STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Andecaliximab (GS-5745) Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma
Name of Test Drug:	Andecaliximab (GS-5745)
Study Number:	GS-US-296-2013
Protocol Version (Date):	Amendment 3
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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CSR	clinical study report
CT	Computerized Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GEJ	gastroesophageal junction
Hb	hemoglobin
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
IHC	immunohistochemistry
ITT	intent to treat
LLOQ	lower limit of quantitation
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
MRI	Magnetic Resonance Imaging

MedDRA	Medical Dictionary for Regulatory Activities
NE	non-evaluable
NN	non-CR/non-PD
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death ligand 1
PR	partial response
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
StD	standard deviation
SI (units)	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
VR	ventricular rate
WHO	World Health Organization

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 follow-up analysis for Study GS-US-296-2013. This SAP is based on the study protocol Amendment 3 dated 16 June 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.

At the time of primary analysis, no clinical study report (CSR) was written. The synoptic CSR for GS-US-296-2013 will be based on the follow-up analysis SAP except for the analysis of efficacy, which will be based on the primary analysis, as described in the SAP for primary analysis.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate and compare the efficacy of andecaliximab (GS-5745) in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma

The secondary objectives of this study are as follows:

- To characterize and compare safety and tolerability of andecaliximab (GS-5745) in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric or GEJ adenocarcinoma

- To characterize the pharmacokinetics (PK) of andecaliximab (GS-5745) in combination with nivolumab

1.2. Study Design

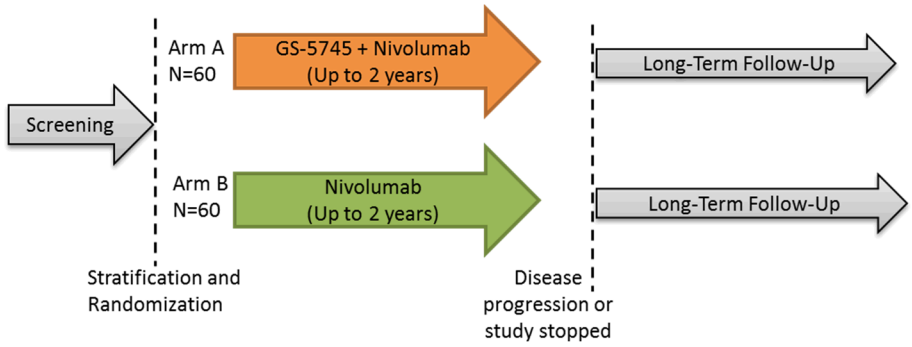
This is a Phase 2, open-label, randomized study comparing andecaliximab (GS-5745) in combination with nivolumab in recurrent gastric and GEJ adenocarcinoma versus nivolumab alone. Approximately 120 subjects will be randomized in a 1:1 manner through an interactive response system (IWRS) to either Treatment Arm A: andecaliximab (GS-5745) + nivolumab or Treatment Arm B: nivolumab alone. The centralized randomization will be stratified by programmed death ligand 1 (PD-L1) positive (≥ 1% tumor cell staining) versus PD-L1 negative (< 1% tumor cell staining).

Subjects randomized to Arm A will receive 800 mg of andecaliximab on Day 1 and every 2 weeks thereafter via intravenous (IV) infusion over approximately 30 minutes in advance of nivolumab. Nivolumab (3 mg/kg) will be administered via IV infusion over approximately 60 minutes following the completion of andecaliximab administration. Subjects meeting eligibility randomized to Arm B will receive 3 mg/kg nivolumab via IV infusion over approximately 60 minutes on Day 1 and every 2 weeks thereafter.

Contrast-enhanced computerized tomography (CT) (without contrast if use of contrast is contraindicated) or gadolinium-enhanced magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis will be performed at screening, every 8 weeks during the study and at the EOS visit if one has not been performed within the last 8 weeks. RECIST 1.1 will be used for assessment of tumor responses with some modifications to account for atypical responses which may occur with immune-based therapies.

Long term follow-up for OS begins once a subject discontinues study for reasons other than death. Subjects will be contacted via phone call every 3 months for determination of long-term survival status.

Figure 1. Study Design



1.3. Sample Size and Power

Assuming the Objective Response Rate (ORR) for subjects treated with nivolumab alone is 25%, 120 subjects in total are needed to detect an improvement of 20% in ORR for subjects treated with andecaliximab (GS-5745) and nivolumab with approximately 83% power at the one-sided significance level of 10% using a Cochran-Mantel-Haenszel (CMH) test with an assumption of common odds ratio for all strata. The assumption of nivolumab ORR is based on the upper bound of the 95% confidence interval of the estimated ORR in CheckMate-032 Study {Le 2016}.

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.

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial review will be conducted after 20 subjects have completed through Week 8. Thereafter, review of safety data will be conducted every 6 months.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Primary Analysis

The primary analysis will occur when the last subject is treated for 6 months or discontinued, whichever is earlier.

2.3. Follow-up Analysis

After the primary analysis, updated analyses of study data including efficacy and safety will be performed to provide long-term efficacy (overall survival) and safety follow-up. P-values for the updated analyses of efficacy are for display purposes only, and no formal hypothesis testing will be conducted.

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 Intent-to-Treat (ITT) 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 randomized 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 treatment group.

3.1.1. Intent-to-Treat Analysis Set

The ITT Analysis Set includes all subjects who were randomized in the study.

This is the primary analysis set for efficacy analyses.

3.1.2. Safety Analysis Set

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

3.1.3. Pharmacokinetic Analysis Set

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

3.1.4. Immunogenicity Analysis Set

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

3.2. Subject Grouping

For analyses based on the ITT Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set and Immunogenicity Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- PD-L1 positive (≥ 1% tumor cell staining) versus PD-L1 negative (< 1% tumor cell staining)

If there are discrepancies in stratification factor values between the IXRS and the Covance lab database, the values recorded in the Covance lab database will be used for analyses.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6.

In the situation where there is insufficient information in a stratum (ie, if there are < 6 subjects or there is no informative event in a stratum by combined treatment arms), the stratification by PD-L1 will not be applied.

3.4. Examination of Subject Subgroups

Primary (ORR) and key secondary (PFS and OS) efficacy endpoints will be examined in the following subgroups if there is sufficient sample size in the subgroup:

- Stratification factor PD-L1 status
  - < 1% tumor cell staining
  - ≥ 1% tumor cell staining
- Overall cell PD-L1 staining at baseline
  - < 1% tumor cell and associated immune cell PD-L1 staining
  - ≥ 1% tumor cell and associated immune cell PD-L1 staining

- Mismatch repair (MMR) status at baseline
  - MMR deficient (Subjects with one or more positive in MSH2, MSH6, MLH1, and PMS2 mutation tests are considered MMR deficient.)
  - MMR proficient (Subjects with all negative in MSH2, MSH6, MLH1, and PMS2 mutation tests are considered MMR proficient.)
- Primary Site of Tumor
  - Gastric
  - GEJ
- Number of Prior Anticancer Therapies
  - 1
  - 2
  - 3
  - 4 and above
- Histological Type
  - Diffuse
  - Other
- Age group
  - < 65
  - ≥ 65
- Gender
  - Male
  - Female

- Race
  - White
  - Non-White

Adverse events and lab abnormalities will be examined in the following subgroups:

- Age group
  - < 65
  - ≥ 65
- Gender
  - Male
  - Female
- Race
  - White
  - Non-White

In the situation where there is no responder in a subgroup, odds ratio of ORR within subgroups will not be estimated.

To graphically display treatment effect changes across subsets, a forest plot of odds ratios and hazard ratios by subject subgroup will be produced.

3.5. Multiple Comparisons

All endpoint tests will be done at the one-sided significance level of 0.1 with no multiplicity adjustment in this proof-of-concept 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.

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 is described in Section 7.1.5.2., for prior and concomitant medications in Section 7.4, and for initiation of new anticancer therapy in Section 6.3.1.

3.6.2. Outliers

Outliers will not be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

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 "01" 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 randomization will be used for analyses and presentation in listings. For screen failures, the date the informed consent was signed will be used for age calculation.

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 transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for plasma/blood concentrations. Plasma concentration values that are below the 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 determination of summary and order statistics.

The following conventions will be used for the presentation of summary and order statistics:

- 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."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug andecaliximab or nivolumab 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 study drug administration.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for chemistry, hematology and vital signs are provided in Table 1. The analysis windows for urinalysis, pregnancy test, ECG, and ECOG are provided in Table 2. The analysis windows for Thyroid Function Tests (TSH, T3, and free T4) are provided in Table 3. The analysis windows for tumor assessments are provided in Table 4.

Table 1. Analysis Visit Windows for Chemistry, Hematology and Vital Signs

Analysis Visit	Study Day	Lower Limit (inclusive)	Upper Limit (inclusive)
Baseline	1	-28	1 (before 1st dose)
Week 2	15	1 (after first dose)	21
Week 4	29	22	35
Week 6	43	36	49
Week X=8, 10, …	7*x+1	7x-6	7*x + 7
Safety Follow-up		max (andecaliximab end date, Nivo end date) + 1	max(andecaliximab end date + 30 days, Nivo end date + 5 months)

Table 2. Analysis Visit Windows for Urinalysis, Pregnancy Test, ECG, and ECOG

Analysis Visit	Study Day	Lower Limit (inclusive)	Upper Limit (inclusive)
Baseline	1	-28	1 (before 1st dose)
Week 4	29	1 (after first dose)	42
Week 8	57	43	70
Week 12	85	71	98
Week X=16, 20, …	7*x+1	7x-13	7*x + 14
Safety Follow-up		max (andecaliximab end date, Nivo end date) + 1	max(andecaliximab end date + 30 days, Nivo end date + 5 months)

Note. For pregnancy test, use results from serum test for screening and results from urine test for post-screening visit.

Table 3. Analysis Visit Windows for Thyroid Function Tests (TSH, T3, free T4)

Analysis Visit	Study Day	Lower Limit (inclusive)	Upper Limit (inclusive)
Baseline	1	-28	1 (before 1st dose)
Week 8	57	1 (after first dose)	84
Week 16	113	85	140
Week 24	169	141	196
Week 32, 40, ….	7*x+1	7x-27	7*x + 28
Safety Follow-up		max (andecaliximab end date, Nivo end date) + 1	max (andecaliximab end date + 30 days, Nivo end date + 5 months)

Table 4. Analysis Visit Windows for Tumor Assessments

Analysis Visit	Nominal Study Day	Lower Limit (inclusive)	Upper Limit (inclusive)
Baseline	-28	Randomization date - 60	Randomization date
Week 8	57	1	84
Week 8 confirmatory	Day of Week 8 visit + 28	Day of Week 8 visit + 28	
Week 16	113	85	140
Week 16 confirmatory	Day of Week 16 visit + 28	Day of Week 16 visit + 28	
Week 24	169	141	196
Week 24 confirmatory	Day of Week 24 visit + 28	Day of Week 24 visit + 28	
Week X=32, 40, …	7*x+1	7x-27	7*x + 28
Week X=32, 40, … confirmatory	Day of Week 32, 40, … visit +28	Day of Week 32, 40, … visit +28	

Note: In the rare cases where the screening assessments are after the randomization date but prior to the first dose of study drug, the assessments will be considered as baseline.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For post baseline values:

  — The record closest to the nominal day for that visit will be selected.

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, 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 similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects. If there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

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

- Safety Analysis Set
- Randomized but never dosed
- Completed study drug
- Did not complete study drug with reasons for discontinuation of study drug
- Completed tumor assessment
- Discontinued tumor assessment before Disease Progression
- Completed long-term follow-up
- Did not complete long-term follow-up with reasons for discontinuation of long-term follow-up

For the status of study drug and study completion and reasons for 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 ITT Analysis Set corresponding to that column.

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

- Reasons for study drug, tumor assessment, and long-term follow-up discontinuation

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol by component (andecaliximab/nivolumab).

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 14, regardless of any 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 date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for subjects included in the final analyses.

The total duration of exposure to study drug will be summarized using descriptive statistics. Summaries will be provided by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The total number of doses administered will be summarized using descriptive statistics.

4.2.2.1. On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen, Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (e.g., {< 75%, ≥ 75 to < 90%, ≥ 90%}) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but 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 treatment group based on the ITT 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 treatment group for the ITT Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

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 treatment group 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 ITT 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

Other baseline characteristics include, ECOG, PD-L1 status, and MMR status at screening. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the ITT Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

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

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

5.3.1. Disease History

A summary of disease-specific medical history will be provided by treatment and overall for the ITT Analysis Set. No formal statistical testing is planned. Variables to be summarized include:

- Primary tumor site
- Histology of gastric cancer
- Disease stage at screening
- Differentiation at screening
- Time since diagnosis (months)

The denominator for the percentage of histology of gastric cancer is the number of subjects with gastric cancer. The denominators for the percentage of other variables are the number of subjects in the ITT analysis set corresponding to that column.

A by-subject listing of disease history and surgical procedures will be provided by subject ID number in ascending order.

5.4. Chemotherapy and Radiotherapy Therapy

Prior (neoadjuvant, adjuvant, and metastatic) chemotherapy and radiotherapy will be summarized using descriptive statistics by treatment arm using ITT analysis set.

A by-subject listing of prior anticancer therapy and radiotherapy will be provided by subject ID number in ascending order. A by-subject listing of post-treatment chemotherapy will be provided by subject ID number and time in ascending order.

A by-subject listing of all radiotherapy will be provided by subject ID number and time in ascending order.

6. EFFICACY ANALYSES

Efficacy analysis will be performed based on the ITT Analysis Set. The investigator assessments will be used for analyses of efficacy endpoints.

P-values for the updated analyses of efficacy are for display purposes only, and no formal hypothesis testing will be conducted. Formal hypothesis testing had been conducted at the primary analysis per the SAP for primary analysis. Efficacy results in the CSR will be based on the primary analysis.

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is objective response rate (ORR), defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR) after starting study drug but before starting any new chemotherapy or radiotherapy based on revised RECIST 1.1.

As sensitivity analysis, confirmed ORR, defined as the proportion of subjects with best overall response of confirmed CR or confirmed partial response (PR) after starting study drug but before starting any new anti-cancer therapy based on revised RECIST 1.1, will also be analyzed. The confirmatory response is required at least 4-week later after the initial CR/PR for confirmed ORR.

Overall response for each visit is derived in the following process. The rules should be applied by the order listed below.

- Response assessments occurring after new anticancer therapy (including radiation therapy), after missing two previous consecutive tumor scans, or after confirmed progressive disease (PD) will not be included for ORR analysis.

- If overall response for the first time point of a visit is an imaging PD, in order to differentiate "pseudo-progression (pseudo-PD)" from "definitive progression", the first imaging PD requires confirmation either by another imaging PD at the confirmatory visit at least 4 weeks apart or by the subsequent clinical PD/ radiation therapy. The first imaging PD will be considered as "confirmed PD" by any of the following:

  — The overall response at the confirmatory visit is also PD;

  — No more tumor assessment is available that is 4 weeks apart;

  — The overall response at the confirmatory visit is non-evaluable (NE) and no more tumor assessments follow the confirmatory visit;

  — First imaging PD is followed by subsequent clinical PD or radiation therapy.

Otherwise, the first imaging PD will be "Pseudo PD".

- Both clinical PD and radiation therapy are considered as PD, and no confirmation is required.

The best overall response for each subject across the time points is derived based on the rank CR > PR > SD > pseudo-PD > PD (including clinical PD, confirmed imaging PD, and radiation therapy) > NE.

For confirmed overall response for each visit, in addition to the rules listed above, the following rules should also be applied.

- If overall response of a visit is CR or PR, a confirmatory visit at least 4 weeks later is required. Overall response for the visit is derived based on overall response at the first time point and overall response at the confirmatory visit.

- If overall response of a visit is SD/NE, no confirmatory visit is required and the overall response for the visit is SD/NE correspondingly.

The rule for deriving confirmed overall response at each visit is specified in Table 5. The best confirmed overall response for each subject across the time points is derived based on the rank CR confirmed > PR confirmed > CR not confirmed > PR not confirmed > SD > pseudo-PD > PD (including clinical PD, confirmed imaging PD, and radiation therapy) > NE.

Table 5. Confirmed Overall Response Derivation

Overall Response at First Visit	Overall Response at Confirmatory Visit	Overall Response for the Time Point	Date of Response
CR	CR	CR confirmed	First visit
	Responses other than CR or there is no confirmatory visit	CR not confirmed	First visit
PR	CR/PR	PR confirmed	First visit
	Responses other than CR/PR or there is no confirmatory visit	PR not confirmed	First visit
PD	PD/ clinical PD/ radiation therapy, or there is no confirmatory visit	PD	First visit
	NE	PD	First visit
	Responses other than PD/clinical PD/ radiation therapy/NE	pseudo-PD	First Visit
NE	Not required	NE	First visit
SD	Not required	SD	First visit

Note: Response after treatment discontinuation does not need to be confirmed.

6.1.1. Statistical Hypothesis for the Primary Efficacy Endpoint

The primary efficacy hypothesis is that there is no difference between Treatment Group (Group T) and Control Group (Group C) in ORR. Using R_T and R_C to denote the objective response rate of Treatment Group (Group T) and Control Group (Group C), respectively, the statistical hypotheses to be tested in this study will be:

H_0: $R_T = R_C$

H_1: $R_T > R_C$ (Group T is superior to Group C in terms of ORR)

6.1.2. Analysis for the Primary Efficacy Endpoint

The ORR endpoint will be tested at a two-sided alpha level of 0.2. The ORR will be presented with corresponding 2-sided 80% and 95% exact confidence intervals (CIs) calculated using the Clopper-Pearson method. Odds ratio will also be presented with corresponding 80% and 95% CIs be calculated using the exact CMH Chi-square test stratified by screening PD-L1 status. Subjects who do not have sufficient baseline or on-study tumor assessments to characterize response will be counted as non-responders and included in the denominator only.

In addition, the confirmed ORR, defined as the proportion of subjects with best overall response of confirmed CR/confirmed PR will also be presented as a sensitivity analysis. The same analysis methods as for ORR mentioned above will be applied for confirmed ORR.

The analysis for the ORR and confirmed ORR will be performed based on the ITT Analysis Set.

6.2. Secondary Efficacy Endpoint

6.2.1. Progression-Free Survival

Progression free survival (PFS), defined as the interval from the date of randomization to the earlier of the first definitive PD (as defined in Section 6.2.1) or death from any cause. The first definitive PD is defined as the first radiation therapy, the first clinical PD, and the first confirmed imaging PD, whichever comes first. Pseudo-PD will not be considered as definitive PD.

Data will be censored on the date of last adequate tumor assessment for subjects (including assessments with a NE outcome):

- who do not have definitive PD or die before study discontinuation, or
- who start new anticancer therapy prior (radiation therapy excluded) to definitive PD or death, or
- who have ≥ 2 consecutive missing tumor assessments before definitive PD or death.

Subjects without any adequate baseline tumor assessment are censored on the randomization date. The adequate baseline tumor assessment is defined as the window from (randomization date - 35 days) to randomization date.

PFS in months will be calculated as (date of event/censoring – date of randomization + 1) / 30.4375.

Survival function of PFS is estimated using Kaplan-Meier method and compared using the log-rank test stratified by PD-L1 status at screening. PFS rates at 1, 2, 3, 6, 9, 12 months, and the median with 95% CIs will be derived using Kaplan-Meier methods by treatment arm. Kaplan-Meier curves will also be provided. In addition, hazard ratio (HR) and corresponding 95% CI will be estimated for PFS using the Cox proportional hazards regression model stratified by PD-L1 status at screening.

Follow-up time in months for PFS will be summarized as a continuous variable with descriptive statistics.

- For a subject who is censored from PFS and has discontinued from tumor assessment, duration of PFS follow-up = (Date of Censoring – randomization date +1)/30.4375

- For subjects with a definitive PFS event and censored subject with ongoing tumor assessment, duration of PFS follow-up = (Date of last tumor assessment in the database – randomization date +1)/30.4375

For subjects who have imaging examinations on various dates that are nevertheless assigned to the same nominal visit, the following rules apply for the calculation of the endpoint date:

- The response date will be the last date associated with that particular imaging time point.

- The progression date will be the first date associated with that particular imaging time point.

Incomplete or missing dates of initiation of anticancer therapy other than the study treatment are imputed as follows:

- If the day is missing but the month and year are available, then the imputed day will be the last day of the month.

- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the month for the last adequate disease assessment if they have the same year, whichever is later.

The analysis of PFS will be performed based on the ITT Analysis Set.

6.2.2. Overall Survival

Overall survival (OS) is defined as interval from the date of randomization to death from any cause. Subjects alive are censored at the last time the subject was known alive.

The survival function of OS is estimated using Kaplan-Meier method and compared using the log-rank test stratified by PD-L1 status at screening. The median, Q1, Q3 estimate of OS and probability of survival at 3, 6, 12, 18, and 24 months from randomization will be provided along with the corresponding 95% CI. In addition, hazard ratio (HR) and corresponding 95% CI will be estimated using Cox proportional hazard regression method stratified by screening PD-L1 status.

Follow-up time in months for OS will be summarized as a continuous variable with descriptive statistics by treatment arm.

- For subjects who discontinued study without death event, duration of OS follow-up = (date of last follow-up – randomization date +1)/30.4375
- For subjects who died, duration of OS follow-up = last available date in the database – randomization date +1

The analysis of OS will be performed based on the ITT Analysis Set.

6.2.3. Duration of Response

Duration of response (DOR) is defined for subjects in the ITT analysis set who are CR/PR prior to new anti-cancer therapy (including radiation therapy) as the interval from the date of the first objective response achieved to the earlier of the first definitive disease progression or death from any cause. The first definitive disease progression is defined in Section 6.2.1. The same censoring rules as for PFS will be applied to DOR.

DOR in months = (date of event/censoring – date of first response [CR or PR] + 1) / 30.4375.

Median DOR and 95% CIs will be estimated using Kaplan-Meier methods by treatment arm. Kaplan-Meier curves will also be provided.

6.3. Exploratory Efficacy Endpoints

CCI [redacted]

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) and preferred term (PT) 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 toxicity criteria specified in the protocol. 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 as determined by the investigator. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health 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 both of the following:

- Any AEs with an onset date on or after the study drug start date and up to 30 days after permanent discontinuation of andecaliximab or 5 months after permanent discontinuation of nivolumab
- Any AEs leading to premature discontinuation of andecaliximab or 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 andecaliximab or 5 months after the date of the last dose of nivolumab

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.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- All TE treatment-related AEs
- TEAEs of Grade 3 or higher (by maximum severity)
- TE Treatment-related AEs of Grade 3 or higher (by maximum severity)
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to discontinuation of any study drug
- All TEAEs leading to study treatment interruption or dose interruption
- All TEAEs leading to death

A brief, high-level summary of AEs described above will be provided by treatment group 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, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

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

Deaths will be summarized by whether it is considered treatment emergent and the cause of the death (AE, due to PD, or other reasons).

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- AEs with Grade 3 or higher
- SAEs
- AEs leading to death
- All deaths
- AEs leading to discontinuation of study drug
- AEs leading to treatment interruption/dose modification

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed using qualitative methods. Shift from baseline to worst post-baseline assessment and Grade 3 or higher lab abnormalities will be summarized for the Safety Analysis Set and will include data collected up to the last dose of andecaliximab plus 30 days for subjects who have permanently discontinued andecaliximab or up to the last dose of nivolumab plus 5 months for subjects who have permanently discontinued nivolumab. Severity grade for lab abnormalities are defined by CTCAE 4.03.

Only central lab results will be used in the analyses.

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, urinalysis, coagulation, and thyroid function 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. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities CTCAE Version 4.03 will be used to assign 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.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of andecaliximab plus 30 days or nivolumab plus 5 months for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and time point 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.

7.2.2. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to worst post baseline assessment.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

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

7.4. Concomitant Medications

Medications collected during the study will be coded using the current version of the [Gilead-modified] World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

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. Use of 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 treatment group. 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 prior to the date of first dosing date of study drug or a start date 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 Results

7.5.1. Investigator Electrocardiogram Assessment

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

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

PK plasma samples will be collected for Arm A only for andecaliximab PK at 30(± 15) min after the end of infusion on Day 1; prior to dosing and 30(± 15) min after the end of infusion on Day 1 of Weeks 4, 8, 16, 24, every 3 months thereafter, and at the end of treatment (EOT) and end of study (EOS) visits.

8.2. Statistical Analysis Methods

Individual subject concentration for andecaliximab will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual subject concentration data by time point.

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 non-missing 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.

The following tables will be provided for andecaliximab:

- Individual subject concentration data and summary statistics

The following listing will be provided

- PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

9. IMMUNOGENICITY ANALYSES

9.1. ADA Sample Collection

For Arm A only serum samples for anti-andecaliximab antibody will be collected prior to dosing on Day 1 of Week 1, 4, 8, 16, 24, and every 3 months thereafter, EOT, EOS.

9.2. Statistical Analysis Methods

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.

10. BIOMARKER ANALYSES

The following biomarkers will be evaluated for whether they are predictive for treatment efficacy. These analyses are exploratory.

[redacted]

11. REFERENCES

Le DT, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, et al. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study [Abstract 06]. J Clin Oncol (ASCO Annual Meeting Abstracts) 2016.

12. SOFTWARE

SAS® Software Version 9.X. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version X.0. Statistical Solutions, Cork, Ireland.

13. SAP REVISION

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

14. APPENDIX

Appendix 1. List of Laboratory Tests for Safety Analysis

Chemistry	Urinalysis	Hematology	Other
Albumin	Color and appearance	WBC	Serum β-hCG or urine pregnancy test[c]
Alkaline phosphatase	Specific gravity pH	Hemoglobin	
ALT	Occult blood	Hematocrit	Thyroid Function Tests (TSH, T3, and free T4)[d]
AST	Protein	Platelet	
Bicarbonate	Glucose Bilirubin	ANC	
BUN	Leukocyte esterase		
Calcium	Nitrite	Differential	
Chloride	Urobilinogen	Eosinophils	
Creatinine[a]	Ketones Microscopic[b]	Lymphocytes	
Glucose		Monocytes	
Lipase		Neutrophils	
Amylase		**Coagulation**	
Magnesium		PT/INR	
Phosphorus		aPTT	
Potassium			
Sodium			
Total bilirubin			
Direct bilirubin			
Total protein			
CEA			
CA125			

ANC = absolute neutrophil count; ALT = alanine aminotransferase; aPTT = Activated Partial Thromboplastin Time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CEA=carcinoembryonic antigen; β-hCG = beta-human chorionic gonadotropin; INR = International Normalized Ratio; PT = Prothrombin Time; WBC = white blood cell; CA125 = Carbohydrate Antigen 125; TSH = thyroid stimulating hormone; T3 = triiodothyronine; Free T4 = free thyroxine

a Estimated creatinine clearance (CL_{cr})/glomerular filtration rate will be calculated based on the Cockroft-Gault formula using actual body weight: CL_{cr} (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 will be conducted pre-dose on Day 1, every 4 weeks thereafter, at EOT, and EOS, 30-day, and 5-month Safety Follow-up

d TSH, T3, and free T4 will be tested by the central laboratory at screening. From Week 8 and beyond, T3 and T4 will be tested reflexively based on abnormal TSH results.

Appendix 2. Schedule of Assessments

Period	Screening	Randomization [a]	Treatment												EOT[m]	Disease Progression	EOS[n]	30 day Safety Follow-up[o]	5-month Safety Follow-Up[p]	Long Term Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 to 50**						
Week	**-4**	**Day 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 to 96**						
Window (day)	**-28**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			**±7**	**±7**	**±7**	
Informed Consent	X																			
Medical and Medication History	X																			
Physical Examination[b]	X	X		X		X		X		X		X		X[s]	X		X	X		
Vital Signs & Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
ECOG Performance Status[c]	X	X[c]		X		X		X		X		X		X[s]	X		X	X		
12-lead ECG	X	X		X		X		X		X		X		X[s]	X		X			
Adverse events/ Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS Registration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Study Drug/ Nivolumab Administration[e]		X	X	X	X	X	X	X	X	X	X	X	X	X						
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Thyroid Function Tests (TSH, T3, free T4)	X					X				X				X[t]	X		X	X	X	

Period	Screening	Randomization [a]	Treatment												EOT[m]	Disease Progression	EOS[n]	30 day Safety Follow-up[o]	5-month Safety Follow-Up[p]	Long Term Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 to 50**						
Week	**-4**	**Day 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 to 96**						
Window (day)	**-28**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			**±7**	**±7**	**±7**	
Coagulation	X														X		X			
Urinalysis	X	X		X		X		X		X		X		X[s]	X		X	X	X	
Pregnancy Test[f]	X	X		X		X		X		X		X		X[s]	X		X	X	X	
Andecaliximab PK[g]		X		X		X				X				Xr	X		X			
Anti-Andecaliximab Antibody[h]		X		X		X				X				X[r]	X		X			
Blood Biomarkers[i]	X	X	X	X		X				X				X[r]		X[i]	X[i]			
Oral Sampling		X																		
CCI																				
CT or MRI & Treatment Response Assessment[k]	X					X				X				X[t]		X[q]	X			
Tumor Biopsy[l]	X[l]			X[l] (Wk 5 through Wk 9)												X[l]				
Overall Survival and Other Antitumor Therapy																				X[u]

a Day 1 visit must occur within 3 days following randomization.
b Complete physical examination (PE) to be performed at Screening, EOT and EOS. A modified PE capturing changes from prior exams will be performed at subsequent visits. Height is required at Screening only.
c ECOG performance status on Day 1 may be waived if has been conducted during screening within 4 days of Day 1.

d Adverse events will be assessed and concomitant medications will be recorded at each clinic visit from Screening up to and including the 30-day Safety Follow-up visit or EOS visit whichever is later.

e For Arm A: Study drug andecaliximab (800 mg) will be administered via IV infusion every 2 weeks over 30 (± 5) min. Nivolumab (3 mg/kg) will be administered via IV infusion following the completion of andecaliximab every 2 weeks over 60 (± 5) min. For Arm B: Nivolumab alone (3 mg/kg) will be administered via IV infusion every 2 weeks over 60 (± 5) min.

f If applicable (females of child bearing potential). Serum pregnancy testing will be conducted at Screening. Urine pregnancy testing will be conducted pre-dose on Day 1 and every then every 4 weeks, at EOT, and EOS, 30-day, and 5-month Safety Follow-up.

g For Arm A only, plasma samples will be collected for andecaliximab PK at 30(± 15) min after the end of infusion on Day 1. For Weeks 4, 8, 16, and 24 and every 3 months thereafter, PK will be collected prior to dosing and 30(± 15) min after the end of infusion. It will also be collected at EOT and EOS.

h For Arm A only, serum samples for anti-andecaliximab antibody will be collected prior to dosing on Day 1, Week 4, Week 8, Week 16, Week 24, and every 3 months thereafter, EOT and EOS.

i Blood biomarkers will be collected at screening and prior to dosing on Day 1; Week 2; Week 4; Week 8; Week 16; Week 24 and every 3 months thereafter and at progression or EOS.

j [redacted]

k Tumor evaluation by CT or MRI will be performed during screening and approximately every 8 weeks regardless of visit week or dose interruption. Scan at EOS visit is not necessary if restaging scan is performed within the prior 8 weeks. Treatment response assessment will be per RECIST v1.1. For subjects who stop study treatment in the absence of disease progression (eg. experienced unexpected toxicity) and remain on study for follow-up for progression-free survival, tumor evaluation by CT or MRI should continue approximately every 8 weeks until disease progression or initiation of non-study specific anti-neoplastic therapy in the absence of progression, whichever occurs earlier.

l A pretreatment biopsy is requested if archival tumor sample provided to meet Inclusion Criterion #6 is from before the last line of therapy. An on-treatment biopsy is required between Week 5 and Week 9. A biopsy at disease progression is requested, if medically feasible. The sample should be collected by the last clinic visit on study ie EOS or 30 Day Safety Follow-up visit. All biopsies are requested to be from gastric lesions if possible (non-gastric metastatic lesions ok if no gastric lesions possible). See laboratory manual for biopsy specifications and procedures.

m End of treatment (EOT) assessments will be completed only 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 approximately every 8 weeks until disease progression.

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

o The 30-day safety follow-up visit will be performed following the last dose of andecaliximab.

p The 5-month safety follow-up visit will be performed following the last dose of nivolumab.

q 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 (see Protocol Section 6.2.9).

r Starting at Week 24, perform every 12 weeks until EOT/EOS.

s Starting at Week 24, perform every 4 weeks until EOT/EOS.

t Starting at Week 24, perform every 8 weeks until EOT/EOS.

u Perform every 3 months until 5 years.