Western subjects are not expected and it is anticipated that andecaliximab 800 mg IV Q2W monotherapy will be well tolerated in Japanese subjects.

Subjects enrolled in the monotherapy cohort(s) of this study will be evaluated in a 28-day DLT window. Safety and tolerability will be assessed after all subjects have been followed for at least 28 days after the first infusion of andecaliximab. If 2 or more subjects within the cohort of 6 subjects experience DLTs during the first 28 days of andecaliximab dosing, 6 additional subjects will be enrolled at a reduced dose of 600 mg Q2W. If 2 additional DLTs are reported at the 600 mg Q2W dose level, andecaliximab will be considered unsafe and will be discontinued.

Once all subjects in Cohort 1 have completed the 28-day DLT assessment period, an internal safety review team (SRT) will conduct a review of the safety and PK data from all subjects prior to opening the combination therapy cohorts.

In Study GS-US-296-0101, andecaliximab was administered at 1200 mg IV Q3W in combination with chemotherapy for subjects with advanced NSCLC (carboplatin plus pemetrexed for adenocarcinoma (n = 10) and carboplatin plus paclitaxel for squamous histology (n = 10)). Data from these cohorts suggested Q3W dosing of andecaliximab was well tolerated and no new safety signal was identified compared to historic data of carboplatin, paclitaxel, and pemetrexed in a similar population.

Finally, PK data from Study GS-US-296-0101 demonstrated similar trough plasma concentrations of andecaliximab in subjects with advanced pancreatic, gastric/GEJ adenocarcinoma and NSCLC following 800 mg IV Q2W or 1200 mg IV Q3W dosing irrespective of tumor histology or chemotherapy combination. These data support the use of these two alternate doses and schedules to facilitate co-administration with chemotherapies using either Q2W or Q3W dosing.

The SRT completed their review of all available clinical safety and PK data for 6 DLT-evaluable subjects in Cohort 1 on 11 May 2017 and determined the dose for the combination therapy cohorts (Cohorts 2 and 4) to be 800 mg andecaliximab Q2W, and Cohort 3 to be 1200 mg Q3W.

Rationale for Combination Therapy Cohorts in Japanese Subjects:

The combination therapy cohorts (Cohorts 2-4) will evaluate the safety and tolerability of andecaliximab in combination with the following anti-cancer regimens:

- Andecaliximab and SP in subjects with treatment-naïve advanced gastric/GEJ adenocarcinoma (Cohort 2)

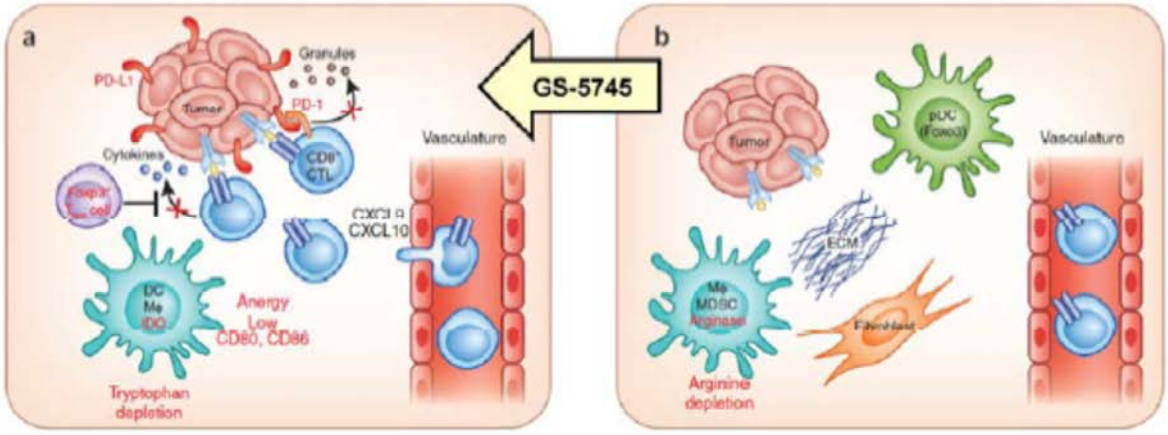
- Andecaliximab and SOX in subjects with treatment-naïve advanced gastric/GEJ adenocarcinoma (Cohort 3)

- Andecaliximab and nivolumab in subjects with advanced gastric/GEJ adenocarcinoma who have progressed on an least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease (Cohort 4)

The SP and SOX regimen were selected for evaluation based on Phase 3 studies of Japanese patients with advanced gastric/GEJ adenocarcinoma and national guidelines {Koizumi 2008}. The safety profile of andecaliximab and a fluoropyrimidine and platinum based regimen has previously been characterized {Shah 2017}.

Nivolumab is a human monoclonal antibody directed against PD-1 that blocks the interaction of PD-1 with PD-L1 and PD-L2 which has demonstrated activity in previously treated advanced gastric cancer {Kang 2017, Le 2015}. Preclinical data suggesting that inhibition of MMP9 activity within tumors may re-balance a myeloid-rich tumor-associated cellular milieu to one that is less repressive to cytotoxic T-cell entry and activity. Additionally, the presence of myeloid suppressor cells may confer resistance to immune checkpoint directed therapy. An anti-MMP9 directed murine surrogate of andecaliximab has shown significant anti-tumor activity in models in which MMP9 is produced by infiltrating myeloid cells. Its anti-tumor activity is associated with reduction of tumor-associated fibrillar collagen and alterations in the immune cell transcript profile in the treated tumors. Inhibition of PD-1 on T cells in the presence of andecaliximab may allow for greater infiltration of activated lymphocytes into the tumor and augment the anti-tumor effect offered by a PD-1 inhibitor alone. This potential synergy provides rationale for combining andecaliximab and nivolumab in subjects with advanced gastric/GEJ adenocarcinoma (see Figure 1-3).

Figure 1-3. Hypothesis for synergy between andecaliximab and nivolumab



Hypothesis for the combination of andecaliximab with nivolumab (figure adapted from Gajewski et al Nature Immunology, {Gajewski 2013}). Treatment with andecaliximab could convert "type b" tumors with dense fibrotic stroma, high myeloid suppressor cell contact, and deficiency of T-cell infiltration into "type a" tumors in which T-cell entry is enabled via remodeling of the microenvironment and re-balancing of suppressive myeloid-derived cytokines and chemokines. T cells in "type a" tumors are susceptible to checkpoint inhibition, which is overcome by treatment with nivolumab.

1.4. Risk/Benefit Assessment for the Study

In Western subjects with advanced solid tumors, there were no DLTs observed with andecaliximab monotherapy doses of up to 1800 mg Q2W. Additionally, combining andecaliximab 800 mg IV Q2W or 1200 mg Q3W with available chemotherapy regimens in non-Japanese subjects with advanced solid tumors enrolled in Study GS-US-296-0101 appeared safe and well-tolerated.

The safety and efficacy profile of SP and SOX in Japanese subjects with advanced gastric/GEJ adenocarcinoma has been established {Koizumi 2008, Yamada 2015}. Phase 1 data combining andecaliximab and mFOLFOX6 in advanced gastric/GEJ adenocarcinoma suggests clinical activity with an acceptable safety profile {Shah 2017}. These data support combining andecaliximab with fluoropyrimidine and platinum doublets commonly used in Japanese subjects with gastric/GEJ adenocarcinoma.

Phase 3 data demonstrating activity and safety of nivolumab monotherapy in Asian subjects with previously treated advanced gastric/GEJ adenocarcinoma {Kang 2017}, preclinical data suggesting potential synergy between andecaliximab and nivolumab, and safety data from the ongoing Phase 2 Study GS-US-296-2013 combining nivolumab and andecaliximab in a similar non-Japanese population (subjects with inoperable locally advanced or metastatic gastric/GEJ adenocarcinoma who have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease) support evaluating the combination in a Japanese population.

Thus, the favorable nonclinical and clinical data outweigh the risks associated with administration of andecaliximab and hence support the evaluation of andecaliximab as monotherapy or in combination with anti-cancer agents in Japanese subjects with advanced gastric/GEJ adenocarcinoma.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To characterize the safety and tolerability of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with inoperable advanced or recurrent gastric or GEJ adenocarcinoma

The secondary objectives of this study are:

- To characterize the PK of andecaliximab
- To evaluate the formation of anti-andecaliximab antibodies

The exploratory objectives of this study are:

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Sections 8.1.2, 8.1.3, and 8.1.4.

3.2. Study Design

This is a Phase 1b, open-label, multicenter study to evaluate the safety and tolerability of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with inoperable advanced or recurrent gastric or GEJ adenocarcinoma. The study will comprise 4 cohorts, 1 monotherapy cohort, and 3 combination therapy cohorts.

Cohort 1 is andecaliximab monotherapy. Cohort 2 is combination therapy of andecaliximab with SP. Cohort 3 is combination therapy of andecaliximab with SOX. Cohort 4 is combination therapy of andecaliximab and nivolumab. Up to 38 subjects are expected to be enrolled in the study.

For Cohorts 1, 2, and 4, computed tomography (CT) or magnetic resonance imaging (MRI) scans will be performed every 8 weeks to evaluate response to treatment by RECIST v1.1. For Cohort 4, response to treatment will also be evaluated using immune-related response criteria recommendations {Wolchok 2009}.

For Cohort 3, CT or MRI scans will be performed every 9 weeks to evaluate response to treatment by RECIST v1.1.

Cohort 1: Andecaliximab Monotherapy

Up to 6 Japanese subjects with inoperable advanced or recurrent gastric or GEJ tumors will be enrolled to receive andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression.

The DLT assessment window is 28 days. The safety and tolerability of the 800 mg dose will be assessed after all 6 subjects have been followed for at least 28 days after the first infusion of andecaliximab. If 2 or more subjects within the cohort of 6 subjects experience DLTs during the first 28 days of andecaliximab dosing, up to 6 additional subjects will be enrolled at a reduced dose of 600 mg Q2W. If 2 additional DLTs occur at 600 mg, andecaliximab will be considered unsafe and will be discontinued. Therefore, a total of up to 12 subjects may be enrolled in Cohort 1.

A DLT is a toxicity defined below, considered possibly related to andecaliximab occurring during the DLT assessment window (Day 1 through Day 28).

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/µL) for > 7 days, or febrile neutropenia (per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 definition) regardless of duration

- Primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is not permitted during the first cycle of study treatment. G-CSF may be used at any time at the discretion of the investigator in response to treatment emergent neutropenia. Subjects who develop Grade 4 neutropenia related to andecaliximab will be considered a DLT (subjects may receive G-CSF at the discretion of the investigator in response to treatment emergent neutropenia).

- Grade 4 thrombocytopenia, Grade 3 thrombocytopenia associated with bleeding, or Grade 3 or 4 thrombocytopenia requiring platelet transfusion

- Grade 3 or 4 non-hematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care)

- Non-hematologic toxicity of ≥ Grade 2 (at any time during treatment) that, in the judgment of the investigator and the medical monitor, is dose-limiting

- Treatment delay of > 14 days due to unresolved toxicity

- For certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion between the investigator, medical monitor, and the sponsor may take place to determine if this adverse event (AE) should be assessed as a DLT necessitating dose reduction

After all 6 subjects in Cohort 1 have completed the 28-day DLT assessment window and 1 or 0 out of 6 subjects experienced DLTs, an internal SRT will conduct a review of the safety and PK data from all subjects prior to proceeding with the combination therapy cohorts to evaluate andecaliximab with other anti-cancer agents.

The SRT completed their review of all available clinical safety and PK data for 6 DLT-evaluable subjects in Cohort 1 on 11 May 2017 and determined the dose for the combination therapy cohorts (Cohorts 2 and 4) to be 800 mg andecaliximab Q2W. See Section 1.3 for rationale of dose selection for Cohort 3 (1200 mg andecaliximab Q3W). The internal SRT consisted of Gilead study team members including the Medical Monitor, representatives from Clinical Operations, Drug Safety and Public Heath (DSPH), and Biostatistics.

Cohorts 2, 3 and 4: Andecaliximab Combination Therapy Cohorts

Japanese subjects with inoperable advanced or recurrent gastric or GEJ tumors will be enrolled in each combination therapy cohort to receive andecaliximab in combination with anti-cancer agents. Dosage and frequency of treatment in these cohorts will be as follows:

- Cohort 2: combination therapy andecaliximab and SP

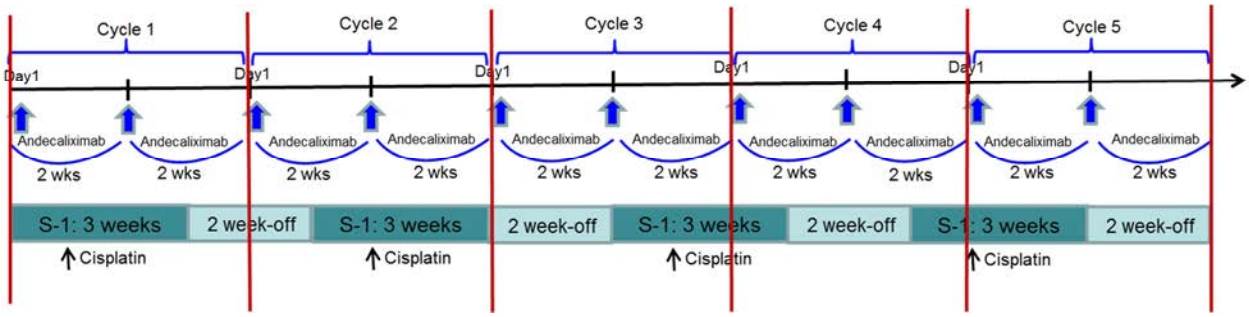
  — Andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression. The dose is based on the safety data from Cohort 1. Andecaliximab treatment will be administered in 28-day cycles.

— S-1 administered orally twice daily: dosage and regimen will be based on subject condition, investigator discretion, institutional practice and/or the in-country label (see Figure 3-1)

— Cisplatin administered by IV infusion on Day 8 of every 5 weeks: dosage and regimen will be based on subject condition, investigator discretion, institutional practice and/or the in-country label (see Figure 3-1)

— Up to 6 subjects will be enrolled in this cohort

Figure 3-1. Cohort 2 (Combination Therapy Andecaliximab and SP) Proposed Regimen



- Cohort 3: combination therapy andecaliximab and SOX

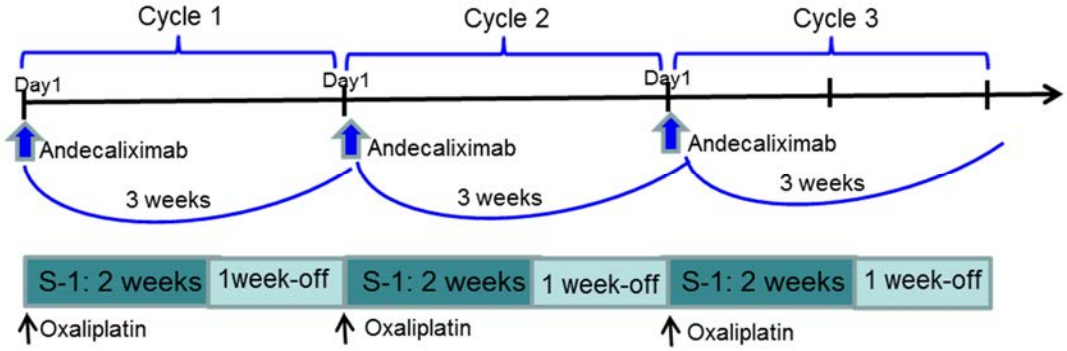
— Andecaliximab 1200 mg via IV infusion over approximately 30 (± 5) minutes Q3W until disease progression. The dose is based on safety data from Cohort 1 and other ongoing Phase 1 studies of andecaliximab. Andecaliximab treatment will be administered in 21-day cycles.

— S-1 administered orally twice daily at 80 mg/day for body surface area (BSA) < 1.25m^2, 100 mg/day for BSA ≥ 1.25 to < 1.5m^2, and 120 mg/day for BSA ≥ 1.5m^2 for the first 14 days of the 21-day cycle (See Figure 3-2)

— Oxaliplatin administered by IV infusion at 100 mg/m^2 over 2 hours on Day 1 of each 21-day cycle (See Figure 3-2)

— Up to 10 subjects will be enrolled in this cohort

Figure 3-2. Cohort 3 (Combination Therapy Andecaliximab and SOX) Regimen



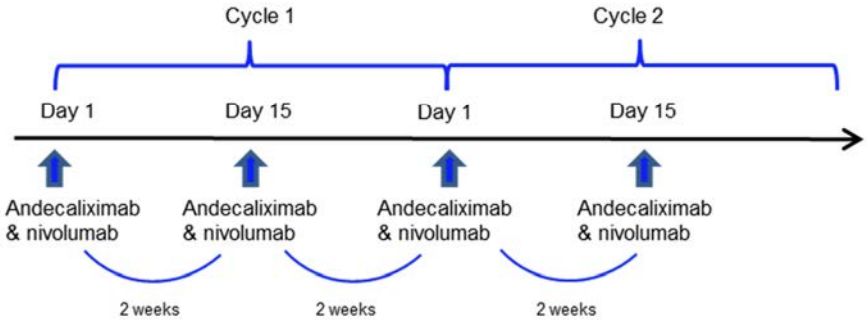
- Cohort 4: combination therapy andecaliximab and nivolumab

  — Andecaliximab 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression. The dose is based on safety data from Cohort 1. Andecaliximab treatment will be administered over in 28-day cycles.

  — Nivolumab 3mg/kg Q2W via IV infusion over 60 (± 5) minutes following the completion of andecaliximab administration (See Figure 3-3). Dose is adjusted if the weight changes more than 10% from the baseline dosing weight.

  — Up to 10 subjects will be enrolled in this cohort

Figure 3-3. Cohort 4 (Combination Therapy Andecaliximab and Nivolumab) Regimen



The cohort dose levels for andecaliximab and associated combination anti-cancer agents are summarized below in Table 3-1:

Table 3-1. Cohort Dose Levels

Cohort	Number of Subjects	Andecaliximab Dose	Andecaliximab Dosing Interval	Combination Anti-Cancer Agent(s)
1	6 to 12	800 mg or 600 mg	Q2W	N/A
2	Up to 6	800 mg	Q2W	SP
3	Up to 10	1200 mg	Q3W	SOX
4	Up to 10	800 mg	Q2W	Nivolumab

Abbreviations: SOX = S-1 and oxaliplatin; SP = S-1 and cisplatin; Q2W = every 2 weeks; Q3W = every 3 weeks

3.3. Study Treatments

Subjects meeting eligibility will receive andecaliximab by IV infusion over approximately 30 (± 5) minutes. Administration of SP, SOX and nivolumab for the combination therapy cohorts are described in Section 3.2.

Safety and efficacy assessments will occur on an outpatient basis, and will include the following: assessment of tumor response, physical examinations (PEs), vital signs, electrocardiograms (ECGs), collection of blood samples (for routine safety laboratory analyses, andecaliximab PK, anti-andecaliximab antibodies, tumor markers, thyroid function tests (for Cohort 4 only: combination therapy andecaliximab and nivolumab), and biomarkers at applicable visits), urine pregnancy, urinalysis, and assessment of AEs at the protocol specified time points.

In the combination therapy cohorts, tolerability will be determined by assessing the frequency of andecaliximab interruptions and dose modifications.

3.4. Duration of Treatment

The screening period will be up to 28 days. For Cohorts 1, 2, and 4, each cycle will be 28 days and for Cohort 3, each cycle will be 21 days.

A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving andecaliximab until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5. CT or MRI for assessment of tumor status will be conducted every 8 weeks for Cohorts 1, 2, and 4, and every 9 weeks for Cohort 3. However, tumor response may be assessed prior to the specified every 8- or 9-week time point if clinically indicated.

3.5. Discontinuation Criteria from Study Treatment

Andecaliximab, S-1, cisplatin, oxaliplatin, and nivolumab can be discontinued for any of the following reasons:

- Adverse events
- Pregnancy

- Investigator decision to remove the subject from the study treatment, in consultation with Gilead medical monitor
- Disease progression
- Intercurrent illness, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Initiation of non-study specific anti-neoplastic therapy in the absence of progression
- Subject request to discontinue treatment
- Withdrawal of consent
  - A subject may withdraw consent solely from active participation in the study but still participate in follow up for disease progression and survival
- Death
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC)
- Loss to follow-up
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- In addition to the drug discontinuation criteria above, nivolumab may be discontinued for any reason specified in the prescribing information.

3.6. Premature Discontinuation from Study Treatment

If a subject has discontinued all study treatments prior to definitive disease progression, the subject shall remain on study until at least 1 of the criteria for discontinuation from study is met (Section 3.7). Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks (Cohorts 1, 2, and 4) or every 9 weeks (Cohort 3) until disease progression. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. It is recommended that the investigator consults with the medical monitor prior to removing the subject from study for any reason except subject withdrawal of consent.

3.7. Discontinuation Criteria from Study

Subject study participation may be ended due to any of the following reasons:

- Initiation of non-study specific anti-neoplastic therapy in the absence of progression
- Disease progression

- Intercurrent illness, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Withdrawal of consent
  - A subject may withdraw consent solely from active participation in the study but participate in follow up for survival.
- Non-compliance with study treatments or protocol violation
- Investigator decision to remove the subject from the study treatment, in consultation with Gilead medical monitor
- Death
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC
- Loss to follow up

3.8. End of Study

End of study (EOS) assessments will be completed when the subject meets at least 1 of the criteria for study discontinuation in Section 3.7.

3.9. Long-Term Follow-Up for Overall Survival

After EOS, long-term follow up (LTFU) will be initiated for subjects who discontinue from study due to reasons other than death. The subject shall remain on LTFU for OS until:

- Death
- Withdrawal of consent to participate in LTFU
- Lost to follow up
- End of LTFU period

Every attempt should be made to keep the subject in the LTFU for OS. See Section 6.10.2 for additional information.

The end of the trial will be defined as when all subjects have completed LTFU or discontinued their participation the study due to death, withdrawal of consent or lost to follow up.

3.10. Source Data

The subject identification number assigned by the interactive web response system (IWRS) is considered source data.

3.11. Biomarker Testing

3.11.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to investigate andecaliximab accumulation in tumor tissue and to understand the andecaliximab mechanism of action. Additionally, biomarkers in tumor tissue may be correlated with circulating biomarkers. The specific analyses will include, but will not be limited to, the biomarkers and assays listed in Table 3-2 below. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. Any future testing must be approved by local authorities as applicable according to specific local regulations.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

Table 3-2. Biomarker Objectives and Testing

COHORTS 1 (Andecaliximab Monotherapy) AND 4 (Combination Therapy Andecaliximab and Nivolumab)		
Sample Type	**Objective**	**Test**
Tumor Tissue Biopsies • **PRIOR TO FIRST DOSE Required** • **6 WEEKS (± 1 WEEK) (Cohort 4) or 6 WEEKS (+ 5 DAYS) (Cohort 1) Required** (from same anatomical location as 1st biopsy) [redacted] Endoscopic gastric samples (minimum 4, but 6-8 encouraged) per time-point; metastasis to liver or lymph nodes acceptable as multiple pass 18g needle biopsy as described in the laboratory manual	To provide a baseline for pharmacodynamic and resistance biomarkers and investigate biomarkers at baseline that associate with response to andecaliximab plus nivolumab in Cohort 4 To evaluate pharmacodynamics and mechanism of action of andecaliximab in tumor tissue CCI [redacted]	Tests listed below may be used for all or some of the tumor tissue biopsies: MMP9, PD-L1, other MMPs, Immune Cells and proteins by IHC and other methods Activity of MMP9 Gene expression patterns (RNA) for tumor subtyping and microenvironment characterization, such as IFNγ and immune cell signatures Somatic tumor mutations
Non-Diseased Gastric tissue biopsy • **PRIOR TO FIRST DOSE Required** Endoscopic samples (minimum 4, but 6-8 encouraged) to be processed as described in the laboratory manual; DO NOT collect if stomach is free of tumor	Required to provide a normal comparison for tumor tests, including somatic tumor mutations	MMP9, other MMPs, Immune Cells and proteins by IHC and other methods Activity of MMP9 Gene expression patterns for tumor subtyping and microenvironment characterization
Tumor Tissue – Archival	To evaluate biomarkers in primary disease in comparison to metastatic disease	MMP9, PD-L1, other MMPs and Immune Cells by IHC and other methods Gene expression patterns for microenvironment characterization Somatic tumor mutations

COHORTS 1 (Andecaliximab Monotherapy) AND 4 (Combination Therapy Andecaliximab and Nivolumab)		
Sample Type	**Objective**	**Test**
Endoscopic evaluation • **PRIOR TO FIRST DOSE Required** • **At time of on-treatment biopsy Required** DO NOT perform if stomach is free of tumor	To evaluate new instances of or progression of existing gastritis and dysplasia before biopsies	
Blood	To evaluate pharmacodynamics of andecaliximab	MMP9 cleavage products such as C1M Circulating MMP9 protein
	To evaluate immune cell activation	Circulating cytokines and inflammatory markers
	To evaluate circulating immune cells	Immune monitoring assay by flow cytometry
	To evaluate other biomarkers of andecaliximab activity	Circulating growth factors such as VEGF
	To evaluate less-invasive methods for monitoring response and resistance	Circulating tumor DNA Circulating RNA species

COHORTS 2 (Combination Therapy Andecaliximab and SP) AND 3 (Combination Therapy Andecaliximab and SOX)		
Sample Type	**Objective**	**Test**
Tumor Tissue Biopsies • **PRIOR TO FIRST DOSE Required** • **AT EOS with documented disease progression Required** Endoscopic gastric samples (minimum 4, but 6-8 encouraged) per time-point; metastasis to liver or lymph nodes acceptable as multiple pass 18g needle biopsy as described in the laboratory manual	To provide a baseline for pharmacodynamic and resistance biomarkers CCI [redacted]	Tests listed below may be used for all or some of the tumor tissue biopsies: MMP9, other MMPs, Immune Cells and proteins by IHC and other methods Activity of MMP9 Gene expression patterns for tumor subtyping and microenvironment characterization, such as IFNγ and immune cell signatures Somatic tumor mutations
Non-Diseased Gastric tissue biopsy • **PRIOR TO FIRST DOSE Required** Endoscopic samples (minimum 4, but 6-8 encouraged) to be processed as described in the laboratory manual; DO NOT collect if stomach is free of tumor	Required to provide a normal comparison for tumor tests, including somatic tumor mutations	MMP9, other MMPs, Immune Cells and proteins by IHC and other methods Activity of MMP9 Gene expression patterns for tumor subtyping and microenvironment characterization
Tumor Tissue – Archival	To evaluate biomarkers in primary disease in comparison to metastatic disease	MMP9, other MMPs and Immune Cells by IHC and other methods Gene expression patterns for microenvironment characterization Somatic tumor mutations
Endoscopic evaluation • **PRIOR TO FIRST DOSE Required** DO NOT perform if stomach is free of tumor	To evaluate gastritis and dysplasia before biopsies	

COHORTS 2 (Combination Therapy Andecaliximab and SP) AND 3 (Combination Therapy Andecaliximab and SOX)		
Sample Type	**Objective**	**Test**
Blood	To evaluate pharmacodynamics of andecaliximab	MMP9 cleavage products such as C1M Circulating MMP9 protein
	To evaluate immune cell activation	Circulating cytokines and inflammatory markers
	To evaluate circulating immune cells	Immune monitoring assay by flow cytometry
	To evaluate other biomarkers of andecaliximab activity	Circulating growth factors such as VEGF
	To evaluate less invasive methods for monitoring response and resistance	Circulating tumor DNA isolation and sequencing Circulating RNA species

Abbreviations: DNA = deoxyribonucleic acid; ELISA = enzyme-linked immunosorbent assay; EOT = end of treatment; IFNγ = interferon gamma; IHC = immunohistochemistry; MMP = matrix metalloproteinase; PD-L1 = programmed death-ligand 1; RNA = ribonucleic acid; VEGF = vascular endothelial growth factor

3.11.2. Biomarker Samples for Optional Future Research

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 38 subjects will be enrolled. The target population is Japanese subjects ≥ 20 years of age with histologically confirmed inoperable advanced or recurrent gastric or GEJ adenocarcinoma.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 20 years of age

2) Subjects must have been born in Japan and must not have lived outside of Japan for a period >1 year in the 5 years prior to Day 1

3) Subjects must be able to trace their maternal and paternal ancestry of parents and grandparents as ethnically Japanese

4) Histologically confirmed inoperable advanced gastric adenocarcinoma (including adenocarcinoma of the GEJ) or relapsed gastric adenocarcinoma

5) Cohorts 1 (andecaliximab monotherapy), 2 (combination therapy andecaliximab and SP) and 3 (combination therapy andecaliximab and SOX): Human Epidermal Growth Factor Receptor 2 (HER2)-negative tumor (primary tumor or metastatic lesion). Enrollment in Cohort 4 (combination therapy andecaliximab and nivolumab) is not restricted by HER2 status (subjects with HER2-positive, HER2-negative, or unknown HER2 status are eligible).

6) Cohort 1 (andecaliximab monotherapy): Prior antitumor therapy or cytotoxic chemotherapy is acceptable. Subjects who are not eligible to receive standard treatments should enroll on the study. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 (or baseline) before the start of andecaliximab dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted])

7) Cohorts 2 (combination therapy andecaliximab and SP) and 3 (combination therapy andecaliximab and SOX): Prior antitumor therapy or cytotoxic chemotherapy for metastatic disease is **not** acceptable. Subjects must be chemo-naive in the metastatic setting. Subjects who relapse during adjuvant chemotherapy or within 180 days after adjuvant chemotherapy for their gastric cancer should not be enrolled.

8) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

9) Life expectancy of > 3 months in the opinion of the investigator

10) Adequate baseline organ function (within 28 days prior to Day 1) as shown in the following able:

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	Cohorts 1-3: ≥ 8.0 g/dL (not RBC transfusion dependent)
Hepatic	Serum total or conjugated bilirubin	≤ 1.5 x ULN
	Serum AST and ALT	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
Renal	Serum Creatinine	Cohort 1: ≤ 1.5 x ULN Cohorts 2 and 3: ≤ 1.0 x ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; RBC = red blood cell; ULN = upper limit of normal

11) Coagulation: International Normalized Ratio (INR) ≤ 1.5 (unless receiving anticoagulation therapy). Subjects on full-dose oral anticoagulation must be on a stable dose (minimum duration 14 days). If receiving warfarin, the subject must have an INR ≤ 3.0 and no active bleeding (ie, no bleeding within 14 days prior to first dose of andecaliximab). Subjects on low molecular weight heparin will be allowed

12) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s) (See Appendix 9)

13) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of andecaliximab, throughout the study treatment period, and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s), and to refrain from sperm donation from the start of andecaliximab, throughout the study treatment period, and defined periods following the last dose of andecaliximab and/or anti-cancer agent(s) (See Appendix 9)

14) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

15) Evidence of a personally signed informed consent form

16) In addition to the applicable criteria above, subjects in Cohort 4 (combination therapy andecaliximab and nivolumab) must meet all of the following inclusion criteria to be eligible for participation in this study:

    a) Measureable gastric or GEJ adenocarcinoma according to RECIST v1.1

b) Subject must have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease. All toxicities attributed to prior anti-cancer therapy other than alopecia or fatigue must have resolved to Grade ≤ 1 (NCI CTCAE Version 4) or baseline

c) Adequate baseline organ function (within 28 days prior to Day 1) as shown in the following table:

Organ System	**Parameter**	**Required Value**
Hematopoietic	ANC	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	≥ 9.0 g/dL
Hepatic	Serum total or conjugated bilirubin	≤ 1.5 x ULN
	Serum AST and ALT	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
Renal	Creatinine Clearance	Creatinine clearance (CLcr) ≥ 60 mL/min, estimated based on the Cockroft-Gault formula or measured based on 24 hour urine collection or other reliable method

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CLcr = creatinine clearance; RBC = red blood cell; ULN = upper limit of normal

d) Subjects not receiving anticoagulant medication must have an activated partial thromboplastin (aPTT) ≤ 1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the aPTT is within therapeutic limits (according to the medical standard in the institution) and the subject has been on stable dose of anticoagulants for at least 1 week at the time of enrollment

e) Thyroid function tests (thyroid-stimulating hormone (TSH), T3, free T4) should be within normal limits. Subjects with underlying thyroid disease are eligible if they are receiving appropriate medication and are clinically stable.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) History or evidence of a clinically significant disorder, condition, or disease that, in the opinion of the investigator and medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

2) Pregnant or lactating. Enrollment of lactating females after discontinuation of breastfeeding is **not** acceptable.

3) Subjects with known central nervous system (CNS) metastases, unless metastases are treated and stable and the subject does not require systemic steroids

4) Radiotherapy within 28 days of Day 1; subjects given palliative radiotherapy to peripheral sites (eg, bone metastasis) may enter the study before 28 days have elapsed if subject has recovered from any acute, reversible effects

5) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of Day 1

6) History of major surgery within 28 days prior to Day 1

7) Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics

8) Cohort 1 (andecaliximab monotherapy): Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of Day 1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{½}$ > 10 days)

9) Clinically significant bleeding within 28 days of Day 1

10) Subjects known to be positive for human immunodeficiency virus (HIV), hepatitis C infection (per local standard diagnostic criteria), or acute or chronic hepatitis B infection (per local standard diagnostic criteria)

11) Known hypersensitivity to any of the study drugs or components or to Chinese hamster ovary cell products or to recombinant human or humanized antibodies

12) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; asymptomatic prostate cancer without known metastatic disease, with no requirement for therapy or requiring only hormonal therapy, and with normal prostate-specific antigen for ≥ 1 year prior to Day 1; adequately treated Stage 1 or 2 cancer currently in complete remission; or any other cancer that has been in complete remission for ≥ 5 years

13) Known alcohol or drug abuse or any other medical or psychiatric condition which contraindicates participation in the study

14) Subject is expected to require any form of systemic or localized antineoplastic therapy while on study

15) In addition to the applicable criteria above, subjects in Cohort 4 (combination therapy andecaliximab and nivolumab) who meet any of the following exclusion criteria will not be enrolled in this study:

    a) Subjects who have received only neoadjuvant or adjuvant therapy for gastric adenocarcinoma

    b) Chronic daily treatment with oral corticosteroids (dose of > 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of Day 1. Inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed

c) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of Day 1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{½}$ > 10 days)

d) Prior treatment with anti-CTLA-4 agents (eg, ipilimumab), anti-PD-1 or anti-PD-L1 agents (eg, pembrolizumab, nivolumab, atezolizumab), anti-PD-L2 agents, anti-MMP agents, or other immunomodulatory therapies

e) Prior therapy with anti-tumor vaccines or other immuno-modulatory antitumor agents

f) Current or history of pneumonitis or interstitial lung disease

g) Active known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

h) History of bone marrow, stem cell, or allogeneic organ transplantation

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

It is the responsibility of the investigator to ensure that subjects are eligible for the study prior to enrollment. Subjects will be assigned a unique screening number via an interactive web response system (IWRS). Once eligibility is confirmed subjects will be assigned a unique subject number via IWRS. The IWRS will be used to maintain a central log documenting screening, to implement enrollment, to assess current inventories of andecaliximab and nivolumab, to initiate necessary resupply of drug and to document discontinuation of drug.

This is an open-label study.

The IWRS will assign kit numbers and provide instructions for dispensing of andecaliximab (Cohorts 1-3) or andecaliximab and nivolumab (Cohort 4). It is anticipated that subjects will usually begin treatment immediately after enrollment in IWRS.

All baseline tests and procedures must be completed prior to the administration of the first dose of andecaliximab on Day 1. Once a subject number is assigned to a subject, it will not be reassigned to another subject.

5.2. Description and Handling of Study Treatments

5.2.1. Formulation

5.2.1.1. Andecaliximab

Andecaliximab is formulated as a sterile, aqueous buffered solution containing acetate at pH 5.0, with sucrose and polysorbate 20 added for stabilization. Each 10 mL vial contains 400 mg andecaliximab at a concentration of 40 mg/mL.

5.2.1.2. S-1

S-1 is commercially sourced. Additional information regarding the formulation can be found in the current prescribing information.

5.2.1.3. Cisplatin

Cisplatin is commercially sourced. Additional information regarding the formulation can be found in the current prescribing information.

5.2.1.4. Oxaliplatin

Oxaliplatin is commercially sourced. Additional information regarding the formulation can be found in the current prescribing information.

5.2.1.5. Nivolumab

Nivolumab is commercially sourced. Additional information regarding the formulation can be found in the current prescribing information.

5.2.2. Packaging and Labeling

Andecaliximab (labeled as GS-5745) will be supplied in 10 mL glass vials with coated elastomeric stoppers and aluminum crimp overseals with a flip-off cap.

Andecaliximab to be distributed to centers in Japan shall be labeled to meet applicable requirements of the local regulations as applicable.

S-1, cisplatin, and oxaliplatin to be used in this study will be obtained from available commercial supplies at each study site.

Commercially available nivolumab will be used for this study and provided by Gilead. Nivolumab to be distributed to centers in Japan shall be labeled to meet applicable requirements of the local regulations.

5.2.3. Storage and Handling

Andecaliximab should be stored at 2°C - 8 ºC. Storage conditions are specified on the andecaliximab label. Until dispensed to subjects, all drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, the drug should be stored in the containers and packaging in which it was supplied until administration to the subjects.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

Commercial product of S-1, cisplatin oxaliplatin, and nivolumab will be used for the study. Further information regarding storage, handling, and preparation are available in the prescribing information for commercial products.

Information regarding preparing andecaliximab IV infusions can be found in the pharmacy manual.

5.3. Dosage and Administration of Andecaliximab, S-1, Cisplatin, Oxaliplatin, and Nivolumab

The target dose of andecaliximab will be administered by preparing a sterile IV solution. The target dose of 600 mg or 15 mL of andecaliximab 40 mg/mL will be prepared from two 10 mL vials. The target dose of 800 mg or 20 mL of andecaliximab 40 mg/mL will be prepared from two 10 mL vials. The target dose of 1200 mg or 30 mL of andecaliximab 40 mg/mL will be prepared from three 10 mL vials. Andecaliximab will be administered via IV infusion over approximately 30 (± 5) minutes at the research clinic by a qualified staff member.

For Cohort 2, combination therapy andecaliximab and SP: Andecaliximab 800 mg will be administered via IV infusion over approximately 30 (± 5) minutes on Days 1 and 15 of each 28-day cycle. S-1 will be administered orally twice daily with the dosage and regimen based on subject condition, investigator discretion, institutional practice and/or the in-country label. Cisplatin will be administered by IV infusion on Day 8 of every 5 weeks with the dosage and regimen based on subject condition, investigator discretion, institutional practice and/or the in-country label.

For Cohort 3, combination therapy andecaliximab and SOX: Andecaliximab 1200 mg will be administered via IV infusion over approximately 30 (± 5) minutes on Days 1 of each 21-day cycle. S-1 will be administered orally twice daily at 80 mg/day for BSA < 1.25m^2, 100 mg/day for BSA ≥ 1.25 to < 1.5m^2, and 120 mg/day for BSA ≥ 1.5m^2 for the first 14 days of the 21-day cycle. Oxaliplatin will be administered by IV infusion at 100 mg/m^2 over 2 hours on Day 1 of each 21-day cycle.

For Cohort 4, combination therapy andecaliximab and nivolumab: Andecaliximab 800 mg will be administered via IV infusion over approximately 30 (± 5) minutes on Days 1 and 15 of each 28-day cycle. Following administration of andecaliximab, nivolumab will be administered via IV infusion over approximately 60 (± 5) minutes on Day 1 and 15 of each 28 day cycle. Dose is adjusted if the weight changes more than 10% from the baseline dosing weight.

Documentation of andecaliximab, S-1, cisplatin, oxaliplatin, and nivolumab administration will be noted on the electronic case report form (eCRF) and in the source documentation.

The investigator or a qualified designee must be present during administration. Subjects should be observed following end of infusion and discharged at the discretion of the investigator or qualified designee.

Details of preparing and administering andecaliximab and nivolumab are included in the Pharmacy Binder provided by Gilead.

5.3.1. Dose Interruption and Reduction

If an AE is attributed to only 1 drug (ie, study drug or other anti-cancer agent), the investigator's discretion will be used to determine if the drug not attributed to the AE will be withheld based on the investigator's assessment of risk-benefit of withholding 1 or both drugs.

5.3.1.1. Andecaliximab

In Cohort 1 (andecaliximab monotherapy), if a subject experiences a DLT (see Section 3.2 for the definition of a DLT), andecaliximab treatment will be postponed until the toxicity is resolved to Grade 0 or 1 (as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 or returns to the subject's baseline value. If the toxicity is resolved to Grade 0 or 1, or returns to the subject's baseline value within 28 days from the start of the event, the subject may resume andecaliximab at 50% of the originally assigned dose level. If the subject experiences a recurrence of the toxicity meeting criteria for DLT after restarting andecaliximab

or if the toxicity does not resolve within 28 days, treatment with andecaliximab will be discontinued. Alternatively, if there is no recurrence of the toxicity, the dose of andecaliximab may be increased to 100% of the originally assigned level after discussion with the medical monitor.

Dose modification or delay of andecaliximab following adverse events that do not meet the criteria for a DLT (either during the DLT window or afterwards for subjects in Cohort 1) may be permitted at the discretion of the Investigator after discussion with the medical monitor.

For subjects enrolled in the combination therapy cohorts (Cohorts 2-4), dose delay of andecaliximab following adverse events may be permitted at the discretion of the Investigator after discussion with the medical monitor. Dose modification of andecaliximab is not permitted in the combination therapy cohorts without prior discussion with the medical monitor.

Additionally, in the combination therapy cohorts, subjects in whom anti-cancer agent (SP, SOX, or nivolumab) administration must be delayed may continue to receive andecaliximab while anti-cancer agent(s) are held, in the absence of disease progression. If anti-cancer agent treatment (SP, SOX, or nivolumab) is permanently discontinued, andecaliximab treatment must be permanently discontinued. Subjects enrolled in Cohorts 2 and 3 may permanently discontinue 1 of the 2 anti-cancer agents (ie, cisplatin or oxaliplatin) for reasons other than disease progression, and still continue treatment with S-1 and andecaliximab until they meet 1 of the discontinuation criteria in Protocol Section 3.5 or 3.7.

Subjects who discontinue andecaliximab for reasons other than disease progression may continue to receive anti-cancer agent treatment (SP, SOX, or nivolumab) until disease progression.

If the subject was not receiving andecaliximab at the time disease progression was documented (eg, due to reversible toxicity), after discussion with the medical monitor, andecaliximab may be re-started if the criteria for resuming treatment as described in Section 5.3.1.1 are met and the investigator feels it is in the subject’s best interest to do so.

Dose delay of andecaliximab due to holidays, site closures and subject availability may be permitted after discussion with the medical monitor. The reason for interruption or delay should be documented in the subject's study record.

5.3.1.2. S-1 and Cisplatin

Administration of S-1 and cisplatin, along with anti-emetic administration and pre and post anti-cancer agent hydration must follow the institutional practice for these agents and the in-country label. Dose reductions of the drugs must also agree with their clinical practice and the country-specific label. Sites may also follow their institutional practice and the country specific label for dose reductions.

5.3.1.3. S-1 and Oxaliplatin

Administration of S-1 and oxaliplatin must follow the institutional practice for these agents and the in-country label. Dose reductions of the drugs must also agree with their clinical practice and the country-specific label. Sites may also follow their institutional practice and the country specific label for dose reductions.

5.3.1.4. Nivolumab

Administration of nivolumab must follow the institutional practice for these agents and the in-country label. Dose reductions of the drugs must also agree with their clinical practice and the country-specific label/prescribing information. Sites may also follow their institutional practice and the country specific label for dose reductions.

5.4. Prior and Concomitant Medications

At Screening, all medication taken up to 28 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (eg, anti-emetics), and vitamins and minerals.

In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and recorded on the eCRF.

During the course of the clinical trial, subjects are anticipated to continue the use of prescribed medications identified during screening procedures, consistent with the study inclusion and exclusion criteria.

Non-study anticancer chemotherapy or immunotherapy (approved or investigational) is not permitted during the trial. If administered, the subject may be removed from the trial.

Inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed; however, chronic daily treatment with oral corticosteroids (dose of > 10 mg/day prednisone equivalent) are not allowed.

5.5. Accountability for Andecaliximab and Andecaliximab/Nivolumab

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product during the study. This includes acknowledgement of receipt of each shipment of andecaliximab and nivolumab (quantity and condition) and tracking of vials assigned/utilized for subject dosing.

Andecaliximab and andecaliximab/nivolumab accountability records will be provided to each study site to:

- Record the date received and quantity of andecaliximab and nivolumab vials

- Record the date, subject number, subject initials, the vial number(s) dispensed
- Record the date, quantity of used and unused andecaliximab and nivolumab vials returned, along with the initials of the person recording the information.

Dispensing records will include the initials of the person dispensing the andecaliximab or nivolumab or supplies.

5.5.1. Investigational Medicinal Product Return or Disposal

Andecaliximab, S-1, cisplatin, oxaliplatin, and nivolumab should be disposed of at the site as per local standard operating procedures. Please see Section 9.1.7 for additional instructions.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2-Appendix 5 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, PEs, vital signs, and special safety assessments like ECGs.

6.1. Subject Enrollment and Treatment Assignment

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 28 days before Day 1 to determine eligibility for participation in the study.

Subject eligibility will be established at the conclusion of the screening evaluations. Subjects will be assigned a unique screening number at the time of consent. Subject eligibility must be determined by results received from the central lab with exceptions made for re-screening and HER2 testing as described in Sections 6.12.2 and 6.12.8.2. It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment.
Once eligibility is confirmed subjects will be assigned a unique subject number.

The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history (including review of disease under study, prior surgeries, and prior anti-cancer therapies)
- Review of prior/concomitant medication(s)
- Complete PE including, body weight, and height
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status

- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - Serum pregnancy test for females of childbearing potential (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - Urinalysis
  - For Cohort 4 (combination therapy andecaliximab and nivolumab): Thyroid function tests (See Section 6.12.8)
- CT or MRI (scans taken as part of standard medical practice within 28 days of Day 1 are acceptable)
- Record any serious adverse events (SAEs) and all AEs related to protocol mandated procedures occurring after signing of the consent form.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic on Day 1 (within 28 days after screening) for enrollment into the study.

6.3. Treatment Assessments – Cohort 1 (Andecaliximab Monotherapy)

6.3.1. Day 1 of Each 28-Day Cycle

The following will be performed and documented on Day 1.

Pre Dose:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)

  - Coagulation (See Section 6.12.8)
  - Andecaliximab concentration (Cycles 2, 3, 5, 7 and every 3 cycles thereafter) (See Section 6.12.8)
  - Anti-andecaliximab antibodies (Cycles 1, 2, 3, 5, 7 and every 3 cycles thereafter) (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - Urine pregnancy test for females of childbearing potential (Day 1 of Cycle 1 only) (See Section 6.12.8)
  - Urinalysis (See Section 6.12.8)
- Obtain tumor tissue biopsy (Day 1 of Cycle 1 Pre Dose) and perform endoscopic evaluation noting extent and grade of disease and new instances of, or progression of, existing gastritis and dysplasia before biopsies
- Obtain normal gastric tissue biopsy (Day 1 of Cycle 1 Pre Dose)
- Collection of archival tumor tissue specimen as applicable: efforts to acquire a tissue sample should begin on Day 1
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

Dosing:

- Administer andecaliximab via IV infusion over approximately 30 (± 5) minutes

Post Dose: End of Infusion (EOI)

- Obtain blood samples for:
  - Andecaliximab concentration (30 ± 15 minutes for Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
- Record any SAEs and all AEs related to protocol mandated procedures

6.3.2. Cycle 1 Day 2 and Cycle 1 Day 4

The following will be performed and documented Cycle 1 Day 2 and Cycle 1 Day 4 (± 1 day):

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status

- Obtain blood samples for:
  - Andecaliximab concentration (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.3.3. Cycle 1 Day 8

The following will be performed and documented on Day 8 (± 1 day):

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology(See Section 6.12.8)
  - Andecaliximab concentration (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.3.4. Day 15 of Each 28-Day Cycle

The following will be performed and documented on Day 15 (± 1 day):

Pre Dose:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)

- Hematology (See Section 6.12.8)
- Coagulation (See Section 6.12.8)
- Andecaliximab concentration (Day 15 of Cycle 1 only) (See Section 6.12.8)
- Blood biomarkers (See Section 3.11)
- Obtain tumor tissue biopsy (Day 15 of Cycle 2 (+5d) only) and perform endoscopic evaluation noting extent and grade of disease and new instances of, or progression of, existing gastritis and dysplasia before biopsies
- Urinalysis (See Section 6.12.8)

- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

Dosing:

- Administer andecaliximab via IV infusion over approximately 30 (± 5) minutes

Post Dose: End of Infusion (EOI)

- Obtain blood samples for:
  - Andecaliximab concentration (30 ± 15 minutes, Day 15 of Cycle 1 only) (See Section 6.12.8)
- Record any SAEs and all AEs related to protocol mandated procedures

6.3.5. Cycle 1 Day 29/Cycle 2 Day 1

The Cycle 1 Day 29 visit, which overlaps with the Cycle 2 Day 1 visit, is the end of the DLT assessment window. In order for a subject to be evaluable for the DLT observation, the subject must have received the first dose of andecaliximab, completed all safety procedures through Day 28, or have experienced a DLT prior to Day 28. Assessments should be performed as listed in Section 6.3.1 for Day 1 of each 28-day cycle. Additionally, see Section 6.5 for Continuation of Treatment Assessments.

6.4. Treatment Assessments – Cohorts 2, 3 and 4 (Combination Therapy Cohorts)

The below assessments outline study procedures to occur at each visit with andecaliximab dosing (Days 1 and 15 of each 28-day cycle for Cohorts 2 and 4; Day 1 of each 21-day cycle for Cohort 3).

6.4.1. Day 1 of Each 28-Day Cycle for Cohort 2 (Combination Therapy Andecaliximab and SP) and Cohort 4 (Combination Therapy Andecaliximab and Nivolumab)

The following will be performed and documented on Day 1 (± 1 day). C1D1 must occur within 3 days following enrollment in IWRS.

Pre Dose:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - Andecaliximab concentration (Cycles 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8
  - Anti-andecaliximab antibodies (Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - Urine pregnancy test for females of childbearing potential (See Section 6.12.8)
  - Urinalysis (See Section 6.12.8)
- Obtain tumor tissue biopsy (within 28 days prior to or on Day 1 of Cycle 1 Pre Dose only) and perform endoscopic evaluation noting extent and grade of disease and new instances of, or progression of, existing gastritis and dysplasia before biopsies
- Obtain normal gastric tissue biopsy (within 28 days prior to or on Day 1 of Cycle 1 Pre Dose only)
- Collection of archival tumor tissue specimen as applicable: efforts to acquire a tissue sample should begin on Day 1

- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

Dosing:

- Administer andecaliximab via IV infusion over approximately 30 (± 5) minutes
- For Cohort 2 (combination therapy andecaliximab and SP): S-1 and cisplatin chemotherapy administration will follow dosage and regimen based on subject condition, investigator discretion, institutional practice and/or the in-country label. Due to expected variation in administration schedules, chemotherapy dosing may or may not take place on Days 1 and 15 of each 28-day cycle.
- For Cohort 4 (combination therapy andecaliximab and nivolumab): Following administration of andecaliximab, administer nivolumab via IV infusion over approximately 60 (± 5) minutes

Post Dose: End of Infusion (EOI)

- Obtain blood samples for:
  - Andecaliximab concentration (30 ± 15 minutes for Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
- Record any SAEs and all AEs related to protocol mandated procedures

6.4.2. Day 1 of Each 21-Day Cycle for Cohort 3 (Combination Therapy Andecaliximab and SOX)

The following will be performed and documented on Day 1 (± 1 day). C1D1 must occur within 3 days following enrollment in IWRS.

Pre Dose:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)

  - Coagulation (See Section 6.12.8)
  - Andecaliximab concentration (Cycles 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8
  - Anti-andecaliximab antibodies (Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - Urine pregnancy test for females of childbearing potential (See Section 6.12.8)
  - Urinalysis (See Section 6.12.8)

- Obtain tumor tissue biopsy (within 28 days prior to or on Day 1 of Cycle 1 Pre Dose only) and perform endoscopic evaluation noting extent and grade of disease and new instances of, or progression of, existing gastritis and dysplasia before biopsies
- Obtain normal gastric tissue biopsy (within 28 days prior to or on Day 1 of Cycle 1 Pre Dose only)
- Collection of archival tumor tissue specimen as applicable: efforts to acquire a tissue sample should begin on Day 1
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

Dosing:

- Administer andecaliximab via IV infusion over approximately 30 (± 5) minutes
- S-1 to be administered orally twice daily for the first 14 days of the 21-day cycle
- Administer Oxaliplatin by IV infusion over 2 hours

Post Dose: End of Infusion (EOI)

- Obtain blood samples for:
  - Andecaliximab concentration (30 ± 15 minutes for Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
- Record any SAEs and all AEs related to protocol mandated procedures

6.4.3. Cycle 1 Day 8 for Cohort 4 (Combination Therapy Andecaliximab and Nivolumab)

The following will be performed and documented on Day 8 (± 1 day):

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Andecaliximab concentration (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.4.4. Day 15 of Each 28-Day Cycle for Cohort 2 (Combination Therapy Andecaliximab and SP) and Cohort 4 (Combination Therapy Andecaliximab and Nivolumab)

The following will be performed and documented on Day 15 (± 1 day):

Pre Dose:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - For Cohort 2 (combination therapy andecaliximab and SP): Andecaliximab concentration (Day 15 of Cycle 1 only) (See Section 6.12.8)

- For Cohort 4 (combination therapy andecaliximab and nivolumab): Andecaliximab concentration (Day 15 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter) (See Section 6.12.8)
- Blood biomarkers (Day 15 of Cycle 1 and Cycle 2 only) (See Section 3.11)
- For Cohort 4 (combination therapy andecaliximab and nivolumab): Obtain tumor tissue biopsy (at 6 weeks (± 1 week) after the first dose of andecaliximab) and perform endoscopic evaluation noting extent and grade of disease and new instances of, or progression of, existing gastritis and dysplasia before biopsies
- Urine pregnancy test (females of childbearing potential) (See Section 6.12.8)
- Urinalysis (See Section 6.12.8)

- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

Dosing:

- Administer andecaliximab via IV infusion over approximately 30 (± 5) minutes
- For Cohort 2 (combination therapy andecaliximab and SP): S-1 and cisplatin chemotherapy administration will follow dosage and regimen based on subject condition, investigator discretion, institutional practice and/or the in-country label. Due to expected variation in administration schedules, chemotherapy dosing may or may not take place on Days 1 and 15 of each 28-day cycle.
- For Cohort 4 (combination therapy andecaliximab and nivolumab): Following administration of andecaliximab, administer nivolumab via IV infusion over approximately 60 (± 5) minutes

Post Dose: End of Infusion (EOI)

- Obtain blood samples for:
  - Andecaliximab concentration (30 ± 15 minutes for Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter for Cohort 4) (See Section 6.12.8)
- Record any SAEs and all AEs related to protocol mandated procedures

6.5. Continuation of Treatment

Study drug dosing will continue in the absence of disease progression or toxicity warranting discontinuation therapy.

6.5.1. Every 8 Weeks for Cohorts 1, 2 and 4
Every 9 Weeks for Cohort 3

For subjects continuing treatment, or subjects who discontinue all treatment prior to disease progression but remain on study, the following will be performed and documented every 8 weeks (± 5 days) for subjects in Cohorts 1 (andecaliximab monotherapy), 2 (combination therapy andecaliximab and SP), and 4 (combination therapy andecaliximab and nivolumab), and every 9 weeks (± 5 days) for subjects in Cohort 3 (combination therapy andecaliximab and SOX):

- Assessment of tumor response
  - CT or MRI
- If not collected in the last 2 weeks, obtain blood samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - For Cohort 4 (combination therapy andecaliximab and nivolumab): Thyroid function tests (See Section 6.12.8)
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.6. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.6). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. It is recommended that the investigator consults with the medical monitor prior to removing the subject from study for any reason except subject withdrawal of consent.

6.7. Criteria for Discontinuation of Study Treatment

See Sections 3.5 and 3.7 for discontinuation criteria.

6.8. End of Treatment

EOT assessments will be requested from subjects in all cohorts who discontinue all treatment prior to disease progression. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks (for Cohorts 1, 2, and 4) or every 9 weeks (for Cohort 3) until disease progression.

The following will be performed and documented at the EOT visit:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- If not conducted in the last 2 weeks, obtain blood samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - Andecaliximab concentration (See Section 6.12.8)
  - Anti-andecaliximab antibodies (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
  - For Cohort 4 (combination therapy andecaliximab and nivolumab): Thyroid function tests (See Section 6.12.8)
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.9. End of Study Visit

The following will be performed and documented at the EOS visit:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Coagulation (See Section 6.12.8)
  - Andecaliximab concentration (See Section 6.12.8)

- Anti-andecaliximab antibodies (See Section 6.12.8)
- Blood biomarkers (See Section 3.11)
- Urine pregnancy test for females of childbearing potential (See Section 6.12.8)
- Urinalysis (See Section 6.12.8)
- For Cohort 4 (combination therapy andecaliximab and nivolumab): Thyroid function tests (See Section 6.12.8)

- CT or MRI (if not conducted within the previous 28 days)
- Tumor tissue biopsy (at progression for Cohorts 2 and 3, CCI [redacted])
- Review of concomitant medication(s)
- Record any SAEs and all AEs related to protocol mandated procedures

6.10. Follow-up Visits

6.10.1. 30-Day Safety Follow-Up

A safety follow-up visit will be performed 30 days (± 7 days) after the last dose of andecaliximab. The 30-day safety follow-up visit may be substituted by a scheduled study visit if it occurs within the same window. The following will be performed and documented at the 30-day follow-up visit:

- Modified PE capturing changes from prior examinations and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Anti-andecaliximab antibodies (See Section 6.12.8)
  - Urine pregnancy test for females of childbearing potential (See Section 6.12.8)
  - Urinalysis (See Section 6.12.8)
  - For Cohort 4 (combination therapy andecaliximab and nivolumab): Thyroid function tests (See Section 6.12.8)
  - For Cohort 4 (combination therapy andecaliximab and nivolumab): Blood biomarkers (See Section 3.11)

- Review of concomitant medication(s)
- Record any SAEs and all AEs

For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

6.10.2. Cohort 4 (Combination Therapy Andecaliximab and Nivolumab) Only: 5-Month Safety Follow-Up

A safety follow-up visit will be performed 5 months (± 7 days) following the last dose of nivolumab for subjects in Cohort 4 (combination therapy andecaliximab and nivolumab). The 5-month follow-up visit may be substituted by a scheduled study visit if it occurs within the same window. The following will be performed and documented at the 5-month follow-up visit:

- Obtain blood and/or urine samples for:
  - Chemistry (See Section 6.12.8)
  - Hematology (See Section 6.12.8)
  - Anti-andecaliximab antibodies (See Section 6.12.8)
  - Urine pregnancy test for females of childbearing potential (See Section 6.12.8)
  - Urinalysis (See Section 6.12.8)
  - Thyroid function tests (See Section 6.12.8)
  - Blood biomarkers (See Section 3.11)
- Review of concomitant medication(s)
- Record any SAEs and all AEs

6.10.3. Long Term Follow-Up

Long term follow-up (LTFU) for OS begins after the EOS visit, or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy, cancer-related surgery for up to 5 years after the EOS visit.

Subjects who are not deceased by the time Gilead has made the determination the study will be ended will receive a final follow-up phone call to assess survival status and communicate the sponsor's decision.

The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect survival information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject (ie, dates of phone calls, registered letters, etc).

6.11. Replacement of Subjects

In Cohort 1 (andecaliximab monotherapy), if a subject is withdrawn from the study for any reason other than a DLT prior to completion of the DLT assessment window, a replacement subject will be enrolled.

6.12. Description of Study Procedures

6.12.1. Informed Consent

All subjects must sign and date the most recent IRB/IEC-approved informed consent form before any study specific procedures are performed. CCI [redacted]

6.12.2. Re-Screening Criteria

Subjects who fail to meet eligibility or complete the initial screening will be permitted to rescreen provided that the reason for screen failure has been resolved and no new exclusions have been identified. If the subject is rescreened > 28 days from their original screening date (date of informed consent), all screening activities, including informed consent, need to be repeated.

Subject eligibility must be determined by results received from the central lab. However, if there have been 2 failed attempts to obtain test results from the central lab, eligibility may be determined using local lab results, with documentation of failed attempts, local lab results and sponsor approval.

6.12.3. Medical & Medication History

A complete medical and surgical history will be obtained by the investigator or designee at screening, including disease history, and recorded on the electronic case report form (eCRF).

All medications taken within 28 days prior to screening and during the screening period will be obtained prior to Day 1 and recorded on the eCRF. For all cohorts, at each study visit the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, vitamins and minerals.

In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and recorded on the eCRF.

6.12.4. Physical Examination

A complete PE will be performed for all cohorts at screening. This will include assessment of clinical signs and symptoms. The exam will be performed by a physician or designee qualified to perform assessments. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the healthcare provider.

For Cohorts 1, 2, and 4, a modified physical exam capturing changes from prior exams will be performed on Day 1 and 15 of each 28-day cycle, at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit.

For Cohort 3, a modified physical exam capturing changes from prior exams will be performed on Day 1 of each 21-day cycle, at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit.

Weight (without shoes) should be measured with each PE (complete and modified) and reported in kilograms. Height (without shoes) should be measured at screening only and reported in centimeters. Weight will be collected any time a complete or modified PE is performed.

Pre dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from pre dose baseline PE which represent a clinically significant deterioration will be documented on the AE page of the eCRF.

6.12.5. Vital Signs

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured by the investigator or qualified designee as per standard institutional guidelines at each study visit as indicated in Appendix 2-Appendix 5.

All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.12.6. Electrocardiogram Assessment

For all cohorts, a single 12-lead ECG will be collected at screening, on Day 1 of each cycle, and at the EOS Visit, per standard practice.

The investigator or qualified designee will review all ECGs and retain the tracing with the source documents. Appropriate data will be reported on the eCRF.

6.12.7. Performance Status

Performance status will be scored using the ECOG performance status scale index at each study visit (for all cohorts) as indicated in Appendix 2-Appendix 5. ECOG used to determine eligibility must be the performance status during the screening period.

6.12.8. Laboratory Assessments

The central laboratory will be responsible for chemistry, hematology, coagulation, urinalysis, and serum pregnancy testing (per Table 6-1) as well as processing and/or storage of other study samples. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual.

If central laboratory results are not available, local laboratories may be used for dosing decisions. Local laboratory assessments resulting in a dose change or as part of an adverse event assessment, which is not supported by central lab results, will be reported on the eCRF.

Urine pregnancy test will be performed at the site.

The date and time of blood and/or urine sample collection will be recorded in the subject's source documentation and reported to the central laboratory. Screening laboratory samples should be obtained within 28 days prior to enrollment. Specified Day 1 pre dose samples may be drawn up to 2 days prior to the Day 1 visit (see Appendix 2-Appendix 5). The tests will be analyzed using standard procedures. White blood cell differentials will be reported as absolute counts.

Blood samples will be obtained for chemistry, hematology, coagulation, pregnancy testing for female subjects, andecaliximab concentration and anti-andecaliximab antibodies, and serum and plasma biomarkers as indicated in Appendix 2-Appendix 5. Urine samples will be obtained for urinalysis and pregnancy testing for female subjects as indicated in Appendix 2-Appendix 5.

Table 6-1. Analytes

Serum Chemistry	Urinalysis	Hematology	Other
Albumin	Color and appearance	WBC	Serum β-hCG[c] (females)
Alkaline phosphatase	Specific gravity	Hemoglobin	Urine pregnancy test[c] (females)
ALT	pH	Hematocrit	Andecaliximab concentration
AST	Occult blood	Platelet	Anti-andecaliximab antibodies
Bicarbonate	Protein	ANC	Serum and plasma biomarkers
BUN	Glucose		
Calcium	Bilirubin	Differential	***COHORT 4 ONLY:*** Thyroid Function Tests: (TSH, T3, free T4)[d]
Chloride	Leukocyte esterase	Eosinophils	
Creatinine[a]	Nitrite	Lymphocytes	
Glucose	Urobilinogen	Monocytes	
Amylase	Ketones	Neutrophils	
Lipase	Microscopic[b]		
Magnesium		**Coagulation**	
Phosphorus			
Potassium		PT/INR	
Sodium		aPTT	
Total bilirubin			
Direct bilirubin			
Total protein			
CA19-9			
CEA			
hsCRP			
COHORTS 3 & 4 ONLY:			
AFP			

Abbreviations: AFP = alpha-fetoprotein; ANC = absolute neutrophil count; ALT = alanine aminotransferase; aPTT = Activated Partial Thromboplastin Time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; β-hCG = betahuman chorionic gonadotropin; HER2 = human epidermal growth factor receptor 2; INR = International Normalized Ratio; hsCRP = High sensitivity C-Reactive protein; PT = Prothrombin Time; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Estimated creatinine clearance (CLcr)/glomerular filtration rate will be calculated based on the Cockroft-Gault formula using actual body weight: CLcr (mL/min) = (140 – age [years])* weight (kg) / (serum creatinine [mg/dL]*72). If the subject is female, multiply the quantity by 0.85.

b Reflex testing based on other abnormalities

c Females of child-bearing potential only. Serum pregnancy will be conducted at Screening. Urine pregnancy tests will be performed at the time points specified in Section 6.12.8.1 and Appendix 2-Appendix 5.

d TSH, T3, free T4 will be test by the central laboratory at screening. At the every 8 week visit and beyond, T3 and T4 will be tested reflexively based on abnormal TSH results.

At any time during the study, abnormal laboratory parameters that are clinically relevant (eg, lead to clinical symptoms or signs, require therapeutic intervention), and constitute an AE must be recorded in the eCRF. All laboratory tests must be reviewed for clinical significance by the investigator or qualified designee.

6.12.8.1. Pregnancy Test

All females of childbearing potential (see Appendix 9) will have a serum pregnancy test at screening.

For female subjects in Cohort 1 (andecaliximab monotherapy), urine pregnancy tests will be performed on Cycle 1 Day 1 Pre Dose, at the EOS visit and at the 30-day safety follow-up visit.

For female subjects in Cohort 2 (combination therapy andecaliximab and SP), urine pregnancy tests will be performed Pre Dose on Days 1 and 15 of each 28-day cycle, at the EOS visit, and at the 30-day safety follow-up visit.

For female subjects in Cohort 3 (combination therapy andecaliximab and SOX), urine pregnancy tests will be performed Pre Dose on Day 1 of each 21-day cycle, at the EOS visit, and at the 30-day safety follow-up visit.

For female subjects in Cohort 4 (combination therapy andecaliximab and nivolumab), urine pregnancy tests will be performed Pre Dose on Days 1 and 15 of each 28-day cycle, at the EOS visit, and at the 30-day and 5-month safety follow-up visits.

The results must be confirmed as negative prior to administration of study drug on the respective days the test is performed.

6.12.8.2. HER2 Testing

Prior to enrollment in Cohorts 1 (andecaliximab monotherapy), 2 (combination therapy andecaliximab and SP), and 3 (combination therapy andecaliximab and SOX), the subject's tumor should have been tested for HER2 status with approved IHC and in situ hybridization (ISH) kits. HER2 positivity is defined as IHC3+ or IHC2+/ISH+ (ISH positivity is defined as HER2:CEP17 ratio of ≥ 2.0). Results for HER2 status obtained prior to signing informed consent are acceptable if obtained with approved IHC and ISH kits. HER2 status may be determined during screening by testing the tumor at the central lab or a local lab with approved IHC and ISH kits.

6.12.8.3. Andecaliximab Pharmacokinetics

For Cohort 1 (andecaliximab monotherapy), plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (±15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit. Additionally, PK plasma samples will be collected at the following time points in Cycle 1 only: 30 (±15) minutes after the end of infusion on Day 1; anytime on Days 2, 4, and 8; prior to dosing and 30 (±15) minutes after the end of infusion on Day 15.

For Cohort 2 (combination therapy andecaliximab and SP), plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (±15) minutes after the end of andecaliximab infusion on Day 1 and prior to andecaliximab dosing on Day 15. Additionally, plasma samples for

andecaliximab PK will be collected prior to andecaliximab dosing and 30 (±15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter, and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.

For Cohort 3 (combination therapy andecaliximab and SOX), plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (±15) minutes after the end of andecaliximab infusion on Day 1. Additionally, plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (±15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter, and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.

For Cohort 4 (combination therapy andecaliximab and nivolumab), plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (± 15) minutes after the end of andecaliximab infusion on Day 1, anytime on Day 8, and prior to andecaliximab dosing and 30 (± 15) minutes after the end of infusion on Day 15. Additionally, plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (±15) minutes after the end of infusion on Day 1 and Day 15 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter, and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.

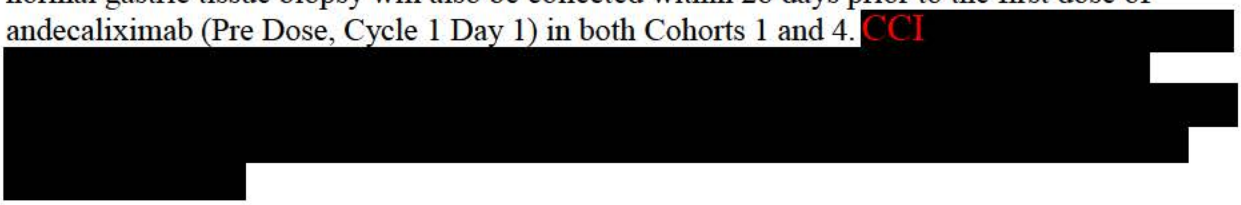
6.12.8.4. Anti-Andecaliximab Antibodies

For all cohorts, blood samples for anti-andecaliximab antibodies will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter, at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, and at the 30 day safety follow-up visit.

For Cohort 4 (combination therapy andecaliximab and nivolumab), blood samples for anti-andecaliximab antibodies will also be collected at the 5-month safety follow-up visit.

6.12.8.5. Tumor Tissue Biopsy

Cohorts 1 (andecaliximab monotherapy) and 4 (combination therapy andecaliximab and nivolumab): Tumor tissue biopsy will be collected within 28 days prior to the first dose of andecaliximab (Pre Dose, Cycle 1 Day 1) in both Cohorts 1 and 4, on Cycle 2 Day 15 (+ 5 days) for Cohort 1, and at 6 weeks (± 1 week) after the first dose of andecaliximab for Cohort 4. A normal gastric tissue biopsy will also be collected within 28 days prior to the first dose of andecaliximab (Pre Dose, Cycle 1 Day 1) in both Cohorts 1 and 4. CCI



Cohorts 2 (combination therapy andecaliximab and SP) and 3 (combination therapy andecaliximab and SOX): Tumor tissue biopsy will be collected within 28 days prior to the first dose of andecaliximab (Pre Dose, Cycle 1 Day 1) and at EOS with documented disease progression. A normal gastric tissue biopsy will also be collected within 28 days prior to the first dose of andecaliximab (Pre Dose, Cycle 1 Day 1). Endoscopic samples (minimum 4, but 6-8

encouraged) or 18 gauge needle biopsies (4 passes) of metastases to liver or lymph nodes are acceptable and are to be processed as described in the laboratory manual.

6.12.8.6. Archival Tumor Tissue

Archival tumor tissue formalin-fixed paraffin embedded (FFPE) blocks will be collected from all subjects and shipped to the central laboratory for sectioning. If blocks are not available to be shipped, 15 x 5-micron slides and 5 x 10-micron slides prepared within 2 weeks from the archival tissue block are requested. Efforts to acquire the archival tissue should begin on Day 1 of Cycle 1.

6.12.8.7. Biomarkers

Samples for biomarker analysis will be obtained as indicated in Section 3.11.

6.12.9. Tumor Response Assessment

6.12.9.1. Tumor Imaging

Either contrast-enhanced CT or gadolinium-enhanced MRI of the chest, abdomen, and pelvis will be performed at screening (scans taken as part of medical practice within 28 days of Day 1 are acceptable), every 8 weeks (for Cohorts 1, 2, and 4) or every 9 weeks (for Cohort 3), and at the EOS visit if one has not been performed within the previous 28 days. Tumor burden will be evaluated solely based on radiographic imaging per RECIST v1.1. Chest x-ray, ultrasound, endoscopy, laparoscopy, positron-emission tomography, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up.

Scans taken as part of standard medical practice up to 28 days prior to enrollment can be used for screening as long as they meet all study requirements. During the treatment phase, scans may be performed at time points other than every 8 or 9 weeks as clinically indicated to assess tumor progression.

If a subject has discontinued all study treatments prior to definitive disease progression, the subject shall remain on study until at least 1 of the criteria for discontinuation from study is met (Section 3.7). Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks (for Cohorts 1, 2, and 4) or every 9 weeks (for Cohort 3) until disease progression. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. It is recommended that the investigator consults with the medical monitor prior to removing the subject from study for any reason except subject withdrawal of consent.

6.12.9.2. Efficacy Measurements for Cohort 4 (Combination Therapy Andecaliximab and Nivolumab) ONLY

RECIST version 1.1 {Eisenhauer 2009} (Appendix 10) will be used for assessment of tumor responses for the purposes of study evaluation, managing patients on protocol treatment, and decision making for discontinuation of study therapy due to disease progression, with some modifications to account for atypical responses which may occur with immune-based therapies {Swaika 2015}. Given that anti PD-1 agents produce antitumor effects by potentiating endogenous cancer-specific immune responses, the response patterns seen with these agents may extend beyond the typical time course of responses seen with cytotoxic agents. In addition, anti-PD-1 therapies can occasionally manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions ("tumor flare" or "pseudoprogression") {Topalian 2014}. In these cases, standard RECIST may not provide an accurate response assessment of anti PD-1 agents.

Therefore, for subjects enrolled in Cohort 4, RECIST 1.1 will be used (Appendix 10) with the following adaptations:

If imaging shows a CR or PR, tumor imaging should be repeated at least 4 weeks (≥4 weeks) later to confirm response, per RECIST 1.1 guidelines. Subjects will then return to regular scheduled imaging every 8 weeks starting with the next protocol-specified imaging time-point (every 8 weeks from Day 1).

Subjects who obtain a confirmatory scan do not need to undergo scheduled imaging assessment ≤ 2 weeks later (eg, if a subject obtains a scan at Week 22 to confirm a Week 16 response, they will not also be required to complete the scheduled Week 24 scan).

If imaging shows progressive disease (PD), it is at the discretion of the investigator to keep the subject on study treatment or to stop study treatment until imaging is repeated ≥4 weeks later in order to confirm PD (adapted from the immune-related response criteria recommendations) {Wolchok 2009}. Patients that are deemed clinically unstable or who have biopsy-proven new metastatic lesions are not required to have repeat imaging for confirmation. The decision to continue a subject on study while awaiting PD confirmation will be based on clinical judgment of a subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

At a minimum, subjects must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

- Absence of signs and symptoms (including worsening laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or of progressive disease at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Study treatment may continue under the following circumstances after repeat/confirmatory imaging (≥4 weeks after initial scan showing PD):

- If repeat imaging shows < 20% tumor burden increase compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued and/or resumed (PD is not confirmed).

- If repeat imaging confirms PD due to any of the scenarios listed below, subjects will be discontinued from study therapy with the following exception: if the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging compared to the initial PD assessment, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed at the protocol specified intervals.

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

If repeat imaging shows an objective response or stable disease relative to nadir, treatment with study medication may continue and subjects will return to regular scheduled imaging every 8 weeks starting with the next protocol-specified imaging time-point. Subjects who obtain a confirmatory scan do not need to undergo scheduled imaging assessment ≤ 2 weeks later (eg, if a subject obtains a scan at Week 14 to confirm a Week 8 PD and progression is not confirmed, they will not also be required to complete the scheduled Week 16 scan).

Progressive Disease is confirmed at repeat imaging if:

- Tumor burden remains ≥ 20% (and at least 5 mm absolute increase) compared to nadir

- Non-target disease resulting in initial PD is worse (qualitative)

- New lesion(s) resulting in initial PD is worse (qualitative)

- Additional new lesion(s) since last evaluation

If repeat imaging confirms PD, subjects will be discontinued from study therapy.

Table 6-2. Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by RECIST (see modifications in protocol)	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR, or CR by RECIST (see protocol for details)	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 8 week imaging schedule

In subjects who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following guidelines for end of study follow-up (Section 6.6).

When feasible, subjects should not be discontinued until progression is confirmed; investigators should discuss with the Gilead Medical Monitor prior to subject discontinuation.

6.12.10. Study Drug and Anti-Cancer Agent Administration

For Cohort 1, andecaliximab 800 mg (or 600 mg if applicable) will be administered via IV infusion over approximately 30 (± 5) minutes on Days 1 and 15 of each 28-day cycle. For Cohorts 2, and 4, andecaliximab 800 mg will be administered via IV infusion over approximately 30 (± 5) minutes on Days 1 and 15 of each 28-day cycle. For Cohort 3, andecaliximab 1200 mg will be administered via IV infusion over approximately 30 (± 5) minutes on Day1 of each 21-day cycle. Study drug dosing must be documented on the eCRF.

Subjects in Cohort 2 will also be administered S-1 orally twice daily, and cisplatin administered by IV infusion on Day 8 of every 5 weeks, with the dosage and regimen based on subject condition, investigator discretion, institutional practice and/or the in-country label. Chemotherapy dosing and regimen changes must be documented on the eCRF.

Subjects in Cohort 3 will also be administered S-1 orally twice daily at 80 mg/day for BSA $< 1.25m^2$, 100 mg/day for BSA ≥ 1.25 to $< 1.5m^2$, and 120 mg/day for BSA $\geq 1.5m^2$ for the first 14 days of the 21-day cycle. Oxaliplatin will be administered by IV infusion at 100 mg/m^2 over 2 hours on Day 1 of each 21-day cycle. Chemotherapy dosing and regimen changes must be documented on the eCRF.

Subjects in Cohort 4 will also be administered nivolumab 3 mg/kg via IV infusion over approximately 60 (± 5) minutes following administration of andecaliximab.

6.12.11. Adverse Events

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures on the adverse events eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.12.12. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Unscheduled procedures, including, but not limited to, vital signs, 12-lead ECG, and CT or MRI may be conducted at these visits. Data generated during an unscheduled visit will be collected on the eCRF.

6.12.13. Protocol Deviations

Gilead's policy prohibits exemptions from protocol inclusion/exclusion criteria. In the event of a significant deviation related to gross non-compliance from the protocol or incidences that impose significant risk to subject safety, the investigator or designee must notify Gilead and/or its designee immediately. The site will be required to document deviations in accordance with Gilead's procedures and in accordance with the site's procedures and processes.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre or post treatment complications that occur as a result of protocol specified procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for chemotherapy infusion per institutional guidelines, elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization (Note: Hospitalization for chemotherapy infusion or other 'social hospitalization' per institutional guidelines will not be considered an SAE)

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

To maintain the integrity of the study, disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

In addition, events that are indicative of the following disease-related SAEs that are assessed as unrelated to study drugs will not be reported as expedited reports by Gilead during the study:

- Progression of gastric cancer

- Death related to disease progression

These events will be exempt from global expedited reporting requirements for the duration of the study as they are the primary endpoints of this study. They will be reported as appropriate in the final clinical study report as well as any relevant aggregate safety report.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the

definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (eg, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication)
- **Yes**: There is reasonable possibility that the event may have been caused by the study drug

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 in the study manual.

If a CTCAE term is not available for the AE/SAE, the severity will be graded using Grade 1 through Grade 5 as defined in the CTCAE definitions.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe (Grade 3) reaction is not necessarily a serious reaction.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF):

- All SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, until 30 days after last administration of andecaliximab and 5 months post-treatment of nivolumab, must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible.

Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol required post treatment follow-up period, must be reported to the eCRF database and Gilead DSPH as instructed. This also includes any SAEs resulting from protocol associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of andecaliximab and 5 months post-treatment of nivolumab, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period, however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline

- SAEs will be reported using an electronic SAE (eSAE) system

7.3.2.1. Electronic Serious Adverse Events (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database within 24 hours of the investigator's knowledge of the event. Immediately after SAE data are recorded in the database, Gilead DSPH and Gilead Japan DSPH are notified via email that new SAE data are available. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH

Fax: PPD
Email: PPD

Gilead DSPH will immediately forward the information received to DSPH at Gilead Japan.

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form

7.3.2.2. Communication of Study Safety Information to Study Sites

Gilead Japan will conduct weekly calls with study investigators in Japan. During these calls, reviews of safety events observed in all subjects in the study will be reviewed. Additionally, safety data will be collected and distributed to sites per the appropriate Gilead Standard Operating Procedures and local GCP. In the event of major safety events, Gilead Japan will urgently contact investigators via email or phone. Study monitoring will be performed by the local CRO, Gilead Japan, and Gilead USA (available by phone, email, or fax as described in the protocol). The following table outlines the methods for sharing emerging safety alert in Study GS-US-296-1884 with investigators.

Major Safety Information	Other Safety Information
Urgent/emergent communication via email/phone with investigators within 24 hours of determining an urgent safety measure needs to be disseminated to investigators	Weekly investigator calls with minutes distributed to all participants
Weekly investigator calls with minutes distributed to all participants	Updates to informed consent form (ICF)
Updates to ICF	Updates to Investigator Brochure if there is any safety signal identified and routine annual updates
Updates to Investigator Brochure if there is any safety signal identified	Expedited reporting
	Investigator Safety Letter is required for all suspected unexpected serious adverse reactions (SUSARs) occurring in any GSI sponsored conventional clinical trials and compassionate use trials. Those safety letters will be distributed to all investigators accordingly.

7.3.2.3. Communication of Andecaliximab Safety Information from Other Studies

Safety information related to andecaliximab from other than the proposed study will be collected according to the same processes as for this study. For non-serious safety information, adverse events are collected through electronic data capture (EDC) system and databased in Gilead's clinical database. Pre-clinical safety data that is non-urgent in nature will be presented to DSPH for inclusion in periodic aggregate reports. SAEs are collected/databased into both the Gilead safety (DSPH) database and clinical database according to the timelines specified in the clinical protocol or, in the event that a CRO is involved in safety reporting, per relevant Clinical Trial Safety Reporting Procedure.

Urgent safety issues from any source are presented to Gilead clinical and safety representatives as urgently as possible for cross functional committee review. Safety data will be collected at night/after business hours/holidays via the eCRF system and will be assessed by Gilead immediately. If the eCRF database is not available, data should be collected via a paper reporting form, for SAEs this data should be recorded within 24 hours. Protocol Section 7.3 describes this process in more detail.

In the event of a major safety event, Gilead Japan will urgently contact investigators via email or phone within 24 hours of determining an urgent safety measure needs to be disseminated to investigators. Routine safety data from other studies will be shared in annual investigator brochure updates. The following table outlines the methods for sharing emerging safety information with Study GS-US-296-1884 investigators.

Major Safety Information	Other Safety Information
Urgent/emergent communication via email/phone with investigators within 24 hours of determining an urgent safety measure needs to be disseminated to investigators	Updates to ICF
Weekly investigator calls with minutes distributed to all participants	Updates to Investigator Brochure if there is any safety signal identified and routine annual updates
Updates to ICF	Investigator Safety Letter is required for all SUSARs occurring in any GSI sponsored conventional clinical trials and compassionate use trials. All investigators receive a copy of the investigator safety letters.
Updates to Investigator Brochure if there is any safety signal identified	

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE (version 4.03).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences medical monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results. Laboratory abnormalities (eg, thiamine deficiency) identified at screening/baseline and during study participation should be treated at the investigators discretion.

Any questions regarding toxicity management should be directed to the Gilead Sciences medical monitor or designee.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Gilead DSPH contact information is as follows:	Email: Fax:	PPD PPD

Refer to Appendix 9 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective is:

- To characterize the safety and tolerability of andecaliximab as monotherapy and in combination with anti-cancer agents in Japanese subjects with inoperable advanced or recurrent gastric or GEJ adenocarcinoma

The secondary objectives are:

- To characterize the PK of andecaliximab
- To evaluate the formation of anti-andecaliximab antibodies

The exploratory objectives are:

[redacted]

8.1.2. Primary Endpoint

The primary endpoint is safety, which will be evaluated by clinical laboratory test findings, PEs, 12-lead ECGs, vital signs measurements, and incidence of AEs in each treatment dose level/cohort.

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Plasma concentrations and PK parameters (e.g. C_{max}, AUC) of andecaliximab
- Incidence rate of positive anti-andecaliximab antibodies

8.1.4. Other Endpoints of Interest

Exploratory endpoints of interest are:

[redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least 1 infusion at any dose of andecaliximab. This analysis set will be used for both safety and efficacy analyses.

8.2.1.2. Pharmacokinetic/Pharmacodynamic Analysis Set

The PK/PD Analysis Set is defined as all subjects in the Safety Analysis Set who have the necessary baseline and on study measurements to provide interpretable results for specific parameters of interest.

8.2.1.3. Biomarkers

Refer to Section 8.8 for Biomarker Analysis.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 90% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n,

percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2 sided. Data will be described and summarized by dose level/cohort, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier (KM) curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pretreatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

The following censoring conventions will be applied to tumor control endpoints:

- PFS: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive progression was objectively documented. Data from subjects who have disease progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of definitive disease progression was objectively documented.

- OS: Data from surviving subjects will be censored at the last time that the subject was known to be alive.

- DOR: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive disease progression was objectively documented. Data from subjects who have disease progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of definitive disease progression was objectively documented.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized for the Safety Analysis Set by treatment dose level/cohort using standard descriptive methods

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height and body mass index.

8.5. Efficacy Analysis

The efficacy of andecaliximab when used as monotherapy or in combination with chemotherapy will be evaluated using the Response Evaluation Criteria in Solid Tumors RECIST Version 1.1.

8.5.1. Categorical Endpoints

Categorical endpoints, such as ORR and DCR will be summarized. The corresponding 90% exact CIs may be present if appropriate.

8.5.2. Time-to-Event Endpoints

Time-to-event endpoints, such as PFS, OS, and DOR, will be analyzed using KM methods. The KM estimate of the survival function will be computed and the results will be presented using KM curves. The median will be provided along with the corresponding 90% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided.

8.5.3. Continuous Endpoints

Continuous endpoints, such as TTR and change in tumor size, will be summarized using descriptive statistics as standard. Waterfall plots may be used.

8.6. Safety Analysis

All safety data collected on or after the date that andecaliximab and if applicable, nivolumab was first administered up to 30 days after the last dose of andecaliximab or if applicable, 5 months post-treatment of nivolumab (whichever is later), will be summarized by treatment dose level/cohort. Data for the pre-treatment and post-treatment follow-up period will be included in data listings.

For categorical safety data including incidence of adverse events and categorizations of laboratory data, count and percent of subjects will be summarized. For continuous safety data including laboratory data, sample size, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized.

8.6.1. Extent of Exposure

Data on a subject's extent of exposure to study treatments (andecaliximab, S-1, cisplatin, oxaliplatin, and nivolumab) will be generated from the drug administration eCRF pages respectively. Exposure data will be summarized by treatment dose level/cohort.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term, and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of andecaliximab up to 30 days after the last dose of andecaliximab.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment dose level/cohort.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the CTCAE Version 4.03.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point post baseline will be summarized by treatment cohort. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of andecaliximab or after the subject has been discontinued from treatment for at least 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Similar general approaches to the AE and clinical laboratory data will be utilized to summarize other safety measures.

8.7. Pharmacokinetic Analysis

The plasma concentration data of andecaliximab will be summarized by nominal sampling time using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum) by dose level/cohort. Pharmacokinetic parameters (C_{max}, C_{last}, t_{max}, t_{last}, λ_z, AUC_{last}, AUC_{inf}, CL, V, and $t_{½}$, as applicable) will be listed and summarized using descriptive statistics by dose level/cohort. Plasma concentrations of andecaliximab over time may be plotted in semi logarithmic and linear formats as mean ± standard deviation by dose level/cohort.

The number and percentage of positive or negative anti-andecaliximab antibody values at each specified timepoint will be summarized. The effect of anti-andecaliximab antibodies on andecaliximab PK, safety, and efficacy may be evaluated.

8.8. Biomarker Analysis

8.8.1. Pharmacodynamic Analysis

The pharmacodynamic biomarkers of interest are described in Section 3.11. The baseline level and change over time from baseline level will be evaluated. Descriptive statistics will be provided at each sampling time, by dose level.

8.8.2. Exploratory Biomarker Analysis

CCI [redacted]

[redacted]

8.9. Sample Size

The sample size of 6 subjects in Cohort 1 allows a relatively high probability (> 65%) to observe 2 or more subjects with DLT when the true underlying probability of DLT is greater than 33.3% at current dose level.

Up to 6 subjects will be enrolled in Cohort 1 to receive 800 mg andecaliximab Q2W, and based on safety assessments, an additional 6 subjects may be enrolled in Cohort 1 to receive 600mg andecaliximab Q2W prior to proceeding with the combination therapy cohorts. Based on the dose level selected by Cohort 1, up to 6 subjects will be enrolled in Cohort 2 (combination therapy andecaliximab and SP), and up to 10 subjects will be enrolled in Cohorts 3 (combination therapy andecaliximab and SOX) and 4 (combination therapy andecaliximab and nivolumab), respectively.

Therefore, up to 38 subjects will be enrolled in the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written

informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, PE, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data

verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Used and unused study drug supplies should be destroyed on site if the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead. The site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies on site. The investigator must maintain accurate records for all study drug destroyed at the site. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If destruction of study drug on site is not possible, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. The monitor will provide further instructions for the return.

The study monitor will review IMP supplies and associated records at study monitoring visits.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 1b Study to Evaluate the Safety and Tolerability of Andecaliximab (GS-5745) as Monotherapy and in Combination with Chemotherapy in Japanese Subjects with Gastric or Gastroesophageal Junction Adenocarcinoma

GS-US-296-1884, Amendment 3, 14 July 2017

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD
PPD
Medical Monitor

PPD

14Jul2017
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table – Cohort 1 (Andecaliximab Monotherapy)

	Cohort 1 (Andecaliximab Monotherapy)											
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Cycle 1**				**Every 8 Weeks[k]**	**EOT[l]**	**EOS**	**30-Day Safety Follow-Up[m]**	**5-Year LTFU[r]**
Cycle Day	**Screening**	**1**	**15**	**2**	**4**	**8**	**29/Cycle 2 Day 1[q]**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**		**± 1**		**± 1**	**± 1**		**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Study Assessments												
Informed Consent	X											
Medical History[a]	X											
Physical Exam[b]	X	X	X				X		X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X		X	X	X	
12-Lead ECG	X	X					X			X		
ECOG Performance Status	X	X	X	X	X	X	X		X	X	X	
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	
AEs[d]	X	X	X	X	X	X	X	X	X	X	X	
CT or MRI[e]	X							X		X		
Collect Archival Tumor Tissue (if Available)[f]		X										
Sample Collection												
Chemistry	X	X[h]	X			X	X	X	X	X	X	
Hematology	X	X[h]	X			X	X	X	X	X	X	

	Cohort 1 (Andecaliximab Monotherapy)											
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Cycle 1**				**Every 8 Weeks[k]**	**EOT[l]**	**EOS**	**30-Day Safety Follow-Up[m]**	**5-Year LTFU[r]**
Cycle Day	**Screening**	**1**	**15**	**2**	**4**	**8**	**29/Cycle 2 Day 1[q]**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**		**± 1**		**± 1**	**± 1**		**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Coagulation	X	X[h]	X				X	X	X	X		
Urinalysis	X	X[h]	X				X			X	X	
Pregnancy test[g]	X	X[h]								X	X	
Andecaliximab Concentration[i]		X	X	X	X	X	X		X	X	X	
Anti-Andecaliximab Antibodies[j]		X					X		X	X		
Blood Biomarkers[n]	X	X	X	X	X	X	X	X	X	X		
Tumor Tissue Biopsy[o]		X	X									
Normal Gastric Tissue Biopsy[p]		X										
Overall Survival and Other Antitumor Therapy												X (Every 3 months)
Study Drug Dosing												
Andecaliximab IV Dosing		X	X				X					

EOS = End of Study (visit); EOT = End of treatment (visit); LTFU = Long Term Follow Up; PE = physical examination; PK: pharmacokinetics

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at screening. A modified PE capturing changes from prior exams will be performed on Day 1 and 15 of each 28-day cycle, and at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d AEs will be assessed before and after andecaliximab dosing during applicable visits.

e Tumor evaluation by CT or MRI will be performed during screening (scans taken as part of standard medical practice within 28 days of Day 1 are acceptable), every 8 weeks, and at the EOS visit (if not conducted within the previous 28 days). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject.

f Archival tumor tissue FFPE blocks will be collected from all subjects. Efforts to acquire archival tissue block should begin on Cycle 1 Day 1.

g For females of childbearing potential, a serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Cycle 1 Day 1 Pre Dose, at the EOS visit, and at the 30-day safety follow-up visit.

h Day 1 pre dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

i Plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (±15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter, at the EOT visit (if not conducted in the last 2 weeks), and EOS visit. Additionally, PK plasma samples will be collected at the following time points in Cycle 1 only: 30 (±15) minutes after the end of infusion on Day 1; anytime on Days 2, 4, and 8; prior to dosing and 30 (±15) minutes after the end of infusion on Day 15

j Blood samples for anti-andecaliximab antibodies will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter, at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, and at the 30-day safety follow-up visit.

k Every 8 Weeks (± 5 days) assessments will be performed for subjects continuing treatment, or subjects who discontinue all treatment prior to disease progression but remain on study. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), and blood samples for chemistry, hematology, coagulation, and blood biomarkers (if not collected in the last 2 weeks) every 8 weeks until disease progression.

l EOT assessments will be requested by subjects who discontinue all treatment prior to disease progression. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks until disease progression. Blood samples for hematology, coagulation, chemistry, blood biomarkers, andecaliximab concentration and anti-andecaliximab antibodies should only be collected if not conducted in the last 2 weeks.

m A safety follow-up visit will be performed 30 days (± 7 days) after the last dose of andecaliximab. The 30-day safety follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.

n Blood samples for biomarkers will be collected Pre Dose on Day 1 of each cycle, Day 15 of Cycles 1 and 2, and every 8 weeks, at the EOT (if not conducted in the last 2 weeks) visit, and EOS visit. Additionally, blood samples for biomarkers will be collected on Days 2, 4, and 8 of Cycle 1.

o Tumor tissue biopsy must be collected within 28 days prior to first dose and on Cycle 2 Day 15 (+ 5 days). Endoscopic samples (minimum 4, but 6-8 encouraged) to be processed as described in the laboratory manual.

p Normal gastric tissue biopsy must be collected within 28 days prior to first dose (Day 1 of Cycle 1 Pre Dose). Endoscopic samples (minimum 4, but 6-8 encouraged) to be processed as described in the laboratory manual.

q The Cycle 1 Day 29 visit, which overlaps with the Cycle 2 Day 1 visit, is the end of the DLT assessment window. In order for a subject to be evaluable for the DLT observation, the subject must have received the first dose of GS-5745, completed all safety procedures through Day 28, or have experienced a DLT prior to Day 28. Assessments should follow schedule for Day 1 of each 28-day cycle.

r LTFU for OS begins after the EOS visit or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy, cancer-related surgery for up to 5 years after the EOS visit.

Appendix 3. Study Procedures Table – Cohort 2: Combination Therapy Andecaliximab and SP

Cohort 2: Combination Therapy Andecaliximab and SP								
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Every 8 Weeks[r]**	**EOT[s]**	**EOS[t]**	**30-Day Safety Follow-Up[u]**	**5-Year LTFU[v]**
Cycle Day	**Screening**	**1**	**15**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[q]**	**± 1**	**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Study Assessments								
Informed Consent	X							
Medical History[a]	X							
Physical Exam[b]	X	X	X		X	X	X	
Vital Signs[c]	X	X	X		X	X	X	
12-Lead ECG	X	X				X		
ECOG Performance Status	X	X	X		X	X	X	
Prior/Concomitant Meds	X	X	X	X	X	X	X	
AEs[d]	X	X	X	X	X	X	X	
CT or MRI[e]	X			X		X		
Collect Archival Tumor Tissue[f]		X						
Sample Collection								
Chemistry	X	X[h]	X	X	X	X	X	
Hematology	X	X[h]	X	X	X	X	X	
Coagulation	X	X[h]	X	X	X	X		
Urinalysis	X	X[h]	X			X	X	

Cohort 2: Combination Therapy Andecaliximab and SP								
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Every 8 Weeks[r]**	**EOT[s]**	**EOS[t]**	**30-Day Safety Follow-Up[u]**	**5-Year LTFU[v]**
Cycle Day	**Screening**	**1**	**15**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[q]**	**± 1**	**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Pregnancy test[g]	X	X[h]	X			X	X	
Andecaliximab Concentration[i]		X	X		X	X		
Anti-Andecaliximab Antibodies[j]		X			X	X	X	
Blood Biomarkers[k]	X	X	X	X	X	X		
Tumor Tissue Biopsy[l]		X				X		
Normal Gastric Tissue Biopsy[m]		X						
Endoscopic Evaluation[n]		X						
Overall Survival and Other Antitumor Therapy								X (Every 3 months)
Dosing								
Andecaliximab IV Dosing[o]		X	X					
S-1 Dosing[p]								
Cisplatin Dosing[p]								

EOS = End of Study (visit); EOT = End of treatment (visit); LTFU = Long Term Follow Up; PE = physical examination; PK = pharmacokinetics

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at screening. A modified PE capturing changes from prior exams will be performed on Day 1 and 15 of each 28-day cycle, at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.
d AEs will be assessed before and after andecaliximab dosing during applicable visits.
e Tumor evaluation by CT or MRI will be performed during screening (scans taken as part of standard medical practice within 28 days of Day 1 are acceptable), every 8 weeks, and at the EOS visit (if not conducted within the previous 28 days). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject.
f Archival tumor tissue will be collected from all subjects with available tissue. Efforts to acquire archival tissue should begin on Cycle 1 Day 1.
g For females of childbearing potential, a serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Pre Dose on Days 1 and 15 of each cycle, at the EOS visit, and at the 30-day safety follow-up visit
h Day 1 pre dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
i Plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (± 15) minutes after the end of infusion on Day 1 and prior to andecaliximab dosing on Day 15. Additionally, plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (± 15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.
j Blood samples for anti-andecaliximab antibodies will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter; at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, and at the 30-day safety follow-up visit.
k Blood samples for biomarkers will be collected Pre Dose on Day 1 of every cycle, Day 15 of Cycles 1 and 2, and every 8 weeks; at the EOT visit (if not conducted in the last 2 weeks), and at the EOS visit.
l Tumor tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose and at EOS with documented disease progression.
m Normal gastric tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose. Do not collect if stomach is free of tumor.
n An endoscopic evaluation must be performed alongside tissue biopsy collection 28 days prior to or on Day 1 of Cycle 1 Pre Dose. Do not perform if stomach is free of tumor.
o Andecaliximab to be administered by IV infusion over 30 (± 5) minutes
p The dosage and regimen of S-1 and cisplatin will be based on subject condition, investigator discretion, institutional practice and/or in the in country label. Due to expected variation in administration schedules, chemotherapy dosing may or may not take place on Days 1 and 15 of each 28-day cycle. See Appendix 6 for proposed regimen.
q C1D1 must occur within 3 days following enrollment in IWRS. A ± 1 day window applies to visits following Cycle 1 Day 1.
r Every 8 Weeks (± 5 days) assessments will be performed for subjects continuing treatment, or subjects who discontinue all treatment prior to disease progression but remain on study. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), and blood samples for chemistry, hematology, coagulation, and blood biomarkers (if not collected in the last 2 weeks) every 8 weeks until disease progression.
s EOT assessments will be requested from subjects who discontinue all treatment prior to disease progression. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks until disease progression. Blood samples for hematology, coagulation, chemistry, blood biomarkers, andecaliximab concentration and anti-andecaliximab antibodies should only be collected if not conducted in the last 2 weeks.
t EOS assessments will be completed when the subject meets at least 1 criterion for study discontinuation in Section 3.7.
u A safety follow-up visit will be performed 30 days (± 7 days) after the last dose of andecaliximab. The 30-day safety follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.
v LTFU for OS begins after the EOS visit or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy, cancer-related surgery for up to 5 years after the EOS visit.

Appendix 4. Study Procedures Table – Cohort 3: Combination Therapy Andecaliximab and SOX

Cohort 3: Combination Therapy Andecaliximab and SOX							
Study Phase	**Screening**	**Each Cycle (21 Days)**	**Every 9 Weeks[s]**	**EOT[t]**	**EOS[u]**	**30-Day Safety Follow-Up Visit[v]**	**5-Year LTFU[w]**
Cycle Day	**Screening**	**1**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[r]**	**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Study Assessments							
Informed Consent	X						
Medical History[a]	X						
Physical Exam[b]	X	X		X	X	X	
Vital Signs[c]	X	X		X	X	X	
12-Lead ECG	X	X			X		
ECOG Performance Status	X	X		X	X	X	
Prior/Concomitant Meds	X	X	X	X	X	X	
AEs[d]	X	X	X	X	X	X	
CT or MRI[e]	X		X		X		
Collect Archival Tumor Tissue[f]		X					
Sample Collection							
Chemistry	X	X[h]	X	X	X	X	
Hematology	X	X[h]	X	X	X	X	
Coagulation	X	X[h]	X	X	X		
Urinalysis	X	X[h]			X	X	

Cohort 3: Combination Therapy Andecaliximab and SOX							
Study Phase	**Screening**	**Each Cycle (21 Days)**	**Every 9 Weeks[s]**	**EOT[t]**	**EOS[u]**	**30-Day Safety Follow-Up Visit[v]**	**5-Year LTFU[w]**
Cycle Day	**Screening**	**1**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[r]**	**± 5**	**N/A**	**N/A**	**± 7**	**N/A**
Pregnancy test[g]	X	X[h]			X	X	
Andecaliximab Concentration[i]		X		X	X		
Anti-Andecaliximab Antibodies[j]		X		X	X	X	
Blood Biomarkers[k]	X	X	X	X	X		
Tumor Tissue Biopsy[l]		X			X		
Normal Gastric Tissue Biopsy[m]		X					
Endoscopic Evaluation[n]		X					
Overall Survival and Other Antitumor Therapy							X (Every 3 months)
Dosing							
Andecaliximab IV Dosing[o]		X					
S-1 Dosing[p]		X					
Oxaliplatin Dosing[q]		X					

EOS = End of Study (visit); EOT = End of treatment (visit); LTFU = Long Term Follow Up; PE = physical examination; PK = pharmacokinetics

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at screening. A modified PE capturing changes from prior exams will be performed on Day 1 of each 21-day cycle and at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at screening only and reported in centimeters.
c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.
d AEs will be assessed before and after andecaliximab dosing during applicable visits.
e Tumor evaluation by CT or MRI will be performed during screening (scans taken as part of standard medical practice within 28 days of Day 1 are acceptable), every 9 weeks, and at the EOS visit (if not conducted within the previous 28 days). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject.
f Archival tumor tissue will be collected from all subjects with available tissue. Efforts to acquire archival tissue should begin on Cycle 1 Day 1.
g For females of childbearing potential, a serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Pre Dose on Day 1of each 21-day cycle, at the EOS visit, and at the 30-day safety follow-up visit.
h Day 1 pre dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
i Plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (± 15) minutes after the end of andecaliximab infusion on Day 1. Additionally, plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (± 15) minutes after the end of infusion on Day 1 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.
j Blood samples for anti-andecaliximab antibodies will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter; at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, and at the 30-day safety follow-up visit.
k Blood samples for biomarkers will be collected Pre Dose on Day 1 of every cycle, and every 9 weeks; at the EOT visit (if not conducted in the last 2 weeks), and at the EOS visit.
l Tumor tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose and at EOS with documented disease progression.
m Normal gastric tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose. Do not collect if stomach is free of tumor.
n An endoscopic evaluation must be performed alongside tissue biopsy collection 28 days prior to or on Day 1 of Cycle 1 Pre Dose. Do not perform if stomach is free of tumor.
o Andecaliximab to be administered via IV infusion over 30 (± 5) minutes
p S-1 to be administered orally twice daily for the first 14 days of the 21-day cycle
q Oxaliplatin to be administered by IV infusion over 2 hours on Day 1 of each 21-day cycle
r C1D1 must occur within 3 days following enrollment in IWRS. A ± 1 day window applies to visits following Cycle 1 Day 1.
s Every 9 Weeks (± 5 days) assessments will be performed for subjects continuing treatment, or subjects who discontinue all treatment prior to disease progression but remain on study. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), and blood samples for chemistry, hematology, coagulation, and blood biomarkers (if not collected in the last 2 weeks) every 9 weeks until disease progression.
t EOT assessments will be requested from subjects who discontinue all treatment prior to disease progression. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 9 weeks until disease progression. Blood samples for hematology, coagulation, chemistry, blood biomarkers, andecaliximab concentration and anti-andecaliximab antibodies should only be collected if not conducted in the last 2 weeks.
u EOS assessments will be completed when the subject meets at least 1 criterion for study discontinuation in Section 3.7.
v A safety follow-up visit will be performed 30 days (± 7 days) after the last dose of andecaliximab. The 30-day safety follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.
w LTFU for OS begins after the EOS visit or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy, cancer-related surgery for up to 5 years after the EOS visit.

Appendix 5. Study Procedures Table – Cohort 4: Combination Therapy Andecaliximab and Nivolumab

Cohort 4: Combination Therapy Andecaliximab and Nivolumab										
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Cycle 1**	**Every 8 Weeks[s]**	**EOT[t]**	**EOS[u]**	**30-Day Safety Follow-Up[v]**	**5-Month Safety Follow-Up[w]**	**5-Year LTFU[x]**
Cycle Day	**Screening**	**1**	**15**	**8**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[r]**	**± 1**	**± 1**	**± 5**	**N/A**	**N/A**	**± 7**	**± 7**	**N/A**
Study Assessments										
Informed Consent	X									
Medical History[a]	X									
Physical Exam[b]	X	X	X			X	X	X		
Vital Signs[c]	X	X	X	X		X	X	X		
12-Lead ECG	X	X					X			
ECOG Performance Status	X	X	X	X		X	X	X		
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	X	
AEs[d]	X	X	X	X	X	X	X	X	X	
CT or MRI[e]	X				X		X			
Collect Archival Tumor Tissue[f]		X								
Sample Collection										
Chemistry	X	X[h]	X	X	X	X	X	X	X	
Hematology	X	X[h]	X	X	X	X	X	X	X	
Coagulation	X	X[h]	X		X	X	X			
Urinalysis	X	X[h]	X				X	X	X	
Pregnancy test[g]	X	X[h]	X				X	X	X	

Cohort 4: Combination Therapy Andecaliximab and Nivolumab										
Study Phase	**Screening**	**Each Cycle (28 Days)**		**Cycle 1**	**Every 8 Weeks[s]**	**EOT[t]**	**EOS[u]**	**30-Day Safety Follow-Up[v]**	**5-Month Safety Follow-Up[w]**	**5-Year LTFU[x]**
Cycle Day	**Screening**	**1**	**15**	**8**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Window (Days)	**−28**	**± 1[r]**	**± 1**	**± 1**	**± 5**	**N/A**	**N/A**	**± 7**	**± 7**	**N/A**
Thyroid Function Tests (TSH, T3, free T4)[i]	X				X	X	X	X	X	
Andecaliximab Concentration[j]		X	X	X		X	X			
Anti-Andecaliximab Antibodies[k]		X				X	X	X	X	
Blood Biomarkers[l]	X	X	X	X	X	X	X	X	X	
Tumor Tissue Biopsy[m]		X	X				X			
Normal Gastric Tissue Biopsy[n]		X								
Endoscopic Evaluation[o]		X	X							
Overall Survival and Other Antitumor Therapy										X (Every 3 months)
Dosing										
Andecaliximab IV Dosing[p]		X	X							
Nivolumab Dosing[q]		X	X							

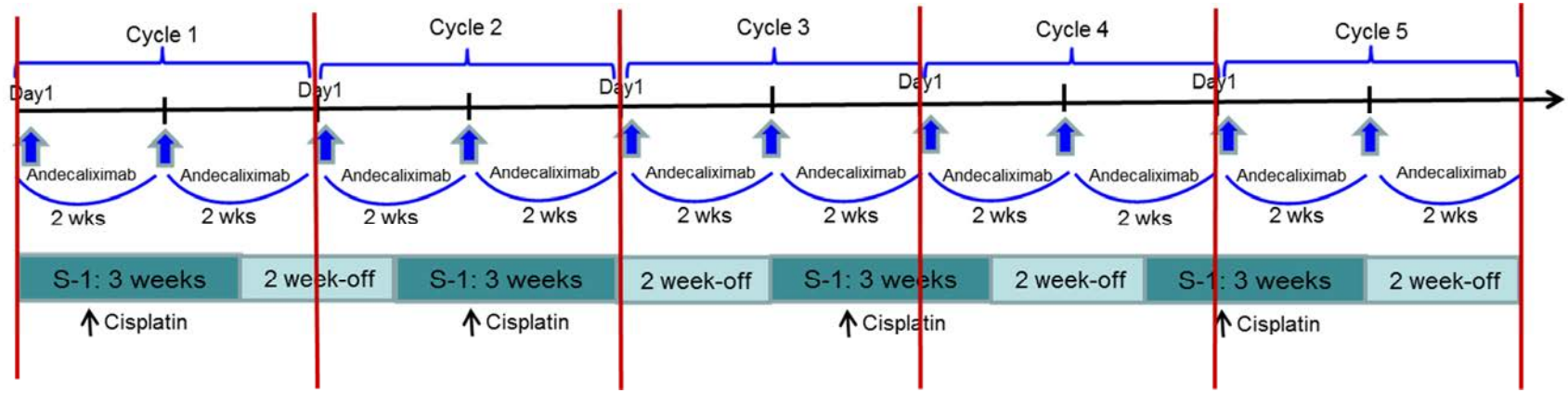
EOS = End of Study (visit); EOT = End of treatment (visit); LTFU = Long Term Follow Up; PE = physical examination; PK = pharmacokinetics; TSH = thyroid-stimulating hormone

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

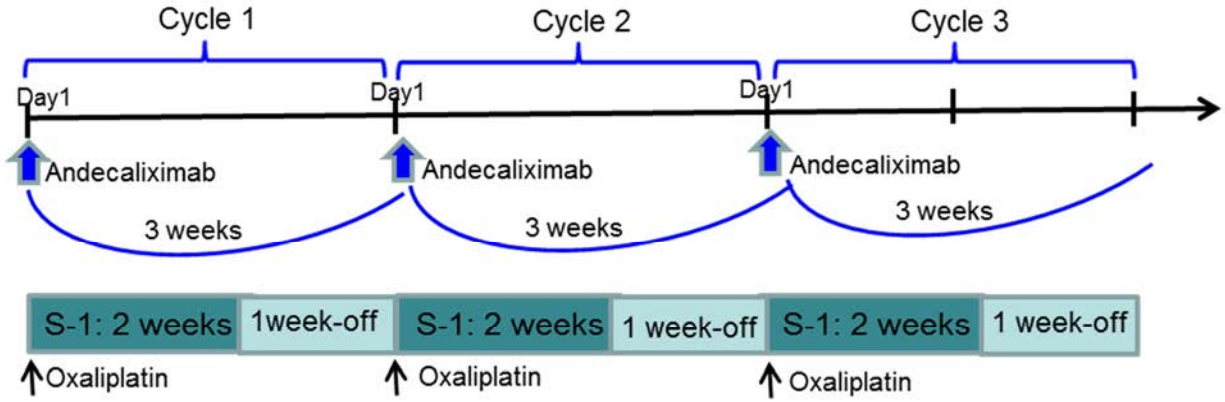
b A complete PE will be performed at screening. A modified PE capturing changes from prior exams will be performed on Day 1 and 15 of each 28-day cycle and at the EOT visit, at the EOS visit, and at the 30-day safety follow-up visit. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.
d AEs will be assessed before and after andecaliximab dosing during applicable visits.
e Tumor evaluation by CT or MRI will be performed during screening (scans taken as part of standard medical practice within 28 days of Day 1 are acceptable), every 8 weeks, and at the EOS visit (if not conducted within the previous 28 days). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject.
f Archival tumor tissue will be collected from all subjects with available tissue. Efforts to acquire archival tissue should begin on Cycle 1 Day 1.
g For females of childbearing potential, a serum pregnancy test will be performed at screening and urine pregnancy tests will be performed on Pre Dose on Days 1 and 15 of each cycle, at the EOS visit and at the 30-day and 5-month safety follow-up visits.
h Day 1 pre dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
i Blood samples for thyroid function tests will be collected at screening, every 8 weeks (± 5 days) if not performed in the last 2 weeks, at the EOT visit, at the EOS visit, and at the 30-day and 5-month safety follow-up visits.
j Plasma samples for andecaliximab PK in Cycle 1 will be collected 30 (± 15) minutes after the end of andecaliximab infusion on Day 1, anytime on Day 8, and prior to andecaliximab dosing and 30 (± 15) minutes after the end of infusion on Day 15. Additionally, plasma samples for andecaliximab PK will be collected prior to andecaliximab dosing and 30 (± 15) minutes after the end of infusion on Day 1 and Day 15 of Cycles 2, 3, 5, 7, and every 3 cycles thereafter and anytime at the EOT visit (if not conducted in the last 2 weeks), and EOS visit.
k Blood samples for anti-andecaliximab antibodies will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, 5, 7, and every 3 cycles thereafter; at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, and at the 30-day and 5-month safety follow-up visits.
l Blood samples for biomarkers will be collected Pre Dose on Day 1 of every cycle, Day 8 of Cycle 1, Day 15 of Cycles 1 and 2, every 8 weeks, at the EOT visit (if not conducted in the last 2 weeks), at the EOS visit, at the 30-day safety follow-up visit, and at the 5-month safety follow-up visit.
m Tumor tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose and at 6 weeks (± 1 week) after the first dose of andecaliximab. The on-treatment tumor tissue biopsy and endoscopic evaluation are performed at 6 weeks (± 1 week) after the first dose of andecaliximab. These assessments are not repeated at each Cycle Day 15 visit. CCI [redacted]
n Normal gastric tissue biopsy must be collected within 28 days prior to or on Day 1 of Cycle 1 Pre Dose. Do not collect if stomach is free of tumor.
o An endoscopic evaluation must be performed alongside tissue biopsy collection 28 days prior to or on Day 1 of Cycle 1 Pre Dose and between 5 and 8 weeks after the first dose of andecaliximab. Do not perform if stomach is free of tumor.
p Andecaliximab to be administered via IV infusion over 30 (± 5 minutes)
q Following administration of andecaliximab, administer nivolumab via IV infusion over approximately 60 (± 5) minutes
r C1D1 must occur within 3 days following enrollment in IWRS. A ± 1 day window applies to visits following Cycle 1 Day 1.
s Every 8 Weeks (± 5 days) assessments will be performed for subjects continuing treatment, or subjects who discontinue all treatment prior to disease progression but remain on study. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), and blood samples for chemistry, hematology, coagulation, thyroid function tests, and blood biomarkers (if not collected in the last 2 weeks) every 8 weeks until disease progression.
t EOT assessments will be requested from subjects who discontinue all treatment prior to disease progression. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study and continue to perform tumor evaluation by CT or MRI every 8 weeks until disease progression. Blood samples for hematology, coagulation, chemistry, blood biomarkers, andecaliximab concentration and anti-andecaliximab antibodies should only be collected if not conducted in the last 2 weeks.
u EOS assessments will be completed when the subject meets at least 1 criterion for study discontinuation in Section 3.7.
v A safety follow-up visit will be performed 30 days (± 7 days) after the last dose of andecaliximab. The 30-day safety follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.
w A safety follow-up visit will be performed 5 months (± 7 days) following the last dose of nivolumab. The 5-month follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.
x LTFU for OS begins after the EOS visit or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy, cancer-related surgery for up to 5 years after the EOS visit.

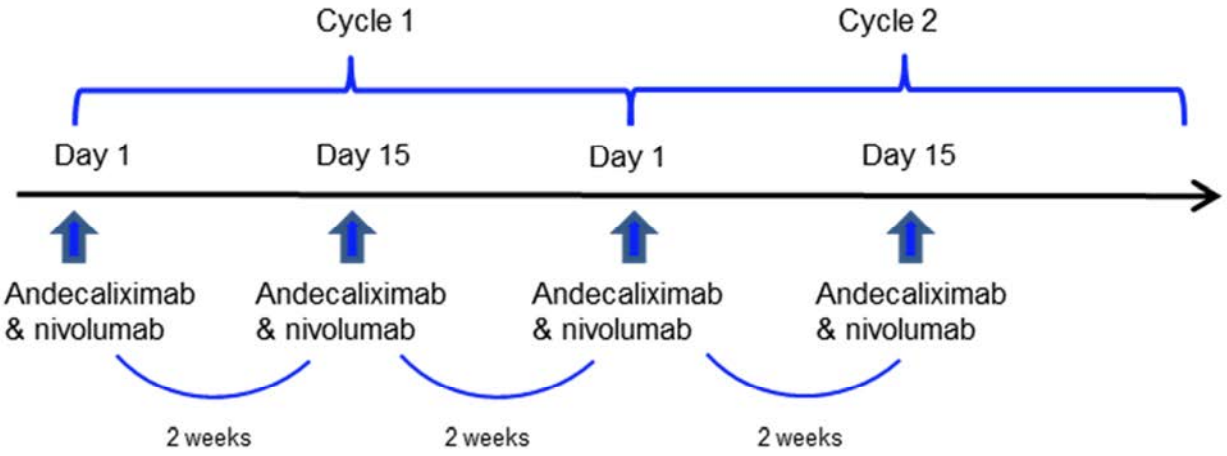
Appendix 6. Proposed Regimen for Combination Therapy Andecaliximab and SP



Appendix 7. Regimen for Combination Therapy Andecaliximab and SOX



Appendix 8. Regimen for Combination Therapy Andecaliximab and Nivolumab



Appendix 9. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with andecaliximab during pregnancy have not been evaluated in humans. The potential for genotoxicity and embryofetal toxicity is considered to be low based on nonclinical toxicological studies. In both the rat and rabbit definitive embryo-fetal developmental toxicity studies, there were no andecaliximab-related effects on embryo-fetal survival and growth and no fetal anomalies. In a fertility study in male and female rats, no test article-related effects on reproductive performance and intrauterine survival were observed at any dosage level.

Please refer to the latest version of the IB for additional information on andecaliximab.

In addition, please also refer to the latest version of the regional prescribing information for the potential risks of treatment with S-1, cisplatin, oxaliplatin, and nivolumab.

2) Definitions

a. Definition of Female of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause.
In addition, women of any age with amenorrhea of $\geq$ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy, and are without an alternative medical cause for amenorrhea.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile potential after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

3) Contraception Requirements for Female Subjects

a. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures, outlined below. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the Cycle 1 Day 1 visit prior to the first dose of study

drug. Pregnancy tests will be performed at protocol specified intervals thereafter. Female subjects must agree to one of the following methods of birth control from screening and throughout the study until 90 days following the last dose of andecaliximab and S-1, 6 months following the last dose of cisplatin and oxaliplatin, and 5 months following the last dose of nivolumab, whichever occurs later.

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure). This is not yet approved in Japan.
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  OR

- Consistent and correct use of 1 hormonal method and 1 barrier method:
  - Hormonal methods
    - Oral contraceptives (either combined estrogen/progestin or progesterone only)
    - Injectable progesterone. This is not yet approved in Japan.
    - Implants of levonorgestrel
    - Transdermal contraceptive patch. This is not yet approved in Japan.
    - Contraceptive vaginal ring
  - Barrier methods
    - Male or female condom, with or without spermicide
    - Diaphragm with spermicide
    - Cervical cap with spermicide. This is not yet approved in Japan.
    - Sponge with spermicide. This is not yet approved in Japan.

Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 90 days following the last dose of andecaliximab and S-1, 6 months following the last dose of cisplatin and oxaliplatin, and 5 months following the last dose of nivolumab, whichever occurs later.

4) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days following the last dose of andecaliximab, nivolumab and S-1, 6 months following the last dose of cisplatin and oxaliplatin, whichever occurs later. Additional contraception recommendations should also be considered for the female partner if she is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days following the last dose of andecaliximab, nivolumab and S-1, and 6 months following the last dose of cisplatin and oxaliplatin, whichever occurs later.

5) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

6) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 90 days following the last dose of andecaliximab and S-1, 6 months following the last dose of cisplatin and oxaliplatin, and 5 months following the last dose of nivolumab. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 10. Revised RECIST Guideline (Version 1.1)

Please see reference (E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) European Journal of Cancer 45(2009) 228-247.) for full RECIST guidelines.

Measurable Lesions:

- Tumor ≥10 mm in longest diameter (LD) on an axial image on CT or MRI with ≤5 mm reconstruction interval If slice thickness >5 mm, LD must be at least 2 times the thickness
- Tumor ≥20 mm LD by chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferred (even without contrast)
- Tumor ≥10 mm LD on clinical evaluation (photo) with electronic calipers; skin photos should include ruler Lesions which cannot be accurately measured with calipers should be recorded as non-measurable
- Lymph nodes ≥15 mm in short axis on CT (CT slice thickness no more than 5 mm)
- Ultrasound cannot be used to measure lesions

Note: only patients with measureable disease at baseline should be enrolled onto the study.

Non-Measurable Lesions:

- All other definite tumor lesions
  - Masses <10 mm
  - Lymph nodes 10-14 mm in short axis
  - Leptomeningeal disease
  - Ascites, pleural or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
  - Abdominal masses or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques
- Benign findings are NEVER included. Also, do not include equivocal (“cannot exclude”) findings

Target Lesions:

- Choose up to 5 lesions (up to two (2) per organ)
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the "sum of the longest diameters" (SLD)

Time point response: patients with target (+/- non target) disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = Progressive disease, and NE = inevaluable.

Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = Progressive disease, and NE = inevaluable.
a "Non-CR/non-PD' is preferred over "stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) E.A. Eisenhauer,*, P. Therasseb, J. Bogaertsc, L.H. Schwartzd, D. Sargente, R. Fordf, J. Danceyg, S. Arbuckh, S. Gwytheri, M. Mooneyg, L. Rubinsteing, L. Shankarg, L. Doddg, R. Kaplanj, D. Lacombec, J. Verweijk