Clinical Trial Protocol

Clinical Trial Protocol Number	EMR 100070-008
Title	A Phase III open-label, multicenter trial of avelumab (MSB0010718C) as a third-line treatment of unresectable, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma
Short Trial Name	JAVELIN Gastric 300
Phase	III
IND Number	IND 126285
EudraCT Number	2015-003301-42
Coordinating Investigator	Yung-Jue Bang, MD, PhD Seoul National University Hospital Department of Internal Medicine 101 Daehak-ro Jongno-gu Seoul 110-744, South Korea Telephone number: +82 2 2072 2390
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA
Clinical Trial Protocol Version	28 March 2018/Version 8.0 including amendments 1.0 to 7.0.
Replaces Version	Version 7.0

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List of Abbreviations

ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC_{tau}	Area Under the Concentration-time Curve
β-hCG	β-human Chorionic Gonadotropin
BOR	Best Overall Response
BSC	Best Supportive Care
CI	Confidence Interval
C_{max}	Maximum Concentration Observed
C_{min}	Minimum Trough Concentration
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5-dimensions and 5-levels Questionnaire
EuroQOL	European Quality of Life
FFPE	Formalin-fixed Paraffin-embedded
FOLFIRI	Triplet Therapy Consisting of Fluorouracil, Leucovorin, and Irinotecan
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HER2	Human epidermal growth factor receptor 2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IPMP	Integrated Project Management Plan
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intention-to-Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death 1 (receptor)
PD-L (1 and 2)	Programmed Death Ligand (1 and 2)
PFS	Progression-free Survival
PGt	Pharmacogenetics
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety (Analysis Set)

SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Terminal Half-life
T4	Free Thyroxine
TEAE	Treatment-emergent Adverse Event
TLS	Tumor Lysis Syndrome
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal
USA	United States of America

1 Synopsis

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Trial centers/regions	The trial will be conducted at approximately 170 sites globally in North America, South America, Asia, Australia, and Europe, with approximately 28 sites in the USA.
Planned trial period (first subject in-last subject out)	First subject in: Q4, 2015 Last subject out: Q3, 2018
Trial Registry	ClinicalTrials.gov/NCT02625623

Objectives:

Primary objective

The primary objective is to demonstrate superiority with regard to overall survival (OS) of avelumab plus best supportive care (BSC) versus physician's choice (chosen from a pre-specified list of therapeutic options) plus BSC.

Secondary objectives

Secondary objectives are as follows:

- To compare avelumab plus BSC versus physician's choice plus BSC in regard to the following:
  - Progression-free survival (PFS) based on an Independent Review Committee (IRC) assessment
  - Objective response rate (ORR) based on IRC assessment
  - Subject-reported outcomes/quality of life (QoL) using the European Quality of Life (EuroQOL) 5-dimensions and 5-levels questionnaire (EQ-5D-5L), and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-STO22.
- To determine the safety and tolerability of avelumab.

Exploratory objectives

Exploratory objectives are as follows:

- To determine duration of response of avelumab plus BSC versus physician's choice plus BSC based on IRC assessment
- To determine time to response of avelumab plus BSC versus physician's choice plus BSC based on IRC assessment
- To evaluate tumor shrinkage in target lesions at each time point from Baseline based on IRC assessment
- To evaluate the disease control rate (DCR)
- To evaluate programmed death 1 ligand (PD-L1) expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarker with their relation to selected clinical response parameters
- To evaluate clinical response parameters (best overall response [BOR], DCR, PFS, and OS) based on PD-L1 status
- To assess individual drug exposures based on sparse pharmacokinetic (PK) sampling as a basis for exposure response analysis
- To characterize exposure response (exposure safety and exposure efficacy) for avelumab with respect to selected safety and efficacy endpoints
- To characterize the immunogenicity of avelumab

- To explore molecular, cellular, and soluble markers (for example, but not limited to, changes in gene expression profiles, microsatellite instability status, tumor-infiltrating lymphocytes and cytokine levels) in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab.

Methodology: This is a multicenter, international, randomized, open-label Phase III trial in subjects with unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or of the gastroesophageal junction who have failed or relapsed from 2 prior chemotherapeutic regimens administered for the treatment of unresectable, recurrent, locally advanced or metastatic disease.

All subjects in both arms will receive BSC as background therapy. Subjects will receive BSC with either avelumab or physician's choice chemotherapy from among a prespecified list of therapeutic options or BSC alone with no active therapy.

Approximately 330 subjects will be randomized, stratified by region (Asia versus non-Asia), in a 1:1 ratio to receive BSC with either avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks or physician's choice chemotherapy from the following options:

- Paclitaxel as monotherapy (80 mg/m^2 on Days 1, 8, and 15 of a 4-week treatment cycle)
- Irinotecan as monotherapy (150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle)
- Subjects who are not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above will receive BSC once every 3 weeks.

Subjects will return to the clinic at regular intervals for assessments. Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks for the first 12 months and every 12 weeks thereafter to determine response to treatment. A central imaging laboratory will be used to read and interpret all CT/MRI data. Response will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and as adjudicated by a blinded IRC. Treatment will continue until:

- Disease progression
- Significant clinical deterioration (clinical progression)
- Unacceptable toxicity, or
- Any criterion for withdrawal from the trial or trial treatment is fulfilled.

For subjects receiving avelumab plus BSC, treatment may continue past the initial determination of disease progression per RECIST v1.1 as long the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of trial treatment
- Stable Eastern Cooperative Oncology Group performance status (ECOG PS)
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

Subjects receiving avelumab plus BSC who have experienced a complete response (CR) should continue to receive avelumab for at least 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. To be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedules of Assessments (see Table 1).

Subjects receiving physician's choice chemotherapy plus BSC or BSC alone will receive trial treatment until progressive disease (PD) per RECIST v1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, or if any criterion for withdrawal from the trial or trial treatment is fulfilled. Subjects receiving physician's choice plus BSC will not be offered to cross over to avelumab plus BSC.

Investigators must specify which of the physician's choice treatment regimens will be selected prior to randomization.

Assessments will be made by the Investigators for the purpose of subject management, but the disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.

Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments.

The primary endpoint of the trial is OS, defined as the time (in months) from randomization to the date of death, regardless of the actual cause of the subject's death.

Safety endpoints include adverse events (AEs) assessed throughout the trial and evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, physical examination findings, clinical laboratory assessments, vital signs, and electrocardiograms (ECGs).

Planned number of subjects: Approximately 330 subjects are planned to be enrolled.

Primary endpoints: The primary endpoint of the trial is OS, defined as the time (in months) from randomization to the date of death, regardless of the actual cause of the subject's death.

Secondary endpoints: The secondary endpoints include PFS according to RECIST v1.1 and as adjudicated by the IRC, BOR as adjudicated by the IRC, subject-reported outcomes/QoL (assessed by the EQ-5D-5L, EORTC QLQ-C30, and EORTC module QLQ-STO22 questionnaires) and safety endpoints (including AEs, physical examination findings, clinical laboratory assessments, vital signs, ECG parameters, and ECOG PS).

Exploratory endpoints: Exploratory endpoints include the following:

- Duration of response
- Time to response
- Tumor shrinkage in target lesions at each time point from Baseline

- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at Baseline with their relation to selected clinical response parameters
- DCR
- Clinical response in PD-L1-positive subjects
- Population PK of avelumab and individual drug exposures based on sparse PK sampling
- Exposure response (exposure safety and exposure efficacy) for avelumab with respect to selected safety and efficacy endpoints
- Immunogenicity of avelumab
- Molecular, cellular and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab.

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria

Male or female subjects aged ≥ 18 years, with an ECOG PS of 0 to 1 at trial entry, with the availability of a formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 7 slides (preferably 10) unstained tumor slides suitable for PD-L1 expression assessment, and with histologically confirmed unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction and 2 prior courses of systemic treatment for unresectable, recurrent, locally advanced or metastatic gastric cancer. Subjects must have progressed after the second line.

First-line therapy may consist of any of the following:

- Fluoropyrimidine-platinum-based doublet
  - Fluoropyrimidine components can consist of S1, 5-fluorouracil, or capecitabine
  - Platinum component can consist of either oxaliplatin or cisplatin
- Fluoropyrimidine-platinum-based triplets consisting of the addition of docetaxel or epirubicin to a fluoropyrimidine-platinum-based doublet
- FOLFIRI, which consists of the administration of fluorouracil, leucovorin, and irinotecan
- Adjuvant or neo-adjuvant fluoropyrimidine-platinum-containing doublets will be considered as a first-line if relapse occurs within 6 months after the last administration of the platinum salt.

Second-line therapy is defined as any of the following:

- Another line of a platinum-based treatment or FOLFIRI if the disease has progressed more than 6 months after completion of the first-line platinum-based treatment or FOLFIRI
- Ramucirumab (as a single agent or in combination)
- Docetaxel (as a single agent or in combination)
- Paclitaxel (as a single agent or in combination) (nab-paclitaxel is acceptable)

- Irinotecan (as a single agent or in combination)

Trastuzumab in combination with first-line therapy or second-line therapy listed above for human epidermal growth factor receptor 2 (HER2) – neu overexpressing adenocarcinoma is acceptable.

Key exclusion criteria

Prior therapy with any antibody or drug targeting T-cell coregulatory proteins, concurrent anticancer treatment, or immunosuppressive agents. Other exclusion criteria include severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), brain metastases (except those treated locally, have not been progressing at least 2 months after completion of therapy, those with no steroid maintenance therapy required, and no ongoing neurological symptoms related to brain localization of the disease), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma) and persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v4.03 (except neuropathy and alopecia).

Investigational Medicinal Product: dose/mode of administration/dosing schedule: Avelumab will be administered as a 1-hour IV infusion at 10 mg/kg once every 2-week treatment cycle until PD or unacceptable toxicity. To mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Reference therapy: dose/mode of administration/dosing schedule: Subjects will receive BSC plus physician's choice chemotherapy selected from one of the following options:

- Paclitaxel as monotherapy (80 mg/m^2 on Days 1, 8, and 15 of a 4-week treatment cycle). Subjects should be premedicated with 20 mg dexamethasone orally approximately 12 and 6 hours prior to injection, 50 mg diphenhydramine (or equivalent) IV 30 to 60 minutes prior to injection, and 300 mg cimetidine or 50 mg ranitidine IV 30 to 60 minutes prior to injection. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
- Irinotecan as monotherapy (150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle). Subjects should be premedicated with anti-emetics, such as 10 mg prochloroperazine orally, 30 minutes prior to beginning therapy. If subjects have cholinergic symptoms, premedicate with 0.2 to 0.3 mg atropine subcutaneously. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
- Subjects who are not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above will receive BSC once every 3 weeks.

The Investigator will determine what systemic therapy will be administered to the subjects.

In the absence of unequivocal data on the doses and schedules of drugs that should be used as a third-line treatment of gastric cancer, the doses and schedules will be determined by the Investigator according to institutional guidelines.

Treatment will be administered until disease progression or unacceptable toxicity.

Physician's choice plus BSC will be stopped after the first on-treatment radiological evaluation of disease progression.

Planned trial and treatment duration per subject: Treatment with avelumab plus BSC will continue until disease progression or unacceptable toxicity. For subjects receiving avelumab plus BSC, treatment may continue past the initial determination of disease progression according to RECIST v1.1 if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment (see criteria above). Additionally, subjects receiving avelumab plus BSC who have experienced a CR should continue to receive avelumab for a minimum of 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. Physician's choice plus BSC will be administered until disease progression or unacceptable toxicity.

Statistical methods: The sample size of this trial is driven by the primary endpoint (OS); therefore, the trial is event driven and the primary analysis will take place after 256 deaths and a minimum of 6 months follow-up since the last subject randomized have occurred to ensure sufficient follow-up for all subjects for the primary analysis of OS. With 256 OS events, the trial provides 90% power to demonstrate an improvement of 2 months median OS time (i.e., median OS time of 6 months in the avelumab plus BSC arm versus 4 months in the control arm, which is equivalent to a reduction of 33% in hazard rate, i.e., hazard ratio of avelumab versus control = 0.67, at the 1-sided 2.5% overall significance level). Assuming a randomization ratio of 1:1 (avelumab plus BSC versus physician's choice plus BSC), an exponential distribution of OS time, a uniform distribution of subject accrual period over 15 months, an additional 6 months' minimum follow-up period for all subjects, and an expected 5% overall drop-out rate, the trial should enroll approximately 330 subjects (n=165 subjects/arm) to achieve 256 OS events in total.

The primary endpoint is OS and will be analyzed using a stratified 1-sided log-rank test. The primary analysis set will be the Intention-to-Treat (ITT) Analysis Set. The type I error rate for the primary endpoint (OS) and 2 key secondary endpoints (PFS and BOR) will be controlled at 2.5% (1-sided) level using a gatekeeping procedure. The primary hypothesis (OS) will serve as a gate keeper and be tested at an overall 1-sided type I error of 2.5%. Only if it is significant, the 2 key secondary endpoints (PFS and BOR) will be tested, and the Hochberg procedure will be used to control the type I error rate at 2.5% (1-sided) for PFS and BOR. The stratification factor used for the stratified statistical analysis in the analysis of the primary and key secondary endpoints will be region (Asia versus non-Asia).

Table 1 Schedules of Assessments

Avelumab Plus Best Supportive Care Arm

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -28 to Randomization	D1	D15	D29	D43	D57	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
Written informed consent	X												
Tumor tissue availability (biopsy/surgery)[e]	X												
Inclusion/exclusion criteria	X												
Medical history, including disease and treatment history[f]	X												
Demographic data	X												
HBV and HCV testing	X												
Subject-reported outcomes/quality of life assessments[g]	X	X[g]	X		X			X	6 weeks	X	X		
Physical examination	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs, including height at Screening	X	X	X	X	X	X	X	X	2 weeks	X	X		
Weight	X	X	X	X	X	X	X	X	2 weeks	X	X		
ECOG PS	X	X[h]	X	X	X	X	X	X	2 weeks	X	X		
Enrollment (if eligible)[i]	X												
12-lead ECG[j]	X									X			
Hematology and hemostaseology	X	X	X	X	X	X	X	X	2 weeks	X	X		
Core serum chemistry[k]		X	X	X	X	X	X	X	2 weeks				
Full serum chemistry[l]	X									X	X		
Urinalysis[m]	X	X			X			X	12 weeks	X	X		

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -28 to Randomization	D1	D15	D29	D43	D57	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
β-hCG pregnancy test[n]	X	X		X		X		X	4 weeks	X	X		
Tumor evaluation/staging (CT scan/MRI/other established methods)[o]	X				X			X	6 weeks for the first 12 months, and every 12 weeks thereafter[o]	X[p]			
Concomitant medications and procedures[q]	X	X	X	X	X	X	X	X	X	X	X		
AE collection	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	
SAE collection	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
T4 and TSH[r]	X				X			X	6 weeks	X	X		
Pretreatment and trial treatment administration[s]		X	X	X	X	X	X	X	2 weeks				
Whole blood for PGt[t]	X												

ADA=anti-drug antibody, AE=adverse events, β-hCG=β-human chorionic gonadotropin, CR=complete response, CT=computed tomography, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC=European Organization for Research and Treatment of Cancer, EQ-5D-5L=European Quality of Life 5-dimensions and 5-levels Questionnaire, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IMP=investigational medicinal product, IRC=Independent Review Committee, IV=intravenous, MRI=magnetic resonance imaging, PD=progressive disease, PGt=pharmacogenetics, PK=pharmacokinetic, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=week.

a. A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. The calculation of the dose of avelumab will be based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation. Subjects should start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call.

b. All subjects will have an End of Treatment visit within 7 days after the decision to discontinue trial treatment. All AEs will be documented until the 30-day Safety Follow-Up visit. Subjects with an ongoing SAE at the 30-day Safety Follow-up visit must be monitored and followed up until stabilization or until the outcome is known. After this visit, all SAEs and all treatment related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it

occurs, irrespective of the time elapsed since the last administration of IMP. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).

c. Tumor evaluation at the End of Treatment visit should only be performed if no disease progression has been documented previously.

d. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-Up visit should be conducted, if possible, prior to the start of this new therapy.

e. A biopsy should be collected unless tissue from an archival specimen (biopsy or surgery) is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details).

f. Medical history should include history of gastric cancer, previous and ongoing medications, previous surgeries and radiotherapies, and Baseline medical condition.

g. The subject-reported outcomes/quality of life questionnaires (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-STO22) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The questionnaires should be conducted at Screening; in the event that this does not occur, it can be done at Visit 1 (Day 1) prior to first treatment.

h. If the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.

i. Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

j. 12-lead ECG should be assessed during screening and at the End of Treatment visit.

k. Core serum chemistry and other laboratory assessments are detailed in Table 7.

l. Full chemistry panel, which includes core serum chemistry, and other laboratory assessments are detailed in Table 7. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

m. Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End of Treatment visits.

n. β-hCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to the next administration of trial treatment.

o. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST v1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days) and ± 5 days after the End of Treatment visit. Disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.

p. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).

q. Concomitant medications and procedures will be documented at each trial visit until the 30-day Safety Follow-Up visit.

r. Blood samples for T4 and TSH will be collected at the times indicated from all subjects. Assessments for PK, ADA, and biomarker samples are detailed in Table 2.

s. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

t. Whole blood sample for PGt will be collected before or on Day 1 for subjects who provide separate informed consent.

Physician's Choice: Best Supportive Care Plus Irinotecan

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -28 to Randomization	D1	D15	D29	D43	D57	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
Written informed consent	X												
Tumor tissue availability (biopsy/surgery)[e]	X												
Inclusion/exclusion criteria	X												
Medical history, including disease and treatment history[f]	X												
Demographic data	X												
HBV and HCV testing	X												
Subject-reported outcomes/quality of life assessments[g]	X	X[g]	X		X			X	6 weeks	X	X		
Physical examination	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs, including height at Screening	X	X	X	X	X	X	X	X	2 weeks	X	X		
Weight and BSA calculation	X	X	X	X	X	X	X	X	2 weeks	X	X		
ECOG PS	X	X[h]	X	X	X	X	X	X	2 weeks	X	X		
Enrollment (if eligible)[i]	X												
12-lead ECG[j]	X									X			
Hematology and hemostaseology	X	X	X	X	X	X	X	X	2 weeks	X	X		
Core serum chemistry[k]		X	X	X	X	X	X	X	2 weeks				
Full serum chemistry[l]	X									X	X		
Urinalysis[m]	X	X			X			X	12 weeks	X	X		

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -28 to Randomization	D1	D15	D29	D43	D57	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
β-hCG pregnancy test[n]	X	X		X		X		X	4 weeks	X	X		
Tumor evaluation/staging (CT scan/MRI/other established methods)[o]	X				X			X	6 weeks for the first 12 months, and every 12 weeks thereafter[o]	X[p]			
Concomitant medications and procedures[q]	X	X	X	X	X	X	X	X	X	X	X		
AE collection	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	
SAE collection	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
T4 and TSH[r]	X				X			X	6 weeks	X	X		
Pretreatment and trial treatment administration[s]		X	X	X	X	X	X	X	2 weeks				
Whole blood for PGt[t]	X												
Blood for soluble factors[u]		X											
Blood for gene expression profiling[u]		X											
Plasma sample for biomarkers[u]		X											

AE=adverse events, β-hCG=β-human chorionic gonadotropin, BSA=body surface area, CR= complete response, CT=computed tomography, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC=European Organization for Research and Treatment of Cancer, EQ-5D-5L=European Quality of Life 5-dimensions and 5-levels Questionnaire, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IMP=investigational medicinal product, IRC=Independent Review Committee, IV=intravenous, MRI=magnetic resonance imaging, PD=progressive disease, PGt=pharmacogenetics, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=week.

a. A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. The calculation of the dose of irinotecan will be calculated based on the BSA determined within 72 hours prior to the day of drug administration. The dose of irinotecan used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation as allowed by local standards. Subjects should start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call.

b. All subjects will have an End of Treatment visit within 7 days after the decision to discontinue trial treatment. All AEs will be documented until the 30-day Safety Follow-Up visit. Subjects with an ongoing SAE at the 30-day Safety Follow-up visit must be monitored and followed up until stabilization or until the outcome is known. After this visit, all SAEs and all treatment related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).
c. Tumor evaluation at the End of Treatment visit should only be performed if no disease progression has been documented previously.
d. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-Up visit should be conducted, if possible, prior to the start of this new therapy.
e. A biopsy should be collected unless tissue from an archival specimen (biopsy or surgery) is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details).
f. Medical history should include history of gastric cancer, previous and ongoing medications, previous surgeries and radiotherapies, and Baseline medical condition.
g. The subject-reported outcomes/quality of life questionnaires (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-STO22) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The questionnaires should be conducted at Screening; in the event that this does not occur, it can be done at Visit 1 (Day 1) prior to first treatment.
h. If the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.
i. Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).
j. 12-lead ECG should be assessed during Screening and at the End of Treatment visit.
k. Core serum chemistry and other laboratory assessments are detailed in Table 7.
l. Full chemistry panel, which includes core serum chemistry, and other laboratory assessments are detailed in Table 7. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).
m. Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End of Treatment visits.
n. β-hCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to the next administration of trial treatment.
o. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST v1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days) and ± 5 days after the End of Treatment visit. Disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.
p. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).
q. Concomitant medications and procedures will be documented at each trial visit until the 30-day Safety Follow-Up visit.
r. Blood samples for T4 and TSH will be collected at the times indicated from all subjects.
s. Irinotecan will be administered on Days 1 and 15 of a 4-week treatment cycle. Subjects receiving irinotecan should be premedicated with anti-emetics, such as 10 mg prochloroperazine orally, 30 minutes prior to beginning therapy. If subjects have cholinergic symptoms, premedicate with 0.2 to 0.3 mg atropine subcutaneously. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.

t. Whole blood sample for PGt will be collected before or on Day 1 for subjects who provide separate informed consent.
u. Blood samples for soluble factors and gene expression profiling, and plasma samples for biomarkers will be collected within 2 hours prior to trial treatment infusion at Week 1.

Physician's Choice: Best Supportive Care Plus Paclitaxel

Measure	Screening/ Baseline Assessments	Treatment Phase[a]											End of Treatment Visit	Safety Follow-up Visit		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10					
		W1	W2	W3	W5	W6	W7	W9	W10	W11	W13					
	Day -28 to Randomization	D1	D8	D15	D29	D36	D43	D57	D64	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
Written informed consent	X															
Tumor tissue availability (biopsy/surgery)[e]	X															
Inclusion/exclusion criteria	X															
Medical history, including disease and treatment history[f]	X															
Demographic data	X															
HBV and HCV testing	X															
Subject-reported outcomes/quality of life assessments[g]	X	X[g]		X			X				X	6 weeks	X	X		
Physical examination	X	X	X	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs, including height at Screening	X	X	X	X	X	X	X	X	X	X	X	Every week for the first 3 weeks of each 4-week cycle	X	X		
Weight and BSA calculation[h]	X	X	X	X	X	X	X	X	X	X	X		X	X		
ECOG PS	X	X[i]	X	X	X	X	X	X	X	X	X		X	X		
Enrollment (if eligible)[j]	X															
12-lead ECG[k]	X												X			
Hematology and hemostaseology	X	X	X	X	X	X	X	X	X	X	X	Every week for the first 3 weeks of each 4-week cycle	X	X		
Core serum chemistry[l]		X	X	X	X	X	X	X	X	X	X					
Full serum chemistry[m]	X												X	X		
Urinalysis[n]	X	X					X				X	12 weeks	X	X		

Measure	Screening/ Baseline Assessments	Treatment Phase[a]											End of Treatment Visit	Safety Follow-up Visit		Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10					
		W1	W2	W3	W5	W6	W7	W9	W10	W11	W13					
	Day -28 to Randomization	D1	D8	D15	D29	D36	D43	D57	D64	D71	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
β-hCG pregnancy test[o]	X	X			X			X			X	4 weeks	X	X		
Tumor evaluation/staging (CT scan/MRI/other established methods)[p]	X						X				X	6 weeks for the first 12 months, and every 12 weeks thereafter[p]	X[q]			
Concomitant medications and procedures[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	
SAE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
T4 and TSH[s]	X						X				X	6 weeks	X	X		
Pretreatment and trial treatment administration[t]		X	X	X	X	X	X	X	X	X	X	Every week for the first 3 weeks of each 4-week cycle				
Whole blood for PGt[u]	X															
Blood for soluble factors[v]		X														
Blood for gene expression profiling[v]		X														
Plasma sample for biomarkers[v]		X														

AE=adverse events, β-hCG=β-human chorionic gonadotropin, BSA=body surface area, CR= complete response, CT=computed tomography, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC=European Organization for Research and Treatment of Cancer, EQ-5D-5L=European Quality of Life 5-dimensions and 5-levels Questionnaire, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IMP=investigational medicinal product, IRC=Independent Review Committee, IV=intravenous, MRI=magnetic resonance imaging, PD=progressive disease, PGt=pharmacogenetics, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=week.

a. A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. The calculation of the dose of paclitaxel will be based on the BSA of the subject determined within 72 hours prior to the day of drug administration. The dose of paclitaxel used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation as allowed by local standards. Subjects should start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call.
b. All subjects will have an End of Treatment visit within 7 days after the decision to discontinue trial treatment. All AEs will be documented until the 30-day Safety Follow-Up visit. Subjects with an ongoing SAE at the 30-day Safety Follow-up visit must be monitored and followed up until stabilization or until the outcome is known. After this visit, all SAEs and all treatment related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).
c. Tumor evaluation at the End of Treatment visit should only be performed if no disease progression has been documented previously.
d. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-Up visit should be conducted, if possible, prior to the start of this new therapy.
e. A biopsy should be collected unless tissue from an archival specimen (biopsy or surgery) is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details).
f. Medical history should include history of gastric cancer, previous and ongoing medications, previous surgeries and radiotherapies, and Baseline medical condition.
g. The subject-reported outcomes/quality of life questionnaires (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-STO22) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The questionnaires should be conducted at Screening; in the event that this does not occur, it can be done at Visit 1 (Day 1) prior to first treatment.
h. The BSA will be calculated for subjects receiving paclitaxel.
i. If the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.
j. Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).
k. 12-lead ECG should be assessed during Screening and at the End of Treatment visit.
l. Core serum chemistry and other laboratory assessments are detailed in Table 7.
m. Full chemistry panel, which includes core serum chemistry, and other laboratory assessments are detailed in Table 7. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).
n. Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End of Treatment visits.
o. β-hCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to the next administration of trial treatment.
p. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST v1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days) and ± 5 days after the End of Treatment visit. Disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.
q. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).

r. Concomitant medications and procedures will be documented at each trial visit until the 30-day Safety Follow-Up visit.
s. Blood samples for T4 and TSH will be collected at the times indicated from all subjects.
t. Paclitaxel will be administered on Days 1, 8, and 15 of a 4-week cycle. Subjects should be premedicated with 20 mg dexamethasone orally approximately 12 and 6 hours prior to injection, 50 mg diphenhydramine (or equivalent) IV 30 to 60 minutes prior to injection, and 300 mg cimetidine or 50 mg ranitidine IV 30 to 60 minutes prior to injection. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
u. Whole blood sample for PGt will be collected before or on Day 1 for subjects who provide separate informed consent.
v. Blood samples for soluble factors and gene expression profiling, and plasma samples for biomarkers will be collected within 2 hours prior to trial treatment infusion at Week 1.

Physician's Choice: Best Supportive Care Only

Measure	Screening/ Baseline Assessments	Treatment Phase[a]						End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5					
		W1	W4	W7	W10	W13					
	Day -28 to Randomization	D1	D22	D43	D64	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
Written informed consent	X										
Tumor tissue availability (biopsy/surgery)[e]	X										
Inclusion/exclusion criteria	X										
Medical history, including disease and treatment history [f]	X										
Demographic data	X										
HBV and HCV testing	X										
Subject-reported outcomes/quality of life assessments[g]	X	X[g]	X	X		X	6 weeks	X	X		
Physical examination	X	X	X	X	X	X	6 weeks	X	X		
Vital signs, including height at Screening	X	X	X	X	X	X	3 weeks	X	X		
Weight and BSA calculation	X	X	X	X	X	X	3 weeks	X	X		
ECOG PS	X	X[h]	X	X	X	X	3 weeks	X	X		
Enrollment (if eligible)[i]	X										
12-lead ECG	X										
Hematology and hemostaseology	X	X	X	X	X	X	3 weeks	X	X		
Core serum chemistry[j]		X	X	X	X	X	3 weeks				
Full serum chemistry[k]	X							X	X		
Urinalysis[l]	X	X		X		X	12 weeks	X			
β-hCG pregnancy test[m]	X										

Measure	Screening/ Baseline Assessments	Treatment Phase[a]						End of Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5					
		W1	W4	W7	W10	W13					
	Day -28 to Randomization	D1	D22	D43	D64	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[c]	Visit 30 Days after Last Treatment (± 5 days)[d]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 weeks)
Tumor evaluation/staging (CT Scan/MRI/other established methods)[n]	X			X		X	6 weeks for the first 12 months, and every 12 weeks thereafter[n]	X[o]			
Concomitant medications and procedures[p]	X	X	X	X	X	X	X	X	X		
AE collection	X	X	X	X	X	X	X	X	X[b]	X[b]	
SAE collection	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
T4 and TSH[q]	X			X		X	6 weeks	X	X		
Whole blood for PGt[r]	X										
Blood for soluble factors[s]		X									
Blood for gene expression profiling[s]		X									
Plasma sample for biomarkers[s]		X									

AE=adverse events, β-hCG=β-human chorionic gonadotropin, BSA=body surface area, BSC=best supportive care, CR=complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC=European Organization for Research and Treatment of Cancer, EQ-5D-5L=European Quality of Life 5-dimensions and 5-levels Questionnaire, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IMP=investigational medicinal product, IRC=Independent Review Committee, IV=intravenous, MRI=magnetic resonance imaging, PD=progressive disease, PGt=pharmacogenetics, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week.

a. A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. Subjects should start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call. Subjects will receive BSC once every 3 weeks.

b. All subjects will have an End of Treatment visit within 7 days after the decision to discontinue trial treatment. All AEs will be documented until the 30-day Safety Follow-Up visit. Subjects with an ongoing SAE at the 30-day Safety Follow-up visit must be monitored and followed up until stabilization or until the outcome is known. After this visit, all SAEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing

SAEs. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).

c. Tumor evaluation at the End of Treatment visit should only be performed if no disease progression has been documented previously.

d. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-Up visit should be conducted, if possible, prior to the start of this new therapy.

e. A biopsy should be collected unless tissue from an archival specimen (biopsy or surgery) is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details).

f. Medical history should include history of gastric cancer, previous and ongoing medications, previous surgeries and radiotherapies, and Baseline medical condition.

g. The subject-reported outcomes/quality of life assessments (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-STO22) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The questionnaires should be conducted at Screening; in the event that this does not occur, it can be done at Visit 1 (Day 1) prior to first treatment.

h. If the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.

i. Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

j. Core serum chemistry and other laboratory assessments are detailed in Table 7.

k. Full chemistry panel, which includes core serum chemistry, and other laboratory assessments are detailed in Table 7. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

l. Full urinalysis (dipstick plus microscopic evaluation) at the Screening visit.

m. β-hCG should be determined from serum at Screening.

n. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST v1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days) and ± 5 days after the End of Treatment visit. Disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.

o. For subjects without PD at End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation (see Section 7.1.5 for details).

p. Concomitant medications and procedures will be documented at each trial visit until the 30-day Safety Follow-Up visit.

q. Blood samples for T4 and TSH will be collected at the times indicated from all subjects.

r. Whole blood sample for PGt will be collected before or on Day 1 for subjects who provide separate informed consent.

s. Blood samples for soluble factors and gene expression profiling, and plasma samples for biomarkers will be collected within 2 hours prior to trial treatment infusion at Week 1.

Table 2 Schedule of Assessments for Pharmacokinetic, Anti-drug Antibody, and Biomarker Samples for Subjects in the Avelumab Arm

Measure	Screening/ Baseline Assessments	Treatment Phase											End of Treatment Visit	Safety Follow-up Visit
		V1		V2	V3	V4		V7	V10	V13		Until Progression	Within 7 Days of Decision to Discontinue Treatment	30 Days after Last Treatment (± 5 days)
		W1		W3	W5	W7		W13	W19	W25				
		D1		D15	D29	D43		D85	D127	D169				
	Day -28 to Randomiz-ation	Prior to infusion	End of infusion	Prior to infusion	Prior to infusion	Prior to infusion	End of infusion	Prior to infusion	Prior to infusion	Prior to infusion	End of infusion			
PK sampling[a]		X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X	X
ADA (Immunogenicity sampling)[b]		X		X	X	X		X	X	X				X
Blood for soluble factors[c]		X		X	X	X		X				No sample collection	X	
Blood for gene expression profiling[d]		X		X	X								X	
Plasma sample for biomarkers[e]		X		X	X			X	X	X		Every 12 weeks	X	

ADA=anti-drug antibody, PK=pharmacokinetics, V=visit, W=week.

a. Blood samples for PK determinations will be collected from all subjects within 2 hours prior to each trial treatment infusion at Weeks 1, 3, 5, and 7 (every 2 weeks), at Weeks 13, 19 and 25 (every 6 weeks), and then every 12 weeks while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7 and 25. Samples will also be collected at the End of Treatment visit and the 30-day Safety Follow-up visit.

b. Blood samples for ADA (immunogenicity) analysis will be collected within 2 hours prior to trial treatment infusion at Weeks 1, 3, 5, 7 (every 2 weeks), at Weeks 13, 19, and 25 (every 6 weeks), then every 12 weeks while on treatment. Samples will also be collected at the 30-day Safety Follow-up visit. PK and ADA samples collected at the same time point can be used interchangeably if the dedicated sample has insufficient quantity, as the subject or the subject's parent(s)/guardian(s) will have consented to all collections and tests.

c. Blood samples for soluble factors will be collected within 2 hours prior to trial treatment infusion at Weeks 1, 3, 5, and 7 (every 2 weeks), at Week 13, and at the End of Treatment visit.

d. Blood samples for gene expression profiling will be collected within 2 hours prior to trial treatment infusion at Weeks 1, 3, 5, and at the End of Treatment visit.

e. Plasma samples for biomarkers will be collected within 2 hours prior to trial treatment infusion at Weeks 1, 3, and 5 (every 2 weeks), at Weeks 13, 19, and 25 (every 6 weeks), then every 12 weeks while on treatment. Samples will also be collected at the End of Treatment visit.

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with avelumab is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States of America (USA) and Merck KGaA, Darmstadt, Germany, in rest of world.

A contract research organization (CRO), Quintiles Inc., Durham, NC, USA, will undertake the operational aspects of this trial. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP). The IPMP will be prepared by the Quintiles Clinical Project Manager in cooperation with other Quintiles Operational Team Leads.

2.1 Investigational Sites

The trial will be conducted at approximately 170 sites globally in North America, South America, Asia, Australia, and Europe, with approximately 28 sites in the USA.

2.2 Trial Coordination/Monitoring

The Sponsor will coordinate the trial and will enlist the support of CROs for some activities of the trial. The Sponsor will perform oversight of the activities performed by the CROs.

The Clinical Trial Supplies department of the Sponsor will supply or reimburse the trial treatment of avelumab and physician's choice chemotherapy. Packaging and distribution of clinical supplies will be performed by the Clinical Trial Supplies department of the Sponsor.

The Coordinating Investigator (Yung-Jue Bang) represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report. Signature pages for the protocol lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix I.

The trial will appear in the following clinical trial registry: ClinicalTrials.gov (NCT02625623).

Subject enrollment and randomization will be managed by an interactive web response system (IWRS).

Safety laboratory assessments will be performed centrally. Local laboratories may be used at the discretion of the Investigator as clinically needed for safety management of the subject, and results from the local laboratories will be entered in the electronic case report forms (eCRFs) per the eCRF Completion Guidelines; however, central laboratory results must also be collected. Urinalysis and urine pregnancy testing will be done locally only.

A β-human chorionic gonadotropin (β-hCG) should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to next administration of trial treatment.

Pharmacokinetic (PK), exploratory biomarkers (central laboratory), and pharmacogenetic (PGt) assessments will be performed under the responsibility and/or supervision of the Sponsor.

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany, or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs) and serious adverse events (SAEs).

Quality assurance of the trial conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics, Merck KGaA, Darmstadt, Germany, will supervise the statistical analyses, which will be outsourced to a CRO.

2.3 Review Committees

2.3.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be composed of a minimum of 3 members who do not have any conflict of interests with the trial Sponsor, including 2 clinicians and a biostatistician. The IDMC will periodically review safety data. The full membership, mandate, and processes of the IDMC will be detailed in the IDMC charter.

2.3.2 Independent Review Committee

A central facility will read and interpret all radiographic scans for this trial. The data for all images will be transferred from each trial site to the central reading center for evaluation. All scans will be evaluated at the central facility in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (1). The response evaluation data will be transferred to the Sponsor or designee at regular intervals throughout the trial. A manual from the vendor will be provided to each trial site.

The Independent Review Committee (IRC) will perform a blinded determination as to whether the criteria for tumor response or progression according to RECIST v1.1 have been met. The IRC will be composed of a minimum of 3 members, including 1 oncologist. The role of the IRC will be to review radiographic image findings and physical findings for the determination of the time point overall response and date of disease progression according to RECIST v1.1 for each subject.

The IRC determines disease response, including progressive disease (PD) assessments associated with the trial endpoints, which will be supported by tumor assessments performed during the trial.

The full membership, mandate, and processes of the IRC will be detailed in the IRC charter.

3 Background Information

3.1 Gastric Cancer

Globally, gastric cancer is the fifth most common cancer and the third leading cause of cancer death. In 2012, there were approximately 950,000 new cases and 723,000 deaths worldwide (2). Of these cancers, approximately 90% to 95% were adenocarcinomas with the remaining 5% to 10% comprising neuroendocrine tumors, lymphomas, squamous cell cancer, and sarcomas.

The incidence of gastric cancer varies widely by country, with no true global standard treatment established. Higher incidence rates are observed in Asia, Costa Rica, Peru, and Eastern Europe, while Western Europe and the USA have lower incidence rates (3).

The use of chemotherapy to treat gastric cancer has no firmly established standard of care. Some drugs used in gastric cancer treatment include the following, sometimes using drugs in various combinations: fluorouracil and other fluoropyrimidines (capecitabine, S1), doxorubicin, cisplatin, oxaliplatin, taxanes, irinotecan, and others. Currently, combinations of fluoropyrimidine and platinum with or without doxorubicin or docetaxel are the most commonly used as first-line treatment. For patients with human epidermal growth factor receptor 2 (HER2)-positive gastric cancer, trastuzumab plus chemotherapy is the standard of care (4). Recently, the benefit of second-line chemotherapy has been demonstrated by several clinical trials; however, there is no standard treatment for patients after they have progressed on second-line therapy (5-24).

Improvement in overall survival (OS) has been demonstrated for 4 drugs (paclitaxel, ramucirumab with or without paclitaxel, docetaxel, and irinotecan) in the context of a randomized controlled trial in subjects with metastatic gastric cancer who have progressed after 1 line of a platinum-based doublet.

Despite these results, advanced, unresectable, and/or metastatic gastric cancer remains a significant unmet medical need. In addition, there is currently no recommended therapeutic approach for patients who progress after 2 lines of therapy for the treatment of recurrent, locally advanced, or metastatic gastric cancer.

3.2 Programmed Death Receptor and Ligands

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T-cell death and localized immune suppression (25-28), potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate antitumor activity in nonclinical animal models (26, 29).

In the clinical setting, treatment with antibodies that block the PD-1 – anti-PD-L1 interaction have been reported to produce objective response rates (ORRs) of 7% to 38% in subjects with advanced or metastatic solid tumors, with tolerable safety profiles (30-32). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of subjects. Recent trials have

documented the activity of anti-PD-L1 antibodies in subjects with advanced gastric cancer (33, 34).

3.3 Avelumab

The investigational medicinal product (IMP) for the present trial is avelumab (anti-PD-L1 monoclonal antibody MSB0010718C). Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype.

Avelumab selectively binds to PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells and is therefore expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self-tolerance (35). For complete details of the in vitro and nonclinical trials, please refer to the current Investigator's Brochure (IB).

In light of the recent data demonstrating the clinical efficacy of an anti-PD-L1 antibody in advanced gastric cancer, and given the clinical importance of PD-L1 expression in gastric cancer tumor cells (36) and the mode of action of avelumab, avelumab is being developed as a potential therapy for patients with various advanced solid tumors, including gastric cancer. This anti-PD-L1 therapeutic antibody concept is intended to be developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono R&D.

The ongoing clinical trials for avelumab are described in the IB. Of the Phase I studies, 2 of these studies have cohorts of subjects with advanced gastric cancer:

- Trial EMR 100070-001 is "a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, PK, biological, and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors."
- Trial EMR 100070-002 is "a Phase I trial to investigate the tolerability, safety, PK, biological, and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer."

In addition to the trial described in this protocol, EMR 100070-008, another Phase III study in subjects with advanced gastric cancer (EMR 100070-007) is ongoing for 1L switch maintenance treatment.

3.3.1 Safety

Available safety and efficacy data for the avelumab program are discussed in the IB and establish a positive benefit risk for conducting Phase III studies with 10 mg/kg (the dosing used in this trial).

The safety profile of avelumab has been evaluated based on data of more than 1750 subjects, including all subjects treated with 10 mg/kg from studies EMR100070-001 (1650 subjects) and EMR100070-003 Part A (88 subjects) as pooled safety dataset with a data cutoff of 09 June 2016, and subjects in the ongoing local Japanese Phase I Trial EMR100070-002. These safety data from subjects with different tumor types treated with avelumab suggests an acceptable safety profile of

the compound. Most of the observed events were either in line with those expected in subjects with advanced solid tumors or with similar class effects of monoclonal antibody blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders], immune-related nephritis and renal dysfunction and other immune-related AEs [myositis, myocarditis, Guillain-Barré syndrome, uveitis]) have been identified as important risks for avelumab (please see the current IB for details). Detailed guidelines for the management of immune-related adverse events and infusion-related reactions have been implemented in the study protocols, including this one (please see Sections 3.5, 5.1.2, 5.1.3, 6.2.1, 6.4.2, 6.5.4, 6.5.5 and 6.12).

3.3.2 Pharmacokinetic Results

Draft PK assessments have been performed in ongoing Trials EMR 100070-001 and EMR 100070-002. The preliminary results based on the data available as of 19 December 2014 are presented under the individual trial headings.

3.3.2.1 Trial EMR 100070-001

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 57 Caucasian subjects treated in the dose-escalation and expansion cohort of the Phase I Trial EMR 100070-001 by standard non-compartmental analysis based on rich serum concentration-time data obtained over a complete dosing interval of 2 weeks (= tau). The analysis of these data revealed that the exposure parameters maximum concentration observed postdose (C_{max}) and area under the concentration-time curve (AUC_{tau}) increased with the doses in a linear fashion.

The mean (standard deviation [SD]) apparent terminal half-life ($t_{1/2}$) was 69 ± 21 hours for 1 mg/kg, 84 ± 22 hours for the 3 mg/kg, 106 ± 29 hours for 10 mg/kg, and 134 ± 74 hours for the 20 mg/kg dose. Taking into account the variability, the $t_{1/2}$ of the 10 and 20 mg/kg doses can be regarded as similar, indicating that target mediated elimination does not increase at these doses. This implies that target occupancy is likely to be high at these 2 doses throughout the dosing interval.

Minimum trough concentrations (C_{min}) were obtained for the majority of subjects enrolled in the trial. The median C_{min} at the end of the first cycle after administration of the 10 mg/kg dose was 20 µg/mL (n=256). This median C_{min} increased during the subsequent cycles to 24 µg/mL (second cycle; n=233), 26 µg/mL (third cycle; n=167), and remained between 24 and 37 µg/mL during the subsequent cycles (n=22 to 114) indicative for no significant accumulation with the biweekly dosing scheme. Median C_{min} after the 3 mg/kg dose were 3.7 µg/mL after the first dose, 3.9 µg/mL after the second dose and 8.3 µg/mL after the third dose (n=7 to 12), though some trough values below 1 µg/mL were observed, as well as antidrug antibodies in at least 1 subject in this dose group on Day 85 of the treatment period, accompanied by loss of quantifiable exposure. Median trough concentrations after the 20 mg/kg dose were 44, 70, and 77 µg/mL after the first, second, and third dose, respectively (n=14 to 19).

For the 10 mg/kg dose, the mean (SD) volume of distribution was 55 ± 12 mL/kg and total systemic clearance was low (0.38 ± 0.11 mL/h/kg).

3.3.2.2 Trial EMR 100070-002

A preliminary analysis of the PK data was performed based on the serum concentration of avelumab obtained from 5 Japanese subjects treated with 3 mg/kg, 6 Japanese subjects treated with 10 mg/kg, and 6 Japanese subjects treated with 20 mg/kg as a 1-hour intravenously (IV) infusion once every 2 weeks.

Non-compartmental PK parameter calculation was performed based on non-quality-assured concentrations obtained during the first infusion using scheduled sample collection times and infusion duration of 1 hour.

Following the first infusion, serum C_{max} (geometric mean) of 64 µg/mL (range: 50 to 78 µg/mL) for the 3 mg/kg, 179 µg/mL (range: 148 to 228 µg/mL) for the 10 mg/kg, and 459 µg/mL (range: 374 to 533 µg/mL) for the 20 mg/kg were observed at a median time to reach maximum concentration of 1.5, 1.3, and 1.8 hours after infusion start (ranging between 1 and 5 hours). The average AUC_{tau} (geometric mean) over the first dosing interval was 5437 µg/mL·h (range: between 3826 and 7246 µg/mL·h) for the 3 mg/kg dose, 20126 µg/mL·h (range: 12185 to 34390 µg/mL·h) for the 10 mg/kg dose, and 47259 µg/mL·h (range: 37238 to 67591 µg/mL·h) for the 20 mg/kg. Variability in exposure parameters (C_{max} and AUC_{tau}) was in general low as indicated by geometric coefficients of variation of 22% and 27% for the 3 mg/kg dose, 20% and 40% for the 10 mg/kg dose, and 14% and 22% for the 20 mg/kg dose. In regards to C_{max} and C_{min}, inter-individual variability was generally higher than intra-individual variability. The apparent $t_{1/2}$ was 89 hours (range: 52 to 118 hours) for 3 mg/kg, 122 hours (range: 68 to 152 hours) for 10 mg/kg, and 114 hours (range: 92 to 133 hours) for 20 mg/kg. The mean estimated volume of distribution was in the range of 61 to 73 mL/kg, the mean total systemic clearance ranged between 0.37 and 0.51 mL/h/kg.

Mean C_{min} obtained immediately before next infusion and mean C_{max} obtained immediately after infusion end (at Days 15, 29, 43, and 85) remained at fairly constant levels, indicating no accumulation following multiple infusions. This is in line with the calculated apparent $t_{1/2}$ and the applied dosing scheme (once every 2 weeks).

Exposure values C_{max} and AUC increased almost proportional with dose.

Although a formal analysis has not been conducted, it is apparent that the preliminary concentrations obtained over time and the clearance during the first dosing interval were similar in Japanese and Caucasian subjects.

3.3.3 Clinical Pharmacodynamics

Receptor occupancy was measured in vitro by flow cytometry on peripheral blood CD3+ T cells after spiking of human whole blood samples from 8 healthy volunteers with avelumab over a concentration range of 0.003 to 10 µg/mL. In this assay, free receptors were measured in samples spiked over this range and compared with the amount of free receptors in the unspiked sample. A

50% receptor occupancy was observed at a drug concentration (SD) of 0.122 µg/mL ± 0.042 µg/mL, and a plateau indicating at least 95% receptor occupancy was reached in all donor blood samples at 1 µg/mL.

These in vitro data combined with PK data were confirmed in ex vivo samples taken at C_{min} after the first dose (Day 15) in a small number of subjects during the initial dose-escalation part of the Phase Ib Trial EMR 100070-001 (n=9). For doses of 10 mg/kg, target occupancy was greater than 90% for these 4 subjects, at C_{min} levels ranging between 12.69 to 26.87 µg/mL. Also, for doses of 3 mg/kg, available target occupancy data for 2 subjects with trough levels ranging from 4.56 to 6.99 µg/mL, showed greater than 90% target occupancy at trough exposure levels. At dose level 1 mg/kg, 2 out of 3 subjects displayed less than 90% target occupancy at trough serum concentrations. Avelumab serum concentrations were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Based on the observed avelumab serum concentrations in the EMR 100070-001 Phase I clinical trial and the in vitro receptor occupancy data, trough concentrations were sufficient to achieve full target occupancy throughout the entire dosing interval in all of the subjects receiving the 10 mg/kg dose. After the 3 mg/kg dose, C_{min} was insufficient in 3 of the 13 subjects to assure full target occupancy; therefore, in order to achieve target saturation during the whole treatment period in all subjects, the dose of 10 mg/kg every 2 weeks was selected as the dose for further investigation in the Phase Ib expansion cohorts and for the subsequent clinical trials.

3.4 Rationale for the Current Clinical Trial

The safety and clinical efficacy of avelumab have been determined in multiple tumor types (non-small cell lung cancer, ovarian cancer, mesothelioma, melanoma, thymoma, and adrenocorticocarcinoma) (37, 38). The rationale to enroll subjects with unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or gastro-esophageal junction is supported by data reported from other PD-1/PD-L1 agents and from 2 expansion cohorts in 2 avelumab Phase I studies.

3.4.1 Data from Anti-PD-1/PD-L1 Therapies in Gastric Cancer

Data from other anti PD-1/PD-L1 therapies in gastric cancer are as follows:

- Data presented at the American Society for Clinical Oncology Annual Meeting 2014 from a Phase I expansion cohort of 16 subjects with gastroesophageal cancer treated with MEDI4736 (anti-PD-L1), which reported 4 out of 16 responders (33).
- Data presented at the European Society for Medical Oncology Annual Meeting 2014 from a Phase I cohort of 39 PD-L1+ subjects with advanced gastric cancer treated with anti-PD-1 (Keynote012), which reported 12 out of 39 responders (34).

3.4.2 Efficacy Data Generated During the Development of Avelumab

Subjects with advanced gastric cancer have been enrolled in 2 clinical trials: Trial EMR 100070-001 (see Section 3.3.2.1) and Trial EMR 100070-002 (see Section 3.3.2.2).

Efficacy results observed in these trials are below:

- Trial EMR 100070-001: As of the data cutoff of 23 October 2015, in the primary cohort of 151 subjects with unresectable, locally advanced, or metastatic gastric or gastroesophageal junction adenocarcinoma, the ORR in second-line subjects was 9.7% (6/62 subjects; 95% confidence interval [CI], 3.6 to 19.9; all 6 subjects had partial response [PR], and 3 were ongoing at cutoff). In switch-maintenance subjects, ORR was 9.0% (8/89 subjects; 95% CI, 4.0 to 16.9; 2 subjects had complete response [CR], and 6 had PR; 4 subjects were ongoing at cutoff). Stable disease was observed in 12 additional second-line subjects (19.4%) and 43 additional switch-maintenance subjects (48.3%). The median progression-free survival (PFS) was 6.0 weeks and PFS rate at 24 weeks was 8.8% in second-line subjects. In the switch-maintenance subjects, the median PFS was 12.0 weeks and PFS rate at 24 weeks was 25.7%.

- Trial EMR 100070-002: As of the data cutoff of 11 March 2015, Japanese subjects with recurrent or refractory gastric or gastroesophageal junction adenocarcinoma had ORR 15% (3/20 subjects, 95% CI, 3.2 to 37.9), with 3 subjects having a PR. Ten subjects (50%) had stable disease, median PFS was 11.9 weeks, and PFS rate at 12 weeks was 43.3%.

Overall, the data generated in subjects with gastric cancer suggest that the administration of avelumab is well tolerated and clinically active.

The response rate and the duration of response observed compare favorably with those reported with chemotherapy in the second-line gastric cancer setting.

3.5 Summary of the Overall Benefit and Risk

Based on the nonclinical and Phase I data available to date, the conduct of the trial is considered justifiable using the dose and dose regimen of the avelumab as specified in this clinical trial protocol. For details regarding the dose selection rationale, refer to the IB. An IDMC (see Section 2.3.1) will assess the risk-benefit ratio on an ongoing basis. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk benefit relationship that would render continuation of the trial unjustifiable.

The primary known identified risks of exposure to avelumab include:

- Infusion-related reactions
- Immune-related adverse events (irAEs).

As of 05 November 2014, 2 Grade 4 infusion reactions have been reported in 480 subjects (0.4%) treated with avelumab (see Section 3.3.2.1); therefore, already implemented risk mitigation

measures for infusion-related reactions/hypersensitivity have been extended. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome (TLS, see Section 6.5.4.3).

As noted in Section 3.2, trials with antibodies that block the PD-1 – PD-L1 interaction have been reported to produce ORRs of 7% to 38% in subjects with advanced or metastatic solid tumors (30-32), with response durations of 1 year or more for the majority of subjects. More specifically, avelumab has a reported ORR in the range of 10% to 15% for second-line (Trial EMR 100070-001) and third- or fourth-line gastric cancer subjects (Trial EMR 100070-001). While that response rate is similar to that reported by Lee et al (39), it is expected that the responses with avelumab will be long lasting. In addition, the ORR does not recapitulate the clinical benefit provided by checkpoint inhibitors, as previously demonstrated for ipilimumab and nivolumab, for which dramatic improvement of OS and PFS was observed, with ORR usually less than 20%. In the absence of any established therapy for third-line gastric cancer, which has a very poor prognosis (median OS less than 5 months), the administration of avelumab represents an option that carries a favorable risk/benefit.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and the applicable national regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objective is to demonstrate superiority with regard to OS of avelumab plus best supportive care (BSC) versus physician's choice (chosen from a pre-specified list of therapeutic options) plus BSC.

4.2 Secondary Objectives

Secondary objectives are as follows:

- To compare avelumab plus BSC versus physician's choice plus BSC in regard to the following:
  - Progression-free survival based on an IRC assessment
  - ORR based on IRC assessment

- Subject-reported outcomes/quality of life (QoL) using the European Quality of Life (EuroQOL) 5-dimensions and 5-levels questionnaire (EQ-5D-5L), and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-STO22.

- To determine the safety and tolerability of avelumab.

4.3 Exploratory Objectives

- To determine duration of response of avelumab plus BSC versus physician's choice plus BSC based on IRC assessment
- To determine time to response of avelumab plus BSC versus physician's choice plus BSC based on IRC assessment
- To evaluate tumor shrinkage in target lesions at each time point from Baseline based on IRC assessment
- To evaluate PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarker with their relation to selected clinical response parameters
- To evaluate the disease control rate (DCR)
- To evaluate clinical response parameters (best overall response [BOR], DCR, PFS, and OS) based on PD-L1 status
- To assess individual drug exposures based on sparse PK sampling as a basis for exposure response analysis
- To characterize exposure response (exposure safety and exposure efficacy) for avelumab with respect to selected safety and efficacy endpoints
- To characterize the immunogenicity of avelumab
- To explore molecular, cellular, and soluble markers (for example, but not limited to, changes in gene expression profiles, microsatellite instability status, tumor-infiltrating lymphocytes and cytokine levels) in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, international, randomized, open-label Phase III trial in subjects with unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or of the gastroesophageal junction who have failed or relapsed from 2 prior chemotherapeutic regimens administered for the treatment of unresectable, recurrent, locally advanced or metastatic disease.

Subjects will receive BSC with either avelumab or physician's choice from a prespecified list of therapeutic options (paclitaxel plus BSC, irinotecan plus BSC, or BSC alone). The medicinal products irinotecan and paclitaxel are used as chemotherapy agents in this trial. Both substances

are authorized and marketed. Investigators must specify which of the physician's choice treatment regimens will be selected prior to randomization. Before making a decision and starting administration of chemotherapy, the Investigator is required to refer to what is stated in the respective current product information (local label, Summary of Product Characteristics [SmPC]), particularly in regard to contraindications, warnings and precautions for use, dosage adjustments in the event of toxicity, subject monitoring provisions, the duration of the need for contraception, and medicinal products that are prohibited or that must be used with caution. In case of a potential contradiction between the specifications outlined in this clinical trial protocol and the information contained in the product information (local label, SmPC) of irinotecan or paclitaxel, respectively, the local label always prevails. Investigators should check updated labeling information via relevant websites before randomization and before chemotherapy administration.

5.1.1 Overall Design

Approximately 330 subjects will be randomized, stratified by region, in a 1:1 ratio to receive BSC with either avelumab at a dose of 10 mg/kg as a 1-hour IV infusion once every 2 weeks or physician's choice chemotherapy from the following (Table 4):

- Paclitaxel as monotherapy (80 mg/m^2 on Days 1, 8 and 15 of a 4-week treatment cycle). Subjects should be premedicated with 20 mg dexamethasone orally approximately 12 and 6 hours prior to injection, 50 mg diphenhydramine (or equivalent) IV 30 to 60 minutes prior to injection, and 300 mg cimetidine or 50 mg ranitidine IV 30 to 60 minutes prior to injection. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
- Irinotecan as monotherapy (150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle). Subjects should be premedicated with anti-emetics, such as 10 mg prochloroperazine orally, 30 minutes prior to beginning therapy. If subjects have cholinergic symptoms, premedicate with 0.2 to 0.3 mg atropine subcutaneously. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
- Subjects who are not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above will receive BSC once every 3 weeks.

Subjects will return to the clinic at regular intervals for assessments. Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks for the first 12 months and every 12 weeks thereafter to determine response to treatment. A central imaging laboratory will be used to read and interpret all CT/MRI data. Response will be evaluated using RECIST v1.1 and as adjudicated by a blinded IRC. Treatment will continue until:

- Disease progression (see Section 5.5.1)
- Significant clinical deterioration (clinical progression, see Section 5.5.1)
- Unacceptable toxicity, or
- Any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5).

For subjects receiving avelumab plus BSC, treatment may continue past the initial determination of disease progression per RECIST v1.1 as long the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of trial treatment
- Stable Eastern Cooperative Oncology Group performance status (ECOG PS)
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

Subjects receiving avelumab plus BSC who have experienced a CR should continue to receive avelumab for a minimum of 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. To be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedules of Assessments (see Table 1). Subjects who re-initiate treatment will not have to undergo a second Screening visit.

Investigators must specify which of the physician's choice treatment regimens will be selected prior to randomization.

Subjects receiving physician's choice plus BSC will receive trial treatment until PD per RECIST v1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled. Subjects receiving physician's choice plus BSC will not be offered to cross over to avelumab plus BSC.

Assessments will be made by the Investigator for the purpose of subject management, but the disease response endpoint determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC (see Sections 2.3.2 and 7.3).

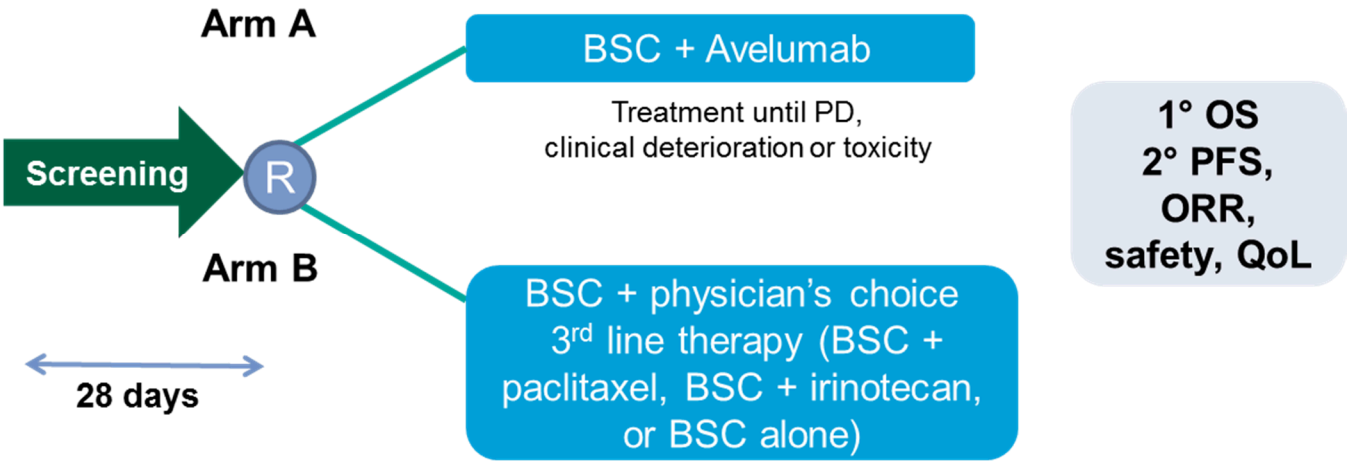
Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments (see Section 7.1.2).

The primary endpoint of the trial is OS, defined as the time (in months) from randomization to the date of death, regardless of the actual cause of the subject's death.

Safety endpoints include AEs assessed throughout the trial and evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, physical examination findings, clinical laboratory assessments, vital signs, and electrocardiograms (ECGs).

The trial design schematic is presented in Figure 1.

Figure 1 Schematic of the Trial Design



BSC=best supportive care, ORR=overall response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, QoL=quality of life, R=randomization.

5.1.2 Trial Treatment Administration and Schedule

The trial Schedules of Assessments are presented in Table 1.

5.1.2.1 Avelumab

Subjects randomized to the avelumab plus BSC arm will receive IV infusion of avelumab (10 mg/kg over 1 hour) once every 2 weeks. To mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

The formulation and packaging information of avelumab is provided in Sections 6.1.1 and 6.6, respectively.

5.1.2.2 Physician's Choice Chemotherapy

Subjects randomized to the physician's choice arm will receive BSC plus physician's choice chemotherapy (paclitaxel or irinotecan monotherapy) until disease progression, unacceptable toxicity, or any of the criteria for withdrawal from trial treatment is fulfilled (Section 5.5). Dosing and regimen of the physician's choice chemotherapy (paclitaxel or irinotecan monotherapy) is summarized in Section 6.2.2.

Additionally, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, subjects will be administered pre-treatment prior to each therapy infusion per local institutional practice.

5.1.2.3 Best Supportive Care

All subjects in both arms will receive BSC as background therapy. Subjects who are not deemed eligible to receive paclitaxel or irinotecan will receive BSC alone with no active therapy once every 3 weeks.

There is no universal definition of BSC that can be applied across institutions, countries, or regions (40). Best supportive care is defined as "treatment administered with the intent to maximize QoL without a specific antineoplastic regimen, which include antibiotics, analgesics, antiemetics, thoracentesis, paracentesis, blood transfusions, nutritional support (including jejunostomy), and focal external-beam radiation for control of pain, cough, dyspnea, or bleeding" (41). Best supportive care will be administered per institutional guidelines. Best supportive care can be administered without any additional therapy.

5.1.3 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

5.1.3.1 Dose Modification for Avelumab

The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

Each subject will stay on the avelumab assigned dose of 10 mg/kg unless treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in Sections 5.1.3.2 and 6.5.4.1. There will be no dose reductions.

5.1.3.2 Adverse Drug Reactions Requiring Avelumab Discontinuation or Modifications

The following adverse drug reactions (ADRs, see Section 7.4.1.1) require permanent treatment discontinuation of avelumab:

- Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management
- Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:
  - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management
  - Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤ 1

- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that resolves to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of trial treatment administration)
- Asymptomatic Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay or discontinuation. The study Medical Monitor should be consulted for such abnormalities.

- Infusion should not be given in case of ongoing Grade 2 ADR on the day of trial treatment administration.

  Treatment can be resumed according to the original schedule once the ADR has resolved to Grade ≤ 1. Up to 2 subsequent trial treatment doses may be omitted to allow for recovery to Grade ≤ 1. If more than 2 doses are skipped, treatment may be resumed after consultation with the trial Medical Monitor.

Infusion-related reactions, hypersensitivity reactions and flu-like symptoms (Grades 1 to 4), TLS, and irAEs should be handled according to guidelines in Sections 6.5.4.1, 6.5.4.2, 6.5.4.3, and 6.5.4.4, respectively.

5.1.3.3 Dose Modification for Physician's Choice Chemotherapy

The starting dose of physician's choice chemotherapy will be determined per local institutional guidelines in the absence of established doses and schedules for these agents when administered in the context of the management of third-line gastric cancer. Suggested dosing is summarized in Section 6.2.2.

Dose modification (dose delays and dose changes) for physician's choice chemotherapy should be performed according to local institutional guidelines.

5.2 Discussion of Trial Design

This is a Phase III, 2-arm, randomized, open-label trial to determine the efficacy and safety of avelumab plus BSC compared with physician's choice of third-line therapy as monotherapy (paclitaxel or irinotecan) plus BSC, or BSC alone in subjects with unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or of the gastroesophageal junction who have failed or relapsed from 2 prior chemotherapeutic regimens.

First-line therapy may consist of any of the following:

- Fluoropyrimidine-platinum-based doublet
  - Fluoropyrimidine components can consist of S1, 5-fluorouracil, or capecitabine

  - Platinum component can consist of either oxaliplatin or cisplatin
- Fluoropyrimidine-platinum-based triplets consisting of the addition of docetaxel or epirubicin to a fluoropyrimidine-platinum-based doublet
- FOLFIRI, which consists of the administration of fluorouracil, leucovorin, and irinotecan
- Adjuvant or neo-adjuvant fluoropyrimidine-platinum-containing doublets will be considered as a first-line if relapse occurs within 6 months after the last administration of the platinum salt.

Second-line therapy is defined as any of the following:

- Another line of a platinum-based treatment or FOLFIRI if the disease has progressed more than 6 months after completion of the first-line platinum-based treatment or FOLFIRI
- Ramucirumab (as a single agent or in combination)
- Docetaxel (as a single agent or in combination)
- Paclitaxel (as a single agent or in combination) (nab-paclitaxel is acceptable)
- Irinotecan (as a single agent or in combination).

Trastuzumab in combination with first-line therapy or second-line therapy listed above for HER2 – neu overexpressing adenocarcinoma is acceptable.

5.2.1 Rationale Supporting the Selection of Eligible First-Line Therapies

Acceptable regimens as first-line treatment of unresectable, recurrent, locally advanced or metastatic gastric cancer are described in Section 5.2.

All of these regimens are considered to be acceptable first-line regimens for the management of unresectable, recurrent, locally advanced or metastatic gastric cancer, as per the National Comprehensive Cancer Network guidelines, the European Society for Medical Oncology, and the Japanese guidelines.

The rationale to consider the administration of an adjuvant or neo-adjuvant platinum-fluoropyrimidine-containing doublet as a first-line therapy if a relapse occurs within 6 months after the last administration of the platinum salt is based on the concept that the subsequent administration of that same chemotherapy would not be adequate.

5.2.2 Rationale Supporting the Selection of Eligible Second-Line Therapies

In addition to the first-line regimens, acceptable regimens as second-line treatment of unresectable, recurrent, locally advanced or metastatic gastric cancer are described in Section 5.2.

The selection of these regimens is based on data (Table 3) demonstrating a statistically significant improvement in OS for irinotecan, docetaxel, paclitaxel, and ramucirumab in second-line advanced gastric cancer subjects compared to BSC.

Table 3 Overall Survival and Progression-free Survival for Subjects Receiving Second-line Chemotherapy

	German AIO N=40	Korean Trial N=202	Cougar 02 N=168	Regard N=355	WJOG 4007 N= 223	Rainbow N=665
Previous treatment (first-line)			Fluoropyrimidine and/or platinum			
Treatment	Irinotecan vs. BSC	Irinotecan or docetaxel (n=133) vs. BSC (n=69)	Docetaxel (n=84) vs. active symptom management	Ramucirumab vs placebo	Paclitaxel (n=108) vs. irinotecan (n=111)	Ramucirumab + weekly paclitaxel (n=330) vs. weekly paclitaxel (n=335)
Second-line subjects	40	148	168	355	219	665
Third-line subjects	NA	54	NA	NA	NA	NA
Median PFS	Irinotecan arm only: 2.6 months					4.4 months (95% CI, 4.2 to 5.3 months) vs. 2.9 months (95% CI, 2·8 to 3·0) HR=0.635 95% CI, 0.536 to 0.752 p<0.0001
Median OS	4.0 months vs. 2.4 months HR=0.48 95% CI, 0.25 to 0.9 p=0.012	5.3 months vs. 3.8 months HR=0.657 95% CI, 0.48 to 0.89 p=0. 007	5·2 months vs. 3.6 months HR=0·67, 95% CI, 0·49 to 0·92 p=0·01	5·2 months vs. 3·8 months HR=0·776, 95% CI, 0·603 to 0·998 p=0·047	9.5 months vs. 8.3 months HR=1.13; 95% CI, 0.86 to 1.49 p=0.38	9.6 months vs. 7.4 months HR=0.807 95% CI, 0.678 to 0.962 p=0.017

Source: Thuss-Patience et al. (42), Kang et al. (43), Ford et al. (44), Fuchs et al. (45), Hironaka et al. (46), Wilke et al. (47).
BSC=best supportive care, CI=confidence interval, HR=hazard ratio, NA=not applicable, OS=overall survival, PFS=progression-free survival.

In addition, the use of another combination therapy in the second-line setting that is not cross-resistant with previously administered first-line therapy is another common therapeutic approach in advanced gastric cancer subjects who have progressed after a first-line of combination therapy (48, 49).

5.2.3 Rationale for Physician's Choice Chemotherapy in the Third-Line Setting

There is no standard of care for the treatment of patients with advanced gastric cancer who have progressed after 2 prior chemotherapies.

Based on this, a study versus BSC may have been considered appropriate; however, there is literature supporting the use of chemotherapy in a third-line advanced gastric cancer trial (39). In particular, data from a cohort of Korean subjects with advanced gastric cancer who were treated with single-agent docetaxel after progression on m-FOLFOX-4 and m-FOLFIRI suggest that chemotherapy in the third line setting is feasible. Therefore, administration of chemotherapy is considered a reasonable option for these patients.

The data from this study are summarized below:

Lee et al. analyzed 33 subjects who had been histologically diagnosed with adenocarcinoma of the stomach and who had progressed after m-FOLFOX-4 and m-FOLFIRI regimens (39). Subjects were treated with docetaxel (75 mg/m^2) on Day 1 every 3 weeks. All subjects were evaluated in terms of tumor response: 5 (15%), 9 (27%), and 19 (58%) subjects experienced PR, stable disease, and PD, respectively. The median time to progression was 2.1 months (95% CI, 1.63 to 2.58 months), and OS was 4.7 months (95% CI, 3.20 to 6.20 months) from the start of the docetaxel regimen. Assessing the subjects' toxicity profiles, the median number of cycles was 2.0 (range, 1.0 to 12.0 cycles). The major hematologic toxicities included Grade 3 or 4 neutropenia (19/33, 58%), Grade 3 or 4 thrombocytopenia (2/33, 6%), and Grade 3 or 4 anemia (5/33, 15%). Neutropenic fever developed in 3 subjects (9%). The nonhematological toxicities were nausea and vomiting (10/33, 30%), abdominal pain (4/33, 12%), skin rash (1/33, 3%), and fluid retention (3/33, 9%). Overall, the conclusion was that docetaxel is a feasible third-line therapy regimen for subjects with advanced gastric cancer after m-FOLFIRI and m-FOLFOX-4 regimens.

Despite these limited data suggesting chemotherapy may be feasible in the third-line setting, BSC may still be considered standard of care for many advanced gastric patients who have progressed after 2 lines of chemotherapy agents. In clinical practice, many patients with gastric cancer develop peritoneal carcinomatosis during the course of their disease, which usually leads to a rapid symptomatic deterioration and chemotherapy intolerance (44). Although data from COUGAR-02 and other trials have shown activity of select therapies after first-line treatment for advanced gastric disease, only a small subset of patients may have an adequate PS after first-line treatment failure that would allow them to be able to tolerate second-line chemotherapy and, therefore, also third line treatment as well.

For patients who are not candidates for chemotherapy, BSC may still be considered a reasonable alternative for patients considered to be unfit for palliative chemotherapy in the second-line setting. Subsequently, BSC should also be considered a reasonable treatment option for third-line patients. Based on this, BSC alone or BSC plus physician's choice of active chemotherapy is considered an appropriate comparator for the proposed target population.

Subjects randomized to the physician's choice plus BSC will receive physician's choice treatment selected from one of the following options:

- Paclitaxel as monotherapy (80 mg/m^2 on Days 1, 8, and 15 of a 4-week treatment cycle)
- Irinotecan as monotherapy (150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle)
- Subjects who are not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above will receive BSC once every 3 weeks.

Dose and regimen of both paclitaxel and irinotecan monotherapy are consistent with recommended regiments in the National Comprehensive Cancer Network guidelines for gastric cancer and based on published Phase III data from the WJOG 4007 trial in advanced gastric cancer (46).

5.2.4 Rationale for the Primary Endpoint

Overall survival was chosen as the primary endpoint because this is an unequivocal measurement of clinical benefit that will not be confounded by the open-label nature of the study.

5.2.5 Rationale for the Expected Treatment Effect

The study sample size has been determined on the hypothesis of a hazard ratio of 0.67.

The expected treatment effect for avelumab plus BSC when compared with physician's choice plus BSC is based on the following considerations:

- The response rate of approximately 15% reported to date in the second-line population of the 2 avelumab Phase I studies is similar with that of chemotherapy in the third-line setting
- Rapid onset of responses has been reported with avelumab, as well as with the other anti-PD-1 and anti-PD-L1 therapies, suggesting that treatment with avelumab will be effective despite the rapid progression of these advanced subjects.

5.2.6 Rationale for Stratification by Region

Region (Asia versus non Asia) has been retained as a stratification factor because it is well established that gastric cancer physiopathology and clinical management differ significantly in Asian countries compared to non-Asian countries (50).

Differences in clinical outcomes between Asian and non-Asian subjects have been reported in the Phase III studies performed with ramucirumab, trastuzumab, and bevacizumab (47, 51, 52).

5.2.7 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Subject enrollment will be randomized and managed by an IWRS (see Section 6.3). Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard patient management

2. Male or female subjects aged ≥ 18 years

3. Availability of a formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 7 slides (preferably 10) unstained tumor slides suitable for PD-L1 expression assessment. PD-L1 expression determination is not a requirement for enrollment and will be done retrospectively

4. Subjects with histologically confirmed unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction

5. Documented objective radiographic or clinical disease progression (e.g., any new or worsening malignant effusion documented by ultrasound examination) that may be confirmed by pathologic criteria (histology and/or cytology)

6. Subjects must have received 2 prior courses of systemic treatment for unresectable, recurrent, locally advanced or metastatic gastric cancer, and must have progressed after the second line

    a. Acceptable regimens as first-line treatment of unresectable, recurrent, locally advanced or metastatic gastric cancer may include the following:

        i. Fluoropyrimidine-platinum-based doublet

            1. Fluoropyrimidine components can consist of S1, 5-fluorouracil, or capecitabine

            2. Platinum component can consist of either oxaliplatin or cisplatin

        ii. Fluoropyrimidine-platinum-based triplets consisting of the addition of docetaxel or epirubicin to a fluoropyrimidine-platinum-based doublet

        iii. FOLFIRI

        iv. Any prior adjuvant or neo-adjuvant treatment is allowed. Treatment with adjuvant or neo-adjuvant fluoropyrimidine-platinum-containing doublets

will be considered as a first-line if relapse occurs within 6 months after the last administration of the platinum salt.

b. Second-line therapy is defined as any of the following:

   i. Another line of a platinum-based treatment or FOLFIRI if the disease has progressed more than 6 months after completion of the first-line platinum-based treatment or FOLFIRI

   ii. Ramucirumab (as a single agent or in combination)

   iii. Docetaxel (as a single agent or in combination)

   iv. Paclitaxel (as a single agent or in combination) (nab-paclitaxel is acceptable)

   v. Irinotecan (as a single agent or in combination)

   Trastuzumab in combination with first-line therapy or second-line therapy listed above for HER2 – neu overexpressing adenocarcinoma is acceptable.

7. ECOG PS of 0 to 1 at trial entry

8. Adequate hematological function defined by white blood cell count $\geq 2.0 \times 10^9$/L with absolute neutrophil count $\geq 1.0 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

9. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 2.5 \times$ ULN for all subjects

10. Adequate renal function defined by an estimated creatinine clearance $\geq$ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

11. Negative blood pregnancy test at Screening for women of childbearing potential. For the purposes of this trial, women of childbearing potential are defined as: "All female subjects after puberty unless they are post-menopausal (age-related amenorrhea $\geq$ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), are surgically sterile, or are sexually inactive"

12. Highly effective contraception (i.e., methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix II or as stipulated in national or local guidelines. Highly effective contraception must be used 15 days prior to first trial treatment administration and for the duration of trial treatment for all subjects. Highly effective contraception must be used at least for 60 days after stopping avelumab treatment and as indicated in the respective label [SmPC] for irinotecan or paclitaxel for subjects receiving chemotherapy or as per label of any other therapy used

as BSC. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately).

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints), such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4. Adjuvant therapy is acceptable as described in Section 5.3.1. Maintenance treatment with oral fluoropyrimidine is acceptable

2. Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy], immune therapy, or cytokine therapy, except for erythropoietin)

3. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of the trial treatment and/or if the subject has not fully recovered from the surgery within 4 weeks of the trial treatment

4. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment (with the exception of subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to < 10 mg prednisone daily). Note:

    a. Subjects receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days before first dose of trial treatment

    b. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be ≤ 10 mg per day of equivalent prednisone

5. All subjects with brain metastases, except those meeting the following criteria:

    a. Brain metastases have been treated locally, have not been progressing at least 2 months after completion of therapy, and no steroid maintenance therapy is required, and

    b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)

6. Previous malignant disease (other than gastric cancer) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (bladder, cervical, colorectal, breast)

7. Prior organ transplantation, including allogeneic stem cell transplantation

8. Significant acute or chronic infections, including, among others:

    a. Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome

    b. Positive test for hepatitis B virus (HBV) surface antigen and/or confirmatory hepatitis C virus (HCV) ribonucleic acid (if anti-HCV antibody tested positive)

    c. Active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical or radiographic findings)

9. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

    a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible

    b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day

    c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)

11. Persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v4.03 (except neuropathy [see exclusion criterion #12] and alopecia)

12. Neuropathy ≥ Grade 3

13. Pregnancy or lactation

14. Known alcohol or drug abuse

15. History of uncontrolled intercurrent illness including but not limited to:

    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)

    b. or, uncontrolled active infection,

    c. or, uncontrolled diabetes (e.g., hemoglobin A1c ≥ 8%)

16. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication (including corrected QT interval prolongation of > 470 msec calculated according to Fridericia and/or pacemaker or prior diagnosis of congenital long QT syndrome)

17. All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment

18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent and that would limit compliance with trial requirements

19. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines)

20. Legal incapacity or limited legal capacity

21. Subjects will be excluded from the treatment with irinotecan or paclitaxel monotherapy if administration of their chemotherapy would be inconsistent with the current local labeling (e.g., in regard to contraindications, warnings/precautions, or special provisions) for that chemotherapy. Investigators should check updated labeling via relevant websites before randomization.

5.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be randomized before treatment start after verification of fulfilling all inclusion criteria without matching any exclusion criteria. Subjects should start treatment administration within 28 days after signing the informed consent form (ICF). Treatment administration will start within 4 days after the randomization call.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

Subjects will be withdrawn from trial treatment for any of the following reasons:

- Subjects meeting the definition of PD while on treatment based on RECIST v1.1 (subjects in the avelumab plus BSC arm who experience disease progression may continue treatment with avelumab if the Investigator believes the subject will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment [see Section 6.2.1]. Such subjects will be withdrawn from treatment if there is a subsequent scan/assessment of PD based on RECIST v1.1.)

- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms
- Unacceptable toxicity
- Withdrawal of consent
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Therapeutic failure requiring urgent additional drug (if applicable)
- Occurrence of any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.1.3.2
- Occurrence of AEs resulting in the discontinuation of the trial treatment being desired or considered necessary by the Investigator and/or the subject
- Occurrence of pregnancy
- Use of a prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the trial treatment
- Noncompliance (see Section 6.9)
- After primary analysis is completed, the subjects may be offered to enroll into a roll-over trial or receive commercial supply.

For subjects receiving avelumab plus BSC, if discontinuation occurs due to progression and a definitive diagnosis/radiographic confirmation is not made at the time of discontinuation, a second imaging scan may be allowed for confirmation of progression. If progression at the second imaging scan is not confirmed and the subject wishes to continue, the subject will be allowed to continue receiving avelumab as long as they meet the criteria for continuation of treatment beyond progression (see Section 6.2.1).

Subjects who withdraw from trial therapy will no longer be followed for survival after the date to discontinue treatment.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. In case of withdrawal from the trial, the assessments scheduled for the last visit (End of Treatment visit) should be performed (see Section 7.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate End of Safety Follow-up eCRF page must be completed. In case of withdrawal, subjects will be asked to continue safety follow-up. Subjects who withdraw from trial therapy will no longer be followed for survival after the date to discontinue treatment.

A subject must be withdrawn if any of the following occur during the trial:

- Withdrawal of the subject's consent

- Participation in any other therapeutic trial during the treatment duration of this trial; however, subjects will continue to be followed for survival

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

If a subject is withdrawn prior to progression for any reason, the subject will not be replaced.

5.6 Premature Termination of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the trial treatment, for example, due to:
  - Evidence of inefficacy of the trial treatment
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions
  - Other unfavorable safety findings.

  (Note: Evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or nonclinical examinations, for example, toxicology.)
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's trial treatment
- After primary analysis is completed, the subjects may be offered to enroll into a roll-over trial.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

5.7 Definition of End of Trial

If the trial is not terminated for a reason given in Section 5.6, the trial is complete after the last subject comes off treatment and completes the safety follow-up. The sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term IMP refers to the investigational drug undergoing a clinical trial, as well as to any comparator drug or placebo (as applicable). In this trial, the IMPs are avelumab and physician's choice chemotherapy (comparator).

6.1 Description of the Investigational Medicinal Product

6.1.1 Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal.

6.1.2 Physician's Choice Chemotherapy

Subjects will receive physician's choice chemotherapy selected from one of the following options as monotherapy in addition to BSC:

- Paclitaxel is a clear, colorless to slightly yellow viscous solution intended for IV administration. It is a white to off-white crystalline powder with a molecular weight of 853.9 kDa
- Irinotecan is a sterile, pale yellow, clear, aqueous solution.

Subjects can also receive BSC alone as described in Section 6.4.1.

6.2 Dosage and Administration

6.2.1 Avelumab Dosage and Administration

Subjects randomized to the avelumab plus BSC arm will receive an IV infusion of avelumab at a dose of 10 mg/kg (over the duration of 1 hour) following pretreatment as described in Section 5.1.2.1 (refer to Table 1). Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4.1. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation. Subjects will receive avelumab once every 2 weeks until the criteria in Sections 5.5 through 5.7 are met.

For subjects receiving avelumab plus BSC, treatment may continue past the initial determination of disease progression per RECIST v1.1 as long as the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of avelumab
- Stable ECOG PS

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

For subjects receiving avelumab plus BSC, if discontinuation occurs due to progression and a definitive diagnosis/radiographic confirmation is not made at the time of discontinuation, a second imaging scan may be allowed for confirmation of progression. If progression at the second imaging scan is not confirmed and the subject wishes to continue, the subject will be allowed to continue receiving avelumab as long as they meet the criteria for continuation of treatment beyond progression.

If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Assessments (Table 1).

Any additional continuation of avelumab plus BSC beyond further progression must be discussed and agreed upon with the medical monitor. Further disease progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered nonmeasurable at the time of initial progression may become measurable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Additionally, subjects receiving avelumab plus BSC who have experienced a CR should continue to receive avelumab for a minimum of 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. To be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab plus BSC therapy. Subjects who re initiate treatment will stay on trial and will be treated and monitored according to the protocol and the “until progression” schedule in the Schedules of Assessments (see Table 1).

6.2.2 Physician's Choice Chemotherapy - Dosage and Administration

Subjects randomized to the physician's choice plus BSC will receive one physician's choice treatment selected from the following options:

- Paclitaxel as monotherapy (80 mg/m^2 on Days 1, 8, and 15 of a 4-week treatment cycle)
- Irinotecan as monotherapy (150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle)
- Subjects who are not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above will receive BSC once every 3 weeks.

The Investigator will determine what systemic therapy will be administered to the subjects. The Investigator can also decide to administer BSC alone without any additional systemic therapy.

In the absence of unequivocal data on the doses and schedules of drugs that should be used as a third-line treatment of gastric cancer, the doses and schedules will be determined by the Investigator according to institutional guidelines.

Therapy will be administered until disease progression or unacceptable toxicity.

Physician's choice plus BSC will be stopped after the first on-treatment radiological evaluation of disease progression.

Monotherapy dosing is summarized below and in Table 4.

- Paclitaxel; 80 mg/m^2 on Days 1, 8, and 15 of a 4-week treatment cycle. Subjects should be premedicated with 20 mg dexamethasone orally approximately 12 and 6 hours prior to injection, 50 mg diphenhydramine (or equivalent) IV 30 to 60 minutes prior to injection, and 300 mg cimetidine or 50 mg ranitidine IV 30 to 60 minutes prior to injection. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.
- Irinotecan; 150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle. Subjects should be premedicated with anti-emetics, such as 10 mg prochloroperazine orally, 30 minutes prior to beginning therapy. If subjects have cholinergic symptoms, premedicate with 0.2 to 0.3 mg atropine subcutaneously. The premedication regimen may be modified based on local treatment standards and guidelines as appropriate.

Table 4 Physician's Choice Chemotherapies

Product Description	Dosage Form	Dose	Dosing Frequency
Paclitaxel	Intravenous	80 mg/m^2	Days 1, 8, and 15 of a 4-week treatment cycle
Irinotecan	Intravenous	150 mg/m^2	Days 1 and 15 of a 4-week treatment cycle

Subjects will receive trial treatment until disease progression per RECIST v1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled.

6.3 Assignment to Treatment Groups

Once the subject has provided a signed ICF and meets inclusion and exclusion criteria, the Investigator or delegate will request the trial treatment assignment using the IWRS. Qualified subjects will be randomized in a 1:1 ratio to receive either avelumab plus BSC or physician's choice plus BSC. The trial is fully controlled by the IWRS, which assigns treatment individual (unique) vial numbers for each subject. The vial number is linked via the Good Manufacturing Practice qualified system to the corresponding treatment as well as to the subject.

Allocation of subjects will be stratified according to region (Asia versus non-Asia). This stratified randomization will be centrally allocated across all trial sites via the IWRS.

Subject identifiers will comprise 17 digits, the first 10 digits representing the trial number, the following 3 digits representing the site number, and the last 4 digits representing the subject number, which is allocated sequentially starting with 0001.

6.4 Non-investigational Medicinal Products to be Used

6.4.1 Best Supportive Care

All subjects in both arms will receive BSC as background therapy. There is no universal definition of BSC that can be applied across institutions, countries, or regions (40). Best supportive care is defined as "treatment administered with the intent to maximize QoL without a specific antineoplastic regimen, which include antibiotics, analgesics, antiemetics, thoracentesis, paracentesis, blood transfusions, nutritional support (including jejunostomy), and focal external-beam radiation for control of pain, cough, dyspnea, or bleeding" (41). Best supportive care will be administered per institutional guidelines. Best supportive care can be administered without any additional therapy.

6.4.2 Other Non-investigational Medicinal Products to be Used

Subjects randomized to receive avelumab plus BSC will receive pretreatment as described in Section 5.1.2.1.

Subjects randomized to receive physician's choice chemotherapy plus BSC will receive pretreatment prior to each infusion per local institutional practice.

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactoid reactions. Following avelumab infusions, subjects must be observed for 2 hours post infusion for potential infusion-related reactions.

As with all monoclonal antibody therapies, there is a risk of allergic reaction. Avelumab should be administered in a setting that allows for immediate access and administration of therapy for severe allergic/hypersensitivity reactions, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1000 dilution), allergy medications (antihistamines), or equivalents should be available for immediate access.

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity and flu-like symptoms according to the NCI are found in Sections 6.5.4.1 and 6.5.4.2, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf (53). Subjects should be instructed to report any delayed reactions to the Investigator immediately.

6.5 Concomitant Medications, Therapies, and Procedures

6.5.1 Permitted Medicines

Any medications, therapies, or procedures (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare and will not interfere with the trial treatment may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.5.4.2.

The Investigator will record all concomitant medications, therapies, and procedures taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF.

Any additional concomitant therapy or procedures that become necessary during the trial and any change to concomitant drugs or procedures must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug as well as the name of the procedure, its start and end date, and reason.

Palliative bone-directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST v1.1 (1) and not based on the necessity for palliative bone-directed radiotherapy.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions, or anticipated emergency situations.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte antigen-4 antibody or concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy*, or radiotherapy administered on superficial lesions], immune therapy, or cytokine therapy except for erythropoietin), major surgery (excluding prior diagnostic biopsy), or concurrent systemic therapy with steroids or other immunosuppressive agents or use of any investigational drug.

* Palliative bone-directed radiotherapy should be within a limited field of radiation and for palliation only. It should be a short course, according to local institutional recommendation, and should be completed at least 7 days prior to the first administration of avelumab.

In addition, the following treatments must not be administered during the trial:

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs is allowed)
- Growth factors for subjects randomized to receive avelumab plus BSC (granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor). Exception: Erythropoietin and darbepoetin alpha may be prescribed at the Investigator's discretion
- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of avelumab or physician's choice

If the administration of a nonpermitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Medical Monitor may be contacted to discuss whether the trial treatment must be discontinued). The subject should complete the End of Treatment visit (Section 7.1.3).

For subjects randomized to physician's choice plus BSC, use of concomitant strong cytochrome P450 3A4 inhibitors and/or inducers should be avoided (for example, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, rifampin, and carbamazepine). For more information on cytochrome P450 3A4 inhibitors and inducers, Investigators are directed to the following URL: http://medicine.iupui.edu/clinpharm/ddis/clinical-table (54).

Medications other than those specifically excluded in this trial may be administered for the management of symptoms associated with the administration of avelumab plus BSC or physician's choice plus BSC as required. These might include analgesics, antinausea medications, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

6.5.3 Other Interventions

The following nondrug therapies must not be administered during the trial (or within 28 days before randomization):

- Major surgery (excluding prior diagnostic biopsy)
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)
- Subjects should not abuse alcohol or other drugs during the trial.

6.5.4 Special Precautions

As a routine precaution, subjects randomized to the avelumab plus BSC arm must be observed for 2 hours post infusion, in an area with resuscitation equipment and emergency agents. At all times during avelumab plus BSC or physician's choice chemotherapy plus BSC treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of avelumab will be stopped in case of Grade ≥ 2 hypersensitivity, inflammatory response, or infusion-related reaction. The treatment recommendations for infusion-related reactions, severe hypersensitivity reactions, and TLS according to the NCI are as outlined in Sections 6.5.4.1, 6.5.4.2, and 6.5.4.3, respectively.

Investigators should also monitor subjects closely for potential irAEs, which may first manifest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. See Section 6.5.4.4 for details on the management of irAEs.

6.5.4.1 Infusion-related Reactions

Symptoms of infusion-related reactions are fever, chills, rigors, diaphoresis, and headache. These symptoms can be managed according to Table 5.

Table 5 Treatment Modification for Symptoms of Infusion-related Reactions Associated With Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. • The total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event (version 4.03), NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should discontinue avelumab treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

6.5.4.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf (53). Subjects should be instructed to report any delayed reactions to the Investigator immediately.

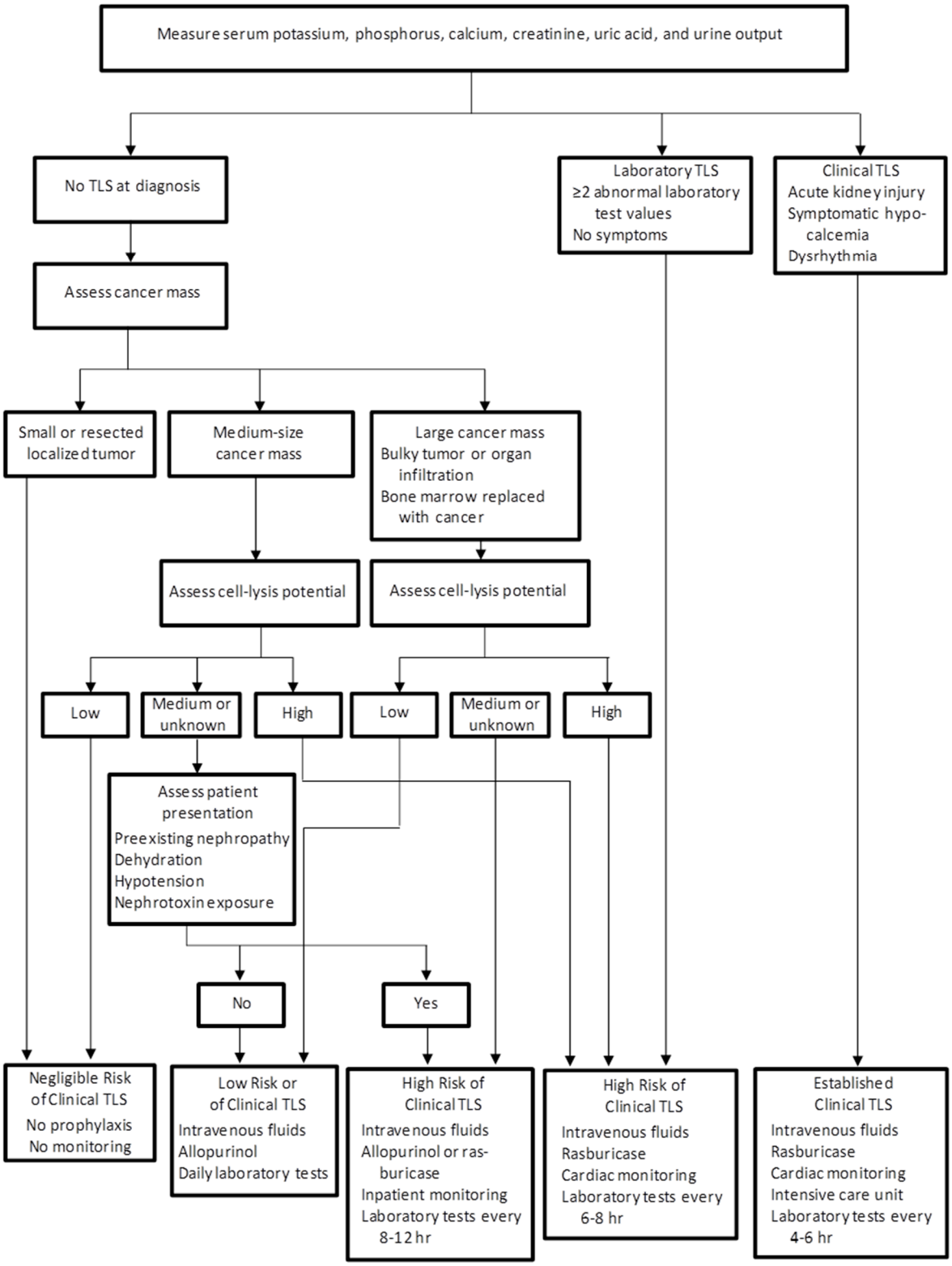
Symptoms include impaired airway, decreased oxygen saturation (< 92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Subjects should be placed on monitor immediately, and the intensive care unit should be alerted for possible transfer if required.

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti-inflammatory drug dose (e.g., 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, acetaminophen) may be given to subjects at the discretion of the Investigator.

6.5.4.3 Tumor Lysis Syndrome

In addition, because avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of TLS. Should this occur, subjects should be treated per the local guidelines and the management algorithm (Figure 2) published by Howard et al (55).

Figure 2 **Assessment and Initial Management of Tumor Lysis Syndrome**



TLS=tumor lysis syndrome.

6.5.4.4 Immune-related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grades 1 to 2 (persistent): manage similar to high grade AE (Grades 3 to 4)
- Grades 3 to 4: treat with high dose corticosteroids.

Treatment of irAEs should follow the guidelines in Table 6.

Table 6 Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.

Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1:

	1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or e.g., ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:**	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	• Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Specialty consult	

ACTH=adrenocorticotropic hormone, ADL=activities of daily living, AHA=American Heart Association, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BNP=B-type natriuretic peptide, CK-MB=creatine kinase MB, CT=computed tomography, ESC=European Society of Cardiology, FSH=follicle-stimulating hormone, FT4=free thyroxine, GH=growth hormone, IGF-1=insulin-like growth factor 1, irAE=immune-related adverse event, IV=intravenous, LH=luteinizing hormone, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, PRL=prolactin, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

The management of irAEs is described in Section 6.5.4.4.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Paclitaxel and irinotecan will be supplied or reimbursed by the Sponsor.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Each box of IMP will contain 1 vial. The information on the label will be in accordance with approved submission documents.

All IMPs will be shipped in suitable transport containers according to each IMP's storage and shipping conditions. Shipments are monitored with temperature control devices.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Avelumab must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each trial site must be stored carefully, safely, and separately from other drugs.

Avelumab stored at room temperature (23°C to 27°C) or at elevated temperatures (38°C to 42°C) for extended periods is subject to degradation. Avelumab must not be frozen. Rough shaking of avelumab must be avoided.

For application in this trial, avelumab must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Pharmacy Manual.

Avelumab must not be used for any purpose other than the trial. The administration of avelumab to subjects who have not been enrolled into the trial is not covered by the trial insurance.

For handling, preparation, and storage of the physician's choice chemotherapy, please refer to local institutional guidelines.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

Storage, handling, preparation, and disposal of IMP should be according to local institutional guidelines.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for avelumab and physician's choice chemotherapy, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of trial treatment, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor or designee. A copy will be retained for the Investigator Site File.
- The dispensing of the trial treatment will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the clinical research associate (CRA) at each monitoring visit.
- Trial treatment accountability records will include:
    1. Confirmation of trial treatment delivery to the trial site
    2. The inventory at the site of trial treatment provided by the Sponsor and prepared at the site
    3. The use of each dose by each subject
    4. The disposition of unused trial treatment
    5. Dates, quantities, batch numbers, expiry dates and (for trial treatment prepared at the site) formulation, as well as the subjects' trial numbers.
- The Investigator should maintain records that adequately document
    1. That the subjects were provided the doses specified by the clinical trial protocol/amendment(s)
    2. That all trial treatment provided by the Sponsor was fully reconciled.

Unused trial treatment must not be discarded or used for any purpose other than the present trial. Any trial treatment that has been dispensed to a subject must not be re-dispensed to a different subject.

The CRA will periodically collect the trial treatment accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the trial site.

At the conclusion or termination of this trial, trial site personnel and the CRA will conduct a final product supply inventory on the investigational drug accountability forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the investigational drug accountability forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- All administered units
- All unused units
- All destroyed units (during the trial)
- All destroyed units at the end of the trial
- Date of destruction(s)
- Name and signature of the Investigator/pharmacist.

It must be ensured at each trial site that the trial treatment is not used:

- After the expiry date
- After the retest date unless the trial treatment is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive trial treatment at the investigational site. Well-trained medical staff will monitor and perform the trial treatment administration. The information of each trial treatment administration including the date, time, and dose of trial treatment will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 1 administration of avelumab, paclitaxel, or irinotecan for nonmedical reasons (see Section 5.5.1). If 1 administration is missed and the interval between the subsequent administration and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

6.10 Blinding

This is an open-label trial; thus, trial treatment is not blinded.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose ≥ 5% over the calculated dose for that particular administration as described in this clinical trial protocol. Any overdose must be recorded in the trial treatment section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or nonserious), must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

There are no known symptoms of avelumab overdose to date. The Investigator should use his or her clinical judgment when treating an overdose of the trial treatment.

In the case of an overdose of paclitaxel, subjects should receive therapeutic granulocyte colony-stimulating factor according to local institutional guidelines as soon as possible. For all physician's choice chemotherapy, Investigators must follow local institutional guidelines for overdose treatment.

6.13 Medical Care of Subjects after End of Trial

After a subject has stopped trial treatment, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs.

Upon withdrawal from trial treatment, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for AEs as specified in Section 7.1.4.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Complete Schedules of Assessments are provided in Table 1.

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2.

7.1.1 Screening and Baseline Procedures and Assessments

The Screening procedures and Baseline assessments will be completed within 28 days before trial treatment starts.

During the Screening period and before any trial-related investigations and assessments are started, subjects will be asked to sign the ICF. The Screening procedures and Baseline assessments will be completed within 28 days of signing the ICF and before randomization. Subjects should also start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call. Failure to establish eligibility within 28 days would

result in screening failure and the subject will be excluded from the trial; however, subjects can be re-entered in the trial based on the Investigator's judgment and following Sponsor approval. In this case, a new ICF will be required to be signed by the subject.

The subjects' information that will be documented during Screening includes the demographic information (birth date, sex, and race) and the complete medical history, including the history of gastric cancer, previous and ongoing medications, and Baseline medical condition (concomitant medications and procedures and AEs will be monitored throughout the trial treatment period). Moreover, an Emergency Medical Support card will be handed out at the Baseline assessments visit.

During Screening, subjects will undergo a complete physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS. The QoL questionnaires will be administered and completed by the subjects at Baseline to collect Baseline data about their health-related QoL; in the event that this does not occur, it can be done at Visit 1 (Day 1) prior to first treatment.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation). Free thyroxine (T4) and thyroid-stimulating hormone (TSH) will also be assessed at Screening for all subjects. The Baseline samples for soluble factors may also be collected at Screening instead of on Day 1 prior to dosing.

During Screening, a serum β-hCG pregnancy test will be performed for females of childbearing potential, and blood HBV and HCV will be performed (may be analyzed locally) for all Screening subjects as these conditions are trial entry exclusion criteria (see Section 5.3.2). Females who are postmenopausal (age-related amenorrhea $\geq$ 12 consecutive months and increased FSH $>$ 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be drawn at Screening.

The tumor evaluation (type and staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) as well as tumor markers or any other established methods (see Section 7.2.4 for details).

Collection of tumor biopsies will also be done during this period, unless tissue (blocks or slides, blocks preferable) is available. For subjects unable to provide a fresh or recent biopsy, archival material is acceptable (blocks preferable). Subjects are required to provide tumor tissue samples, see Section 7.6 for details. Criteria for determining the adequacy of tumor tissue are described in the Study Manual. Subjects who undergo a biopsy specifically as part of the Screening assessments for this protocol will be permitted to participate in the protocol provided they meet all other inclusion criteria and no exclusion criteria.

The whole blood samples for PGt assessments (optional for subjects who sign the separate PGt ICF) will be collected before or on Day 1 before trial treatment starts for subjects randomized to receive BSC and either avelumab or physician's choice.

Assessments will be made by the Investigators for the purpose of subject management, but the disease response determinations, including PD assessments associated with the trial endpoints, will be supported by tumor assessments performed by an IRC.

7.1.2 Treatment Period

In this trial, the treatment will be given until disease progression, significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5.1). For subjects receiving avelumab plus BSC, treatment may continue past the initial determination of disease progression according to RECIST v1.1 if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment (see Section 6.2.1). Additionally, subjects receiving avelumab plus BSC who have experienced a CR should continue to receive avelumab for a minimum of 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedules of Assessments (see Table 1).

Subjects should start treatment administration within 28 days after signing the ICF. Treatment administration will start within 4 days after the randomization call. While on trial treatment, subjects will be asked to visit the trial site at the following schedules according to the Schedule of Assessments:

- Once every 2 weeks until disease progression for subjects randomized to receive avelumab plus BSC
- Once every week for the first 3 weeks of each 4-week cycle until disease progression for subjects randomized to receive paclitaxel plus BSC
- Once every 2 weeks until disease progression for subjects randomized to receive irinotecan plus BSC
- Once every 3 weeks until disease progression for subjects randomized to receive BSC alone with no active therapy.

For avelumab plus BSC, a time window of up to 3 days before or 1 day after the scheduled visit day (-3/ +1 days) will be permitted for all trial procedures; however, the bi-weekly 14-day schedule should be strictly adhered to, and subjects should return to the target date even if the previous visit was off schedule.

For physician's choice plus BSC, a time window of up to 3 days before or 1 day after the scheduled visit day (-3/ +1 days) will be permitted for all trial procedures.

The tumor evaluation (see Section 7.3) will be performed every 6 weeks for the first 12 months and every 12 weeks thereafter with a time window of -5 days for both arms.

Subjects will receive either:

- Avelumab by IV infusion following pretreatment (see Section 5.1.2.1), once every 2 weeks (see Section 6.2.1) plus BSC, or
- Physician's choice chemotherapy by IV infusion following pretreatment as applicable prior to each infusion (see Section 6.2.2) plus BSC or BSC alone.

Assessments to be performed during the treatment period are presented in Table 1 and Table 2.

7.1.3 End of Treatment Visit

Subjects must undergo an End of Treatment visit after discontinuation of treatment. This visit should be performed within 7 days of the decision to discontinue treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier. Please refer to Table 1 and Table 2 for the specific assessments to be performed.

7.1.4 Safety Follow-up

All subjects will have a subsequent Safety Follow-up visit scheduled 30 days (± 5 days) after the last administration of trial treatment. The visit will include an assessment of safety parameters as described in Table 1 and PK parameters for avelumab as described in Table 2. Subjects will also be contacted by telephone 90 days after the last administration of trial treatment to collect information on new or ongoing SAEs and treatment related non-serious AEs.

All AEs will be documented until the 30-day Safety Follow-Up visit. Subjects with an ongoing SAE at the 30-day Safety Follow-up visit must be monitored and followed up until stabilization or until the outcome is known. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call.

If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-up visit should be conducted, if possible, prior to the start of this new therapy.

7.1.5 Long-term Follow-up

All SAEs ongoing at the 90-day Safety Follow-up Phone Call must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up".

For subjects without PD according to RECIST v1.1 at the End of Treatment visit, follow-up for disease progression and survival will end on the date of treatment discontinuation .

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographic Data

At screening, the following demographic data will be collected: date of birth, sex, and race.

7.2.2 Diagnosis of Gastric Cancer

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- Detailed history of the tumor, including histopathological diagnosis, grading, and staging in accordance with the International Union Against Cancer Tumor Node Metastasis Classification of Malignant Tumors at diagnosis
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current cancer signs and symptoms and side effects from current and previous anticancer treatments
- Current cancer disease status.

7.2.3 Medical History

In order to determine the subject's eligibility to the trial, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant nonmalignant diseases and treatments
- All medications (including herbal medications) taken and procedures carried out within 28 days prior to Screening.

For the trial entry, all of the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.4 Computed Tomography or Magnetic Resonance Imaging Scans for Tumor Assessment at Baseline

Baseline imaging will be performed within 28 days prior to randomization in order to establish Baseline disease status of target and nontarget lesions according to RECIST v1.1. Acceptable modalities include CT scans (chest, abdomen, and pelvis), CT chest with contrast together with MRI of the abdomen and pelvis, or positron emission tomography/CT scans. The use of IV contrast is preferred unless there is a history of allergy or other risk in the opinion of the Investigator (chest X-ray is not acceptable and other imaging modalities may be performed at the discretion of the Investigator and as clinically indicated). Baseline tumor burden should be determined as outlined in Section 7.3. In general, lesions detected at Screening/Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

7.2.5 Other Baseline Assessments

All other Baseline measurements, such as vital signs, a complete physical examination, ECOG PS, clinical laboratory parameters, and 12-lead ECG, will be assessed.

7.3 Efficacy Assessments

Radiographic images and physical findings (physical assessments) used for the local determination of disease progression will be read centrally and reviewed by a blinded IRC. The IRC will make a determination as to whether the criteria for tumor response or progression according to RECIST v1.1 have been met.

For each subject, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject. All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each subject, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial must correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedules of Assessments (refer to Table 1).

Treatment decisions will be made by the Investigator based on the Investigator's assessment of tumor status.

For efficacy determination, tumor responses to treatment will be assigned by the IRC based on the evaluation of the response of target, nontarget, and new lesions according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1 (1)).

To assess objective response, the tumor burden at Baseline will be estimated and used for comparison with subsequent measurements. At Baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST v1.1 (1).

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed, preferably at the scheduled 6-week interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD. Subjects who withdraw from the trial for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging. For subjects receiving avelumab plus BSC, if discontinuation occurs due to progression and a definitive diagnosis/radiographic confirmation is not made at the time of discontinuation, a second imaging scan may be allowed for confirmation of progression. If progression at the second imaging scan is not confirmed and the subject wishes to continue, the subject will be allowed to continue receiving avelumab as long as they meet the criteria for continuation of treatment beyond progression.

7.4 Assessment of Safety

The safety profile of the trial treatments will be assessed through the recording, reporting, and analyzing of Baseline medical conditions, AEs, physical examination findings, including vital signs, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). Given the intended mechanism of action of avelumab, particular attention will be given to AEs that may follow the enhanced T cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis.

The reporting period for AEs is described in Section 7.4.1.3.

The safety assessments will be performed according to the Schedules of Assessments (refer to Table 1).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE v4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to trial treatment using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the trial treatment include, but may not be limited to, temporal relationship between the AE and the trial treatment, known side effects of trial treatment, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP. The AE could not medically (pharmacologically/clinically) be attributed to the trial treatment under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. The AE could medically (pharmacologically/clinically) be attributed to the trial treatment under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by

the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

SAEs

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate therapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline medical conditions, and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs or reported as SAEs, if they meet criteria for seriousness.

AESIs

Any AE that is suspected to be a potential irAE will be considered an adverse event of special interest (AESI).

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate report form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the trial treatment, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues for all SAEs and treatment related non-serious AEs through the trial's Safety Follow-up Phone Call, defined at 90 days (± 1 week) after the last trial treatment administration.

Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

7.4.1.4 Procedure for Reporting Serious Adverse Events and Adverse Events of Special Interest

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report From must be provided immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible monitor, although in exceptional circumstances the Global Drug Safety department of the Sponsor may contact the Investigator directly to obtain clarification or to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the 30-day Safety Follow-up Visit. SAEs and treatment-related non-serious AEs are recorded and assessed continuously until the 90-day Safety Follow-up Phone Call.

All SAEs ongoing at the 90-day Safety Follow-up Phone Call must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus AE Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial treatment immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

All laboratory samples, as detailed in the Schedules of Assessments (see Table 1), must be collected and sent to the central laboratory for analysis, except for some samples that may be analyzed locally (Screening pregnancy testing, HBV, and HCV testing). Urinalysis and urine pregnancy testing will be done locally only.

Results from the central laboratory for complete blood count and core chemistry must be available and reviewed prior to randomization. Results of all central laboratory testing will be transferred to the clinical database.

Local laboratory samples may be drawn and if collected are required to be recorded in the eCRFs.

In case of liver function test elevations (AST, ALT, and/or total bilirubin) requiring additional laboratory draws (according to guidelines set forth in Table 6), an unscheduled laboratory draw should be sent to the central laboratory for analysis.

Blood samples will be drawn, processed, and stored in accordance with directions provided in the Study Manual and as per timing shown in the Schedules of Assessments (Table 1).

The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the full safety tests listed in Table 7 will be taken from nonfasted subjects as detailed in the Schedules of Assessments (Table 1). The T4, TSH, and urinalysis will only be assessed at the time points defined in Table 7 and Table 1. If confirmation of a subject's postmenopausal status is necessary, an FSH level will also be performed at Screening, see Section 7.1.1.

Table 7 Clinical Laboratory Assessments

Full Chemistry	Core Chemistry[a]	Hematology
Albumin	Alkaline phosphatase	Absolute lymphocyte count
Alkaline phosphatase	ALT	Absolute neutrophil count
ALT	Amylase	Hematocrit
Amylase	AST	Hemoglobin
AST	BUN/total urea	Platelet count
GGT	Calcium	RBC count
BUN/total urea	Chloride	White blood cell count and differential count
Calcium	Creatine kinase	RBC morphology
Chloride	Creatinine	Reticulocytes
Cholesterol	Glucose	MCH
Creatine kinase	LDH	Mean corpuscular volume
Creatinine	Lipase	MCHC
CRP	Phosphorus/Phosphates	
Glucose	Magnesium	**Hemostaseology**
LDH	Potassium	aPTT
Lipase	Sodium	Prothrombin time/INR
Phosphorus/Phosphates	Total bilirubin	
Magnesium		**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)
Potassium		
Sodium		
Total bilirubin		Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End of Treatment visit.
Total protein		
Uric acid		Totality of binding ADAs
Triglycerides		
		TSH and T4
Hormone		
FSH (yes/no if applicable)		

ADA=anti-drug antibody, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, FSH=follicle-stimulating hormone, GGT=gamma-glutamyltransferase, INR=international normalized ratio, LDH=lactate dehydrogenase, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, RBC=red blood cell, TSH=thyroid-stimulating hormone, T4=free thyroxine.

[a] Core serum chemistries.

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs including body temperature, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest) will be recorded at trial entry.

A complete physical examination (including general appearance, dermatological, head/neck, pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, musculoskeletal system, extremities, eyes [inspection and vision control], nose, throat, and neurologic status) will be performed at Screening and at subsequent visits as documented in the Schedules of Assessments and the results documented in the eCRF. All clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History section and/or Disease History; all abnormalities occurring or worsening after signature of informed consent should be recorded in the AEs section. Abnormal findings are to be reassessed at subsequent visits.

The ECOG PS will be documented during the Screening phase and at each scheduled visit (if the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1) and documented in the eCRF.

Body weight will be recorded at Screening and at subsequent visits as indicated in the Schedules of Assessments and documented in the eCRF. Height will be measured at Screening only.

A 12-lead ECG will be recorded as indicated in the Schedules of Assessments.

All newly diagnosed or worsening conditions, signs, and symptoms observed from Screening, whether related to trial treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, a serum β-hCG pregnancy test will be carried out during the Screening phase and at the visits indicated in the Schedules of Assessments. Subjects who are postmenopausal (age-related amenorrhea $\geq$ 12 consecutive months and FSH $>$ 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

7.5 Pharmacokinetics

Blood samples for population PK determinations will be collected from all subjects receiving avelumab plus BSC within 2 hours prior to each trial treatment administration at Weeks 1, 3, 5, and 7 (every 2 weeks); at Weeks 13, 19, and 25 (every 6 weeks); and then at 12-week intervals thereafter while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7, and 25. Samples will also be collected at the End of Treatment visit and the 30-day Safety Follow-up visit.

The PK Schedule of Assessments for avelumab is provided in Table 2.

7.5.1 Body Fluid(s)

Whole blood sufficient to provide 0.2 mL of serum will be collected for PK assessments. Further details will be summarized in the Laboratory Manual.

7.5.2 Pharmacokinetic Calculations

The software to be used and PK calculations and parameters will be specified in a separate analysis plan.

7.6 Biomarkers

The exploratory biomarkers for the trial include measurements from tumor tissues and analyses of blood samples to explore molecular, cellular, and soluble markers that may be relevant to the mechanism of action of the drug or response/resistance to the drug.

Predictive/prognostic biomarker candidates, e.g., the level of PD-L1 expression in tumor cells and cells of the tumor microenvironment (e.g., infiltrating lymphocytes) from a tumor biopsy will be investigated with a PD-L1 pharmDx investigational assay that is under development.

PD-L1 expression in tumor cells will be assessed retrospectively and used to determine PD-L1 positivity by using an immunohistochemistry-based companion diagnostic (PD-L1 pharmDx) test under development. In addition, the analysis in tumor cells will include the percentage of tumor cells at each staining intensity level (0, 1+, 2+, and 3+). PD-L1 expression in cells of the tumor microenvironment (for example, immune cells/infiltrating lymphocytes) may also be determined to explore possible correlations with outcome to treatment and other biomarker assessments.

A panel of putative markers including molecular, soluble, and cellular markers may be analyzed from tumor biopsy and blood samples at Baseline and/or from post-treatment time points to investigate a possible correlation between clinical efficacy and analyzed markers. The following biomarker assessments may be performed retrospectively:

- Frequency and localization of tumor-infiltrated leukocytes, for example, but may not be limited to, delineation of natural killer cells, B cells, macrophage, neutrophils, myeloid-derived suppressor cells, fibroblast and vascular structure, CD8, and Foxp3 regulatory T cells by immunohistochemistry.
- Exploratory markers related to the mechanism of action of the drug, for example, but may not be limited to, soluble factors, gene expression profiles, microsatellite instability status, tumor mutation/antigen analysis, immune repertoire profiling, and changes in any of the preceding items.

Details of time points and sampling are provided in the Schedules of Assessments (Table 1) and in Table 2 for avelumab.

In order to complete all the assessments on tumor materials and blood samples, the Sponsor or the designated CRO will provide instructions for collection and storage of samples and necessary supplies to the site, including shipping materials and prepaid mailers. Please refer to the respective document for detailed information.

Unless specifically specified, all proposed biomarker analyses are exploratory and dependent on the quality and availability of sufficient materials. Collection and storage of samples will be detailed in the Study Manual. The panel of biomarkers might be adjusted based on results from

ongoing research related to anti-PD-1/PD-L1 therapies and/or safety; therefore, each subject will also be asked whether any remaining tumor tissue and/or blood-derived samples, including back-up serum samples collected for PK and/or anti-drug antibody (ADA) analysis, can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug and/or disease-related aspects. A subject's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the subject's participation in the current trial. Biomarker analyses may be conducted after the conclusion of this trial and may be based on samples derived from multiple studies.

Tissue collection: A biopsy should be collected unless tissue (blocks or slides) from an archival specimen (biopsy or surgery) is available. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suited. Fine needle aspiration biopsies are not suited. Biopsies are only to be obtained from safely accessible tumor tissue/sites.

Provision of samples: 1. Priority: tumor-containing FFPE tissue block; 2. Priority: if the tumor-containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut, 4 µm thick, and mounted on SuperFrost Plus microscope slides. Preferably, 25 slides should be provided; if not possible, a minimum number of 7 (preferably 10) slides is required for PD-L1 expression analysis.

Tissue processing: The cancer tissues should be fixed in 10% neutral buffered formalin, paraffin-embedded, and routinely processed for histological evaluation. Formalin substitutes are not suited as fixative.

Sample and tissue repository: Biomarker samples may be stored beyond the end of the trial and utilized at a later time jointly with samples from other studies in order to investigate actions of the investigational drug or aspects of the disease under study and the commercial development of the immunohistochemistry-based investigational PD-L1 pharmDx assay.

7.6.1 Pharmacogenetics

The PGt assessments will be considered (details for sample processing will be described in the Study Manual) to examine the subject's germline genetic background for DNA sequence variation in genes potentially related to drug response, safety, PK, or mechanism of action. For example, but not limited to, Fc-gamma receptor polymorphism and rearrangements/mutations in genes thought to be related to immune responses may be examined in germline DNA.

Germline DNA will be investigated on DNA extracted from whole blood. For this purpose, an additional amount of whole blood will be collected at Baseline (screening phase or Day 1 prior to first treatment). In exceptional circumstances, the germline DNA sample may be obtained at any other point of time during the trial.

Participation is optional for subjects being recruited at sites who's IRB has approved PGt assessments. A specific PGt ICF will have to be signed by the subject who chooses to participate. Storage and analyses of samples will be handled according to the specification as described in the ICF. The samples may be analyzed in the context of this trial or for the continuing development of

avelumab. The samples will not be used to obtain information about individual genetic risks unrelated to the disease studied. Genetic data obtained during the analysis of the samples will not be reported back to the individual or to his/her healthcare providers.

7.6.2 Anti-drug Antibody Analysis

For subjects randomized to receive avelumab plus BSC, a blood sample for Baseline ADA, previously referred to as "human anti-human antibody," analysis will be collected prior to trial treatment administration on Day 1 (Week 1). Further serum samples for ADA analysis will be collected within 2 hours before infusion at Weeks 3, 5, and 7 (every 2 weeks); at Weeks 13, 19, and 25 (every 6 weeks); and then every 12 weeks thereafter (as long as the subject is receiving trial treatment), and at the 30-day Safety Follow-up visit. Blood samples for ADA analysis should be taken before dose administration, at the same time as PK sample collection. Samples positive for ADAs will be re-analyzed to determine the titer and tested for neutralizing capacity.

7.7 Other Assessments

7.7.1 Subject-reported Outcomes/Quality of Life

Subject-reported outcomes/QoL will be assessed by the EQ-5D-5L, and EORTC QLQ-C30, and module QLQ-STO22. Questionnaires will be completed by the subject at the visits specified in the Schedules of Assessments (Table 1) (details will be provided in the Study Manual).

The subject-reported outcomes/QoL questionnaires should be completed by the subject prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. Subjects may use a site pad to record their responses to these questionnaires.

Data will be collected by the CRO and housed in a database. Analysis of the questionnaires will be described in the Statistical Analysis Plan (SAP).

8 Statistics

8.1 Sample Size

The sample size of this trial is driven by the primary endpoint – OS; therefore, the trial is event-driven and the primary analysis will take place after 256 deaths and a minimum of 6 months follow-up since the last subject randomized have occurred to ensure sufficient follow-up for all subjects for the primary analysis of OS. With 256 OS events, the trial provides 90% power to demonstrate an improvement of 2 months median OS time (i.e., median OS time of 6 months in the avelumab plus BSC arm versus 4 months in the control arm, which is equivalent to a reduction of 33% in hazard rate, i.e., hazard ratio of avelumab plus BSC versus control = 0.67, at the 1-sided 2.5% overall significance level). Assuming a randomization ratio of 1:1 (avelumab plus BSC versus control), an exponential distribution of OS time, a uniform distribution of subject accrual period over 15 months, an additional 6 months minimum follow-up period for all subjects and an

expected 5% overall drop-out rate, the trial should enroll approximately 330 subjects (n=165 subjects/arm) to achieve 256 OS events in total.

8.2 Randomization

The trial is a randomized, active-controlled (based on physician's choice), and open-label trial. Eligible subjects will be randomized into either the avelumab plus BSC arm or control plus BSC arm (physician's choice) in a 1:1 ratio, stratified by region (Asia versus non-Asia). The purpose of the stratification is to ensure balance of the treatment arms within region. Randomization will occur using the IWRS as described in Section 6.3 upon completion of the Screening/Baseline procedures and determination of subject eligibility.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint of the trial is OS, defined as the time (in months) from randomization to the date of death, regardless of the actual cause of the subject's death.

For subjects who are still alive at the time of data analysis or who are lost to follow-up, OS time will be censored at the last recorded date that the subject is known to be alive (date of last contact, last visit date, date of last trial treatment administration, or date of last scan, whichever is the latest) as of the data cut-off date for the analysis.

With the completion of the primary analysis, subjects will no longer be followed for survival.

8.3.2 Secondary Endpoints

8.3.2.1 Progression-free Survival

Progression-free survival is a key secondary endpoint and will be determined according to RECIST v1.1 as adjudicated by an IRC (see Section 2.3.2). It is defined as the time (in months) from date of randomization until date of the first documentation of PD or death by any cause (whichever occurs first).

For the primary analysis, PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects who start new anti-cancer treatment prior to an event, or for subjects with an event after 2 or more missing tumor assessments. Subjects who do not have a Baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the date of randomization unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

As a sensitivity analysis, the following 3 sensitivity analyses of PFS will also be performed:

1. Considering events after start for new anticancer treatment.

2. Clinical progression will be considered as an event

3. PFS based on Investigator assessment

Additional sensitivity analyses may be provided, and details will be documented in the SAP.

8.3.2.2 Best Overall Response

The confirmed BOR will be determined according to RECIST v1.1 and as adjudicated by an IRC. It is defined as the best response obtained among all tumor assessment visits after the date of randomization until documented disease progression, excluding assessments after start of subsequent anticancer therapy, taking requirements for confirmation into account as detailed below. Clinical deterioration will not be considered as documented disease progression. Details of determination of tumor response date at each time point will be provided in the IRC charter.

For a BOR of PR or CR, confirmation of the response according to RECIST v1.1 will be required, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A BOR of stable disease requires that an overall response of stable disease has been determined at a time point at least 6 weeks after randomization.

The ORR is defined as the proportion of all randomized subjects with a confirmed BOR of PR or CR according to RECIST v1.1 and as adjudicated by the IRC.

The confirmed BOR according to Investigator assessment will be derived in the same way as the confirmed BOR according to the IRC.

8.3.2.3 Subject-reported Outcomes/Quality of Life

The following subject-reported outcomes are further secondary endpoints:

- The EQ-5D-5L
- The EORTC QLQ-C30
- The EORTC Module QLQ-STO22

8.3.3 Safety Endpoints

Safety endpoints include AEs, physical examination findings, laboratory assessments, vital signs, ECG parameters, and ECOG PS as described in Section 7.4.

8.3.4 Exploratory Endpoints

Exploratory endpoints include the following:

- Duration of response

- Time to response
- Tumor shrinkage in target lesions at each time point from Baseline
- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at Baseline with their relation to selected clinical response parameters
- DCR
- Clinical response in PD-L1-positive subjects
- Population PK of avelumab and individual drug exposures based on sparse PK sampling
- Exposure response (exposure safety and exposure efficacy) for avelumab with respect to selected safety and efficacy endpoints
- Immunogenicity of avelumab
- Molecular, cellular and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab

8.4 Analysis Sets

Screening Analysis Set

The Screening Analysis Set includes all subjects who signed the ICF.

Intention-to-Treat (ITT) Analysis Set

The ITT Analysis Set will include all subjects who were randomized to trial treatment. Analyses performed on the ITT Analysis Set will take into account subjects' allocation to treatment arms as randomized. The ITT Analysis Set will be the primary analysis set for all primary and secondary efficacy endpoints.

Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will include all ITT subjects who did not have major protocol violations. Major protocol violations will be specified in the trial SAP.

Safety Analysis Set

The Safety (SAF) Analysis Set will include all subjects who were administered at least 1 dose of trial treatment. Analyses performed on the SAF Analysis Set will consider subjects as treated.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Full details of all planned analyses will be described in the trial SAP.

All safety and efficacy endpoints will be summarized by treatment arm.

In order to provide overall estimates of treatment effects, data will be pooled across trial centers. The "center" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of subjects randomized at each center. Region will be considered as a stratification factor for stratified statistical analysis as appropriate.

In general, continuous variables will be summarized using number (n), mean, median, SD, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

The calculation of proportions will be based on the number of subjects in the analysis set of interest, unless otherwise specified in the trial SAP.

Baseline

Baseline is defined as the last measurement taken prior to the first dose of trial treatment for safety endpoints and the last measurement taken prior to randomization for efficacy endpoints.

On-Treatment

The on-treatment period is defined as the time from the first trial treatment administration to the last trial treatment administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.

Multiplicity Adjustment Strategy

The type I error rate for the primary endpoint (OS) and 2 key secondary endpoints (PFS and BOR) will be controlled at 2.5% (1-sided) level using a gatekeeping procedure. The primary hypothesis (OS) will serve as a gate keeper and be tested at an overall 1-sided type I error of 2.5%. Only if it is significant, the 2 key secondary endpoints (PFS and BOR) will be tested, and the Hochberg procedure will be used to control the type I error rate at 2.5% (1-sided) for PFS and BOR (56).

Statistical analyses will be performed using SAS® version 9.2 or higher.

8.5.2 Analysis of Primary Endpoints

Primary Analysis

The primary endpoint is OS and will be considered as confirmatory evidence of efficacy. Analysis of the primary endpoint will occur after 256 events (deaths) have been observed and a minimum of 6 months follow-up since the last subject randomized. The primary analysis set will be the ITT Analysis Set. The OS difference between the 2 treatment arms will be compared using a stratified, 1-sided, log-rank test at an overall 1-sided type I error rate of 2.5%. The stratification factor will be region (Asia vs. non-Asia). The following null hypothesis will be tested:

$$H0: \lambda_A(t) = \theta\lambda_B(t), \theta \geq 1, \text{ versus } H1: \lambda_A(t) = \theta\lambda_B(t), \theta < 1,$$

where λ (t) represents the hazard rate at time t and θ the unknown constant of proportionality of hazards in treatment arms A (avelumab plus BSC) and B (physician's choice plus BSC).

Kaplan-Meier estimates (production-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the survival rate at 3, 6, 9 and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (57) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (58). The estimate of the standard error will be computed using Greenwood's formula.

Note that the statistical conclusion will be drawn from the stratified, 1-sided log-rank test.

A stratified Cox proportional hazards model will be used to assess the magnitude of treatment difference between the 2 treatment arms and to explore the robustness of the primary endpoint confirmatory analysis. The natural parameter of this model is the log hazard ratio. Ties will be handled by replacing the proportional hazards model by the discrete logistic model. The hazard ratio of avelumab versus physician's choice (with physician's choice chemotherapy as reference) together with the corresponding Wald 2-sided 95% CI will be presented.

The validity of the proportional hazards assumption will be assessed visually by plotting log(-log[survival]) versus log(time) by treatment.

Sensitivity Analysis

The primary endpoint analysis described above will be repeated based on the PP Analysis Set as a means of sensitivity analysis if this analysis set includes less than 90% of subjects in the ITT Analysis Set.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Key Secondary Endpoints – Progression-free Survival and Best Overall Response

Secondary efficacy analyses will be performed on the ITT Analysis Set.

Based on the gatekeeping testing strategy described in Section 8.5.1, if the 1-sided p-value from the stratified log-rank test of the primary endpoint OS is less than 0.0250, the key secondary endpoints (i.e., PFS and BOR) will be tested per the Hochberg procedure used to control the type I error rate at 2.5% (1-sided).

8.5.3.1.1 Progression-free Survival

For the key secondary endpoint PFS, the primary statistical analysis will be the same as described for the analysis of OS.

A sensitivity analysis will be performed based on the PP Analysis Set if the PP Analysis Set includes less than 90% of subjects in the ITT Analysis Set. The PFS according to Investigator assessment will be analyzed in the same manner as another means of sensitivity analysis. Other sensitivity analyses based on different censoring rules will be conducted. Details will be provided in the trial SAP.

8.5.3.1.2 Best Overall Response

For the key secondary endpoint analysis of BOR according to RECIST v1.1 and as adjudicated by the IRC, the ORR in terms of having a confirmed BOR of CR or PR will be calculated along with corresponding 2-sided exact Clopper-Pearson 95% CIs for the 2 treatment arms. The Cochran-Mantel-Haenszel test will be performed with the stratum of region to compare the ORR between the 2 treatment arms.

The ORR according to Investigator assessment will be analyzed in the same manner as a means of sensitivity analysis.

8.5.3.2 Other Secondary Endpoints – Subject-reported Outcomes/QoL

8.5.3.2.1 European Quality of Life 5-dimensions and 5-levels Questionnaire

Observed and change from Baseline values for the EQ-5D-5L index score will be summarized descriptively at planned visits during the treatment phase and End of Treatment visit by treatment arm. In addition, change from Baseline values will be compared between the 2 treatment arms using analysis of covariance (ANCOVA) with region and Baseline value as covariates. The EQ-5D-5L Visual Analog Scale scores will be presented by data listing only.

8.5.3.2.2 European Organization for Research and Treatment of Cancer QLQ-C30

Observed and change from Baseline values for the Global health status/QoL scale and each of the 5 QLQ-C30 functional scales (i.e., Physical, Role, Emotional, Cognitive, and Social) will be summarized descriptively at planned visits during the treatment phase and End of Treatment visit by treatment arm. In addition, the best (largest positive change), worst (largest negative change), and last observed on-treatment change from Baseline values will be summarized. Each measure will be compared between the 2 treatment arms using ANCOVA with region and Baseline value as covariates.

8.5.3.2.3 European Organization for Research and Treatment of Cancer QLQ-STO22

Observed and change from Baseline values for each of the 5 QLQ-STO22 gastric cancer module symptom scales (i.e., Dysphagia, Pain, Reflux, Eating, and Anxiety) will be summarized descriptively at planned visits during the treatment phase and End of Treatment visit by treatment

arm. In addition, the best (largest negative change), worst (largest positive change), and last-observed on-treatment change from Baseline values will be summarized. Each measure will be compared between the 2 treatment arms using ANCOVA with region and Baseline value as covariates.

8.5.4 Analysis of Exploratory Endpoints

Exploratory endpoint analyses will be performed on the ITT Analysis Set, unless otherwise specified in the trial SAP.

8.5.4.1 Duration of Response

Duration of response is defined, for patients with an objective response, as the time from the first documentation of observed response (CR or PR) to the date of first documentation of objective PD or death due to any cause. If a patient has not had an event (PD or death), duration of response is censored at the date of last adequate tumor assessment. The censoring rules for duration of response are the same as those for PFS (Section 8.3.2.1). Duration of response will be analyzed descriptively by treatment arm. The Kaplan-Meier estimate of median response duration along with its 95% CI, as well as estimates of the survival function at 3, 6, and 12 months will be presented by treatment arm.

8.5.4.2 Time to Response

Time to response is defined, for subjects with an objective response, as the time (in weeks) from date of randomization to the first documentation of objective response (CR or PR) which is subsequently confirmed. Time to response will be summarized using simple descriptive statistics (mean, SD, median, minimum, maximum, Q1, Q3).

8.5.4.3 Tumor Shrinkage

Tumor shrinkage will be summarized as the percent change from Baseline in target lesions per time point. The tumor response will be based on the IRC assessment. Details of the analysis will be included in the trial SAP.

8.5.4.4 PD-L1 Expression Levels Versus Selected Clinical Response Parameters

The relationship between different PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (e.g., infiltrating lymphocytes) and selected clinical response parameters will be explored. Further details of the analysis will be described in a separate analysis plan.

8.5.4.5 Disease Control Rate

The DCR is defined as the proportion of subjects with confirmed BOR of CR, PR, and stable disease according to RECIST v1.1 and adjudicated by the IRC obtained among all tumor

assessment visits after the date of randomization until documented disease progression in the analysis set of interest.

For a confirmed BOR of CR, PR, or stable disease, confirmation of the response according to RECIST v1.1 will be required, preferably at the regularly scheduled 6-week assessment interval (after 12 months of treatment, 12-week assessment interval will be used), but no sooner than 5 weeks after the initial documentation of CR or PR. A BOR of stable disease requires that an overall response of stable disease has been determined at a time point at least 6 weeks after randomization.

The DCR will be summarized by treatment arm along with its 2-sided exact Clopper-Pearson 95% CI.

8.5.4.6 Selected Clinical Endpoints in PD-L1-positive Subjects

The relationship between PD-L1-positive status and selected clinical endpoints (e.g., OS, PFS, BOR, DCR) will be explored. Further details of these analyses will be described in the trial SAP.

8.5.4.7 Pharmacokinetic Data

The primary PK analysis will include a descriptive summary of avelumab concentrations during the treatment phase. If appropriate, the data may be added to data from other trials for a population PK analysis. Further details of the analysis will be described in a separate analysis plan.

8.5.4.8 Exposure Response

Analyses of exposure-response relationships for avelumab plus BSC with respect to efficacy and safety endpoints may be conducted. Further details of the analysis will be described in a separate analysis plan.

8.5.4.9 Immunogenicity Data

Investigations will be conducted on markers of the immune response (e.g., cytokines) that could be modulated by treatment. Changes in soluble factors (e.g., cytokine profiles) will be summarized. In addition, the incidence of immunogenicity developed in the avelumab plus BSC treatment arm will also be summarized. The immunogenicity testing strategy will be implemented and conducted in keeping with the following:

- Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (2007; EMEA/CHMP/BMWP/14327/2006)
- Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use (2012; EMA/CHMP/BMWP/86289/2010)
- Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins (2014)

A qualified method that uses an acid dissociation step to detect antidrug antibodies in the presence of excess drug in human serum will be applied. The ADA titers of positive samples will be determined and positive samples will be tested for neutralizing capacity of the antidrug antibodies.

Further details of the analysis will be described in a separate analysis plan.

8.5.4.10 Biomarker Data

Analyses of exploratory biomarkers with respect to the mechanism of action of avelumab or response/resistance to the drug may be conducted. Further details of the analysis will be described in a separate analysis plan.

8.5.5 Analysis of Safety Endpoints

All Safety analyses will be performed on the SAF Analysis Set at the time of the final analysis of the primary endpoint (OS). Safety endpoints will be tabulated using descriptive statistics only.

Safety assessments will be based on review of AEs, concomitant medications, central laboratory measurements (serum chemistry, hematology, and urinalysis), ECOG PS, physical examinations, vital signs, and 12-lead ECGs.

Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

Treatment-emergent adverse events (TEAEs) are defined as events with onset dates occurring on-treatment or events which worsen on-treatment (see Section 8.5.1).

The incidence of TEAEs, regardless of relatedness to trial treatment, will be summarized by system organ class and preferred term for each treatment arm. Similar summaries will also be provided for serious TEAEs, TEAEs leading to permanent discontinuation of trial treatment, TEAEs by maximum severity, TEAEs by highest relationship to trial treatment, TEAEs with fatal outcome, and treatment-emergent AESIs, such as irAEs.

Concomitant Medications and Procedures

Concomitant medications (i.e., medications other than trial treatment taken at any time on-treatment) will be summarized using frequencies and percentages within a given drug class and preferred name by treatment arm and overall. Concomitant procedures (i.e., procedures undertaken at any time on-treatment) will be listed only.

Laboratory Values

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-treatment grades for chemistry and hematology laboratory results will be summarized. Shifts in toxicity grading from Baseline to highest grade during the on-treatment period will be displayed.

Results for laboratory tests that are not part of NCI-CTCAE will be presented categorically (e.g., below, within, or above normal limits). Only subjects with post-Baseline laboratory values will be included in these analyses. Urinalysis results will be listed only. Further details of analyses for the laboratory parameters will be provided in the trial SAP.

Eastern Cooperative Oncology Group Performance Status

Shifts from Baseline in ECOG PS score will be presented at planned visits during the treatment phase and End of Treatment visit by number and percentage for each treatment arm. Shifts from Baseline to highest on-treatment ECOG PS score will be summarized in a similar fashion.

Physical Examinations

Clinically significant, abnormal findings from physical examinations before ICF signature are to be reported as pre-existing medical conditions and will be included in summaries of medical history. On the other hand, clinically significant, abnormal findings from physical examinations after ICF signature are to be reported as AEs and will be included in summaries of AEs.

Vital Signs

Maximum on-treatment increase and maximum on-treatment decrease from Baseline values will be summarized by parameter (e.g., body temperature, respiratory rate, heart rate, and blood pressure) using descriptive statistics by treatment arm.

12-Lead Electrocardiograms

Observed and change from Baseline values based on 12-lead ECGs will be summarized at the End of Treatment visit by parameter (e.g., heart rate, PR interval, QRS interval, RR interval, QT interval, and Fridericia-corrected QT interval) and treatment arm for the SAF Analysis Set. In addition, shifts from Baseline in ECG results (e.g., normal, abnormal) will be presented at the End of Treatment visit by parameter and treatment arm.

Further details of safety analyses will be provided in the trial SAP.

8.5.6 Reporting of Other Clinical Data of Interest

Subject Characteristics

Subject characteristics will be obtained prior to randomization and will be summarized by treatment arm and overall for the ITT Analysis Set. Subject characteristics may include, but are not limited to, age, sex, race/ethnicity, height, weight, body mass index, region corresponding to the site at which the subject is enrolled, and ECOG PS.

Disease Characteristics

Information on Baseline disease characteristics collected on the eCRF will be summarized by treatment arm and overall for the ITT Analysis Set. Disease characteristics may include, but are

not limited to, site of primary tumor (i.e., stomach, gastro-esophageal junction), and PD-L1 assay status (i.e., positive, negative).

Enrollment and Disposition

The number and percentage of subjects screened (number only), discontinued prior to randomization (number only), randomized, randomized but not treated, treated, and prematurely discontinued will be summarized by treatment arm and overall. All premature terminations will be summarized by primary reason for treatment discontinuation/withdrawal. The number and percentage of subjects in the ITT Analysis Set with major protocol deviations leading to exclusion from the PP Analysis Set will be presented by treatment arm and reason for exclusion. All major protocol deviations will be listed.

Medical History

Pre-existing medical conditions reported at the time of the Screening/Baseline procedures will be summarized using frequency tables by treatment arm and overall for the SAF Analysis Set.

Treatment Exposure and Compliance

The extent of exposure to trial treatment (avelumab or physician's choice) will be characterized by duration (weeks), number of administrations (avelumab plus BSC arm only), cumulative dose (e.g., mg/kg or mg/m^2), dose intensity (e.g., mg/kg/week or mg/m^2/week), relative dose intensity (actual dose given/planned dose), number of dose delays, number of infusion rate reductions (avelumab plus BSC arm only), and number of dose reductions (physician's choice chemotherapy plus BSC arm only) for the SAF Analysis Set. The number and percentage of non-compliant subjects (see Section 6.9) with regard to trial treatment will be presented by treatment arm based on the SAF Analysis Set.

Anticancer Therapies and Procedures

Prior anticancer therapies (i.e., anticancer medications other than trial treatment taken at any time pre-treatment) will be summarized using frequencies and percentages by drug class and preferred name within treatment arm and overall for the SAF Analysis Set. Prior anticancer procedures (i.e., procedures undertaken at any time pre-treatment) will be listed only.

Post anticancer therapies (i.e., anticancer medications other than trial treatment taken at any time post-treatment) will be summarized using frequencies and percentages by type of therapy collected on the eCRF.

8.6 Interim Analysis

No interim analysis for efficacy is planned for this trial. There will be periodic safety review by the IDMC. Details will be provided in the IDMC charter and the IDMC SAP.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, the Japanese ministerial ordinance on GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the United States Food and Drug Administration), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained. A separate specific PGt ICF will be provided to subjects who are willing to participate in this optional procedure, which refers to the extraction and analysis of germline DNA from blood in order to better understand how gene(s) may affect the efficacy of avelumab.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Blood and tumor tissue samples for PGt and biomarkers will be stored for up to 10 years after trial completion. During this time, the samples may be reanalyzed for newly identified markers or with new or improved technology. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified and the tumor tissue will be returned to the site upon request. If the site does not request the return of the tumor tissue, it will be destroyed.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor or designee for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor or designee provides the appropriate means to contact a Sponsor or delegate physician. This includes the provision of a 24-hour contact

number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (such as the ICF) to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File and a copy will be filed with the CRO.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the IPMP for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

For subject-reported outcome data such as QoL and pain assessments, electronic subject-reported outcome will be used.

The data will be entered into a validated database. The CRO will follow the standards of the Sponsor in the database design and data structure. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's or designee's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end

of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on Clintrials.gov is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

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12 Appendices

Appendix II Guidance on contraception

Birth control methods considered as highly effective

According to the Clinical Trials Facilitation Group (CTFG) "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2]Contraception methods in the context of this guidance are considered to have low user dependency

[3]Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

[4]In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.