GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	116561	
EudraCT Number:	2016-001402-41	
Clinical Trials.gov Identifier:	NCT02864381	
Indication:	Gastric Adenocarcinoma	
Protocol ID:	GS-US-296-2013	
Clinical Program Manager:	Name: Telephone: Email:	PPD PPD PPD
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	116561 2016-001402-41 NCT02864381
Study Centers Planned:	Approximately 50 centers in Australia, North America, and Europe
Objectives:	The primary objective of this study is: • To evaluate and compare the efficacy of andecaliximab (formerly 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: • To characterize and compare safety and tolerability of andecaliximab in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric or GEJ adenocarcinoma • To characterize the pharmacokinetics (PK) of andecaliximab in combination with nivolumab The exploratory objectives of this study are: [redacted]

Study Design:

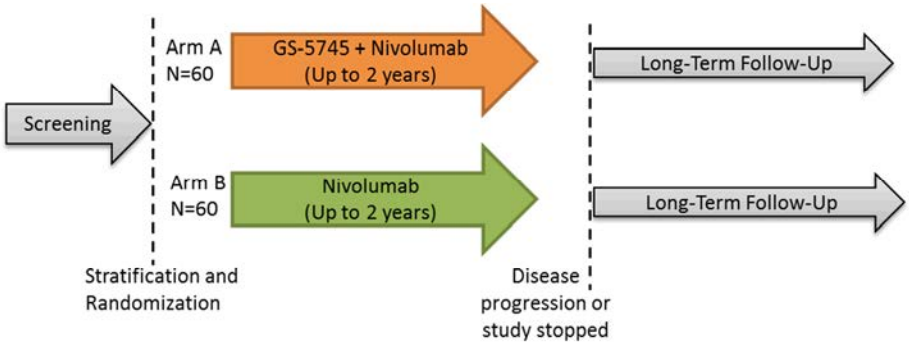
This is a Phase 2, open-label, randomized study comparing andecaliximab in combination with nivolumab in recurrent gastric adenocarcinoma versus nivolumab alone. Approximately 120 subjects will be randomized to either Treatment Arm A: andecaliximab + nivolumab or Treatment Arm B: nivolumab alone.

To evaluate combination drug safety, an independent Data Monitoring Committee (DMC) will be charged with overseeing the study safety. After the first 20 subjects are treated for 12 weeks, the DMC will review all safety data to evaluate for any unexpected toxicities. If the DMC recommends that the combination demonstrates acceptable tolerability, enrollment and randomization will proceed with continued safety oversight from the DMC. Thereafter, review of safety data will be performed at regular intervals as described in the DMC charter.

Randomized study:

Treatment Groups:

- Arm A: andecaliximab + nivolumab
- Arm B: nivolumab



Randomization and Stratification:

- 1:1 allocation to andecaliximab + nivolumab versus nivolumab alone through an interactive web response system (IWRS)
- Fixed-block centralized randomization stratified by:
  - PD-L1 positive versus PD-L1 negative

Number of Subjects Planned:

Approximately 120 subjects

Target Population:	Subjects who are ≥18 years or older with a histologically confirmed inoperable locally advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction (GEJ) and who have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease
Duration of Treatment:	Treatment will be given every 2 weeks and will continue until disease progression, unacceptable toxicity, or withdrawal of consent to a maximum of 2 years duration
Eligibility Criteria:	Inclusion Criteria Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Age ≥18 years 2) Histologically confirmed inoperable locally advanced or metastatic adenocarcinoma of the stomach or GEJ which have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease 3) Eastern Cooperative Oncology Group (ECOG) ≤ 1 4) Measurable disease according to RECIST v1.1 5) Tumor sites that can be accessed for repeat biopsies 6) Archival tumor tissue, preferably obtained from the most recent available biopsy; there must be adequate tissue for a PD-L1 stratification test, as assessed by central pathologist 7) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline 8) Subjects not receiving anticoagulant medication must have an international normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin (aPTT) ≤ 1.5 x upper limit of normal (ULN) prior to randomization. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the subject has been on a stable dose of anticoagulants for at least 1 week at the time of randomization 9) Adequate hematologic function a) neutrophils ≥ 1.5 x 10^9/L b) platelets ≥ 100 x 10^9/L c) hemoglobin ≥ 9 g/dL

10) Adequate hepatic function
    a) Direct or total bilirubin ≤ 1.5 x ULN
    b) ALT and AST ≤ 2.5 x ULN
11) Creatinine clearance (CL_{cr}) ≥ 60 mL/min, estimated based on the Cockroft-Gault formula or measured based on 24-hour urine collection or other reliable method
12) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the screening visit throughout the study treatment period, for 90 days following the last dose of andecaliximab and at least 5 months after the last dose of nivolumab, unless the subject chooses continuous heterosexual abstinence as a lifestyle-choice (see Appendix 4 for more information)
13) For male subjects of reproductive potential having intercourse with females of childbearing potential, willingness to use a protocol recommended method of contraception and to refrain from sperm donation from the start of study drug, throughout the study treatment period, and for 90 days after administration of the last dose of andecaliximab or nivolumab (see Appendix 4 for more information)
14) Breastfeeding females must agree to discontinue nursing before study drug administration
15) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer
16) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions
17) Evidence of a signed informed consent prior to implementation of any protocol specific procedure

Exclusion Criteria

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

1) Subjects that have received only neoadjuvant or adjuvant therapy for gastric adenocarcinoma
2) Radiotherapy within 28 days of randomization; subjects given palliative radiotherapy to peripheral sites (eg, bone metastasis) may enter the study before 28 days have elapsed provided the radiated sites do not contain lesions which may be used to evaluate response, and must have recovered from any acute, reversible effects

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active gastrointestinal bleeding, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by the treating physician
4) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; asymptomatic prostate cancer without known metastatic disease, with no requirement for therapy or requiring only hormonal therapy, and with normal prostate-specific antigen for ≥ 1 year prior to randomization; adequately treated Stage 1 or 2 cancer currently in complete remission; or any other cancer that has been in complete remission for ≥ 5 years
5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days of first dose of study drug
6) Known positive status for human immunodeficiency virus (HIV)
7) Known acute or chronic-active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
8) Chronic daily treatment with oral corticosteroids (dose of > 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed
9) Known or suspected central nervous system metastases
10) Known alcohol or drug abuse or any other medical or psychiatric condition which contraindicates participation in the study
11) Documented myocardial infarction or unstable/uncontrolled cardiac disease (ie, unstable angina, congestive heart failure [New York Heart Association > Class II]) within 6 months of randomization
12) Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires intravenous antibiotics
13) Pregnant or breastfeeding women (pregnancy needs to be excluded by testing of beta-human chorionic gonadotropin [β-hCG])
14) Experimental medical treatment within 28 days prior to randomization
15) Known hypersensitivity to andecaliximab or nivolumab or excipients or to Chinese hamster ovary cell products or to recombinant human or humanized antibodies

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

17) Previous severe hypersensitivity reaction to treatment with another monoclonal antibody therapy

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

19) Prior therapy with anti-tumor vaccines or other immune-modulatory antitumor agents

20) Current or history of pneumonitis or interstitial lung disease

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

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

Study Procedures/ Frequency:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to randomization on Day 1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead ECG, ECOG performance status, prior/concomitant medication review, blood collection for pregnancy test (females), chemistry, hematology, and coagulation, adverse event (AE) assessment, archival or recent biopsy FFPE tissue block collection, and computed tomography (CT) or magnetic resonance imaging (MRI). Baseline tumor lesions will be measured and characterized prior to randomization to assess the subject's disease status prior to beginning treatment. Archival tumor tissue adequate for PD-L1 immunohistochemical stratification test is required at screening.

Treatment:

Treatment will occur every 2 weeks. Subjects who meet eligibility will undergo CT scans or MRI every 8 weeks. Starting on Day 1, subjects randomized to Arm A: andecaliximab + nivolumab will receive andecaliximab via intravenous infusion (IV) over 30 minutes. Nivolumab will be administered via IV over 60 minutes after andecaliximab. Subjects randomized to Arm B: nivolumab only will receive nivolumab via IV over 60 minutes.

Treatment will continue every 2 weeks in the absence of disease progression or toxicity warranting discontinuation of therapy, for up to 2 years. Tumor response may be assessed prior to the specified every 8 weeks, if clinically indicated.

Test Therapy, Dose, and Mode of Administration:	Arm A: 800 mg andecaliximab via IV infusion over approximately 30 minutes in advance of nivolumab 3 mg/kg via IV infusion over approximately 60 minutes on Day 1 and every 2 weeks thereafter. Arm B: nivolumab 3 mg/kg via IV infusion over approximately 60 minutes on Day 1 and every 2 weeks thereafter.
Criteria for Evaluation:	All subjects who meet eligibility criteria, have signed a consent form, and have begun treatment, will be evaluated for response.
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital sign measurements, and by the incidence of AEs.
Efficacy:	• Objective response rate (ORR) will be determined from the subjects' best response during treatment. • Progression free survival (PFS) will be defined as the interval from the date of randomization to the earlier of the first documentation of definitive disease progression or death from any cause. • Duration of response (DOR) will be defined as the interval from the date the first response (CR or PR) is achieved to the earlier of the first documentation of definitive disease progression or death from any cause. • Overall survival (OS) will be defined as the interval from date of randomization to death from any cause.
Pharmacokinetics:	• Blood samples to measure andecaliximab will be collected at the time points specified in the protocol. • Blood samples to measure anti-andecaliximab antibodies will also be collected at the time points specified in the protocol.
Statistical Methods:	
Analysis Methods:	Appropriate analyses sets will be defined. In general, categorical and ordinal data will be summarized by count and percent of subjects. Continuous data will be summarized by descriptive summary statistics (mean, standard deviation, minimum, quartiles, median and maximum). For the analysis of ORR, a Cochran-Mantel-Haenszel (CMH) Chi-square test on odds ratio will be performed to compare the 2 treatment groups.

	The Kaplan-Meier (KM) method and stratified log-rank test will be used to compare the 2 treatment groups for time-to-event endpoints (ie, OS and PFS). A Cox proportional hazard model will be used to estimate the hazard ratio and corresponding 95% confidence interval (CI). DOR will be analyzed using the KM method.
Interim Analysis:	After approximately 20 subjects are treated for 12 weeks, an independent DMC will review safety data on these subjects and recommend to Gilead whether the treatment has demonstrated acceptable tolerability. Thereafter, review of safety data will be performed at regular intervals as described in the DMC charter.
Sample Size:	Assuming the 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 and nivolumab with approximately 83% power at one-sided significance level of 10% using a 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}.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

β-hCG	beta-human chorionic gonadotropin
λz	terminal elimination rate constant; estimated by linear regression of the terminal elimination phase of the log serum/plasma/PBMC concentration versus time curve of the drug
5-FU	5-fluorouracil
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{last}	area under the plasma/serum/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
BSA	body surface area
C_{max}	maximum observed concentration of drug
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last observed quantifiable serum/plasma/PBMC concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed serum/plasma/PBMC concentration of drug
CR	complete response
CRO	contract research organization
CT	computed tomography
Ctau	observed drug concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOS	end of study
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
FDA	Food and Drug Administration

GCP	good clinical practice
GEJ	gastroesophageal junction
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HLT	high-level term
HR	hazard ratio
IB	investigator's brochure
IC_{50}	concentration necessary to achieve 50% inhibition of target
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IRB/IEC	institutional review board or independent ethics committee
ISH	in situ hybridization
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
KM	Kaplan-Meier
LV	leucovorin
LTFU	long-term follow-up
MMP	matrix metalloproteinases
MRI	magnetic resonance imaging
MSS	musculoskeletal syndrome
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcomes
RECIST	Response Evaluation Criteria In Solid Tumors
PT	preferred term
RNA	ribonucleic acid
SADR	serious adverse drug reactions
SAE	serious adverse event
SD	stable disease
SOC	system organ class

SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
TIMPs	tissue inhibitors of metalloproteinases
T_{last}	time (observed time point) of C_{last}
TTR	time to response
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

Matrix metalloproteinases (MMP) comprise a family of at least 23 Zn^{2+}-dependent proteases which are involved in the degradation and remodeling of the extracellular matrix and basement membranes in and activation or degradation of growth factors, cytokines and chemokines in many normal as well as pathologic biological processes. They are typically grouped based on their structure or their primary substrates and include the gelatinases, collagenases, stromelysins, matrilysins, an elastase, and membrane-type MMP, a group of cell surface tethered proteases {Hu 2007, Mott 2004}. The gelatinases comprise MMP2 and MMP9, sometimes referred to as type IV collagenases, which are named for their ability to degrade type IV or basement membrane collagen and gelatin, {Chen 2002, Kridel 2001}. The contrasting roles of MMP9 and MMP2 have been revealed in a variety of studies which support a more ubiquitous expression pattern and associated role for MMP2 in normal tissue homeostasis, as compared to disease-induced and pathology-associated expression and activity of MMP9 {Agrawal 2006, Castaneda 2005, Dubois 1999, Garg 2009, Hu 2007, Itoh 2002, Li 2009, Miyazaki 2011, Naito 2005, Santana 2006}. Various substrates have been identified for MMP9, and the active enzyme can release cytokines, growth factors, and bioactive fragments which in turn modulate inflammation, neovascularization, tumorigenesis and matrix remodeling {Hijova 2005}. MMP9 is an inducible MMP that is secreted as a zymogen and activated in a "cysteine switch" mechanism by the cleavage of the peptidoglycan binding domain {Van Wart 1990}. While activation of MMP9 appears to be carried out by other MMPs, the protease's activity is also regulated by the binding of tissue inhibitors of metalloproteinases (TIMPs), primarily by TIMP1 {Imai 1995, Olson 1997, Vempati 2007}. Elevated MMP9 expression in diseased tissue and plasma is associated with several human diseases. The health and largely normal development of the MMP9 knockout mouse has enabled evaluation in a variety of disease models, and these data support a significant role for MMP9 in a variety of inflammatory, fibrotic, and oncologic processes {Dubois 1999, Hu 2007, Itoh 2002, Itoh 1999, Opdenakker 2003}.

The disease-associated induction and functions of MMP9 render it an attractive therapeutic target. In oncology, MMP9 can contribute to tumor growth through a variety of mechanisms, including remodeling of the microenvironment, promotion of pro-tumorigenic and pro-angiogenic signaling pathways, and blunting of anti-tumor immune responses.

Checkpoint inhibitors, including therapeutic antibodies targeting programmed death-1 (PD-1) receptor such as nivolumab, have shown dramatic and sustained clinical benefit in melanoma, renal cell carcinoma, and subsets of other diverse solid tumors. These findings highlight the importance of immunomodulation in tumorigenesis. However, the response rate to these inhibitors remains limited in some of tumors such as gastric adenocarcinoma {Antonia 2015}. Factors contributing to limitations in response could include access of T cells to tumor cells due to the collagenous tumor desmoplastic reaction and tumor angiogenesis, in addition to repression of anti-tumor T-cell responses in the local tumor microenvironment resulting from the increased presence and activity of myeloid suppressor cells (MSC) and their associated cytokines,

chemokines, and growth factors. The combination of andecaliximab with nivolumab offers an opportunity to broaden and deepen responses in gastric adenocarcinoma. Treatment with andecaliximab may result in productive remodeling of the tumor microenvironment to enable both T-cell and drug access, and the inhibition of both MSC recruitment and activation by andecaliximab may further inhibit tumor growth and promote anti-tumor immunity in combination with nivolumab.

1.1.1. Gastric Adenocarcinoma

Adenocarcinoma of the stomach is the most common gastrointestinal cancer in the world and the third leading cause of cancer death worldwide{Ferlay 2013}. Approximately 22,220 patients are diagnosed annually in the United States, of whom 10,990 are expected to die. While the incidence of distal gastric adenocarcinoma has recently declined in the United States, gastric adenocarcinoma remains quite frequent in certain minority populations and it is still the second most common cause of cancer death worldwide. In addition, adenocarcinoma of the gastroesophageal junction (GEJ) is one of the most rapidly increasing solid tumors in the United States and Western Europe.

Most patients with gastric adenocarcinoma in the United States are symptomatic and already have advanced incurable disease at the time of presentation. At diagnosis, approximately 50 percent have disease that extends beyond locoregional confines, and only one-half of those who appear to have locoregional tumor involvement can undergo a potentially curative resection. Surgically curable early gastric adenocarcinomas are usually asymptomatic and only infrequently detected outside the realm of a screening program. Screening is not widely performed, except in countries which have a very high incidence, such as Japan, Venezuela, and Chile. The common presenting symptoms and diagnostic approaches to gastric adenocarcinoma include weight loss (usually results from insufficient caloric intake rather than increased catabolism) and may be attributable to anorexia, nausea, abdominal pain, early satiety, and/or dysphagia. Abdominal pain is often present which tends to be epigastric, vague, and mild early in the disease but more severe and constant as the disease progresses. Dysphagia is a common presenting symptom in patients with cancers arising in the proximal stomach or at the esophagogastric junction. Patients may also present with nausea or early satiety from the tumor mass or in cases of an aggressive form of diffuse-type gastric adenocarcinoma called linitis plastica, from poor distensibility of the stomach. They may also present with a gastric outlet obstruction from an advanced distal tumor.

Gastric and esophageal adenocarcinomas are chemotherapy sensitive diseases, with several active drug therapy classes, including platinum, fluoropyrimidines, topoisomerases inhibitors, taxanes, and anthracyclines. Despite significant differences in epidemiology and molecular characteristics, cytotoxic chemotherapy combinations have not demonstrated significant differences in efficacy across gastric adenocarcinoma. {Chau 2009}.

Chemotherapy clearly provides a survival advantage over best supportive care in both first-line {Glimelius 1997, Murad 1993, Pyrhonen 1995, Scheithauer 1995} and second-line {Kang 2012, Thuss-Patience 2009} settings. A meta-analysis of first-line chemotherapy versus best supportive case studies reported a hazard ration (HR) of 0.39 (95% CI, 0.28-0.52;p<0.001) for overall survival in favor of chemotherapy. This translates to a benefit of a median of 6 months {Wagner 2006}.

Performance status often declines after first-line therapy. Patients with esophageal cancer often have significant comorbidities, including obesity, heart disease, emphysema, which when coupled with progressive dysphagia and malnutrition, often limit therapeutic opportunities after first-line therapy. Gastric adenocarcinoma patients who develop peritoneal carcinomatosis often have decreased bowel function that then results in GI symptoms and a decline in functional status and therefore limiting treatment options substantially {Power 2010}. However administration of second-line therapy in patients who are sufficiently fit to receive it has demonstrated a survival advantage over supportive care alone. {Kang 2012, Thuss-Patience 2009}. A meta-analysis of these studies demonstrated a HR for OS of 0.73 (95%CI, 058 – 0.960), and in highly functioning patients (ECOG performance status of 0 or 1) the HR was 0.57 (95%CI 0.36-0.91).

For patients who retain an adequate performance status, there is no standard approach for second-line therapy after failure of the first-line regimen. Quality-of-life and minimization of side effects are key considerations when choosing the therapeutic approach. The choice of regimen is empiric. No single regimen has emerged as clearly superior and few trials have compared different regimens {Thallinger 2011, Wesolowski 2009}. Current NCCN guidelines suggest clinical trials in the relapsed setting, and immune checkpoint inhibitors have recently started in these patients.

There is emerging evidence that immunosurveillance is significantly altered in gastroesophageal malignancies {Kono 2006, Lu 2011, Ohigashi 2005}. PD-L1 is a transmembrane protein that was first identified for its role in the maintenance of self-tolerance and prevention of autoimmunity {Fife 2011}. Engagement of PD-L1 on dendritic cells with PD-1 receptor on T cells delivers an inhibitory signal that promotes T-cell anergy or apoptosis {Keir 2008}.Tumor cells overexpress PD-L1 resulting in T-cell anergy and escape from immunosurveillance. Blockade of the interaction between PD-L1 on tumor cells and PD-1 on T cells reverses T-cell suppression within tumors, thereby promoting effective antitumor immune responses. In esophageal cancer, tumor infiltrating lymphocytes correlated with improved survival {Kono 2006, Lu 2011}. Of note, 70% of esophageal adenocarcinomas express PD-L1 and its expression is independently associated with worse survival {Lu 2011}. Immune checkpoint inhibitors are being actively investigated in gastric adenocarcinoma and have yielded promising results.

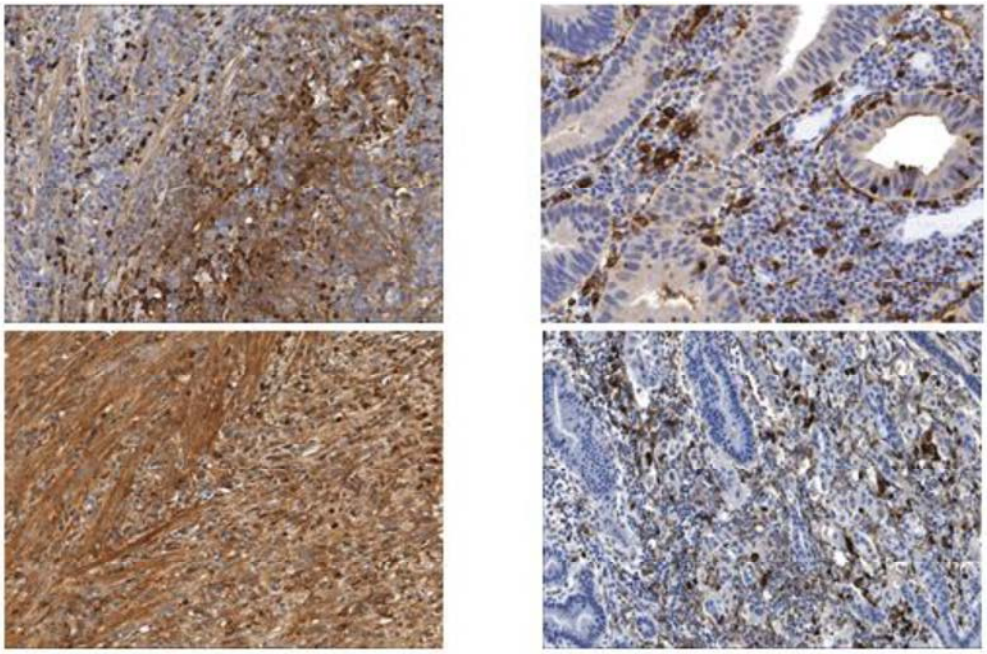
There has been early demonstration of activity of PD-1 antibody immune checkpoint inhibitors in upper GI cancers. Pembrolizumab seems to have some activity in patients with PD-L1 expressing advanced gastric adenocarcinoma as reported at the European Society for Medical Oncology 2014 meeting {Muro 2014}. Of the 39 patients enrolled, 19 were from Asia and 20 were from other areas of the world. At a median follow up of approximately 6 months, the

ORR was 31% in Asians and 30% in non-Asians, suggesting activity. Data more recently presented at ASCO GI in Jan 2016 also confirmed PD-1 inhibition by nivolumab as an effective possible treatment strategy for second-line gastric adenocarcinoma patients with an ORR of 12% and SD of 21%.{Antonia 2015}.

1.1.2. MMP9 Expression in Oncology

Immunohistochemistry (IHC) studies conducted with validated reagents indicate that MMP9 expression is highly prevalent across solid tumors, including gastric adenocarcinoma ($\geq$ 90%, n $\geq$ 30 each for cases of North American, European, and Chinese origin). MMP9 is expressed heterogeneously by tumor epithelia and infiltrating inflammatory cells (predominantly of myeloid type), along with subsets of fibroblastic stroma, and tumor-associated endothelial cells. Heterogeneous expression is apparent within a single tumor, as well as across different tumors. No particular associations with genetic background and MMP9 expression were apparent across different solid tumors.

Figure 1-1. Examples of MMP9 Expression in Gastric Adenocarcinoma (IHC)



Panels on the left show examples of regions with high tumor cell epithelial positivity for MMP9, along with positive stromal areas. In panels on the right, there is less MMP9 expression evident in tumor epithelia, but stromal positivity is apparent. All cases contain MMP9-positive infiltrating inflammatory cells.

1.1.3. General Information

Andecaliximab (formerly GS-5745) is a recombinant chimeric IgG4 monoclonal antibody selective for MMP9. It has been engineered to remove T cell epitopes in an effort to reduce the risk of immunogenicity. Andecaliximab was derived from the murine anti-human MMP9 monoclonal antibody, AB0041, and shares the same binding characteristics. Andecaliximab and AB0041 cross-react with and inhibit rat and cynomolgus monkey MMP9 but not murine MMP9.

AB0046, which cross-reacts with and inhibits murine MMP9, was generated via immunization in MMP9 knockout mice. Epitope mapping analysis revealed that AB0046 binds a similar region in murine MMP9 to that bound by andecaliximab and AB0041 on human MMP9.

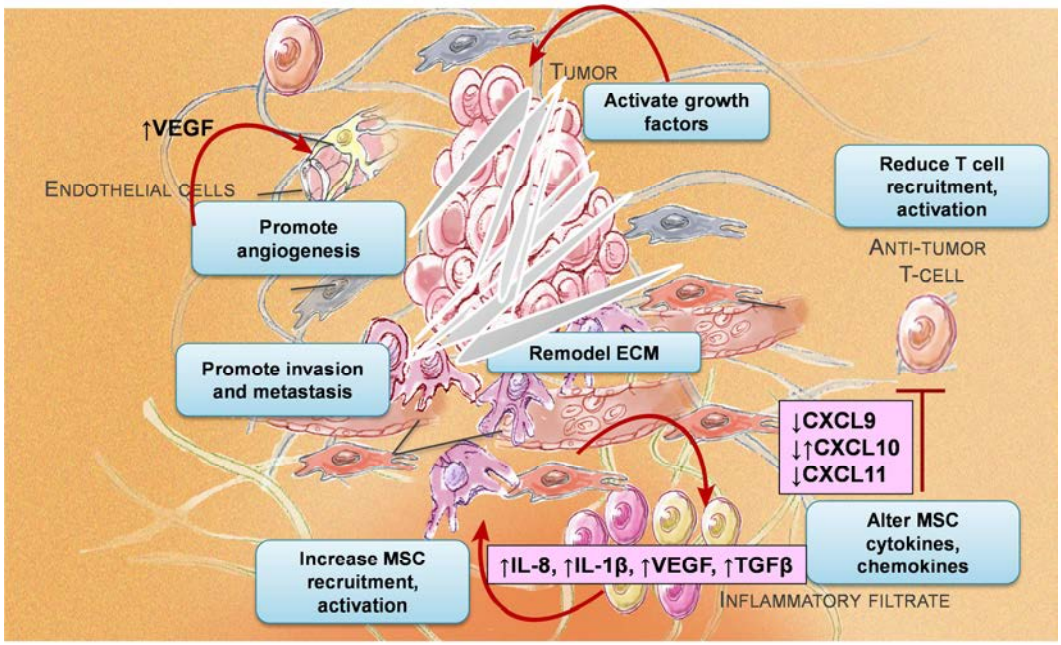
For further information on andecaliximab, refer to the current Investigator's Brochure (IB).

1.1.4. Preclinical Pharmacology and Toxicology

1.1.4.1. Pharmacology

MMP9 enzymatic activity contributes to tumor growth by several mechanisms (Figure 1-2). MMP9 degrades basement membrane collagen and remodels other extracellular matrix (ECM) components and regulates the bioavailability of ECM-sequestered growth factors such as VEGF, FGF-2, as well as membrane-tethered EGF {Ardi 2009, Deryugina 2010, Kessenbrock 2010, Perng 2011}. Proteolytic breakdown of physical barriers to cell invasion plus liberation of factors that activate growth and angiogenesis paves the way for tumor expansion and metastasis, with the accompanying development of neovascularization to support tumor outgrowth. MMP9 expression by tumor-associated myeloid suppressor cells (MSCs) such as macrophages (TAMs), neutrophils (TANs), and myeloid-derived suppressor cells (MDSC) is associated with local pro-tumorigenic immunomodulation and angiogenesis {Farina 2014}. Cytokine and chemokine modulation by MMP9 in the tumor microenvironment promotes further recruitment of MSCs that both promote tumor growth and reduce anti-tumor immune responses by T and NK cells (Figure 1-2) {Condeelis 2006, Heissig 2002, Shih 2006}.

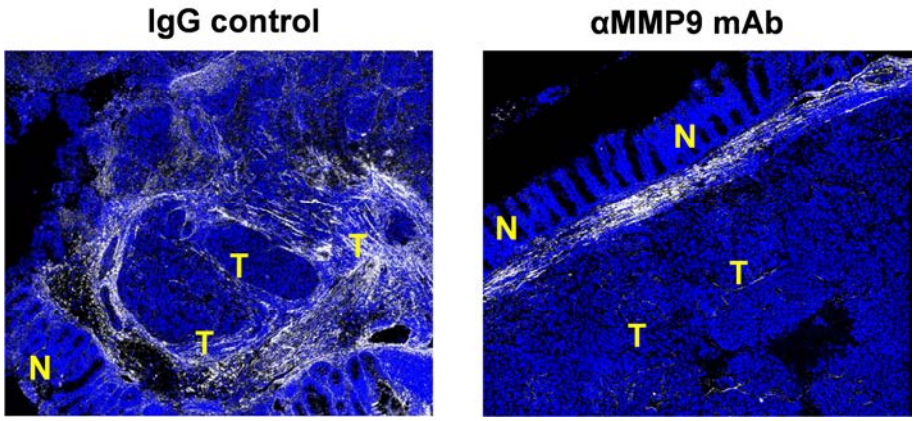
Figure 1-2. Summary of Pro-Tumorigenic Activities of MMP9



Summary of pro-tumorigenic activities of MMP9, which include promoting tumor growth, invasion, and metastasis via effects on both tumor epithelia and the microenvironment. Remodeling of the microenvironment alters the physical properties of tumors. In addition, the action of MMP9 on cytokines and chemokines in the local milieu promote recruitment and activation of myeloid suppressor cells and inhibit anti-tumor T-cell recruitment and responses.

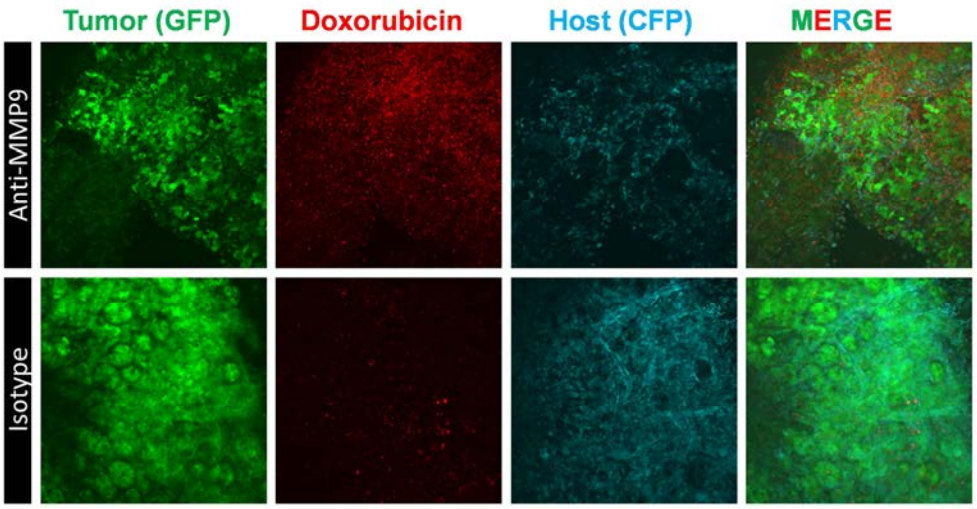
The therapeutic potential of inhibitory antibodies targeting human MMP9 (AB0041) and mouse MMP9 (AB0046) was evaluated in a surgical orthotopic xenograft mouse model of colorectal carcinoma in which tumors were derived from the human tumor cell line HCT116. While MMP9 expression is limited in this tumor model as compared to human gastrointestinal tumors such as gastric and colorectal cancer, with patchy positivity in subsets of tumor epithelia and infiltrating myeloid cells observed, the model nonetheless enables exploration of MMP9 biology in each compartment. Treatment of established tumors with a cocktail of an anti-human MMP9 antibody (targeting MMP9 produced by tumor epithelia) and an anti-mouse MMP9 antibody (targeting MMP9 produced by infiltrating cells) significantly reduced growth of the primary tumor and reduced the incidence of metastases in multiple independent studies. Furthermore, treatment with either agent alone yielded significant anti-tumor efficacy highlighting important roles for both tumor epithelial-derived and stromal/infiltrate-derived MMP9 in primary tumor outgrowth. Of note, in addition to reduction in tumor growth, MMP9 inhibition was associated with changes in the tumor microenvironment, specifically a reduction in the tumor cell-associated fibrillar collagen as measured by second harmonic generation microscopy, a multiphoton method that specifically visualizes crystalline fibrillar collagen (Figure 1-3). Follow up studies in the orthotopic HCT-116 model provide further evidence that inhibition of MMP9-associated remodeling can promote delivery of agents to the tumor (in this example, modeled by injection and imaging of doxorubicin after 2 weeks of therapy with anti-MMP9, Figure 1-4).

Figure 1-3. Changes in Tumor-Associated Fibrillar Collagen



Changes in tumor-associated fibrillar collagen (second harmonic generation microscopy, white) with MMP9 inhibition in an orthotopic model of colorectal cancer (HCT-116-derived). T = tumor, N = normal. Fibrillar collagen adjacent to normal structures was not altered, but tumor-associated fibrillar collagen was reduced.

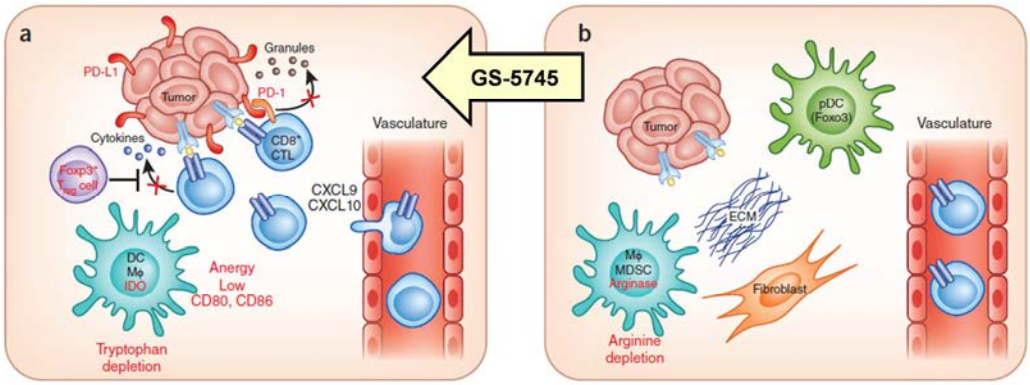
Figure 1-4. Effect of MMP9 Inhibition in the HCT-116 Orthotopic Model of CRC



Exploring the effects of MMP9 inhibition in the HCT-116 orthotopic model of colorectal cancer, in which tumor cells are labeled with green fluorescent protein (GFP, in green) and the host is labeled with cyan fluorescent protein, with bias towards fibroblastic cells (CFP, in blue). After two weeks of treatment of established tumors with anti-MMP9 antibodies or an isotype control, doxorubicin is administered and its natural signal imaged 24 hours later (red). The merged image highlights changes in the physical tumor structure with anti-MMP9, along with evidence of improved delivery of doxorubicin.

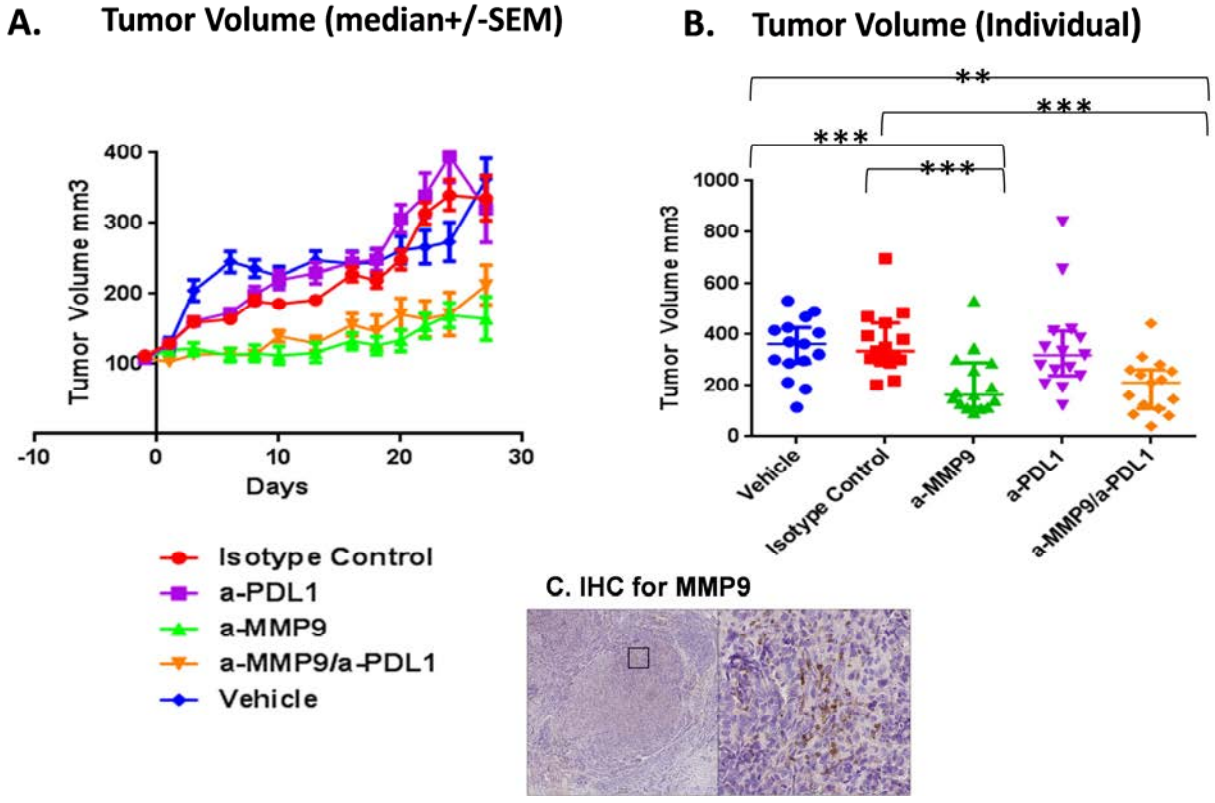
These observations and published data suggest that inhibition of MMP9 could provide benefit with respect to anti-tumor immunity in 2 respects: improved access of both antibodies and T cells themselves to tumor cells to enable synapse formation and cell lysis as a result of remodeling of the tumor microenvironment, and re-balancing of a myeloid-rich tumor-associated cellular milieu to one that is less repressive to cytotoxic T-cell entry and activity (Figure 1-5). To experimentally explore these concepts, a syngeneic mouse model of breast cancer was utilized (HC11-NeuT [HER2]-driven tumors implanted in the mammary fat pad). IHC analysis of HC11-NeuT tumors indicated that MMP9 expression was restricted to the myeloid cell infiltrate with limited to no expression apparent in tumor epithelia (Figure 1-6). While this expression pattern underestimates the MMP9 profile that is observed in human tumors, it nonetheless affords an opportunity to examine the consequences of inhibiting myeloid-derived, tumor-associated MMP9 in mice with an intact immune system. As shown in Figure 1-6, therapeutic administration of anti-murine MMP9 antibody AB0046 resulted in significant inhibition of tumor growth, highlighting the role of myeloid cell-derived MMP9 in promoting tumorigenesis. Conversely, a murine inhibitory antibody targeting the T-cell checkpoint pathway via PD-L1 did not have any impact on tumor growth. The resistance to checkpoint therapy in this model is attributed to the presence of MSC. A combination of anti-MMP9 and anti-PD-1 did not further impact tumor volume in this model, perhaps in part due to the magnitude of effect of anti-MMP9 as a single agent.

Figure 1-5. Hypothesis for Andecaliximab and Nivolumab



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

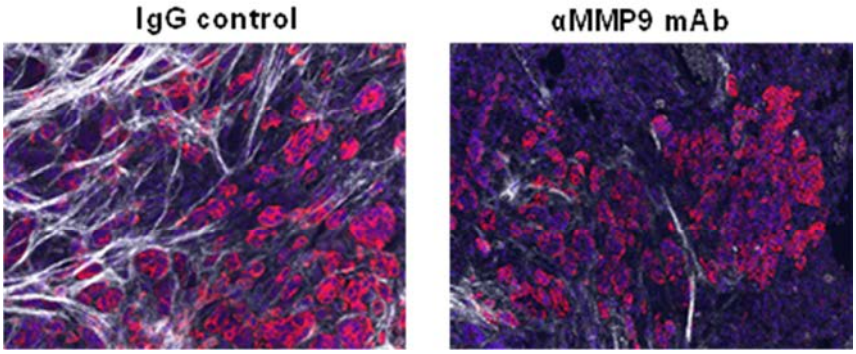
Figure 1-6. Inhibition of MMP9 in Orthotopic HC11-NeuT Model of Breast Cancer



Inhibition of MMP9 is efficacious in the syngeneic, orthotopic HC11-NeuT model of breast cancer. Treatment was initiated at an average tumor volume of 100 mm3. Test articles: vehicle (blue), Isotype control IgG (GS-645864, red), anti-MMP9 (GS-622703 = AB0046, green), anti-PD-L1 (GS-696882, purple), combination of anti-MMP9 and anti-PD-L1 (orange). ** $p < 0.01$, *** $p < 0.005$. Representative IHC for MMP9 expression in this model is shown in C, positive myeloid cell infiltrate.

Collagen fibrils around tumors can impede delivery of therapies and the access of T cells to tumor cells, thus acting as a physical barrier to anti-tumor immunity and contributing to tumor progression. Analysis of tumor-associated fibrillar collagen by second harmonic microscopy was superimposed with images of nuclear staining (Sytox orange) and tumor cell staining (cytokeratin) to provide context for collagen fibril visualization .The cytokeratin staining revealed that the tumors grew in both large masses and small acinar structures and the collagen fibrils in and around both structures appeared to be diminished in the tumors treated with AB0046 (Figure 1-7). Quantification of fibrillar collagen intensity across entire images from this study confirmed the trend in decreased fibrillar collagen in the α-MMP9 treated tumors.

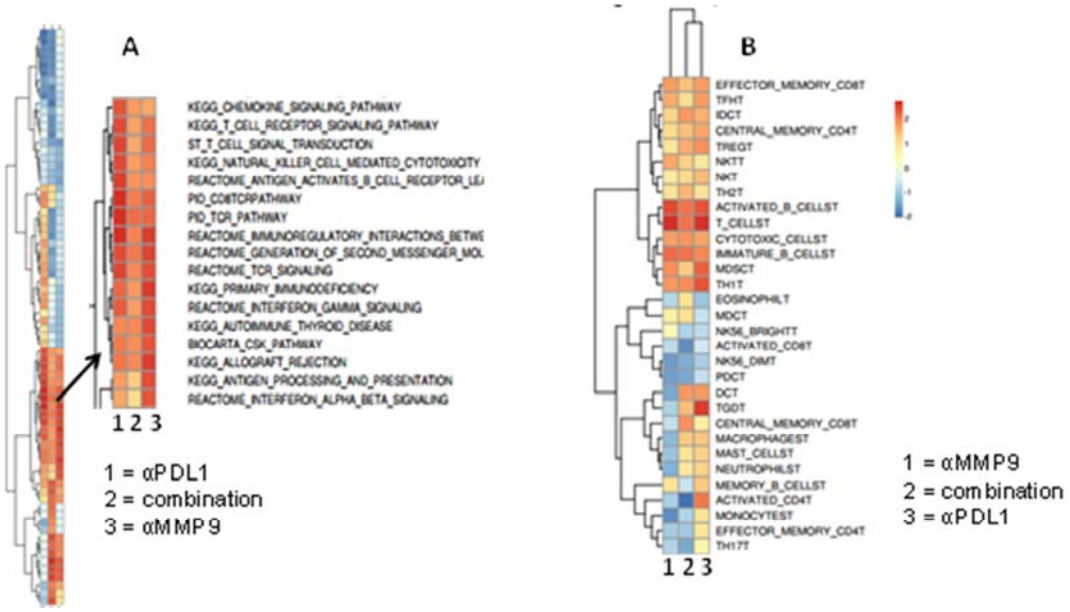
Figure 1-7. Changes in Tumor-Associated Fibrillar Collagen



Changes in tumor-associated fibrillar collagen (second harmonic generation microscopy, white) with MMP9 inhibition in an orthotopic syngeneic model of breast cancer. Tumor cells are stained with a pan-cytokeratin marker (pink), nuclei in DAPI (blue).

Transcript and pathway analysis of treated tumors revealed additional changes in the tumor microenvironment associated with MMP9 inhibition. The top 10 pathways analysis using C2 canonical pathways collections indicated that inhibition of MMP9 lead to an increase in overall immune signature pathways such as interferon gamma and alpha-beta signaling, immunoregulation, antigen processing and presentation, and CD8 and T-cell receptor signaling. For anti-PD-L1 treated tumors, an increase in immune signature was also observed, consistent with the known mechanism of action of this agent (immunoregulatory interactions between lymphoid and non-lymphoid cells, CD8 TCR pathway, TCR pathway, and T-cell signal transduction). As illustrated in Figure 1-8, upregulation of immunomodulatory pathways consistent with T-cell and possibly also NK cell activation was a notable feature of MMP9 inhibition by different pathway analyses, and these patterns were also reflected in the PD-L1 and combination groups. These data are consistent with inhibition of myeloid-produced MMP9 resulting in a microenvironment that is more favorable for T-cell infiltration and activation.

Figure 1-8. Transcriptome and Pathway Analysis of the HC11-NeuT Model



Primary pathways for MMP9 inhibition, from KEGG and Broad collections, reflect activation of T-cell and related immunomodulatory signaling pathways.

The PD-1/PD-L1 axis defines an immune checkpoint that prevents the activation of T cells in the tumor microenvironment. Data from current clinical trials suggests that the tumors that respond most strongly to nivolumab are those that are either particularly immunogenic (eg, tumors with genomic instability) or those with infiltrated T cells in the tumor. For tumors that do not respond, despite the relief of the immune checkpoint by nivolumab, continued repression of T-cell activation due to an immunosuppressive environment may be a possible explanation. andecaliximab is hypothesized to remove the immunosuppressive environment through local suppression of or reduction of myeloid-derived suppressor cells, as well as local inflammation and immunosuppressive cytokines. Additionally, inhibition of MMP9 in the tumor microenvironment is expected to promote lymphocyte and therapeutic access. Thus, combination of andecaliximab with nivolumab is proposed to lead to more activated cytotoxic T cells and provide superior efficacy in advanced gastric cancer relative to nivolumab alone.

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

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

1.1.4.2. Toxicology

The toxicology program consists of completed 4-week repeat-dose IV toxicity studies in both rats and monkeys. The 26-week toxicity studies in rats and cynomolgus monkeys included both IV and SC routes. The rat and rabbit embryo fetal development studies and the rat fertility study have also been completed. At doses of andecaliximab up to 100 mg/kg/dose IV, data indicate no test article-related maternal or fetal effects in rats and rabbits, and no test article-related effects on male or female fertility in rats. Findings associated with andecaliximab treatment in the 4-week repeat-dose toxicity studies have been limited to reversible physeal hypertrophy in rats, and reversible increased adrenal gland weight in female monkeys at all doses, which was associated with slight hypertrophy of the zona fasciculata in a single 100-mg/kg/dose female monkey. The physeal hypertrophy in rats is likely directly attributable to inhibition of MMP9 as similar findings were observed in MMP9 null mice {Vu 1998} and in children with mutations in MMP9 and MMP13 {Lausch 2009}. In both mice and children, this is a transient finding that spontaneously regresses as the bone matures. The physeal hypertrophy noted in rats is not considered relevant to adult humans because the growth plates are closed and longitudinal bone growth is no longer ongoing in adults. In the 26-week studies, there were no findings of toxicological concern in rats or cynomolgus monkeys following weekly IV or SC administration at doses up to 100 mg/kg/dose and 150 mg/kg/dose, respectively. The lack of physeal hypertrophy observed in the rat 26-week study is presumably due to the reversible nature of this finding as longitudinal bone growth and growth plate closure slows/completes. The NOAEL in the rat and monkey 26-week studies was 100 mg/kg/dose (IV) (Rat Week 24 $AUC_{0\text{-}168h}$ 269,000; monkey Week 25 $AUC_{0\text{-}168h}$ 766,000 µg•h/mL) and 150 mg/kg/dose (SC), (Rat Week 24 $AUC_{0\text{-}168h}$ 101,000 µg•h/mL; monkey Week 25 $AUC_{0\text{-}168h}$ 719,000 µg•h/mL), respectively, the highest doses evaluated by each route of administration in each study.

1.1.5. Clinical Trials of Andecaliximab

Andecaliximab is being investigated for the treatment of solid tumors, inflammatory bowel disease, rheumatoid arthritis, cystic fibrosis, and chronic obstructive pulmonary disease. Brief summaries of the solid tumor clinical trials are provided herein.

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

As of January 12, 2016, Study GS-US-296-0101 had enrolled 40 subjects with metastatic gastric adenocarcinoma (14 remain on study). Grade 3 or higher treatment-emergent AEs (TEAEs) included neutropenia (18%), nausea (10%), and neutrophil count decreased (10%). The most common serious TEAEs were abdominal pain, GI hemorrhage, hyponatremia, nausea, pyrexia, and septic shock each occurring in 2 subjects (5%). Median progression free survival (PFS) for all 40 subjects was 7.4 months (90% confidence interval (CI) = [5.0, 12.5]), with a median duration of response (DOR) of 9.4 months and an objective response rate (ORR) of 50%. Of those subjects, 30 were chemotherapy naïve (eg, first-line), and demonstrated a median PFS of 12.0 (90% CI = [5.5, 18.0]) months, with a median DOR of 10.6 months and an ORR of 57%. Collagen neoepitope decreased with continued treatment, demonstrating on-target effects.

This efficacy data combined with the favorable safety profile continues to support evaluation of andecaliximab in a Phase 3 study of this fatal disease where therapeutic options are limited and non-curative.

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

Study GS US-296-1884 is a Phase 1b clinical study of Japanese subjects to evaluate safety and tolerability of GS5745 as monotherapy and in combination with chemotherapy.

Further details on the oncology studies with andecaliximab, as well as the clinical studies outside of oncology, can be found in the andecaliximab IB.

1.1.6. Information about Nivolumab

Nivolumab (OPDIVO) is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with:

- Advanced (unresectable or metastatic) melanoma in adults
- Metastatic non-small cell lung cancer whose disease progressed during or after platinum-based chemotherapy. (US FDA)
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy (US FDA)

Please see local label for updated accurate information about nivolumab.

1.2. Rationale for this Study

Andecaliximab is a monoclonal antibody that inhibits MMP9, an extracellular enzyme involved in matrix remodeling, tumor growth, and metastasis. Preclinical studies demonstrate that MMP9 inhibition alters the tumor microenvironment, is associated with greater chemotherapy penetration, and improved anti-tumor immunity.

MMP9 has been shown to degrade and remodel basement membrane and extracellular matrix and vasculature. It can promote recruitment of tumor-associated macrophages and immune suppressor cells, and locally activate cytokines produced by these cells that impair anti-tumor immunity. The murine surrogate of andecaliximab (anti-MMP9 antibody) has shown significant anti-tumor activity in models in which MMP9 is produced by infiltrating myeloid cells. The anti-tumor activity is associated with reduction of tumor-associated fibrillar collagen, and alterations in the immune cell transcript profile in the treated tumors. PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells. Binding of a PD-1inhibitor to the PD-1 receptor will inhibit the inhibitory signal on T cells and will thus stimulate the

anti-tumor effect. Andecaliximab's ability to alter the collagenous microenvironment may allow for greater infiltration of activated lymphocytes into the tumor and hence augment the anti-tumor effect offered by a PD-1 inhibitor alone. Thus, the combination of removing the negative stimulus on T cells by the PD-1 inhibitor and the enabling of activated T cells to gain access to the tumor cells by remodeling of the microenvironment and reduction of suppressive signals makes this a very attractive combination for cancer therapy.

Nivolumab is a fully human anti-PD-1 IgG4 monoclonal antibody with a favorable safety profile and efficacy in melanoma, non–small-cell lung cancer, and renal cell carcinoma. The Phase 1/2, open-label CheckMate-032 study evaluated nivolumab ± ipilimumab in subjects with solid tumors. At GI ASCO 2016 data were presented for subjects with gastroesophageal or gastric adenocarcinoma receiving nivolumab monotherapy. Fifty-nine subjects were enrolled and treated with single-agent nivolumab; ORR was 12% (n = 7/58; 1 complete response, 6 partial responses, 12 subjects [21%] had stable disease). Among responders, median duration of response was 7.1 months (95% CI, 3.0–13.2) and OS was 6.8 months (95% CI, 3.3–12.4). Thirty-nine percent of tumor samples were PD-L1 positive (≥ 1% cutoff). ORRs in subjects with PD-L1-positive and -negative tumors were 18% and 12%, respectively. The investigators concluded that nivolumab showed activity in second-line gastric adenocarcinoma and should be further investigated.

Somatic mutations have the potential to encode for "non-self" and serve as immunogenic antigens. Tumors with a large number of somatic mutations due to genomic instability have been found to be more susceptible to immune checkpoint blockade. In a trial of 41 subjects with progressive metastatic carcinoma with or without mismatch-repair deficiency, both PFS and OS were significantly improved for subjects treated with a PD-1 inhibitor alone and whose tumors were genomically unstable {Le 2015}.

Randomization in this study will be stratified by PD-L1 status.

1.3. Risk/Benefit Assessment for the Study

There is no clear or demonstrably superior standard regimen for the treatment of advanced gastric adenocarcinoma especially for those who failed first-line chemotherapy; however, further therapy does improve OS. Preliminary data shows that immune checkpoint inhibitors have activity in this difficult disease and with fewer side effects than chemotherapy. Furthermore, many patients cannot take second-line and beyond chemotherapy due to deterioration of performance status or other comorbid conditions and thus immune therapy presents an attractive option for them. Andecaliximab has the potential to augment the response by immune checkpoint inhibitors in 3 distinct ways: (1) allow greater penetration of activated T cells into the tumor bed by remodeling the extracellular matrix, (2) inhibit the MDSCs that are present due to MMP9 physiologic activity, and (3) change the cytokine milieu to be predominantly anti-tumor. This preclinical hypothesis has been tested in mouse models and presents as strong rationale for efficacy in human cancer.

Furthermore, andecaliximab thus far has shown limited toxicity in clinical trials. No MTD dose was reached in the dose-escalation monotherapy Phase 1 study, and the toxicity profile seen when combining andecaliximab with mFOLFOX chemotherapy is similar to that seen with chemotherapy alone. To date there have been no additional toxicities ascribed to andecaliximab.

Preliminary clinical data point to activity of andecaliximab in combination with chemotherapy with a median PFS in chemotherapy-naive subjects of 12 months. Early data similarly shows activity of nivolumab as monotherapy in the refractory gastric adenocarcinoma population with durable response rates and a tolerable safety profile (Grade 3 or 4 treatment-related AEs in ~17% of subjects in the most recent public data from CheckMate-032). It is hypothesized that the 2 agents together, andecaliximab and nivolumab, will have greater activity when combined.

Potential risks are those inherent in participation in any clinical trial, including (but not limited to) the potential for unforeseen toxicity from 1 or more of the study treatments, procedure-associated risks for protocol-specified procedures, and potential to be treated with a less-active therapy regimen.

The favorable nonclinical and clinical data outweigh the risks associated with administration of andecaliximab and nivolumab and support the evaluation of andecaliximab in combination with nivolumab as a second-line treatment in subjects with advanced gastric or GEJ adenocarcinoma.

1.4. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate and compare the efficacy of andecaliximab in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric or GEJ adenocarcinoma

The secondary objectives of this study are:

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

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

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

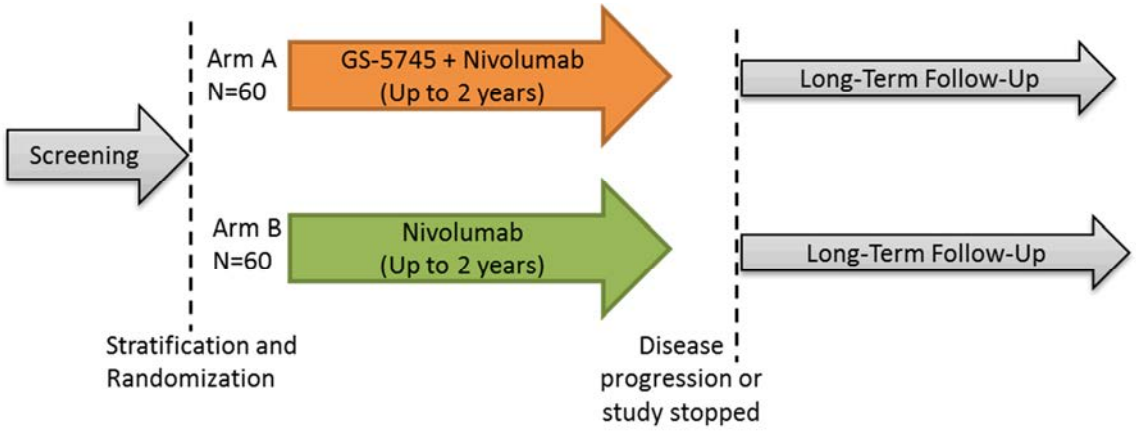
3.2. Study Design

This is a Phase 2, open-label, randomized study comparing andecaliximab in combination with nivolumab versus nivolumab alone in recurrent gastric adenocarcinoma. One hundred and twenty subjects (60 per arm) will be randomized to either Treatment Arm A: andecaliximab + nivolumab or Treatment Arm B: nivolumab alone.

To evaluate combination drug safety, an independent Data Monitoring Committee (DMC) will be charged with overseeing the study safety. After the first 20 subjects are treated for 12 weeks, the DMC will review and evaluate all safety data for any unexpected toxicities. If the DMC determines the combination demonstrates acceptable tolerability, enrollment and randomization will proceed with continued safety oversight from the DMC. Thereafter, review of safety data will be performed at regular intervals as described in the DMC charter.

Treatment Groups:

- Arm A: andecaliximab + nivolumab
- Arm B: nivolumab



Randomization and Stratification:

- 1:1 allocation to andecaliximab + nivolumab versus nivolumab alone through an interactive web response system (IWRS)
- Fixed-block centralized randomization with stratified by:
  - PD-L1 positive versus PD-L1 negative

3.3. Study Treatments

Subjects meeting eligibility 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.

3.4. Duration of Treatment

Starting on Day 1, treatment will be given every 2 weeks and will continue in the absence of disease progression or unacceptable toxicity, consent withdrawal or subject's refusal of treatment, or up to 2 years. There will be a screening period of up to 28 days. Following completion of treatment, subjects will be followed for safety at 30 days after last dose of andecaliximab and 5 months post-treatment of nivolumab, and for survival status approximately every 3 months for up to 5 years total.

3.5. Discontinuation Criteria from Treatment

Andecaliximab and/or nivolumab will be discontinued for any of the following reasons:

- Pregnancy during the study; refer to Appendix 4
- Investigator decision to remove the subject from the study treatment, in consultation with the Gilead Medical Monitor whenever possible
- Confirmed disease progression (see Section 6.2.9 Disease and Response Assessment)
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Initiation of non-study specific anti-neoplastic therapy
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue treatment
- Withdrawal of consent
- Death

- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC)

- Lost to follow up

- Subject non-compliance

Should any study medication discontinuation occur, the reason for discontinuation should be entered in the corresponding study drug completion eCRF. In addition, the subject should continue with the rest of the treatment regimen and the study related procedures per protocol.

3.5.1. Discontinuation Criteria for Nivolumab

In addition to the discontinuation reasons outlined in Section 3.5, please refer to the current nivolumab label or SmPC for your respective region for full discontinuation criteria during treatment with nivolumab.

Nivolumab should also be discontinued for any dosing interruption lasting > 6 weeks with the following exceptions:

- Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Medical Monitor/Study Director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

- Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Sponsor Medical Monitor/Study Director. Prior to reinitiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Medical Monitor/Study Director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

If nivolumab therapy is permanently discontinued for any reason, subjects on Treatment Arm A should also permanently discontinue andecaliximab therapy at the same time. Subjects enrolled on Treatment Arm A who discontinue andecaliximab for reasons other than progression may continue nivolumab after consultation with the Sponsor Medical Monitor/Study Director.

3.6. Premature Discontinuation from Study Treatment

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

3.7. Discontinuation Criteria from Study

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

- Initiation of non-study specific anti-neoplastic therapy in the absence of progression
- Disease progression
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Withdrawal of consent
- Investigator decision to remove the subject from the study, in consultation with the Gilead Medical Monitor
- Death
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC
- Lost to follow up

3.8. Long-Term Follow-Up for Overall Survival

Long-term follow-up (LTFU) will be initiated for subjects who discontinue participation in the study due to reasons other than death. The subject shall remain on LTFU for OS until:

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

Every attempt should be made to keep the subject in the LTFU for OS.

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

3.9. Source Data

The subject identification number and randomization number captured by the interactive web response system (IWRS) are considered source data.

3.10. Biomarker Testing

The PD-1/PD-L1 axis defines an immune checkpoint that prevents the activation of T cells in the tumor microenvironment. Nivolumab inhibits binding of T-cell PD-1 to PD-L1 present on tumor and stromal cells; thus nivolumab inhibits the checkpoint to allow activation of cytotoxic T cells by tumor immunogens. Data from current clinical trials suggests that the tumors that respond most strongly to nivolumab are those that are either immunogenic (tumors with genomic instability) or those with infiltrated T cells in the tumor. For tumors that don't respond, despite the relief of the immune checkpoint by nivolumab, continued repression of T-cell activation due to an immunosuppressive environment may be a possible explanation. Andecaliximab is hypothesized to remove the immunosuppressive environment through local suppression of or reduction of myeloid suppressor cells, local inflammation, and immunosuppressive cytokines. Additionally, inhibition of MMP9 in the tumor microenvironment is expected to promote lymphocyte and therapeutic agent access. Thus, combination of andecaliximab with nivolumab is proposed to lead to more activated cytotoxic T cells and provide superior efficacy in advanced gastric adenocarcinoma relative to nivolumab alone. The biomarker testing described below is designed to address, to the extent possible, these specific hypotheses and to investigate whether non-invasive biomarkers of response can be identified.

3.10.1. Biomarker Samples to Address the Study Objectives:

Biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of gastric adenocarcinoma and/or the validation of a companion diagnostic for andecaliximab. The specific analyses may include, but will not be limited to, the biomarkers and assays listed below. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. Any future testing must be approved by local authorities as applicable according to specific local regulations.

CCI [redacted]

3.10.1.1. PD-L1 Biomarker Test for Stratification

PD-L1 will be assessed by immunohistochemistry (IHC). Archival tumor tissue is required, preferably from the most recent available biopsy or surgical resection. Archival FFPE blocks are preferred. The central laboratory pathologist will certify the presence of sufficient tumor tissue. Tumor tissue is also requested for other biomarker tests in Table 3-1.

3.10.1.2. Pharmacodynamic Biomarkers

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

Table 3-1. Biomarker Objectives and Testing

SAMPLE TYPE	OBJECTIVE	TEST
Tissue Biopsy (archival): Most recently obtained archival tumor biopsy Required	Stratification MANDATORY	• PD-L1 IHC
Tissue Biopsy: Pretreatment; CCI [redacted]	To evaluate potential baseline markers that correlate with response	• MMP9, other MMPs and Immune Cells by IHC and other methods • Tumor gene expression (RNA); IFNγ gene signature, immune cell signatures, • Genomic instability • Somatic tumor DNA mutations
Tissue Biopsy: On-treatment (obtained between Weeks 5-9) Required	To evaluate potential markers that correlate with treatment and/or response	• MMP9, other MMPs, PD-L1 and Immune Cells (to include MDSCs and proliferating T cells) by IHC and other methods • Tumor gene expression patterns (RNA); IFNγ signature, immune cell signatures,
Tissue Biopsy: At Progression If medically feasible	To evaluate potential markers of acquired resistance	• MMP9, other MMPs and Immune Cells • Tumor gene expression patterns (RNA); IFNγ signature, immune cell signatures
Blood	To evaluate pharmacodynamic markers of andecaliximab	• MMP9-mediated collagen cleavage products (C1M)
	To evaluate inflammation and chemokines related to T-cell activation and other protein markers of MMP9 activity	• Circulating cytokines, chemokines and inflammatory markers
	To evaluate circulating immune cells	• Immune cell phenotyping by flow cytometry • Immune cell repertoire
	To evaluate the impact of treatment and/or response on tumor heterogeneity	• Genomic analysis of circulating tumor cells
	To evaluate disease burden and identify mutations correlated with resistance to therapy	• Circulating tumor DNA (ctDNA) isolation and sequencing
Oral sample	To investigate oral microbiome diversity	• Characterization of oral microbiome diversity

3.10.2. Biologic Samples for Optional Future Research

CCI

[redacted]

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 120 subjects will be randomized to receive open-label study drug. The target population is subjects with histologically confirmed inoperable locally advanced or metastatic adenocarcinoma of the stomach or the GEJ and who have received at least1 prior line of therapy.

4.2. Inclusion Criteria

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

1) Age ≥18 years

2) Histologically confirmed inoperable locally advanced or metastatic adenocarcinoma of the stomach or GEJ which have progressed on at least 1 prior systemic therapy or line of treatment for unresectable/metastatic disease

3) Eastern Cooperative Oncology Group (ECOG) ≤ 1

4) Measurable disease according to RECIST v1.1

5) Tumor sites that can be accessed for repeat biopsies

6) Archival tumor tissue, preferably obtained from the most recent available biopsy; there must be adequate tissue for a PD-L1 stratification test, as assessed by central pathologist

7) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline

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

9) Adequate hematologic function

   a) neutrophils ≥ 1.5 x 10^9/L

   b) platelets ≥ 100 x 10^9/L

   c) hemoglobin ≥ 9 g/dL

10) Adequate hepatic function

    a) Direct or total bilirubin ≤ 1.5 x ULN

    b) ALT and AST ≤ 2.5 x ULN

11) Creatinine clearance (CL_{cr}) ≥ 60 mL/min, estimated based on the Cockroft-Gault formula or measured based on 24 hour urine collection or other reliable method

12) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the screening visit throughout the study treatment period, for 90 days following the last dose of andecaliximab and at least 5 months after the last dose of nivolumab, unless the subject chooses continuous heterosexual abstinence as a lifestyle-choice (see Appendix 4 for more information)

13) For male subjects of reproductive potential having intercourse with females of childbearing potential, willingness to use a protocol recommended method of contraception and to refrain from sperm donation from the start of study drug, throughout the study treatment period, and for 90 days after administration of the last dose of andecaliximab or nivolumab (see Appendix 4 for more information)

14) Breastfeeding females must agree to discontinue nursing before study drug administration

15) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer

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

17) Evidence of a signed informed consent prior to implementation of any protocol specific procedure

4.3. Exclusion Criteria

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

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

2) Radiotherapy within 28 days of randomization; subjects given palliative radiotherapy to peripheral sites (eg, bone metastasis) may enter the study before 28 days have elapsed provided the radiated sites do not contain lesions which may be used to evaluate response, and must have recovered from any acute, reversible effects

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active gastrointestinal bleeding, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

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

5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days of first dose of study drug

6) Known positive status for human immunodeficiency virus (HIV)

7) Known acute or chronic-active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)

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

9) Known or suspected central nervous system metastases

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

11) Documented myocardial infarction or unstable/uncontrolled cardiac disease (ie, unstable angina, congestive heart failure [New York Heart Association > Class II]) within 6 months of randomization

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

13) Pregnant or breastfeeding women (pregnancy needs to be excluded by testing of beta-human chorionic gonadotropin [β-hCG])

14) Experimental medical treatment within 28 days prior to randomization

15) Known hypersensitivity to andecaliximab or nivolumab or excipients or to Chinese hamster ovary cell products or to recombinant human or humanized antibodies

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

17) Previous severe hypersensitivity reaction to treatment with another monoclonal antibody therapy

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

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

20) Current or history of pneumonitis or interstitial lung disease

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

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

This is an open-label, randomized study. Randomization to Arm A: andecaliximab + nivolumab or Arm B: nivolumab alone will be based on a randomization schedule prepared by Gilead and/or a designee before the start of the study. Eligible subjects will be randomized via an interactive web response system (IWRS).

The IWRS will be used to maintain a central log documenting screening, to implement randomization, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of the study drug.

The IWRS will assign kit numbers and provide instructions for dispensing of study drug (andecaliximab+nivolmab/nivolumab alone). It is anticipated that subjects will usually begin study drug immediately after randomization.

5.2. Description and Handling of Study Treatments

5.2.1. Formulation

5.2.1.1. Andecaliximab

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

5.2.1.2. Nivolumab

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

5.2.2. Packaging and Labeling

Study drug andecaliximab (labeled as GS-5745) solution will be supplied in 10 mL glass vials with coated elastomeric stoppers and aluminum crimp seals with flip-off caps.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), European Union (EU) guideline to Good Manufacturing Practice – Annex 13 (investigational medicinal Product(s)), and/or other local requirements. Commercially available product of nivolumab will be used for this study.

5.2.3. Storage and Handling

Andecaliximab should be stored at 2 to 8 ºC. Storage conditions are specified on the study drug label. Until dispensed to the subject, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, the study drug should be stored in the containers and packaging in which they were supplied until dosing to the subject.

Commercial nivolumab will be used for the study. Further information regarding preparation, storage, and handling are available in the Prescribing Information or SmPC for nivolumab.

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

5.3. Dosage and Administration of Study Drug

For Arm A, andecaliximab will be administered 800 mg via IV infusion over approximately 30 (± 5) minutes at the research clinic by a qualified staff member on Day 1 and every 2 weeks thereafter. Following administration of andecaliximab, nivolumab will be administered 3 mg/kg via IV infusion over approximately 60 (± 5) minutes on Day 1 and every 2 weeks thereafter.

For Arm B, nivolumab will be administered 3 mg/kg via IV infusion over approximately 60 (± 5) minutes on Day 1 and every 2 weeks thereafter.

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

5.3.1. Dose Adjustments

If an AE is attributed to only 1 drug (andecaliximab or nivolumab), the investigator's discretion will be used to determine if the drug not attributed to the adverse event will be withheld based on the investigator's assessment of risk-benefit of withholding 1 or both drugs.

5.3.1.1. Andecaliximab

If a subject experiences a Grade 3 toxicity or greater that is felt to be due to study drug andecaliximab, treatment will be postponed until the toxicity is resolved to Grade 0 or 1 (as defined by CTCAE v 4.03) or returns to the subject's baseline value. If the toxicity is resolved to Grade 0 or 1 or returns to the subject's baseline value, the subject may resume andecaliximab at the originally assigned dose level. If the subject experiences a recurrence of the Grade 3 or greater toxicity after restarting andecaliximab, treatment with andecaliximab will be discontinued.

5.3.1.2. Nivolumab

Please refer to the current nivolumab label or SmPC for your respective region for recommended dose modification guidelines and full discontinuation criteria with nivolumab.

5.4. Prior and Concomitant Medications

At Screening, all medication taken up to 30 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (eg, anti-emetics), and vitamins and minerals.

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

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

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

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

5.4.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

5.4.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic chemotherapy or biological therapy not specified in the protocol
- Immunotherapy not specified in this protocol
- Investigational agents other than those specified by the protocol

- Radiation therapy

  — Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  — Note: Inhaled steroids are allowed for management of asthma.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5. Accountability for Study Drug

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

Study drug (andecaliximab and or nivolumab) accountability records will be provided to each study site to:

- Record the date received and quantity of study drug vials

- Record the date, subject number, subject initials, the vial number dispensed

- Record the date, quantity of used and unused vials returned, along with the initials of the person recording the information.

Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.5.1. Study Drug Return or Disposal

The study drugs (andecaliximab and nivolumab) should be disposed of at the site as per local standard operating procedures. Please see pharmacy binder for additional instructions (See Section 9.1.7 for details).

6. STUDY PROCEDURES

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

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

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and special safety assessments such as ECGs.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any non-serious AEs related to protocol-mandated procedures on the AEs eCRF. All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF.

6.1. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the screening evaluations. The screening number and/or subject ID will be assigned for that individual subject by the designated IWRS. Subject eligibility must be determined by results received from the central lab as described in Sections 6.2.2 and 6.2.8.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization. A subject will be considered enrolled once he or she has completed randomization.

Subjects will undergo procedures defined in Appendix 2. Details regarding randomization and treatment assignment are in Section 5.1.

6.2. Study Procedure Descriptions

The following sections describe the individual study procedures outlined in subsequent sections and the schedule of assessments. During the treatment period, all visits may be performed within the windows identified in Appendix 2.

6.2.1. Informed Consent

All subjects must sign and date the most recent IRB/IEC-approved informed consent form before any study specific procedures are performed except where noted in the protocol in relation to standard of care procedures. CCI [redacted]

6.2.2. Re-Screening Criteria

Subjects who do not randomize within 28 days of screening will be screen failed.

Re-screening may be allowed. Subjects who are re-screened after 28 days must be re-consented with a new screening number and the screening assessments must be repeated. For subjects that are re-screened within 28 days, assessments with results that would exclude the subject will need to be repeated.

Subject eligibility must be determined by results received from the central lab. However, if there has been at least 1 failed attempt to obtain test results from the central lab, eligibility may be determined using local lab results, with documentation of failed attempts, local lab results, and sponsor approval.

6.2.3. Medical & Medication History

A complete medical and surgical history will be obtained by the investigator or designee at screening, including disease history, and recorded on the eCRF.

All medications taken within 30 days prior to screening and during the screening period will be obtained prior to randomization and recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, vitamins and minerals.

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

6.2.4. Physical Examination

A physical examination (PE) will be performed at screening, end of treatment (EOT), and EOS. This will include assessment of clinical signs and symptoms. The exam will be performed by a physician, a physician's assistant, or nurse practitioner qualified to perform assessments. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the healthcare provider.

A modified physical exam capturing changes from prior exams will be performed on Day 1 and every 4 weeks thereafter, and at the 30-day Safety Follow-up. Height will be collected at Screening only.

6.2.5. Vital Signs & Weight

Vital signs including blood pressure, heart rate, respiratory rate, and oral temperature will be measured by the investigator or qualified designee as per standard institutional guidelines at each study visit as indicated in Appendix 2. Weight will be collected at the same visits vital signs are taken.

6.2.6. Electrocardiogram Assessment

A single 12-lead electrocardiogram (ECG) will be collected at Screening, Day 1, and every 4 weeks thereafter at subsequent visits, and at the EOT and EOS visits, as indicated in Appendix 2. The investigator will review all ECGs and retain the tracing with the source documents.

6.2.7. Performance Status

Performance status will be scored using the ECOG performance status scale index (refer to Appendix 3), at Screening, Day 1 and every 4 weeks thereafter, EOT, EOS, and 30-day Safety Follow-up visits. ECOG used to determine eligibility must be the performance status during the screening period. ECOG performance status on Day 1 may be waived if it was conducted during screening within 4 days of Day 1.

6.2.8. Laboratory Assessments

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

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

Urine pregnancy test will be performed locally at the site.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate BUN Calcium Chloride Creatinine[a] Glucose Lipase Amylase Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein CEA CA125	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic[b\]	WBC Hemoglobin Hematocrit Platelet ANC <u>Differential</u> Eosinophils Lymphocytes Monocytes Neutrophils **Coagulation** PT/INR aPTT	Serum β-hCG or urine pregnancy test[c] Thyroid Function Tests (TSH, T3, freeT4)[d]

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.

Screening laboratory samples should be obtained within 28 days prior to randomization. Blood samples will be obtained for hematology, chemistry, coagulation, thyroid function, and pregnancy testing for female subjects. A urine sample will also be obtained at screening for urinalysis.

Blood samples for hematology and chemistry will be obtained at pre-dose on Day 1 and every 2 weeks thereafter, EOT, EOS, 30-day, and 5-month Safety Follow-up. Blood samples for Thyroid Function Tests (TSH, T3, free T4) will be collected every 8 weeks, and at EOT, EOS, 30-day, and 5-month Safety Follow-up. A urine sample for urinalysis and pregnancy testing for female subjects will also be obtained on Day 1 and every 4 weeks thereafter, EOT, EOS, 30-day, and 5-month Safety Follow-up. Blood samples for coagulation will be obtained at EOT and EOS.

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

6.2.8.1. Pregnancy Test

All females of childbearing potential (see Appendix 4) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed every 4 weeks starting on Day 1, EOT, EOS, 30-day, and 5-month Safety Follow-up.

6.2.8.2. Pretreatment, On-treatment and Progression Biopsies

- If biopsies are endoscopic gastric, at least 4 biopsies at each time-point (pre-treatment, on-treatment, and at progression) should be obtained. If biopsies are from other sites, core needle biopsies, excisional, resections, incisional, or punch biopsies are acceptable. For core needle biopsies, at least 3 cores should be collected. Refer to the laboratory manual for tissue processing instructions. It is preferred that on treatment and progression biopsies be taken from primary (gastric or GEJ tissue) lesions and/or the same site as the pre-treatment (or archival) tissue. If tissue is not available or accessible from the primary lesion (gastric or GEJ tissue), biopsies of metastatic lesions are acceptable. Pre-treatment: To be obtained within the screening window or any time after last line of therapy; The pretreatment biopsy is requested if archival tumor sample provided to meet Inclusion Criterion #6 is from before the last line of therapy

- On-treatment: To be obtained anytime within the window of Week 5 through Week 9

- At progression: To be obtained at disease progression (if medically feasible)

6.2.8.3. Anti-Andecaliximab Antibody

For Arm A only, blood samples for anti-andecaliximab antibody will be collected prior to dosing at the following visits: Day 1, Weeks 4, 8, 16, 24, and every 3 months thereafter, and at the EOT and EOS visits.

6.2.8.4. Andecaliximab Pharmacokinetics

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

6.2.8.5. Biomarkers

Samples for biomarker analysis as listed in Table 3-1 will be collected as follows and in Appendix 2:

- Blood biomarker samples will be collected at screening, prior to dosing on Day 1, Weeks 2, 4, 8, 16, 24, and every 3 months thereafter, and at EOS or at disease progression.
- An oral sample (saliva or other) for characterization of oral microbiome diversity will be collected prior to dosing on Day 1.

[redacted]

6.2.9. Disease and Response Assessment

6.2.9.1. Efficacy Measurement

RECIST version 1.1 {Eisenhauer 2009} [Appendix 5] will be used for assessment of tumor responses for the purposes of study evaluation, managing patients on protocol treatment, and decision making for discontinuation of study therapy due to disease progression, with some modifications to account for atypical responses which may occur with immune-based therapies {Swaika 2015}. Given that anti PD-1 agents produce antitumor effects by potentiating endogenous cancer-specific immune responses, the response patterns seen with these agents may extend beyond the typical time course of responses seen with cytotoxic agents. In addition, anti-PD-1 therapies can occasionally manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions ("tumor flare" or "pseudoprogression") {Topalian 2014}. In these cases, standard RECIST may not provide an accurate response assessment of anti PD-1 agents.

Therefore, RECIST 1.1 will be used [Appendix 5] with the following adaptations:

If imaging shows a CR or PR, tumor imaging should be repeated at least 4 weeks (≥4 weeks) later to confirm response, per RECIST 1.1 guidelines. Subjects will then return to regular scheduled imaging every 8 weeks starting with the next protocol-specified imaging time-point. Subjects who obtain a confirmatory scan do not need to undergo scheduled imaging assessment ≤2 weeks later (eg, if a subject obtains a scan at Week 22 to confirm a Week 16 response, they will not also be required to complete the scheduled Week 24 scan).

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

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

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

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

- If repeat imaging shows < 20% tumor burden increase compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued and/or resumed (PD is not confirmed).
- If repeat imaging confirms PD due to any of the scenarios listed below, subjects will be discontinued from study therapy with the following exception: if the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging compared to the initial PD assessment, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed at the protocol specified intervals.

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

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

Progressive Disease is confirmed at repeat imaging if:

- Tumor burden remains ≥ 20% (and at least 5 mm absolute increase) compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion(s) resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

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

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

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

In subjects who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following guidelines for end of study follow-up (Section 6.2.9.2).

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

6.2.9.2. Tumor Imaging

Contrast-enhanced CT (without contrast if use of contrast is contraindicated) or gadolinium-enhanced 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. CT is the preferred imaging modality for this study. Tumor burden will be evaluated solely based on radiographic imaging per RECIST v 1.1, with the modifications noted in Section 6.2.9.1. Chest x-ray, ultrasound, endoscopy, laparoscopy, positron-emission tomography, radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, it is recommended that the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. Local site study team reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility.

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

For subjects who stop study treatment in the absence of disease progression (eg, experienced unexpected toxicity), scans should continue to be collected approximately every 8 weeks until disease progression or initiation of systemic anti-tumor therapy other than the study treatment, whichever is earlier.

All relevant clinical and radiographic information required to make each assessment must be made available for source verification and submission to a central reader. CCI [redacted] Disease progression will be determined by the investigator or qualified designee.

Imaging should be continued at protocol-specified intervals until whichever of the following occurs first:

- Initial site-assessed disease progression is confirmed
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

6.2.10. Study Drug Administration

For Arm A, andecaliximab will be administered via IV infusion over approximately 30 (± 5) minutes on Day 1 and every 2 weeks thereafter. Following andecaliximab dosing, subjects will also be administered nivolumab via IV infusion over approximately 60 (± 5) minutes.

For Arm B, nivolumab will be administered via IV infusion over approximately 60 (± 5) minutes.

Study drug dosing must be documented on the eCRF.

6.2.11. Adverse Events

From the time of obtaining informed consent through the first administration of study drug, record all SAEs as well as any AEs related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF.

From the time of the first administration of study drug through 30 days post the last administration of andecaliximab and 5 months post-treatment of nivolumab, record any SAEs, and AEs including exacerbation or changes in medical history, on the AE eCRF.

See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Assessments for Premature Discontinuation from Study

If a subject has discontinued all study treatments prior to definitive disease progression, the subject shall remain on study for follow-up for progression-free survival (see Sections 3.5 and 3.6). 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. Subjects will remain on study until disease progression or initiation of non-study specific anti-neoplastic therapy in the absence of progression, whichever occurs earlier.

If it is not possible to keep the subject on study, or acceptable to the subject or investigator, the subject may be withdrawn. It is recommended that the investigator consults with the medical monitor prior to removing the subject from study for any reason except subject withdrawal of consent.

6.4. Criteria for Discontinuation of Study Treatment

See Section 3.5 for discontinuation criteria.

6.5. End of Treatment

End of treatment (EOT) assessments will be completed only by subjects who discontinue all treatment for reasons other than progressive disease, initiation of new anti-neoplastic therapy, or full withdrawal of consent. 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.

6.6. End of Study

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

6.7. 30-Day Safety Follow-Up

A Safety Follow-up visit will be performed 30 days (± 7 days) following 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.

6.8. 5-Month Safety Follow-Up

A Safety Follow-up visit will be performed 5 months (± 7 days) following the last dose of nivolumab. The 5-Month Safety Follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.

6.9. Long-Term Follow-Up

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 and recording of any other anti-cancer therapy and cancer related surgery after the EOS visit.

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

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

6.10. Unscheduled visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Data generated during an unscheduled visit will be collected on the eCRF.

6.11. Protocol Deviations

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

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

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

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

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

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

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

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

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

- Progression of gastric adenocarcinoma

- Death related to disease progression

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

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

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

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

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.6.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

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

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

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

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

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

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

7.3.1. Adverse Events

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

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

7.3.2. Serious Adverse Events

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

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

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

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

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

7.3.2.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

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

  Gilead DSPH: Fax: PPD
  Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

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

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

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

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

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

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

7.6. Toxicity Management

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

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

Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor or designee. Please see Section 5.3 and refer to the regional prescribing information for details of toxicity management with nivolumab.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.
- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.
- Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.
- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).
- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

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

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

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

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

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

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

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate and compare the efficacy of andecaliximab in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric adenocarcinoma

The secondary objectives of this study are:

- To characterize and compare safety and tolerability of andecaliximab in combination with nivolumab versus nivolumab alone in subjects with recurrent gastric adenocarcinoma
- To characterize the PK of andecaliximab in combination with nivolumab

The exploratory objectives of this study are:

[redacted]

8.1.2. Primary Endpoint

The primary endpoint of this study is ORR. ORR will be determined from the subjects' best response during treatment.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

- Progression free survival, defined as the interval from the date of randomization to the earlier of the first documentation of definitive disease progression or death from any cause.
- Overall survival, defined as the interval from date of randomization to death from any cause.

- Duration of response, defined as the interval from the date of the first response (CR or PR) is achieved to the earlier of the first documentation of definitive disease progression or death from any cause.

- Occurrence of adverse events and laboratory abnormalities during treatment.

8.1.4. Other Endpoints of Interest

The exploratory endpoints of this study are:

[redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT analysis set includes data from all randomized subjects. Study drug assignment will be designated according to randomization.

This analysis set will be used in the analyses of subject characteristics, OS, PFS, and ORR. The analysis of ORR based on the ITT analysis set will be considered the primary analysis of the study. The analyses of DOR will be based on the subjects in the ITT analysis set who achieve a CR or PR.

Subjects in the ITT analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, those with best overall responses of not evaluable [NE] or not detected [ND]) will be included in the denominators in calculations of response rates.

8.2.1.2. Safety Analysis Set

The Safety Analysis Set will include data from all subjects who receive ≥1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

This analysis set will be used in the analysis of safety variables as well as study treatment administration. All data collected up to 30 days after the last dose of andecaliximab or 5 months post-treatment of nivolumab, whichever is later, will be included in the safety summaries.

8.2.1.3. Pharmacodynamic and Pharmacokinetic Analysis Sets

The Pharmacodynamics and PK Analysis Sets will include data from subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2 sided. Data will be described and summarized by dose level/cohort, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative.

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

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

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

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

Demographic and baseline characteristics will be summarized using standard descriptive methods.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The null hypothesis is that addition of andecaliximab to nivolumab will not improve ORR. The alternative hypothesis is that addition of andecaliximab to nivolumab will improve ORR.

The Cochran-Mantel-Haenszel (CMH) Chi-square test adjusting for stratification factors will be performed to compare the 2 treatment groups. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. Odds ratios and the corresponding 80% and 95% CIs will be presented.

8.5.2. Secondary Analyses

The KM method and the stratified log-rank test will be used to compare the 2 treatment groups for PFS and OS. A Cox proportional hazard model with the same stratification factors will be used to estimate the hazard ratio and corresponding 95% CI. DOR will be analyzed using the KM method.

8.6. Safety Analysis

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

In general, count and percent of subjects will summarize categorical and ordinal data. Mean, standard deviation, minimum, quartiles, median, and maximum will summarize continuous data.

8.6.1. Extent of Exposure

A subject's extent of exposure to andecaliximab and nivolumab will be generated from the study drug administration eCRF page. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE is defined as any AE with onset date on or after the date of first dose of study drug up to 30 days after permanent study drug discontinuation or any adverse events leading to premature study drug discontinuation.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by treatment group

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the CTCAE (version 4.03). Maximum post-baseline grade will be summarized by count and percent of subjects with each grade.

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

Laboratory abnormalities that occur before the first dose of study drug will be included in data listings.

8.6.4. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

The plasma concentrations of andecaliximab will be summarized by nominal sampling time using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) standard deviation, median, minimum, and maximum). Plasma concentrations of the study drug over time may be plotted in semi logarithmic and linear formats as mean ± standard deviation.

Exposure-response analysis may be explored as appropriate.

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

8.8. Biomarker Analysis

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time for all subjects by treatment arms. CCI [redacted]

8.9. Interim Safety Analysis

After approximately 20 subjects are treated for 12 weeks, a DMC will review safety data on these subjects and recommend to Gilead whether the treatment has demonstrated acceptable tolerability. Thereafter, review of safety data will be performed at regular intervals as described in the DMC charter.

8.10. Sample Size

Assuming the 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 and nivolumab with approximately 83% power at one-sided significance level of 10% using a CMH test. The assumption of nivolumab ORR is based on the upper bound of the 95% CI of the estimated ORR in CheckMate-032 Study {Le 2016}.

8.11. Data Monitoring Committee

In addition to the review of the interim safety analysis after approximately 20 subjects are treated 12 weeks, a DMC will review the progress of the study and perform interim reviews of safety data at intervals as described in the DMC charter and provide recommendations to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

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

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

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

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

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender)

- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)

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

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

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

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

9.1.6. Case Report Forms

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

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

9.1.7. Study Drug Accountability and Return

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

GS-US-296-2013, Amendment 3, 16 June 2017

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

PPD

PPD (Printed)
Gilead Sciences Medical Monitor

PPD

15 Jun 2017
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

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	

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**	
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	
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				X[r]	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																		
[redacted]																				
CT or MRI & Treatment Response Assessment[k]	X					X				X				X[t]		X[q]	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**	
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 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.
[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 for reasons other than progressive disease, initiation of new anti-neoplastic treatment, or full withdrawal of consent. 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 (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 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.

Appendix 3. ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference for ECOG {Oken 1982}

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

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

The risks of treatment with andecaliximab during pregnancy have not been evaluated in humans. The potential for genotoxicity is not expected given that andecaliximab is a monoclonal antibody. In both the rat and rabbit definitive embryo-fetal developmental toxicity studies, there were no andecaliximab-related effects on embryo-fetal survival and growth and no fetal anomalies. In a fertility study in male and female rats, no test article-related effects on reproductive performance and intrauterine survival were observed at any dosage level. A clinically relevant interaction between andecaliximab and contraceptive steroids is not expected because of their distinct metabolic pathways and therefore, hormonal contraception may be used as part of the birth control methods.

Please refer to the latest version of the investigator's brochure for additional information.

Please refer to the regional prescribing information for information on the potential risks of treatment with nivolumab.

2) Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes pubertal females regardless of whether or not she has had a menses (premenarchal, Tanner Stage 3) and perimenopausal women who have had a spontaneous menses in the last 12 months. A woman who has had a tubal sterilization is considered to be of childbearing potential.

- Women ≤ 54 years of age with amenorrhea of any duration will be considered to be of childbearing potential unless they have had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

- Women > 54 years of age with cessation (for ≥12 months) of previously occurring menses due to ovarian failure will not be considered to be of childbearing potential.

3) Contraceptive Requirements for Females

Female subjects of childbearing potential must agree to use protocol specified highly effective method(s) of contraception from the screening/randomization visit throughout the study period, 90 days following the last dose of study drug andecaliximab and 5 months after the last dose of nivolumab unless the subject chooses continuous heterosexual abstinence as a lifestyle choice. The investigator should counsel subjects on the protocol specified method(s) for avoiding pregnancy during the study. See the listed below for the protocol specified contraceptive methods.

Female study subjects who are not heterosexually active must have periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking study drug. The investigator should counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test every 4 weeks starting on Day 1, prior to receiving the dose of study drug. Lactating females must discontinue nursing before study drug administration.

Protocol specified contraceptive methods:

- Complete abstinence from intercourse. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 90 days after last dose of study drug andecaliximab and 5 months after the last dose of nivolumab:

  — intrauterine device (IUD) with a failure rate of < 1% per year

  — female barrier method: cervical cap or diaphragm with spermicidal agent

  — tubal sterilization

  — vasectomy in male partner

  — implants of levonorgestrel

  — injectable progesterone

  — oral contraceptives (either combined or progesterone only)

  — contraceptive vaginal ring

  — transdermal contraceptive patch

Female subjects must agree to refrain from egg donation or egg harvesting for the purpose of fertilization during the course of the study for at least 90 days after the last dose of andecaliximab and 5 months after the last dose of nivolumab.

4) Contraceptive Requirements for Males

Male subjects must agree to use condoms and avoid sperm donation from the screening/randomization visit throughout the study period, and for at least 90 days after administration of the last dose of study drug andecaliximab or nivolumab.

5) Procedures to be Followed in the Event of Pregnancy

Subjects should be instructed to notify the investigator if they (or their partner) become pregnant at any time during the study, or if they become pregnant within 90 days following the last dose of andecaliximab and within 5 months after the last dose of nivolumab. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. The investigator should report all pregnancies to the CRO Safety Department using the pregnancy report form within 24 hours of becoming aware of the pregnancy. The investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting partner pregnancy, pregnancy and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 5. Revised RECIST Guideline (version 1.1)

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

Measurable Lesions:

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

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

Non-Measurable Lesions:

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

Target Lesions:

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

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

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

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

Time point response: patients with non-target disease only

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

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

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

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

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

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