STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Study to Evaluate the Safety and Tolerability of Andecaliximab (ADX) as Monotherapy and in Combination with Anti-Cancer Agents in Japanese Subjects with Gastric or Gastroesophageal Junction Adenocarcinoma
Name of Test Drug:	Andecaliximab (ADX)
Study Number:	GS-US-296-1884
Protocol Version (Date):	Amendment 3 (14 July 2017)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADX	andecaliximab
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLQ	below limit of quantitation
BUN	blood urea nitrogen
CA 19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EDC	electronic data capture
EOS	end-of-study
EOT	end of treatment
FDA	(United States) Food and Drug Administration
g	gram
GCP	Good Clinical Practice (Guidelines)
GEJ	gastroesophageal junction
β-HCG	beta human chorionic gonadotropin
HLGT	high-level group term
HLT	high-level term
ICF	informed consent form
ID	identification
INR	international normalized ratio
IV	intravenous
Kg	kilogram

L	liter
LLT	lower-level term
LTFU	long term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
MRI	magnetic resonance imaging
NN	non-CR/non-PD
ORR	objective response rate
OS	overall survival
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
Q2W	every two weeks
Q3W	every three weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SE	standard error
SOC	system organ class
StD	standard deviation
TTR	time to response
ULN	upper limit of the normal range
WBC	white blood cell count

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve
$AUC_{0\text{-}336h}$	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{336h}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the synoptic clinical study report (CSR) for Study GS-US-296-1884. This SAP is based on the study protocol amendment 3 dated 14 July 2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To characterize the safety and tolerability of ADX 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 as follows:

- To characterize the pharmacokinetics (PK) of ADX
- To evaluate the formation of anti-ADX antibodies

The exploratory objectives of this study are as follows:

[redacted]

1.2. Study Design

This is a Phase 1b, open-label, multicenter study to evaluate the safety and tolerability of ADX 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 ADX monotherapy
- Cohort 2 is combination therapy of ADX with S-1 and cisplatin (SP)
- Cohort 3 is combination therapy of ADX with S-1 and oxaliplatin (SOX)
- Cohort 4 is combination therapy of ADX with nivolumab

Cohort 1: ADX Monotherapy

Up to 6 Japanese subjects will be enrolled to receive ADX 800 mg via 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 ADX. If 2 or more subjects within the cohort of 6 subjects experience DLTs during the first 28 days of ADX 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, ADX will be considered unsafe and will be discontinued. Therefore, a total of up to 12 subjects may be enrolled in Cohort 1.

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

The SRT completed their review of all available clinical safety and PK data for 6 DLT-evaluable subjects in Cohort1 on 11 May 2017 and determined the dose for the combination therapy cohorts (Cohorts 2 and 4) to be 800 mg ADX Q2W, and Cohort 3 to be 1200 mg every three weeks (Q3W).

Cohort 2: combination therapy ADX and SP

- ADX 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. ADX 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 (Figure 1 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 (Figure 1 1)

Cohort 3: combination therapy ADX and SOX

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

Cohort 4: combination therapy ADX and nivolumab

- ADX 800 mg via IV infusion over approximately 30 (± 5) minutes Q2W until disease progression. The dose is based on safety data from Cohort 1. ADX treatment will be administered over in 28-day cycles.
- Nivolumab 3mg/kg Q2W via IV infusion over 60 (± 5) minutes following the completion of ADX administration (Figure 1 3). Dose is adjusted if the weight changes more than 10% from the baseline dosing weight.

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 according to 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 according to RECIST v1.1.

Long term follow-up (LTFU) for overall survival (OS) begins after the end-of-study (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.

Key Inclusion Criteria:

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) Histologically confirmed inoperable advanced gastric adenocarcinoma (including adenocarcinoma of the GEJ) or relapsed gastric adenocarcinoma
4) Cohorts 1 (ADX monotherapy), 2 (combination therapy ADX and SP) and 3 (combination therapy ADX and SOX): Human Epidermal Growth Factor Receptor 2 (HER2)-negative tumor (primary tumor or metastatic lesion). Enrollment in Cohort 4 (combination therapy ADX and nivolumab) is not restricted by HER2 status (subjects with HER2-positive, HER2-negative, or unknown HER2 status are eligible).
5) Cohort 1 (ADX 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 ADX dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).
6) Cohorts 2 (combination therapy ADX and SP) and 3 (combination therapy ADX 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.

7) Subjects in Cohort 4 must meet all of the following additional inclusion criteria:

   a) Measurable 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

Key Exclusion Criteria:

1) Cohort 1 (ADX 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 t½ > 10 days)

2) In addition to the applicable criteria above, subjects in Cohort 4 (combination therapy ADX 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 t½ > 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

Figure 1–1. Cohort 2 (Combination Therapy ADX and SP) Proposed Regimen

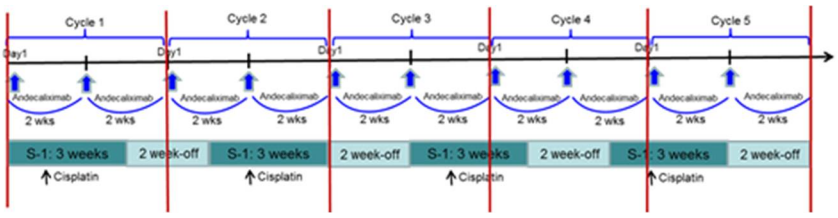


Figure 1–2. Cohort 3 (Combination Therapy ADX and SOX) Regimen

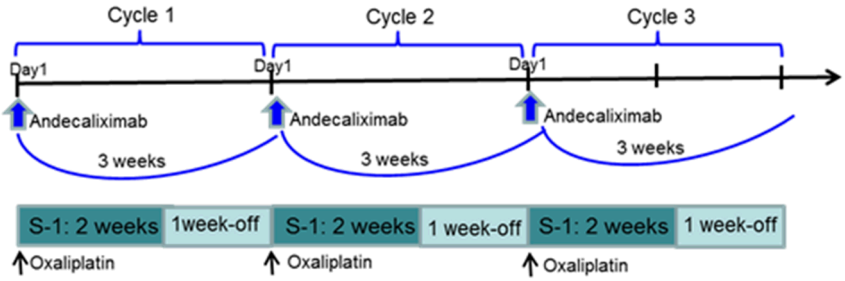
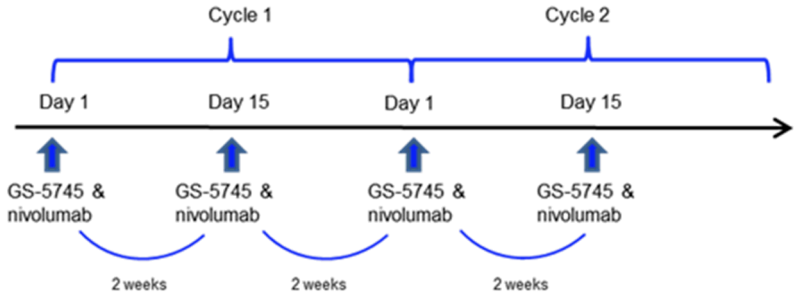


Figure 1–3. Cohort 4 (Combination Therapy ADX and Nivolumab) Regimen



For the details of the schedule of assessments, please refer to Appendix 1 through Appendix 4.

1.3. Sample Size and Power

The sample size of 6 subjects in the monotherapy cohort 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 ADX Q2W, and based on safety assessments, an additional 6 subjects may be enrolled in Cohort 1 to receive 600mg ADX Q2W prior to proceeding with the combination therapy cohorts. Therefore, a total of up to 12 subjects may be enrolled in Cohort 1.

Based on the dose level selected by Cohort 1, up to 6 subjects will be enrolled in Cohort 2 (combination therapy ADX and SP), and up to 10 subjects will be enrolled in Cohorts 3 (combination therapy ADX and SOX) and 4 (combination therapy ADX and nivolumab), respectively.

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

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned.

2.2. Final Analysis

After all subjects have completed/discontinued the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

2.3. Follow-up Analysis

No follow-up analysis is planned for this study.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by cohort and overall.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.3. Dose-Limiting Toxicity (DLT) Analysis Set

DLTs will only be evaluated for subjects in Cohort 1. The DLT Analysis Set includes Cohort 1 subjects in the Safety Analysis Set who complete all study treatment and have safety assessments through the protocol specified DLT assessment window, Day 28, inclusive, or have experienced a DLT prior to Day 28, exclusive. This is the primary analysis set for analyses related to DLTs in Cohort 1. Safety assessments relevant to the DLT analysis set definition will include serum chemistry, hematology and coagulation tests as specified in the protocol.

3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.1.5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose antidrug antibody (ADA) status reported. This is the primary analysis set for all immunogenicity analyses.

3.1.6. Biomarker Analysis Set

The Biomarker Analysis Set will include subjects who took at least 1 dose of study drug and have at least 1 evaluable biomarker measurement available.

3.2. Subject Grouping

Unless otherwise specified, subjects will be grouped by cohort for analyses:

- Cohort 1: 800 mg Q2W ADX monotherapy
- Cohort 2: combination therapy of ADX 800 mg Q2W with S-1 and cisplatin
- Cohort 3: combination therapy of ADX 1200 mg Q3W with S-1 and oxaliplatin
- Cohort 4: combination therapy of ADX 800 mg Q2W with nivolumab

For summaries where the cohorts will be aggregated, the summary results will be presented under the “Total” column.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects.
No covariates will be included in analyses.

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset date is in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Unless otherwise specified, outliers will not be excluded from the analysis in general.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth.
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth.
- If year of birth is missing, then date of birth will not be imputed.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presented in listings. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. For screen failures, the date the first informed consent was signed will be used for the age derivation.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on log-transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for analyzing plasma concentrations and PK parameters. Plasma concentration values that are below limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes. The following conventions will be used for the presentation of summary and order statistics for PK concentrations:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the date of first dose of study drug (ADX) administration and derived as follows:

- For post-dose study days: Assessment Date First Dosing Date + 1

- For days prior to the first dose: Assessment Date First Dosing Date

Therefore, study day 1 is the day of first dose of ADX administration.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the case report form (CRF) will be used when data are summarized by visit.

Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.
- Data collected on an end of treatment (EOT) visit will be summarized as a separate visit, labeled as “End of Treatment Visit”.
- Data collected on an EOS visit will be summarized as a separate visit, labeled as “End of Study Visit”.
- Data collected on a 30-day safety follow-up visit will be summarized as a separate visit, labeled as “30-Day Safety Follow-Up Visit”.
- Data collected on a 5-month safety follow-up visit will be summarized as a separate visit, labeled as “5-Month Safety Follow-Up Visit”.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by cohort for each investigator and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided by cohort and overall, as appropriate. This summary will present the number of subjects screened and the number of subjects enrolled, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- Treated with study drug (ADX) (all cohorts)

  Treatment discontinued

  - Reasons for discontinuation
- Treated with S-1 (cohorts 2 and 3)

  Treatment discontinued

  - Reasons for discontinuation
- Treated with oxaliplatin (cohort 2)

  Treatment discontinued

  - Reasons for discontinuation
- Treated with cisplatin (cohort 3)

  Treatment discontinued

  - Reasons for discontinuation
- Treated with nivolumab (cohort 4)

  Treatment discontinued

  - Reasons for discontinuation
- Completed lesion assessment
- Discontinued lesion assessment before disease progression

Reasons for lesion assessment discontinuation

- Discontinued study (including long-term follow-up for overall survival)

  Reasons for study discontinuation

For the status of study drug, lesion assessment completion, study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug specified in the protocol.

4.2.1. Exposure to Study Drug (ADX)

Exposure to ADX will be summarized by cohort for the Safety Analysis Set.

Duration of Exposure

Duration of exposure to study drug will be defined as (last dose date first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing end date is missing, the last study drug start date will be used to impute the end date of the last study drug.

Duration of exposure to ADX will be summarized using descriptive statistics.

Number of Doses

The total number of doses of ADX that each subject received during the study will be summarized using descriptive statistics. A subject is said to have received a dose of ADX if he/she received any amount of the planed dose of ADX (ie, actual dose > 0) at a visit. Additionally, the number and percentage of subjects receiving a given number of doses category will be summarized, as appropriate.

Actual Dose Amount

In addition, the total and average actual dose amount of ADX in mg that each subject received will be summarized using descriptive statistics.

The average actual dose amount of ADX is defined as (total actual dose amount received in mg) / (number of doses given), regardless of whether the doses were interrupted/completed or full/reduced.

A by-subject listing of study drug (ADX) administration will be provided by subject ID number (in ascending order) and visit (in chronological order), including dosing date/time, planned dosage, actual dosage administered, infusion outcome and reason for dose interruption (if applicable).

4.2.2. Exposure to Chemotherapy

Exposure to chemotherapy agents, including cisplatin, oxaliplatin and nivolumab, will be listed. Duration of exposure and the total number of doses that each subject received during the study will be summarized for each agent in a similar manner as for ADX. Chemotherapy received prior to study enrollment and after the start of other anti-cancer therapy will not be included in the summary.

S-1 was administered orally twice daily. A by-subject listing of S-1 administration will be provided by subject ID number (in ascending order), including dose per administration, dose frequency, start and stop date, and reason for dose interruption or modification (if applicable).

4.2.3. Exposure to Nivolumab

Exposure to nivolumab will be listed. Duration of exposure to nivolumab and the total number of doses of nivolumab that each subject received during the study will be summarized in a similar manner as for ADX.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but were enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by cohort and overall for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by cohort and overall for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

No other baseline characteristics will be summarized.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Disease-specific medical history will be summarized for the variables listed below, by cohort and overall by the number and percentage of subjects with each prepopulated condition. The summary will be provided for the Safety Analysis Set. No formal statistical testing is planned.

Variables to be summarized include:

- Type of cancer
- Pathological subtype of gastric cancer
- Disease stage at diagnosis
- Disease stage at screening
- Differentiation
- Time since diagnosis

The denominators for the percentage will be the numbers of subjects in the Safety Analysis Set corresponding to that column, except that for pathological subtype of gastric cancer, percentages will be calculated based on the number of subjects with gastric cancer in that column.

A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending order.

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

5.4. Prior Anti-cancer Therapy

Prior anti-cancer therapies will be summarized based on the Safety Analysis Set.

Number of subjects who received prior anti-cancer therapies and the number of prior regimens that each subject received will be summarized by cohort and overall using descriptive statistics. The regimens and prior therapies that the subjects received will be summarized by cohort and overall.

Number of subjects who received prior radiotherapies and the number of prior radiotherapies that each subject received will be summarized by cohort and overall.

Number of subjects who received prior surgeries or procedures and the prior surgeries or procedures that the subjects received will be summarized by cohort and overall.

By-subject listings will be provided for prior and post study anti-cancer therapies, radiotherapies, and surgery or procedures by subject ID number in ascending order.

6. EFFICACY ANALYSES

6.1. Exploratory Efficacy Endpoints

6.1.1. Definition of the Exploratory Efficacy Endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

6.1.2. Analysis of the Exploratory Efficacy Endpoints

CCI [redacted]

[redacted]

6.2. Change from Protocol-Specified Efficacy Analyses

For this synoptic CSR, the exploratory efficacy endpoints will not be derived or summarized.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the date that ADX and if applicable, nivolumab was first administered and no later than 30 days after permanent discontinuation of ADX, or if applicable, 5 months after permanent discontinuation of nivolumab (whichever is later).
- Any AEs leading to premature discontinuation of ADX and if applicable, nivolumab.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later).

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT (if applicable), PT, and cohort. For the AE categorizes described below, summaries will be provided by SOC, PT, maximum severity, and cohort:

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs related to ADX
- TEAEs related to S-1
- TEAEs related to oxaliplatin
- TEAEs related to cisplatin
- TEAEs related to nivolumab
- TEAEs related to ADX with Grade 3 or higher
- TE SAEs

- TE SAEs related to ADX
- TE SAEs related to S-1
- TE SAEs related to oxaliplatin
- TE SAEs related to cisplatin
- TE SAEs related to nivolumab
- TEAEs leading to premature discontinuation of ADX
- TEAEs leading to premature discontinuation of S-1
- TEAEs leading to premature discontinuation of oxaliplatin
- TEAEs leading to premature discontinuation of cisplatin
- TEAEs leading to premature discontinuation of nivolumab
- TEAEs leading to death (summarize by SOC and PT as all TEAEs leading to death will be Grade 5.)
- TEAEs leading to dose modification or temporary interruption of ADX
- TEAEs leading to dose modification or temporary interruption of S-1
- TEAEs leading to dose modification or temporary interruption of oxaliplatin
- TEAEs leading to dose modification or temporary interruption of cisplatin
- TEAEs leading to dose modification or temporary interruption of nivolumab

A brief, high-level summary of AEs described above will be provided by cohort and by the number and percentage of subjects who experienced the above AEs.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable) and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, all TEAEs, TEAEs of Grade 3 or higher, TE SAEs and TE ADX-related AEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided as follows:

- All AEs, indicating whether the event is treatment emergent
- All AEs with Grade 3 or higher
- All SAEs
- All AEs leading to death
- All AEs leading to premature discontinuation of any study drug (ADX, S-1, oxaliplatin, cisplatin and nivolumab)
- All AEs leading to dose modification or temporary interruption of any study drug (ADX, S-1, oxaliplatin, cisplatin and nivolumab)
- All AEs related to any study drug (ADX, S-1, oxaliplatin, cisplatin and nivolumab)
- All AEs with Grade 3 or higher related to ADX
- All deaths

7.1.6.2. Summaries of Deaths

A summary (number and percentage of subjects) of deaths will be provided by cohort. The summary will include the following categories:

- All deaths
- Deaths within 30 days of the last dosing of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later)
- Deaths beyond 30 days of the last dosing of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later)

All death will be summarized by the cause of the death (AE, PD, or other reasons).

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

A listing of the DLT AEs will be provided.

A summary of DLTs will be presented by SOC and decreasing frequency of preferred term within SOC using the DLT Analysis Set for Cohort 1.

7.2. Laboratory Evaluations

Laboratory data collected during the study, scheduled and unscheduled, will be analyzed and summarized using qualitative method.

The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

No summaries of numerical laboratory results will be provided.

7.2.2. Graded Laboratory Values

CTCAE version 4.03 will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately. Local labs will be graded based on the central lab normal ranges with in-house macro. In the event where both central and local lab results are collected in the clinical database, baseline flag, worst toxicity and toxicity shift should be derived using both central and local lab results. All central and local laboratory values will be listed.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point, up to 30 days after the last dose of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later). If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and cohort; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Worst treatment-emergent laboratory abnormalities postbaseline grade (Grade 1 to 4 separately, Grade 3 or 4, and Grade 1 to 4)

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after the last dose of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later).

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

7.2.3. Shifts Relative to the Baseline Value

Shift tables will be presented for each cohort by showing change in CTCAE grade from baseline to the worst post-baseline grade.

7.3. Body Weight and Vital Signs

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. High or low values for vital signs will be flagged. Body weight will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications begun before a subject took the first study drug (ADX).

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be considered as prior medication regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be considered as prior medication, unless otherwise specified.

A summary of prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug (ADX). Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class level 2 and preferred name using the number and percentage of subjects for each cohort. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date that is prior to the date of first dosing date of study drug or a start date that is after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram (ECG) Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted.

ECG data collected up to 30 days after the last dose of ADX, or if applicable, 5 months after the last dose of nivolumab (whichever is later), will be included in the summary analysis.

Analyses of ECG data will be provided by cohort using the Safety Analysis set.

7.5.1. Investigator Electrocardiogram Assessment

A by-subject listing for ECG assessment results will be provided by subject ID number and time point in chronological order.

7.5.2. Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds. Per Gilead data collection standard, ventricular rate (VR) is taken as heart rate and will be used to derive RR.

The maximum postdose QTcF interval values obtained during the study will be summarized within the following categories:

- > 450 msec
- > 480 msec
- > 500 msec

The maximum postdose change in QTcF interval values obtained during the study will also be summarized within the following categories:

- > 30 msec
- > 60 msec

7.5.3. PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex. The maximum ventricular rate (VR) and PR and QRS intervals observed during the study will be categorized. The number and percentage of subjects having values in the following ranges will be presented by cohort:

- VR > 100 bpm
- PR interval > 200 msec
- QRS interval > 110 msec

7.6. Other Safety Measures

All post treatment anti-cancer therapies (other than those allowed per-protocol) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order. A summary of post treatment anti-cancer therapies will not be provided.

A data listing will be provided for the results of all pregnancy tests conducted in the study.

7.7. Changes from Protocol-Specified Safety Analyses

Continuous safety data including laboratory data will not be summarized.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Plasma samples will be collected to measure concentrations of ADX at protocol specified time points.

8.1.1. Estimation of PK Parameters

For subjects in Cohort 1, relevant PK parameters will be estimated using Phoenix WinNonlin® software and utilizing standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible. Descriptive statistics will be presented for PK parameters of ADX by cohort.

All predose sample times before time-zero will be converted to 0. For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile by profile basis.

Pharmacokinetic parameters such as λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.1.2. PK Parameters

The PK parameters for ADX presented in the table below will be computed for all subjects in the PK Analysis Set, as applicable.

The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{last} and C_{max} of ADX. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-1. PK Parameters for Each Analyte

Analyte	PK Parameters
ADX	C_{eoi}, C_{max}, T_{max}, AUC_{last}, $AUC_{0\text{-}336h}$, , C_{336h}, C_{last}, T_{last}, λ_z, $T_{1/2}$

Individual subject concentration data and individual subject PK parameters for ADX will be listed and summarized using descriptive statistics by cohort. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by treatment. Moreover, the geometric mean, 95% CI, and the mean and StD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by cohort:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics for Cohort 1

The following figures will be provided for each analyte for Cohort 1:

- Mean (± StD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age
- Individual data on determination of serum half-life and corresponding regression correlation coefficient

9. IMMUNOGENICITY ANALYSES

9.1. ADA Sample Collection

Serum samples will be collected to measure anti-ADX antibody (ADA) at protocol specified time points.

9.2. ADA Status

A by-subject listing for ADA status at each time point and the titer for subjects with positive ADA status will be provided by subject ID number and time point in chronological order.

Immunogenicity data will be listed for all subjects in the Immunogenicity Analysis Set.

10. BIOMARKER ANALYSES

Binding of ADX to MMP9 will be evaluated in the periphery and additional biomarkers will be explored in blood and tumor tissue. A comprehensive analysis may be documented separately.

Biomarker Analysis Set will be used for biomarker analysis.

10.1. Statistical Analysis Methods

All summaries will be presented in tabular or graphical form. Descriptive statistics refers to number of subjects, mean, median, standard deviation (StD), 1st quartile (Q1), 3rd quartile (Q3), minimum, and maximum for continuous measurements and number and percentage of subjects in each level of a categorical measurement.

Tables will be provided for the following:

- Descriptive Statistics for free and total MMP9 by visit for Cohort 1
- Descriptive Statistics for the baseline level for biomarkers including EBV, MMR, and PD-L1 for Cohort 4

Figures will be provided for the following:

- Mean (± StD) Plot for free and total MMP9 over time for Cohort 1
- Median (Q1, Q3) Plot for free and total MMP9 over time for Cohort 1

Listings will be provided for the following:

- Free and total MMP9 for Cohort 1
- EBV, MMR, and PD-L1 for Cohort 4

11. REFERENCES

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15 (23):7412-20.

12. SOFTWARE

SAS® Software Version 9.4. (SAS Institute Inc., Cary, NC, USA.) is to be used for all programming of tables, listings, and figures.

WinNonlin® (Pharsight Corporation, Mountain View, CA, USA.) is to be used for all PK analyses.

13. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

14. APPENDICES

SCHEDULE OF ASSESSMENTS

Appendix 1. 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										

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**
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	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 2. 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 of the Study Protocol 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 of the Study Protocol.
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 3. 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 of the Study Protocol.
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 4. 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 of the Study Protocol.
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.