Clinical Trial Protocol

Clinical Trial Protocol Number	EMR100070-007
Title	A Phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction
Short Trial Name	JAVELIN Gastric 100
Phase	III
IND Number	CCI [redacted]
EudraCT Number	2015-003300-23
Coordinating Investigator	PPD
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 01821-3936, USA Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821-3936, USA +1 978 435 1253
Clinical Trial Protocol Version	17 July 2019/ Version 7.0
Replaces Version	21 June 2018 / Version 6.0

[redacted]

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List of Abbreviations

5-FU	fluorouracil
CCI	[redacted]
ADCC	antibody-dependent cell-mediated cytotoxicity
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}	trough concentration
CHMP	Committee for Medicinal Products for Human Use
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	cardiac troponin I
cTnT	cardiac troponin T
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 5 Levels Questionnaire
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEJ	gastro-esophageal junction
GGT	gamma-glutamyltransferase
H1	histamine H1 receptor
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2+	human epidermal growth factor receptor 2 positive
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IPMP	Integrated Project Management Plan
irAE	immune-related adverse event
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
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
CCI [redacted]	
CCI [redacted]	
PP	per-protocol
PR	partial response
QoL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	standard of care
SUSAR	suspected unexpected serious adverse reactions
SwM	switch-maintenance
$t_{1/2}$	terminal half-life
T_4	free thyroxine
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USA	United States of America

1 Synopsis

Clinical Trial Protocol Number	EMR100070-007
Title	A Phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction
Trial Phase	III
IND Number	CCI [redacted]
FDA covered trial	Yes
EudraCT Number	2015-003300-23
Coordinating Investigator	PPD
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, Massachusetts 01821-3936 USA
Trial centers/countries	The trial will be conducted at approximately 230 sites globally in North America, South America, Asia Pacific, and Europe, with approximately 47 sites in the USA.
Planned trial period (first subject in-last subject out)	First subject in: Q4, 2015 Last subject out: Q3, 2019
Trial Registry	ClinicalTrials.gov

Objectives:

Primary objectives: The primary objectives are to demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to Overall Survival (OS) in all randomized subjects or in PD-L1+ subjects who have not progressed on first-line chemotherapy.

Secondary objectives:

- To demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to Progression-Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) according to Investigator assessment.
- To demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to objective response rate (ORR) as per RECIST v1.1 and per Investigator assessment.
- To compare the subject-reported outcomes / quality of life (QoL) of subjects when treated with avelumab versus continuation of first-line chemotherapy as assessed by the European QoL 5-dimensions 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.

CCI

Methodology:

This is a multicenter, international, randomized, open-label Phase III trial of avelumab in subjects with advanced (unresectable, locally advanced or metastatic) adenocarcinoma of the stomach, or of the gastroesophageal junction (GEJ) who are treatment naïve and have not yet received chemotherapy for the treatment of metastatic or locally advanced disease.

This study includes a Screening period, Induction Phase, Maintenance Phase, and Follow-up Phase.

The actual number of subjects enrolled in the Induction Phase will be driven by observed induction failure rates and will be such to allow for approximately 466 subjects to be randomized in the Maintenance Phase. Subjects enrolled in the Induction Phase will receive induction chemotherapy comprised of oxaliplatin and either 5-fluorouracil (5-FU) or capecitabine (Induction Phase) for 12 weeks. Following the Induction Phase, subjects who experience a complete response (CR), partial response (PR), or stable disease (SD) will enter the Maintenance Phase and be randomly assigned to receive either avelumab, or continuation of the same chemotherapy regimen from the Induction Phase (Maintenance Phase).

The dose and schedule of the chemotherapy during the Induction Phase are as follows or in accordance to the label instructions and per local guidelines:

- Oxaliplatin at 85 mg/m^2 intravenous (IV) on Day 1 with leucovorin 200 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1, given every 2 weeks (for up to 12 weeks)

  OR

- Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 400 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Days 1 and 2) given every 2 weeks (for up to 12 weeks)

  OR

- Oxaliplatin at 130 mg/m^2 IV on Day 1 with capecitabine at 1000 mg/m^2, twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks (for up to 12 weeks).

Local label and guidelines should be followed for specific starting doses due to renal or hepatic impairments and for subsequent dose modifications due to different toxicities.

Upon completion of chemotherapy in the Induction Phase, subjects without disease progression (subjects with SD, PR, or CR) will be eligible for randomization to the Maintenance Phase where they will receive either avelumab, or continue the same regimen of chemotherapy from the Induction Phase.

Treatment during the Maintenance Phase are as follows:

1. For subjects randomly assigned to avelumab: avelumab will be given at a dose of 10 mg/kg as a 1-hour IV infusion once every 2 weeks until disease progression

2. For subjects randomly assigned to chemotherapy: the same regimen of oxaliplatin-fluoropyrimidine doublet as in the Induction Phase will be continued until disease progression.

    - Subjects who are not deemed eligible to receive further chemotherapy will receive best supportive care (BSC) alone with no active therapy. Prior to randomization, Investigators must specify BSC treatment for these subjects.

    - For subjects receiving chemotherapy (oxaliplatin + 5-FU or oxaliplatin + capecitabine), dose modifications after the starting dose are allowed if the continuation of the oxaliplatin-fluoropyrimidine doublet, or a component thereof, is prohibited by toxicity. For subjects intolerant to further oxaliplatin, single-agent capecitabine or 5-FU + leucovorin will be an option for dose modification.

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. Clinical decision making and study endpoint evaluation will be based on Investigator assessment of the scans using RECIST v1.1.

Study treatment will continue until:

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

Subjects receiving avelumab may continue treatment past the initial determination of disease progression per RECIST version 1.1 as long the following criteria are met:

- Investigator-assessed clinical benefit, without any rapid disease progression
- Tolerance of trial treatment
- Stable Eastern Cooperative Oncology Group performance status (ECOG PS [PS=0 or 1])
- 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 avelumab treatment beyond progression should be discussed with the Medical Monitor and documented in the study records.

For subjects continuing avelumab after initial progressive disease (PD), 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, 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 restart, 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.

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 increase in tumor burden of 20% and $\geq$ 5 mm absolute increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions.

Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months or until disease progression or unacceptable toxicity, after confirmation of response. 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 after agreement with the Medical Monitor. To be eligible for retreatment, 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 follow the Schedule of Assessments until disease progression.

Subjects in the maintenance chemotherapy arm 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.

On-study subject management and study endpoint evaluation will be based on Investigator assessments.

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

After completion of the Maintenance Phase, subjects will enter the Follow-up Phase.

Planned number of subjects:

Approximately 466 subjects are planned to be randomly assigned into the Maintenance Phase. The actual number of subjects enrolled in the Induction Phase will be driven by observed induction failure rates and will be such to allow for approximately 466 patients to be randomized in the Maintenance Phase. At the time of this protocol amendment, subject

enrollment in the Maintenance Phase is complete, with 499 subjects randomized into the Maintenance Phase.

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.

Secondary endpoints:

The key secondary endpoints are:

- PFS defined as the time (in months) from randomization to the date of the first documentation of disease progression (per RECIST v1.1 and as evaluated by Investigator) or death due to any cause (whichever occurs first).
- Best Overall Response (BOR) in Maintenance Phase according to RECIST v1.1 and per Investigator assessment.

Other secondary endpoints include subject-reported outcomes / QoL (assessed by the EQ-5D-5L, EORTC QLQ-C30, and EORTC module QLQ-STO22 questionnaires).

[redacted]

Safety endpoints:

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 examinations, clinical laboratory assessments, concomitant medications, vital signs, electrocardiogram (ECG) parameters, and ECOG PS.

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 recently-obtained (within 6 months) biopsy from a non-irradiated area, formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 10 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression assessment, at least 1 measurable tumor lesion, and with histologically confirmed unresectable, locally advanced or metastatic, adenocarcinoma of the stomach or the GEJ.

Key exclusion criteria

Prior therapy with any antibody or drug targeting T-cell coregulatory proteins, concurrent anticancer treatment, or immunosuppressive agents. Other exclusion criteria: 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), persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v4.03 and prior chemotherapy for unresectable locally advanced or metastatic adenocarcinoma of the stomach or GEJ.

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, premedicate patients with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. 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 and has to be recorded as concomitant medication.

Reference therapy: dose/mode of administration/dosing schedule: Chemotherapy during the Maintenance Phase will be administered according to the following rules:

1. For subjects randomly assigned to chemotherapy: the same regimen of oxaliplatin-fluoropyrimidine doublet as in the Induction Phase will be continued until disease progression.

    - Subjects who are not deemed eligible to receive further chemotherapy will receive BSC alone with no active therapy. Prior to randomization, Investigators must specify BSC treatment for these subjects.

    - For subjects receiving chemotherapy (oxaliplatin + 5-FU or oxaliplatin + capecitabine) dose modifications after the starting dose are allowed if the continuation of the oxaliplatin-fluoropyrimidine doublet, or a component thereof, is prohibited by toxicity. For subjects intolerant to further oxaliplatin, single-agent capecitabine or 5-FU + leucovorin will be an option for dose modification.

Therapy will be administered until disease progression, unacceptable toxicity, or for the accepted maximal duration of the agent(s) selected.

Therapy will be stopped after the first on-treatment radiological evaluation of disease progression.

Planned trial and treatment duration per subject:

In this trial, treatment with chemotherapy during the Induction Phase will last for 12 weeks, followed by the Maintenance Phase with either avelumab or continuation of the same regimen of chemotherapy from the Induction Phase, which will continue until disease progression or unacceptable toxicity. Subjects receiving avelumab during the Maintenance Phase may continue treatment past the initial determination of disease progression according to RECIST v1.1 if they meet the criteria presented under Methodology (Investigator-assessed benefit; tolerance of treatment; stable ECOG PS; and does not delay other imminent intervention). Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months or until disease progression or unacceptable toxicity, after confirmation of response.

Statistical methods:

The primary objectives of this trial are to demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to OS in all randomized subjects or in PD-L1+ subjects who have not progressed on first-line chemotherapy. The primary endpoint in this study is OS. An imbalanced type I error allocation will be used for the 2 primary hypotheses and control overall family wise type I error rate at 2.5% (1-sided) with 0.5% (1-sided) allocated to PD-L1+ subjects and 2% (1-sided) allocated to all randomized subjects.

The sample size for this study is driven by the primary endpoint of OS. The sample size is based on calculation assuming an 18-month enrollment period in the Maintenance Phase and follow-up of approximately 18 months after enrollment completion. Approximately 466 subjects will be enrolled and randomized using 1:1 randomization ratio, stratified by region (Asia vs. non-Asia) in the Maintenance Phase. The actual number of subjects enrolled in the Induction Phase will be driven by observed induction failure rates and will be such to allow for approximately 466 patients to be randomized in the Maintenance Phase. At the time of this protocol amendment, subject enrollment in the Maintenance Phase is complete, with 499 subjects randomized into the Maintenance Phase.

For the OS in all randomized subjects, assuming a median duration of 10.5 months in the control arm and 15 months in the avelumab arm corresponding to a hazard ratio of 0.70 and a drop-out rate of 5%, then 356 events are required to achieve 90% power of the log-rank test at a 1-sided overall 2% alpha level.

The data cut-off for the primary analysis will take place on a prospectively-determined date, upon which the target number of 356 OS events in all randomized subjects are projected to have been reached and the last subject randomized in the study has been followed for at least 18 months from randomization. This calculation includes an interim efficacy analysis and assumes it will be performed after 75% of OS events have been observed. For OS in all

randomized subjects, the interim and primary analyses will follow a sequential alpha spending function approach developed by Lan and DeMets using an O'Brien and Fleming boundary function. Applying this approach with an assumed 267 and 356 observed events, respectively, 1-sided significance levels of 0.0072 and 0.0178 for the interim and final analyses will preserve an overall type I error rate of 2% for OS in all randomized subjects.

For OS in PD-L1+ subjects, at planning stage a prevalence rate of 35% in all randomized subjects was assumed, and a median OS of 19.3 months in the avelumab arm corresponding to a hazard ratio of 0.54.

The study will be considered successful if the null hypothesis testing for OS in either all randomized subjects or PD-L1+ subjects will be rejected as statistically significant.

Table 1 **Schedule of Assessments – Screening and Induction Phase (Open-label Chemotherapy Treatment Phase) for Oxaliplatin + Capecitabine**

	Screening	Induction Phase (-4/+2 days)[a]				End-of-Treatment[b]	Safety Follow-up Visit
		Cycle 1	Cycle 2	Cycle 3	Cycle 4[c]	Within 7 Days of Decision to Discontinue Treatment	30 Days after Last Treatment (± 5 days)
		W1	W4	W7	W10		
	Day-28 to Enrollment	D1	D22	D43	D64		
Written informed consent	X						
Inclusion / exclusion criteria	X						
Medical history	X						
Disease history	X						
Demographic data	X						
Subject-reported outcomes / quality of life assessments[d]	X	X[d]					
Physical examination	X	X	X	X	X	X	
Vital signs (including height at Screening)	X	X	X	X	X	X	
Weight[e]	X	X	X	X	X	X	
ECOG PS[f]	X	X	X	X	X	X	
12-lead ECG	X					X	
Concomitant medications	Collected from Screening through End-of-Treatment Visit						
Concomitant procedures	Collected from Screening through End-of-Treatment Visit						
AE and SAE collection	Collected from Informed Consent through End-of-Treatment Visit[b]						X
Samples and Laboratory Assessments							
Hematology and hemostaseology[g]	X	X	X	X	X	X	X
Full serum chemistry[h]	X					X	
Core serum chemistry[h]		X	X	X	X		X
Urinalysis[i]	X					X	X
β-hCG pregnancy test[j]	X	X	X	X	X	X	
HBV and HCV test[k]	X						
T_4 and TSH	X			X		X	

[redacted]

Dosing							
Premedication[p]		X	X	X	X		
Chemotherapy administration		X	X	X	X		

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CT = computed tomography; D = day; ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; [redacted]; [redacted]; RNA = ribonucleic acid; SAE = serious adverse event; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; W = week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b Subjects who discontinue the Induction Phase due to any reason will have an EOT visit within 7 days of the decision to discontinue chemotherapy. All subjects who do not enter the Maintenance Phase will have a 30-day after last treatment Safety Follow-up visit. Subjects entering the Maintenance Phase will have the Re-baseline visit (Table 3 to Table 6 as applicable). Subjects with an AE ongoing at the EOT visit must be followed up for final outcome until the 30-day Safety Follow-up visit. Subjects with an SAE ongoing at the 30-day Safety Follow-up visit 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."

c Subjects who complete Cycle 4 will return to clinic for the Re-baseline visit (see Table 3 to Table 6 depending on regimen). The Re-baseline visit is to occur -10 to -1 days before the first administration in the Maintenance Phase.

d Subject-reported outcomes / quality of life assessments should be completed by subjects after the ICF is signed and prior to any study-related procedures at the indicated visits. The assessments should be conducted at Screening; in the event that this doesn't occur, it can be done at Cycle 1 (Day 1) prior to treatment.

e The dose of chemotherapy will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration.

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

g Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

h Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

i A full urinalysis is required at Screening and the EOT visit (see Table 12 for details).

j β-hCG must be determined from serum at Screening and from either urine or serum sample thereafter as required per local guidelines. Results of the most recent pregnancy test has to be available prior to next dosing.

k An HBV surface antigen and anti-HCV tests must be performed at Screening to exclude subjects with hepatitis infection. If the anti-HCV antibody test is positive, the infection must be confirmed by an HCV RNA test.

[redacted]

- Anti-emetic premedications should be administered in accordance with either the 2006 American Society of Clinical Oncology guidelines or local institutional guidelines.

Table 2 **Schedule of Assessments – Screening and Induction Phase (Open-label Chemotherapy Treatment Phase) for Oxaliplatin + 5-Fluorouracil (5-FU)**

	Screening	Induction Phase (-4/+2 days)[a]						End-of-Treatment[b]	Safety Follow-up Visit
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6[c]	Within 7 Days of Decision to Discontinue Treatment	30 Days after Last Treatment (± 5 days)
	Day-28 to Enrollment	W1	W3	W5	W7	W9	W11		
		D1	D15	D29	D43	D57	D71		
Written informed consent	X								
Inclusion / exclusion criteria	X								
Medical history	X								
Disease history	X								
Demographic data	X								
Subject-reported outcomes / quality of life assessments[d]	X	X[d]							
Physical examination	X	X	X	X	X	X	X	X	
Vital signs (including height at Screening)	X	X	X	X	X	X	X	X	
Weight[e]	X	X	X	X	X	X	X	X	
ECOG PS[f]	X	X	X	X	X	X	X	X	
12-lead ECG	X							X	
Concomitant medications	Collected from Screening through End-of-Treatment Visit								
Concomitant procedures	Collected from Screening through End-of-Treatment Visit								
AE and SAE collection	Collected from Informed Consent through End-of-Treatment Visit[b]								X
Samples and Laboratory Assessments									
Hematology and hemostaseology[g]	X	X	X	X	X	X	X	X	X
Full serum chemistry[h]	X							X	
Core serum chemistry[h]		X	X	X	X	X	X		X
Urinalysis[i]	X							X	X
β-hCG pregnancy test[j]	X	X		X		X		X	

HBV and HCV test[k]	X								
T_4 and TSH	X				X			X	
CCI									
Response Assessments									
CCI									
Dosing									
Premedication[p]		X	X	X	X	X	X		
Chemotherapy administration		X	X	X	X	X	X		

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CT = computed tomography; D = day; ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; CCI CCI; RNA = ribonucleic acid; SAE = serious adverse event; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; W = week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b Subjects who discontinue the Induction Phase due to any reason will have an EOT visit within 7 days of the decision to discontinue chemotherapy. All subjects who do not enter the Maintenance Phase will have a 30-day after last treatment Safety Follow-up visit. Subjects entering the Maintenance Phase will have the Re-baseline visit (Table 3 to Table 6 as applicable). Subjects with an AE ongoing at the EOT visit must be followed up for final outcome until the 30-day Safety Follow-up visit. Subjects with an SAE ongoing at the 30-day Safety Follow-up visit 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."

c Subjects who complete Cycle 6 will return to clinic for the Re-baseline visit (see Table 3 to Table 6 depending on regimen). The Re-baseline visit is to occur -10 to -1 days before the first administration in the Maintenance Phase.

d Subject-reported outcomes / quality of life assessments should be completed by subjects after the ICF is signed and prior to any study-related procedures at the indicated visits. The assessments should be conducted at Screening; in the event that this doesn't occur, it can be done at Cycle 1 (Day 1) prior to treatment.

e The dose of chemotherapy will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration.

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

g Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

h Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

i A full urinalysis is required at Screening and the End-of-Treatment visit (see Table 12 for details).

j β-hCG must be determined from serum at Screening and from either urine or serum sample thereafter as required per local guidelines. Results of the most recent pregnancy test has to be available prior to next dosing

k An HBV surface antigen and anti-HCV tests must be performed at Screening to exclude subjects with hepatitis infection. If the anti-HCV antibody test is positive, the infection must be confirmed by an HCV RNA test.

[redacted]

p Anti-emetic premedications should be administered in accordance with either the 2006 American Society of Clinical Oncology guidelines or local institutional guidelines.

Table 3 Schedule of Assessments –Maintenance Phase and Follow-Up – Oxaliplatin + Capecitabine

		Maintenance Phase (-4/+2 days)[a]						End of Treatment	Follow-up[b]		
	Re-baseline (Day -10 to Day -1)[c]	V1 W1 Day 1	V2 W4 Day 22	V3 W7 Day 43	V4 W10 Day 64	V5 W13 Day 85	Until Progression	End-of-Treatment Visit Within 7 Days of Decision to Discontinue Treatment[d]	Safety Follow-up Visit 30 Days after Last Treatment (±5 days)[e]	Safety Follow-up Phone Call 90 Days after Last Treatment (± 1 week)	Long-term Follow-up Every 12 Weeks after Last Treatment (± 2 week)
Study Procedures											
Review eligibility Criteria[f]	X										
Physical examination[g]	X	X	X	X	X	X	6 weeks	X	X		
Vital signs	X	X	X	X	X	X	3 weeks	X	X		
Weight[h]	X	X	X	X	X	X	3 weeks	X	X		
ECOG PS[i]	X	X	X	X	X	X	3 weeks	X	X		

		Maintenance Phase (-4/+2 days)[a]						End of Treatment	Follow-up[b]		
		V1	V2	V3	V4	V5		End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up
	Re-baseline (Day -10 to Day -1)[c]	W1 Day 1	W4 Day 22	W7 Day 43	W10 Day 64	W13 Day 85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (±5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
12-lead ECG	X							X			
Subject-reported outcomes / quality of life assessments[j]	X	X[j]	X	X		X	6 weeks	X	X		
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit										
Anti-cancer therapy[b]									X	X	X
AE collection	All AEs are collected through the 30-day Safety Follow-up Visit; Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call[b]									X	
SAE collection	All SAEs are documented until the 90-day Safety Follow-up Phone Call; Ongoing SAEs at the 90-day Safety Follow-up Call will be followed[b]									X	
Samples and Laboratory Assessments											
Hematology and hemostaseology[k]	X	X	X	X	X	X	3 weeks	X	X		
Full serum chemistry[l]	X							X	X		
Core serum chemistry[l]		X	X	X	X	X	3 weeks				
Urinalysis[m]	X	X		X		X	12 weeks	X	X		
β-hCG pregnancy test[n]	X	X	X	X	X	X	3 weeks	X	X		
T_4 and TSH	X			X		X	6 weeks	X	X		
Cardiac troponin[o]	X	X	X	X	X	X					
[redacted]											
Response Assessments											

		Maintenance Phase (-4/+2 days)[a]						End of Treatment	Follow-up[b]		
	Re-baseline (Day -10 to Day -1)[c]	V1	V2	V3	V4	V5		End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up
		W1 Day 1	W4 Day 22	W7 Day 43	W10 Day 64	W13 Day 85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (±5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
CCI											
Randomization[f]	X										
Dosing											
Pretreatment		X	X	X	X	X	3 weeks				
Chemotherapy administration		X	X	X	X	X	3 weeks				

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CR = complete response; CT = computed tomography; ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; IMP = investigational medicinal product; ICF = informed consent form; CCI PD = progressive disease; CCI PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; W = week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b All subjects will have an EOT visit within 7 days after the decision to discontinue study 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 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±1 week], and after 12 months every 12 weeks [±1 week]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further anti-cancer therapy). The survival follow-up will continue until 5 years after the last subject receives the last dose of trial drug (see Section 7.1.5 for details).

c Subjects who discontinue treatment due to any reason during the Re-baseline period and before randomization will have an EOT visit within 7 days of the decision to discontinue chemotherapy and a 30-day Safety Follow-up visit in accordance with the Induction Phase Schedule of Assessments.

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

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

f Enrollment and randomization into the Maintenance Phase will be done after the confirmation of fulfilling all inclusion criteria (Section 5.3.1) without matching any exclusion criteria (Section 5.3.2).

g The physical examination will occur every 3 weeks until Week 13, and every 6 weeks thereafter.

h The dose of chemotherapy will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration.

i If the Re-baseline ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1.

j Subject-reported outcomes / quality of life assessments should be completed by subjects prior to any study-related procedures at the indicated visits. The assessments should be conducted at Re-baseline; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

k Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

l Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

m A full urinalysis is required at the End-of-Treatment visit and the Re-baseline visit and a basic urinalysis at all other indicated visits (see Table 12 for details).

n β-hCG should be determined from either urine or serum sample. Results of the most recent pregnancy test has to be available prior to next dosing.

o Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase (see Table 11)

CCI [redacted]

Table 4 Schedule of Assessments –Maintenance Phase and Follow-Up - Oxaliplatin + 5-Fluorouracil (5-FU)

		Maintenance Phase (-4/+2 days)[a]								End of Treatment	Follow-up[b]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up
	Re-baseline (Day -10 to Day -1)[c]	W1 Day 1	W3 Day 15	W5 Day 29	W7 Day 43	W9 Day 57	W11 Day 71	W13 Day 85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
Study Procedures													
Review of eligibility criteria[f]	X												
Physical examination[g]	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs	X	X	X	X	X	X	X	X	2 weeks	X	X		
Weight[h]	X	X	X	X	X	X	X	X	2 weeks	X	X		
ECOG PS[i]	X	X	X	X	X	X	X	X	2 weeks	X	X		
12-lead ECG	X									X			
Subject-reported outcomes / quality of life assessments[j]	X	X[j]	X		X			X	6 weeks	X	X		
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit												
Anti-cancer therapy[b]											X	X	X
AE collection	AEs are collected through the 30-day Safety Follow-up Visit; Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call[b]											X	
SAE collection	All SAEs are documented until the 90-day Safety Follow-up Phone Call, Ongoing SAEs at the 90-day Safety Follow-up Call will be followed [b]											X	
Samples and Laboratory Assessments													
Hematology and hemostaseology[k]	X	X	X	X	X	X	X	X	2 weeks	X	X		
Full serum chemistry[l]	X									X	X		
Core serum chemistry[l]		X	X	X	X	X	X	X	2 weeks				
Urinalysis[m]	X	X			X			X	12 weeks	X	X		
β-hCG pregnancy test[n]	X	X		X		X		X	4 weeks	X	X		

Document No. CCI [redacted]
Object No. CCI [redacted]

		Maintenance Phase (-4/+2 days)[a]								End of Treatment	Follow-up[b]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up
	Re-baseline (Day -10 to Day -1)[c]	W1 Day 1	W3 Day 15	W5 Day 29	W7 Day 43	W9 Day 57	W11 Day 71	W13 Day 85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
T_4 and TSH	X				X			X	6 weeks	X	X		
Cardiac troponin[o]	X	X	X	X	X	X	X	X					
CCI													
Response Assessments													
CCI													
Randomization[r]	X												
Dosing													
Pretreatment		X	X	X	X	X	X	X	2 weeks				
Chemotherapy administration		X	X	X	X	X	X	X	2 weeks				

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CR = complete response; CT = computed tomography; ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; IMP = investigational medicinal product; ICF = informed consent form; CCI ; PD = progressive disease; CCI PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; W = week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b All subjects will have an EOT visit within 7 days after the decision to discontinue study 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 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±1 week], and after 12 months, every 12 weeks [±1 week]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further anti-cancer therapy). The survival follow-up will continue until 5 years after the last subject receives the last dose of trial drug (see Section 7.1.5 for details).

c Subjects who discontinue treatment due to any reason during the Re-baseline period and before randomization will have an EOT visit within 7 days of the decision to discontinue chemotherapy and a 30-day Safety Follow-up visit in accordance with the Induction Phase Schedule of Assessments.

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

e 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 any new therapy.

f Enrollment and randomization into the Maintenance Phase will be done after the confirmation of fulfilling all inclusion criteria (Section 5.3.1) without matching any exclusion criteria (Section 5.3.2).

g The physical examination will occur every 2 weeks until Week 13, and every 6 weeks thereafter.

h The dose of chemotherapy will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration.

i If the Re-baseline ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1.

j Subject-reported outcomes / quality of life assessments should be completed by subjects prior to any study-related procedures at the indicated visits. The assessments should be conducted at Re-baseline; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

k Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

l Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

m A full urinalysis is required at the End-of-Treatment visit and the Re-baseline visit and a basic urinalysis at all other indicated visits (see Table 12 for details).

n β-hCG should be determined from either urine or serum sample. Results of the most recent pregnancy test need to be available prior to next dosing.

o Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase (see Table 11).

[redacted]

Table 5 Schedule of Assessments: Maintenance Phase and Follow-Up - Best Supportive Care Only

	Re-baseline (Day -10 to Day -1)[c]	Treatment Phase (-4/+2 days)[a]						End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5					
		W1	W4	W7	W10	W13					
		D1	D22	D43	D64	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
Study Procedures											
Review eligibility criteria[f]	X										
Physical examination[g]	X	X	X	X	X	X	6 weeks	X	X		
Vital signs	X	X	X	X	X	X	3 weeks	X	X		
Weight[h]	X	X	X	X	X	X	3 weeks	X	X		
ECOG PS[i]	X	X	X	X	X	X	3 weeks	X	X		
12-lead ECG	X							X			
Subject-reported outcomes / quality of life assessments[j]	X	X[j]	X	X		X	6 weeks	X	X		
Anti-cancer therapy[b]									X	X	X
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit										
AE collection	AEs are collected through the Safety Follow-up Visit; Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call[b]									X	
SAE collection	All SAEs are documented until the 90-day Safety Follow-up Phone Call, Ongoing SAEs at the 90-day Safety Follow-up Call will be followed[b]									X	
Samples and Laboratory Assessments											
Hematology and hemostaseology[k]	X	X	X	X	X	X	3 weeks	X	X		
Full serum chemistry[l]	X							X	X		
Core serum chemistry[l]		X	X	X	X	X	3 weeks				
Urinalysis[m]	X	X		X		X	12 weeks	X	X		
B-hCG pregnancy test[n]	X										
T_4 and TSH	X			X		X	6 weeks	X	X		
Cardiac troponin[o]	X	X	X	X	X	X					

	Re-baseline (Day -10 to Day -1)[c]	Treatment Phase (-4/+2 days)[a]						End-of-Treatment Visit	Safety Follow-up		Long-term Follow-up[b]
		V1	V2	V3	V4	V5					
		W1	W4	W7	W10	W13					
		D1	D22	D43	D64	D85	Until Progression	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
CCI											
Randomization[r]	X										

AE = adverse event, β-hCG = β-human chorionic gonadotropin, CR = complete response, CT = computed tomography, D = Day, ECG = electrocardiogram, EOT = end of treatment; ECOG-PS = Eastern Cooperative Oncology Group Performance Status, ICF = informed consent form, IMP = investigational medicinal product, CCI PD = progressive disease, CCI, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors version 1.1, SAE = serious adverse event, SD = stable disease, T_4 = free thyroxine, TSH = thyroid stimulating hormone, V = visit, W = Week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b All subjects will have an EOT visit within 7 days after the decision to discontinue study 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 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±1 week], and after 12 months every 12 weeks [±1 week]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further anti-cancer therapy). The survival follow-up will continue until 5 years after the last subject receives the last dose of trial drug (see Section 7.1.5 for details).

c Subjects who discontinue treatment due to any reason during the Re-baseline period and before randomization will have an EOT visit within 7 days of the decision to discontinue chemotherapy and a 30-day Safety Follow-up visit in accordance with the Induction Phase Schedule of Assessments.

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

e 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.

f Enrollment and randomization into the Maintenance Phase will be done after the confirmation of fulfilling all inclusion criteria (Section 5.3.1) without matching any exclusion criteria (Section 5.3.2).

g The physical examination will occur every 3 weeks until Week 13, and every 6 weeks thereafter.

h The dose of BSC will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration.

i If the Re-baseline ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1.

j Subject-reported outcomes / quality of life assessments should be completed by subjects prior to any study-related procedures at the indicated visits. The assessments should be conducted at Re-baseline; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

k Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

l Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

m A full urinalysis is required at the End-of-Treatment visit and the Re-baseline visit and a basic urinalysis at all other indicated visits (see Table 12 for details).

n β-hCG should be determined from either urine or serum sample. Results of the most recent pregnancy test needs to be available prior to next dosing.

o Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase see Table 11).

[redacted]

Table 6 Schedule of Assessments – Maintenance Phase and Follow-up – Avelumab

	Avelumab Treatment (-4/+2 days)[a]									End of Treatment	Follow-up[b]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up
	Re-baseline (Day -10 to Day -1)[c]	W1 Day 1	W3 Day 15	W5 Day 29	W7 Day 43	W9 Day 57	W11 Day 71	W13 Day 85	Until Progres-sion	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
Study Procedures													
Eligibility criteria[f]	X												
Physical examination[g]	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs	X	X	X	X	X	X	X	X	2 weeks	X	X		
Weight[h]	X	X	X	X	X	X	X	X	2 weeks	X	X		
ECOG PS[i]	X	X	X	X	X	X	X	X	2 weeks	X	X		
12-lead ECG	X									X			
Subject-reported outcomes / quality of life assessments[j]	X	X[j]	X		X			X	6 weeks	X	X		
Anti-cancer therapy[b]											X	X	X
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit												
AE collection	AEs are collected through the Safety Follow-up Visit Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call[b]											X	
SAE collection	All SAEs are documented until the 90-day Safety Follow-up Phone Call, Ongoing SAEs at the 90-day Safety Follow-up Call will be followed[b]											X	
Samples and Laboratory Assessments													
Hematology and hemostaseology[k]	X	X	X	X	X	X	X	X	2 weeks	X	X		
Full serum chemistry[l]	X									X	X		
Core serum chemistry[l]		X	X	X	X	X	X	X	2 weeks				
Urinalysis[m]	X	X			X			X	12 weeks	X	X		

	Avelumab Treatment (-4/+2 days)[a]								End of Treatment	Follow-up[b]		
		V1	V2	V3	V4	V5	V6	V7	End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up
	Re-baseline (Day -10 to Day -1)[c]	W1 Day 1	W3 Day 15	W5 Day 29	W7 Day 43	W9 Day 57	W11 Day 71	W13 Day 85	Within 7 Days of Decision to Discontinue Treatment[d]	Visit 30 Days after Last Treatment (± 5 days)[e]	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks after Last Treatment (± 2 week)
β-hCG pregnancy test[n]	X	X		X		X		X	4 weeks	X	X		
T_4 and TSH	X				X			X	6 weeks	X	X		
Cardiac troponin[o]	X	X	X	X	X	X	X	X					
Response Assessments													
CCI													
Randomization[r]	X												
Dosing													
Pretreatment[s]		X	X	X	X	X	X	X	2 weeks				
Avelumab[s,t]		X	X	X	X	X	X	X	2 weeks				

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CR = complete response; CT = computed tomography; ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; IMP = investigational medicinal product CCI ; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; W = week.

a A time window of up to 4 days before or 2 days after the scheduled Day 1 visit (-4 / +2 days) will be permitted for all trial procedures for the Day 1 visit of each cycle. Subjects should also return to the trial site as per local institutional practice for any additional routine assessments during chemotherapy.

b All subjects will have an EOT visit within 7 days after the decision to discontinue study 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 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±1 week], and after 12 months, every 12 weeks [±1 week]) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further anti-cancer therapy). The survival follow-up will continue until 5 years after the last subject receives the last dose of trial drug (see Section 7.1.5 for details).

c Subjects who discontinue treatment due to any reason during the Re-baseline period and before randomization will have an EOT visit within 7 days of the decision to discontinue chemotherapy and a 30-day Safety Follow-up visit in accordance with the Induction Phase Schedule of Assessments.

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

e 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.

f Enrollment and randomization into the Maintenance Phase will be done after the confirmation of fulfilling all inclusion criteria (Section 5.3.1) without matching any exclusion criteria (Section 5.3.2).

g The physical examination will occur every 2 weeks until Week 13, and every 6 weeks thereafter.

h 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.

i If the Re-baseline ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1.

j Subject-reported outcomes / quality of life assessments should be completed by subjects prior to any study-related procedures at the indicated visits. The assessments should be conducted at Re-baseline; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

k Hematology (including Complete Blood Count) and hemostaseology assessments are detailed in Table 12. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1). Complete blood count results must also be available and reviewed prior to dose administration.

l Full chemistry and core serum chemistry samples are detailed in Table 12. Samples for chemistry results must be available and reviewed prior to dose administration.

m A full urinalysis is required at the End-of-Treatment visit and the Re-baseline visit and a basic urinalysis at all other indicated visits (see Table 12 for details).

n β-hCG should be determined from either urine or serum sample. Results of the most recent pregnancy test needs to be available prior to next dosing.

o Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase. (See Table 11)

[redacted]

s Premedicate patients with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. 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 and has to be recorded as concomitant medication.

t Subjects will receive avelumab as long as ECOG PS remains stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms. Subjects receiving avelumab will remain on-treatment until PD. Subjects who have experienced initial disease progression may continue treatment with avelumab if the following criteria are met: Investigator believes that the subject will experience clinical benefit from the treatment; there is no unacceptable toxicity resulting from the treatment; the subject's ECOG PS is stable (PS = 0 or 1); and treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression.

Table 7 **Schedule of Assessments – CCI , CCI , and CCI Sampling during Maintenance and Open-label Treatment Phases (Avelumab arm only)**

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CCI ; EOT = end of treatment; Hrs = hours; CCI ; PK = pharmacokinetics; V = visit; W = Week.

a. Subjects completing the last cycle of the Induction Phase will enter the Re-baseline period prior to Day 1 of the Maintenance Phase.

b. 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.

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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) PPD (formerly PPD PPD 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) maintained by PPD. The IPMP will be prepared by the PPD Clinical Project Manager in cooperation with other PPD Operational Team Leads.

2.1 Investigational Sites

The trial will be conducted at approximately 230 sites in North America, South America, Asia Pacific, and Europe, with approximately 47 sites in the USA.

2.2 Trial Coordination / Monitoring

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

The Clinical Trial Supplies department of the Sponsor will supply the trial medication of avelumab. Packaging and distribution of clinical supplies will be performed by the Clinical Trial Supplies department of the Sponsor. First-line chemotherapy will be supplied by the study center or by the Sponsor, according to local laws and regulations.

Subject enrollment will be managed by an interactive web response system (IWRS). The Coordinating Investigator PPD epresents 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 sign-off of the clinical trial protocol.

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.

CCI CCI and CCI 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 Research & Development Quality Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the CCI data analyses), which will be outsourced to a CRO. The trial will appear in the following clinical trial registry: ClinicalTrials.gov

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 Radiologist

An independent radiologist verifies and confirms eligibility to enter the Maintenance Phase.

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 (Stewart 2014). Of these cancers, approximately 90% to 95% were adenocarcinomas with the remaining 5% to 10% comprising of 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 (Globocan 2012).

Chemotherapy is routinely used to treat metastatic gastric cancer; however, there is no single standard regimen that is used globally. Common chemotherapy agents used to treat gastric cancer, either as monotherapy or in combination, include the following: fluorouracil (5-FU) and other fluoropyrimidines (eg, capecitabine, S1), carmustine, semustine and doxorubicin, mitomycin C, cisplatin, oxaliplatin, taxanes, and irinotecan. The relative benefits of these different drugs, alone and in combination, are unclear (NCCN 2015). Recently, trastuzumab has become available for use with chemotherapy for the treatment of patients whose tumors overexpress the human epidermal growth factor receptor 2 gene (Hudis 2007). Despite the availability of these agents, advanced, unresectable, and/or metastatic gastric cancer remains a significant unmet medical need.

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 (Dong 1999; Dong 2002; Freeman 2000; Topalian 2012a), potentially providing an immune-tolerant environment for tumor development and growth. CCI [redacted]

In the clinical setting, treatment with antibodies that block the PD-1 – anti-PD-L1 interaction have been reported to produce objective response rates (ORR) of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles (Hamid 2013; Brahmer 2012; Topalian 2012b). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients. Recent studies have documented the activity of anti-PD-L1 antibodies in subjects with advanced gastric cancer (Muro 2014; Lutzky 2014).

3.3 Avelumab

The investigational medicinal product (IMP) for the present trial is avelumab. Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-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 (Latchman 2001). For complete details of the in vitro and nonclinical trials, please refer to the 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 (Oki 2014) 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 trials for avelumab are described in the IB. Avelumab is currently in clinical development with 2 ongoing Phase I trials in subjects with solid tumors, one ongoing Phase II trial in Merkel cell carcinoma (MCC), and 2 Phase III trials in non-small cell lung cancer (NSCLC). Of the ongoing studies, 2 of these studies have cohorts of patients with advanced gastric cancer:

- Trial EMR100070-001 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 EMR100070-002 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, EMR100070-007, another Phase III study in patients with advanced gastric cancer (EMR100070-008) is ongoing for third-line 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 from data of more than 1,750 subjects, including all subjects treated with 10 mg/kg from studies EMR100070-001 (1,650 subjects) and EMR100070-003 Part A (88 subjects as pooled safety dataset with a data cut-off of 09 June 2016) and subjects in the ongoing local Japanese Phase I 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 antibodies 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-Barre syndrome, uveitis]) have been identified as important risks for avelumab (please see current IB for details). Detailed guidelines for the management of immune-related AEs and infusion-related reactions have been implemented in the study protocols, including this one (please see Section 3.5, Section 5.1.2.2.1, Section 5.1.3.2, Section 6.2.1, Section 6.4, Section 6.5.4, Section 6.5.5, and Section 6.12).

3.3.2 Pharmacokinetic Results

Draft PK assessments have been performed in ongoing Trials EMR100070-001 and EMR100070-002. The preliminary results based on the data available as of 19 December 2014 are presented under the individual trial headings.


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3.4 Rationale for the Current Clinical Trial

The safety and clinical efficacy of avelumab have been determined in multiple tumor types (NSCLC, ovarian cancer, mesothelioma, melanoma, thymoma, and adrenocorticocarcinoma) (Disis 2015, Gulley 2015). The rationale to enroll subjects with unresectable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction (GEJ) 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 (Lutzky 2014).
- 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 (Muro 2014).

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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. 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).

To mitigate the risk of infusion-related reactions, premedicate patients with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. 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 (ADCC), there is a potential risk of tumor lysis syndrome (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 ORR of 7% to 38% in patients with advanced or metastatic solid tumors, with response durations of 1 year or more for the majority of patients.

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 objectives of this trial are to demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to Overall Survival (OS) in all randomized subjects or in PD-L1+ subjects who have not progressed on first-line chemotherapy.

4.2 Secondary Objectives

Secondary objectives are as follows:

- To demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to PFS as per RECIST v1.1 according to Investigator assessment.
- To demonstrate superiority of maintenance therapy with avelumab versus continuation of first-line chemotherapy with regard to the ORR as per RECIST v1.1 and per Investigator assessment
- To compare the subject-reported outcomes / quality of life (QoL) of subjects when treated with avelumab versus continuation of first-line chemotherapy as assessed by the European QoL 5-dimensions 5 Level 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.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, international, randomized, open-label Phase III trial comparing maintenance therapy with avelumab with continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the GEJ (See Sections 5.1.2.1 and 5.1.2.2 for details).

The medicinal products oxaliplatin, 5-FU and capecitabine are used as chemotherapy agents in the Induction Phase and the Maintenance Phase of this trial. All three substances are accepted as standard of treatment for the indication under study. Before administering any of these substances, the Investigator is required to refer to what is stated in the 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, patient 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 oxaliplatin, 5-FU, or capecitabine, the local label always prevails. Investigators should check updated labeling via relevant websites before enrollment, randomization, and chemotherapy administration in the Induction Phase and the Maintenance Phase.

This study is conducted with a Screening period and an Induction Phase, Maintenance Phase, and Follow-up Phase.

5.1.1 Overall Design

Approximately 466 subjects are planned to be enrolled in the Maintenance Phase. The actual number of subjects enrolled in the Induction Phase will be driven by observed induction failure rates and will be such to allow for approximately 466 patients to be randomized in the Maintenance Phase. At the time of this protocol amendment, subject enrollment in the Maintenance Phase is complete, with 499 subjects randomized into the Maintenance Phase. Subjects enrolled in the Induction Phase will receive a first-line therapy comprised of oxaliplatin and either 5-FU or capecitabine (Induction Phase) for 12 weeks (see Section 5.1.2.1).

Following the Induction Phase, subjects who experience a CR, PR, or SD after 12 weeks (approximately 466 subjects) will be randomly assigned (Maintenance Phase) to receive either avelumab (see Section 5.1.2.2.1) or continuation of the same regimen of chemotherapy from the Induction Phase (see Section 5.1.2.2.2). Subjects who are not deemed eligible to receive further chemotherapy will receive best supportive care (BSC) alone with no active therapy.

Prior to randomization, Investigators must specify which of treatments (continuation of the same regimen of chemotherapy from the Induction Phase versus BSC) will be selected for subjects in chemotherapy control arm.

CCI [redacted] After the Induction Phase, all subjects will be evaluated for eligibility into the Maintenance Phase by an independent radiologist using RECIST v1.1.

Study treatment will continue until:

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

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

- Investigator-assessed clinical benefit, without any rapid disease progression
- Tolerance of trial treatment
- Stable Eastern Cooperative Oncology Group (ECOG) performance status (PS) (PS = 0 or 1)
- 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 avelumab treatment beyond progression should be discussed with the Medical Monitor and documented in the study records.

For subjects continuing avelumab after initial progressive disease (PD), 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, 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 restart, 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 3).

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 increase in tumor burden of 20% and ≥ 5 mm absolute increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions.

Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months or until disease progression or unacceptable toxicity, after confirmation of response. 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 after agreement with the Medical Monitor. To be eligible for retreatment, 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 follow the Schedule of Assessments until disease progression (see Table 3).

Subjects receiving maintenance chemotherapy will receive trial treatment until PD per RECIST version 1.1, for the accepted maximal duration of the agent(s) selected, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled.

On-study subject management and study endpoint evaluation will be based on Investigator assessments (see Section 7.3).

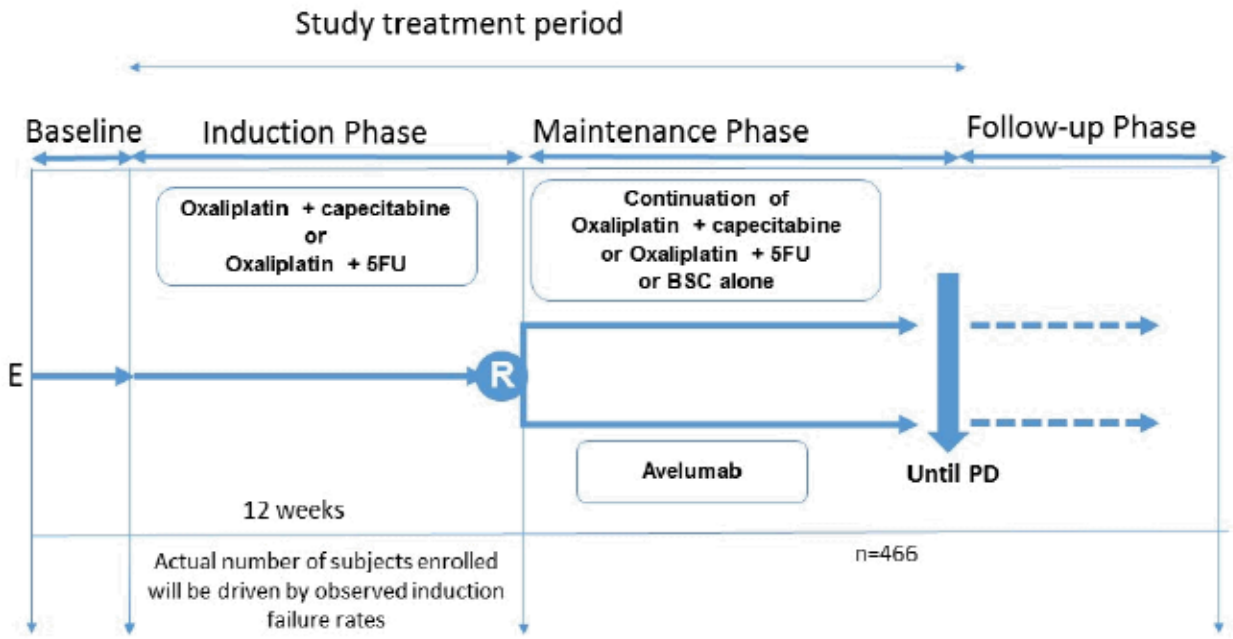
Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments (see Section 7.1).

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. The primary endpoint OS will be tested in all randomized subjects (intent-to-treat [ITT] Analysis Set) and in PD-L1+ subjects (PD-L1+ Analysis Set). The PD-L1 expression status will be determined according to the conventional tumor-cell (cell number-based percentage) scoring method where subjects with PD-L1 tumor expression ≥ 1% are considered to be PD-L1+.

Safety endpoints include AEs, assessed throughout the trial and evaluated using the NCI-CTCAE v4.03; physical examinations; clinical laboratory assessments; concomitant medications; vital signs; electrocardiogram (ECG) parameters; and ECOG PS.

The trial design schematic is presented in Figure 1.

Figure 1 **Schematic of Trial Design**



All subjects in both arms will receive BSC as background therapy as specified in Section 6.1.4.
BSC=best supportive care; 5-FU=5-fluorouracil; n=number of subjects; PD=progressive disease.

5.1.2 Trial treatment Administration and Schedule

The trial Schedule of Assessments are presented in Table 1 to Table 7.

5.1.2.1 Induction Chemotherapy

Subjects enrolled in this trial will start with a 12-week chemotherapy Induction Phase comprised of oxaliplatin and either 5-FU or capecitabine (according to the dosing schedule in Section 6.2.2 and Table 1 and Table 2 or in accordance to the label instructions and per local guidelines).

- Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 200 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1, given every 2 weeks (for up to 12 weeks, Table 2).

  OR

  Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 400 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Days 1 and 2) given every 2 weeks (for up to 12 weeks)

  OR

- Oxaliplatin at 130 mg/m^2 IV on Day 1 with capecitabine at 1000 mg/m^2, twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks (for up to 12 weeks, Table 1).

Local label and guidelines should be followed for specific starting doses due to renal or hepatic impairments and for subsequent dose modifications due to different toxicities.

Subjects who experience a CR, PR, or SD after 12 weeks will be randomly assigned to either avelumab or continue the same regimen of chemotherapy from the Induction Phase. Subjects who demonstrate a response during the Induction Phase that renders their measurable disease no longer measurable at the time of the Maintenance Phase can be randomized.

5.1.2.2 Maintenance Therapy

5.1.2.2.1 Avelumab Arm

Subjects randomly assigned to the avelumab arm will receive IV infusion of avelumab (10 mg/kg over 1 hour) once every 2 weeks (see Table 6).

To mitigate infusion-related reactions, premedicate patients with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. 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 Section 6.1.2, Section 6.1.1 and Section 6.6, respectively.

5.1.2.2.2 Chemotherapy Arm

Subjects randomly assigned to the maintenance chemotherapy arm will receive first-line chemotherapy according to the dosing schedule (see Section 6.2 and Table 3 to Table 4) or in accordance to the label instructions and per local guidelines) until disease progression, unacceptable toxicity, for the accepted maximal duration of the agent(s) selected, or any of the criteria for withdrawal from trial treatment is fulfilled (Section 5.5).

The dose and schedule during the Maintenance Phase are as follows:

Subjects randomly assigned to chemotherapy will continue the same regimen of oxaliplatin-fluoropyrimidine doublet as they received during the Induction Phase until disease progression.

- Subjects who are not deemed eligible to receive further chemotherapy will receive BSC alone with no active therapy. Prior to randomization, Investigators must specify BSC treatment for these subjects (see Table 5)

- For subjects receiving chemotherapy (oxaliplatin + 5-FU or oxaliplatin + capecitabine), dose modifications after the starting dose are allowed if the continuation of the oxaliplatin-fluoropyrimidine doublet, or a component thereof, is prohibited by toxicity. For subjects intolerant to further oxaliplatin, single-agent capecitabine or 5-FU + leucovorin will be an option for dose modification.

Additionally, in order to reduce the incidence and severity of nausea and vomiting as well as the severity of hypersensitivity reactions, subjects will be administered pretreatment prior to each therapy infusion per local institutional practice.

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 Section 5.1.3.2 and Section 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 ($\leq$ 6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management
  - Transient ($\leq$ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade $\leq$ 1
  - Single laboratory values out of normal range (excluding Grade $\geq$ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate
  - Grade 3 skin toxicity
  - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
  - Change in ECOG PS to $\geq$ 3 that resolves to $\leq$ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is $\geq$ 3 on the day of trial treatment administration).
  - Asymptomatic Grade $\geq$ 3 lipase or amylase elevation not associated with clinical manifestations of pancreatitis. Medical Monitor must be consulted for such lipase and amylase abnormalities.
- Any Grade 2 ADR should be managed as follows:
  - If a Grade 2 ADR resolves to Grade $\leq$ 1 by the last day of the current cycle, treatment may continue.
  - If a Grade 2 ADR does not resolve to Grade $\leq$ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with an avelumab ADR (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
  - Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

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

5.1.3.3 Dose Modification for Chemotherapy

During the Induction Phase, dose modifications (dose delays and dose changes) for toxicity after the starting dose are allowed and should be made in accordance with labeling instructions and local institutional guidelines. Subjects on chemotherapy in the Maintenance Phase will continue with the same dose they had at the end of the Induction Phase (starting dose or reduced dose). During the Maintenance Phase, dose modifications are also allowed for toxicity.

The dose of chemotherapy will be calculated based on the weight or body surface area, as applicable, of the subject determined within 72 hours prior to the day of drug administration (see Table 9).

Dose modification guidelines (dose delays and dose changes) after the starting dose for chemotherapy are provided in Table 8. For specific starting doses due to renal or hepatic impairment and for subsequent dose modifications due to different toxicities, please follow the local label and guidelines.

For subjects intolerant to further oxaliplatin, single-agent capecitabine or 5-FU + leucovorin will be an option for dose modification.

Table 8 Dose Modification General Guidelines for Chemotherapy

Maintenance Therapy	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
5-FU (2600 mg/m^2 dose over 24 hours)	1950 mg/m^2 - 2080 mg/m^2 over 24 hours	1300 mg/m^2 (1560 mg/m^2 over 24 hours)	Discontinue
5-FU (2400 mg/m^2 dose) over 46-48 hours	1800 mg/m^2 - 1920 mg/m^2 over 46-48 hours	1200 mg/m^2 -1440 mg/m^2 over 46-48 hours	Discontinue
Capecitabine	75% of starting dose	50% of starting dose	Discontinue
Oxaliplatin (85 mg/m^2 dose)	64 to 68 mg/m^2 in accordance with local label/institutional guidelines	42.5 mg/m^2 in accordance with local label/institutional guidelines	Discontinue
Oxaliplatin (130 mg/m^2 dose)	98 to 104 mg/m^2 in accordance with local label/institutional guidelines	65 mg/m^2 in accordance with local label/institutional guidelines	Discontinue

5-FU=5-fluorouracil

5.2 Discussion of Trial Design

5.2.1 Rationale Supporting the Choice of the First-line Chemotherapy

There is no consensus on what should be the optimal first-line chemotherapy for the management of advanced gastric cancer. A platinum fluoropyrimidine doublet is considered as an acceptable option by the National Comprehensive Cancer Network (NCCN), ESMO, and Japanese guidelines for the management of that disease (Waddell 2013). In the proposed study, all subjects will receive a platinum fluoropyrimidine doublet consisting of capecitabine or 5-FU and oxaliplatin. Subjects whose disease is at least stable will be randomly assigned to receive either avelumab (active arm) or will, per the judgment of the Investigator, receive subsequent cycles of the initial chemotherapy regimen until unacceptable toxicities or disease progression.

The administration of oxaliplatin and capecitabine or 5-FU as a first-line regimen for the treatment of advanced gastric cancer is acceptable for the following reasons:

- Study REAL-2 (Cunningham 2008) demonstrated that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively in patients with previously untreated gastric cancer. In terms of safety, oxaliplatin administration resulted in lower incidence of Grade 3 and 4 neutropenia, renal toxicity and thromboembolism but to slightly higher incidence of Grade 3 and 4 diarrhea and neuropathy. The safety profiles of 5-FU and capecitabine were similar.
- Capecitabine or 5-FU in combination with a platinum-based antineoplastic agent (cisplatin) was the chemotherapy backbone used in the TOGA study that supported the approval of trastuzumab for patients with gastric cancer with human epidermal growth factor receptor 2 positive (HER2+) disease.

- Oxaliplatin triggers a particular type of apoptotic deaths that is considered to be immunogenic and was preferred to cisplatin for the platinum component of the required chemotherapy doublet (Tesniere 2010).
- To have only oxaliplatin as the platinum salt will limit the risk of having a confounding factor on the primary endpoints as REAL-2 did not completely rule-out that cisplatin and oxaliplatin had exactly the same clinical efficacy.

5.2.2 Rationale for Exclusion of HER2 Positive Population

Subjects with human epidermal growth factor receptor 2-positive disease are excluded from this trial. This rationale for excluding these subjects is that the current standard of care (SOC) for HER2 positive subjects is different than HER2 negative subjects and would require addition of trastuzumab to the induction chemotherapy choices. Inclusion of HER2 positive subjects would also result in an additional option for maintenance therapy and thus result in greater subject heterogeneity.

5.2.3 Rationale for Switching Subjects from Chemotherapy to Avelumab

The proposal to switch subjects assigned to the experimental arm after they have completed 12 weeks of chemotherapy is appropriate for the following reasons:

- There is no data supporting that additional chemotherapy beyond 4 to 6 cycles (up to 12 weeks of treatment) will result in improved survival in the context of a disease where it is common practice to re-induce patients at the time of disease progression. Patients who have not responded to or who will cease to respond to avelumab will be re-induced either with platinum-based doublets or with drugs that have shown clinical benefit as a second-line therapy. Subjects will be monitored every 6 weeks and rescue therapy may be administered once disease progression is established.
- Treatment of patients with avelumab has resulted in an ORR of 15% in patients with gastric cancer from Asian and non-Asian regions. Some of these responses were long lasting and a number of subjects with prolonged SD were also observed. Based on these data, it is reasonable to interrupt chemotherapy after 12 weeks to initiate an immunotherapy that has been reported to induce prolonged responses in advanced gastric cancer patients who will ultimately progress after initial chemotherapy regimens.
- For subjects randomly assigned to receive additional chemotherapy in the Maintenance Phase, it is recommended that the chemotherapy regimen does not to exceed 6 cycles. This is supported by the previously established regimen in the registration study for trastuzumab (TOGA). In conclusion, switching subjects after 12 weeks of chemotherapy to receive avelumab treatment is considered appropriate.

5.2.4 Justification of Open-label Study Design

The open-label study design is justified based on the following:

Double-blind controlled study would be impossible due to differences in treatment schedule and toxicity profile that would unmask treatment assignment.

5.2.5 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.

Overall survival in PD-L1+ subjects was chosen as one of the primary objectives based on results from the EMR100070-001, Phase Ib, gastric primary cohort. In the group of GC/GEJC subjects who did not progress on or after first-line chemotherapy, a difference in median OS of 4.3 months was observed in subjects with PD-L1 tumor cells ≥ 1% compared to the overall subjects.

5.2.6 Trial Periods

The study will consist of (i) Screening/baseline evaluation, (ii) induction, (iii) maintenance, and (iv) post-treatment follow-up period.

i) During Screening/baseline (Day -28 to Day 1), informed consent will be obtained and subject compliance with the inclusion/exclusion criteria will be ascertained.

ii) During the Induction Phase, subjects will receive 4 cycles of chemotherapy comprised of oxaliplatin and capecitabine every 3 weeks OR 6 cycles of chemotherapy comprised of oxaliplatin and 5-FU every 2 weeks.

Induction Chemotherapy:

Subjects enrolled in this trial will receive chemotherapy comprised of oxaliplatin and either 5-FU or capecitabine. Subjects who experience a CR, PR, or SD after 12 weeks will be randomly assigned to either avelumab or continuation of the same first-line chemotherapy they received during the Induction Phase. Subjects who demonstrate a response during the Induction Phase that renders their measurable disease no longer measurable at the time of the Maintenance Phase can be randomized.

iii) During the Maintenance Phase, subjects will be randomly assigned to receive either avelumab or continuation of the same chemotherapy regimen from the Induction Phase, until disease progression, unacceptable toxicity, or for the accepted maximal duration of the agent(s) selected.

Maintenance Avelumab Arm:

Subjects receiving avelumab will continue on-treatment until disease progression or unacceptable toxicity. Subjects receiving avelumab during the Maintenance Phase may continue treatment past the initial determination of disease progression according to RECIST v1.1 if they meet the criteria presented in Section 6.2.1 (Investigator-assessed benefit; tolerance of treatment; stable ECOG PS; and does not delay other imminent intervention).

Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months or until disease progression or unacceptable toxicity, after confirmation of response.

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 after agreement with the Medical Monitor. In order to be eligible for retreatment, 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.

Maintenance Chemotherapy Arm:

Maintenance chemotherapy will continue until disease progression or unacceptable toxicity or until the maximum acceptable dosing is achieved at the discretion of the Investigator.

Subjects who are not deemed eligible to receive further chemotherapy will receive BSC alone with no active therapy until disease progression. Prior to randomization, Investigators must specify BSC treatment for these subjects.

iv) The Follow-up Phase will include a post-treatment period and long-term follow-up visits. During the post-treatment period (from treatment discontinuation to Safety Follow-up), a Safety Follow-up visit will be scheduled 30 days after last treatment and a phone call will occur 90 days after treatment discontinuation.

A long-term follow-up visit will occur every 12 weeks for 5 years after the last subject receives the last dose of study drug (see Section 7.1.7 for details).

During Screening, induction, maintenance and post-treatment periods, subject will undergo visits and assessment procedures as per described in the Schedule of Assessments (Table 1 to Table 7).

5.2.7 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

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. Has read, understood and signed written informed consent before any trial-related procedure is undertaken that is not part of the standard subject management
2. Male or female subjects aged ≥ 18 years
3. Availability of a recently-obtained (within 6 months) biopsy from a non-irradiated area, formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue or a minimum

number of 10 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression assessment.

4. Disease must be measurable per RECIST v1.1
5. Subjects with histologically confirmed unresectable locally advanced or metastatic adenocarcinoma of the stomach or GEJ
6. ECOG PS of 0 to 1 at trial entry
7. Estimated life expectancy of more than 12 weeks
8. Adequate hematological function defined by white blood cell (WBC) count $\geq 2.5 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/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) range 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 ≥ 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 postmenopausal for at least 2 years, are surgically sterile, or are sexually inactive."
12. Highly effective contraception (ie, 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 Guidance on Contraception 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 oxaliplatin, 5-FU or capecitabine for subjects receiving chemotherapy [in the Induction Phase and the Maintenance Phase], 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 (CTLA-4)
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. Prior chemotherapy for unresectable locally advanced or metastatic adenocarcinoma of the stomach or GEJ
4. Tumor shown to be HER2+ by immunohistochemistry (IHC $\geq$ 3+) and/or by fluorescence in situ hybridization (FISH) (IHC 2+, FISH +)
5. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of enrollment and/or if the subject has not fully recovered from the surgery within 4 weeks of enrollment
6. 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 $\leq$10 mg prednisone daily). Note: 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 $\leq$ 10 mg per day of equivalent prednisone
7. 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)
8. 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 (eg, bladder, cervical, colorectal, breast)
9. Prior organ transplantation, including allogeneic stem-cell transplantation
10. Significant acute or chronic infections including, among others:
    a. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
    b. Positive test for HBV surface antigen and / or confirmatory HCV ribonucleic acid (RNA) test if the anti-HCV antibody test is positive.
    c. Active tuberculosis (TB) (history of exposure or history of positive TB test; plus presence of clinical symptoms, physical or radiographic findings)
11. 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 $\leq$ 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

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)
13. Persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v 4.03 except alopecia
14. Neuropathy Grade ≥ 3.
15. Pregnancy or lactation
16. Known alcohol or drug abuse
17. History of uncontrolled intercurrent illness including but not limited to:

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

    b. Uncontrolled active infection, or

    c. Uncontrolled diabetes (eg, hemoglobin A1c ≥ 8%)

18. Clinically significant (ie, 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 [QTc] prolongation of > 470 ms and/or pacemaker) or prior diagnosis of congenital long QT syndrome
19. 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
20. Any psychiatric condition that would prohibit the understanding or rendering of informed consent and that would limit compliance with study requirements
21. Vaccination with live or live/attenuated viruses within 55 days (5 half-lives x 127 hours + 30 days) of first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines)
22. Legal incapacity or limited legal capacity
23. Patients will be excluded from the Induction Phase and the Maintenance Phase if administration of their chemotherapy would be inconsistent with the current local labeling (SmPC) (eg, in regard to contraindications, warnings/precautions or special provisions) for that chemotherapy. Investigators should check updated labeling via relevant websites at the time of entry into the Induction Phase and the Maintenance Phase.

5.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria without matching any exclusion criterion.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

Subjects will be withdrawn from trial treatment during the Induction and/or Maintenance Phase for any of the following reasons:

- Subjects meeting the definition of PD while on-treatment based on RECIST v1.1. Subjects in the Maintenance Phase receiving avelumab who experience disease progression may continue treatment with avelumab if they meet the criteria presented in Section 6.2.1 (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 the 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 $\geq$ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.1.3.2 for subjects receiving avelumab.
- Occurrence of AEs, resulting in the discontinuation of the trial drug being desired or considered necessary by the Investigator and / or the subject
- Occurrence of pregnancy
- Use of a nonpermitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the trial drug
- Noncompliance (see Section 6.9).

For subjects receiving avelumab, 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 restart, the subject will be allowed to continue receiving avelumab as long as they meet the criteria for continuation of treatment beyond progression. For more information, see Section 6.2.1.

Subjects who withdraw from trial therapy will continue to be followed for survival and new anti-cancer therapies. The survival follow-up of all subjects will continue until 5 years after the last subject receives the last dose of avelumab. Under some circumstances, the subjects may not be

followed for 5 years for survival in this study, eg, the subjects may be offered to enroll into a roll-over study, or the Sponsor may terminate the study early.

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 7.1.5), 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 and survival follow-up, which includes the collection of data on survival, subject-reported outcomes/QoL questionnaires, and subsequent anticancer therapy.

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 (see Section 7.1.7).

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 drug, for example, due to:
  - Evidence of inefficacy of the trial drug
  - 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 CCI *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 IMP
- After the interim analysis, the IDMC declares superior efficacy in the avelumab treatment arm compared with those randomly assigned to continue on first-line chemotherapy and recommends that the trial be stopped early.

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 survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab.

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 investigational drug is avelumab and the comparator is a chemotherapy regimen administered after randomization.

6.1 Description of the Investigational Medicinal Product

6.1.1 Induction Chemotherapy

Subjects will receive an oxaliplatin-fluoropyrimidine doublet comprised of oxaliplatin and either 5-FU or capecitabine during the Induction Phase, whichever is approved and used as the SOC at the Investigator's institution.

- Oxaliplatin is a sterile lyophilized powder or concentrate for solution for infusion intended for infusion, and is slightly soluble in water. The molecular weight of oxaliplatin is 397.2858 g/mol
- 5-FU is a sterile solution intended for IV administration. It is a white to practically white crystalline powder which is sparingly soluble in water. The molecular weight of fluorouracil is 130.08 kDa.
- Capecitabine is a white to off-white crystalline powder supplied as a tablet formulation intended for oral administration. Tablets should be swallowed with water within 30 minutes after a meal. The molecular weight of capecitabine is 359.35 g/mol.

6.1.2 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.

6.1.3 Maintenance Chemotherapy

Subjects will continue the same regimen of oxaliplatin-fluoropyrimidine doublet as in the Induction Phase (see Section 6.1.1).

6.1.4 Best Supportive Care

All subjects in both arms will receive BSC as background therapy. Subjects who are not deemed eligible to receive further chemotherapy will receive BSC alone with no active therapy. There is no universal definition of BSC that can be applied across institutions, countries, or regions (Zafar 2008). 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), stents for dysphagia, and focal external-beam radiation for control of pain, cough, dyspnea, or bleeding" (Jassem 2008). Best supportive care will be administered per institutional guidelines and can be administered without any additional therapy.

6.2 Dosage and Administration

6.2.1 Avelumab Dosage and Administration

Subjects 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 5.1.2.2.1 (Table 3). 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.

CCI [redacted]

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

- Investigator-assessed clinical benefit, without any rapid disease progression
- 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 avelumab treatment beyond progression should be discussed with the Medical Monitor and documented in the trial records.

For subjects continuing avelumab after initial PD, 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, 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 restart, 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 3).

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 increase in tumor burden of 20% and ≥ 5 mm absolute increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions or the development of new measurable lesions.

New lesions are considered measureable 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 measureable 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 who have experienced a CR should be treated for a minimum of 12 months and/or until disease progression or unacceptable toxicity, after confirmation of response. 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 after agreement with the Medical Monitor. To be eligible for retreatment, 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 follow the Schedule of Assessments until disease progression (see Table 3).

6.2.2 Chemotherapy Dosage and Administration

Induction chemotherapy will be administered according to the following rules.

Therapy will be administered at the dose and schedule shown in Table 1 and Table 2 or in accordance to the label instructions and per local guidelines. The dosing frequency is summarized below:

- Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 200 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1, given every 2 weeks (for up to 12 weeks),

  OR

Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 400 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Days 1 and 2) given every 2 weeks (for up to 12 weeks)

OR

- Oxaliplatin at 130 mg/m^2 IV on Day 1 with capecitabine at 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks (for up to 12 weeks).

Local label and guidelines should be followed for specific starting doses due to renal or hepatic impairments and for subsequent dose modifications due to different toxicities.

Chemotherapy during Maintenance Phase will be administered according to the following rules:

- Subjects will receive continuation of the same regimen of oxaliplatin-fluoropyrimidine doublet as in the Induction Phase.
- Subjects who are not deemed eligible to receive further chemotherapy will receive BSC alone with no active therapy. Prior to randomization, Investigators must specify BSC treatment for these subjects.
- For subjects receiving chemotherapy (oxaliplatin + 5-FU or oxaliplatin + capecitabine), dose modifications after the starting dose are allowed if the continuation of the oxaliplatin-fluoropyrimidine doublet, or a component thereof, is prohibited by toxicity. For subjects intolerant to further oxaliplatin, single-agent capecitabine or 5-FU + leucovorin will be an option for dose modification.

Therapy will be administered until disease progression, or unacceptable toxicity, or for the accepted maximal duration of the agent(s) selected.

Therapy will be stopped after the first on-treatment radiological evaluation of disease progression.

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

Table 9 Allowed Therapy Regimens

Product Description	Dosage Form	Dose	Dosing Frequency
5-fluorouracil (5-FU)	Intravenous (IV)	Leucovorin 200 mg/m^2 followed by 5-FU 2600 mg/m^2	On Day 1 every 2 weeks.
		Leucovorin 400 mg/m^2 followed by 5-FU 400 mg/m^2 intravenous push (IVP) followed by 2400 mg/m^2 IV	Leucovorin on Day 1 5-FU IVP on Day 1 5-FU IV over 46-48 hours on Day 1 and Day 2
Capecitabine	Tablet	1000 mg/m^2	Twice daily for 2 weeks followed by a 1-week rest period, given in 3-week cycles
Oxaliplatin	Intravenous (IV)	85 mg/m^2 with 5-FU	On Day 1 every 2 weeks
		130 mg/m^2 with capecitabine	On Day 1 every 3 weeks. Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

6.3 Assignment to Treatment Groups

Once the subject has provided a signed informed consent form (ICF) and meets inclusion and exclusion criteria, and has completed the Induction Phase as specified in this protocol, the Investigator or delegate will request the trial treatment assignment using the IWRS. Qualified subjects will be randomly assigned in a 1:1 ratio to receive either avelumab or maintenance chemotherapy. The trial is fully controlled by the IWRS, which assigns treatment individual (unique) kit numbers for each subject. The kit number is linked via the Good Manufacturing Practice qualified system to the corresponding treatment as well as to the subject.

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

Subjects randomly assigned to receive avelumab will receive pretreatment as described in Section 5.1.2.2.1.

Subjects randomly assigned to receive maintenance chemotherapy 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 anaphylactic 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. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications (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 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 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.

Palliative bone-directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST v1.1 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.

Medicinal products known to prolong the QTc must be used with caution in subjects receiving oxaliplatin.

Bisphosphonate or denosumab treatment is allowed during the study provided that they are administered as concomitant palliative and supportive care for disease-related symptoms. Disease

progression should be completely ruled out and the exact reason for the use of these therapies must clearly be documented.

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 within 28 days before starting study treatment.

* 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 steroids (that is, for allergic reactions or the management of irAEs is allowed)
- Growth factors for subjects randomly assigned to receive avelumab (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: erythropoietin and darbepoetin alpha may be prescribed at the Investigator's discretion.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Sponsor may be contacted to discuss whether the trial treatment must be discontinued). The subject should complete the End of Treatment visit (Section 7.1.5) and be followed for survival according to Section 7.1.6.

Medications other than those specifically excluded in this trial (see above) may be administered for the management of symptoms associated with the administration of avelumab or maintenance chemotherapy as required. These might include analgesics, anti-nausea medications, antihistamines, diuretics, antianxiety 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 randomly assigned to the avelumab arm must be observed in an area with resuscitation equipment and emergency agents. At all times during avelumab or maintenance chemotherapy 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 tumor lysis syndrome according to the NCI are as outlined in Section 6.5.4.1, Section 6.5.4.2, and Section 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. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like antinuclear antibodies or antineutrophil cytoplasmic antibodies. 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 10.

Table 10 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade v4.03	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.
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, 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. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

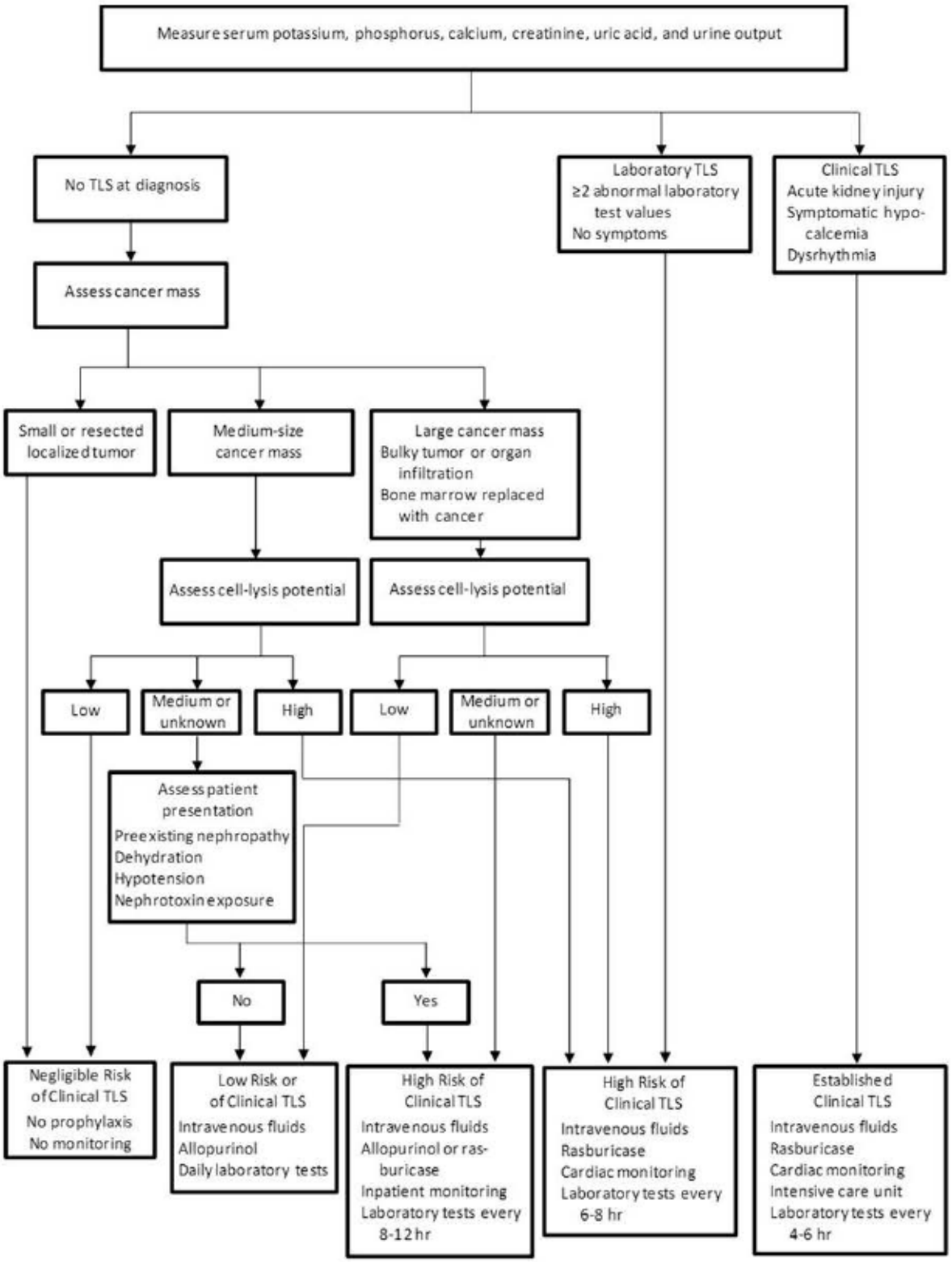
Symptoms include impaired airway, decreased oxygen saturation (< 92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Subjects should be placed on monitor immediately, and the intensive care unit should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

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti-inflammatory drug dose (eg, 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 (eg, paracetamol/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 ADCC, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm (Figure 2) published by Howard (2011).

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 11.

Table 11 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 (eg, 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 activities of daily living (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 5 mg/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 Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 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 Grades 3 to 4
Grades 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	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

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If not improving after 2 weeks or worsening or for recurrent Grade 2: 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 × ULN and/or total bilirubin > ULN to 1.5 × ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grades 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × 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 × ULN and/or total bilirubin > 3 × 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 increase 1.5 x baseline or Creatinine increased > ULN to 1.5 × 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 x baseline and ≤ 6 × ULN or Creatinine > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤ 1: 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 × 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 (eg, troponin, CK-muscle/brain, 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-related myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, restart avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

Immune-related 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 (eg, azathioprine, cyclosporine A)
* Local guidelines, or eg, European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association 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 (ie, 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 (ie, 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 (ie, subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone): • 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:** • 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.	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.
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 restarting 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	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BNP=B-type natriuretic peptide, CK =creatine kinase, CT=computed tomography, FSH=follicle-stimulating hormone, GH=growth hormone, IGF-1=insulin-like growth factor 1, irAE=immune-related adverse event, IV=intravenous, LH=luteinizing hormone, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, PRL=prolactin, 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 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.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Avelumab will be packed in boxes each containing 1 vial. The information on the trial treatment will be in accordance with approved submission documents.

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Oxaliplatin, 5-FU, and capecitabine, will be supplied by the study center or by the Sponsor, according to local laws and regulations.

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 CCI to CCI 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 CCI or at elevated temperatures CCI 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 IPMP.

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.

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 maintenance chemotherapy, including reconciliation 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. 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 re-analyzed 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 study treatment administration for nonmedical reasons (see Section 5.5.1). If 1 study treatment administration is missed and the interval between the subsequent treatment and the last study treatment visit 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 ≥ 10% 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.

For all maintenance 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 SOC and generally accepted medical practice and depending on the subject's individual medical needs.

Upon withdrawal from trial treatment, subjects may receive the type of care they and their physicians agree upon. Subjects will be followed for survival and AEs as specified in Section 7.1.6.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments for the Screening period and the Induction Phase is provided in Table 1 and Table 2, for the Maintenance and Follow-up Phase in Table 3 to Table 6, and for CCI

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. 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 ethnicity) and the complete medical history, including the history of gastric cancer, previous and ongoing medications, and baseline medical condition (the information of concomitant medications and AEs and SAEs 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 (Table 1 and Table 2). The QoL questionnaires will be administered and completed by the subjects at baseline to collect baseline data about their health-related QoL.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation). Free thyroxine (T_4) and thyroid-stimulating hormone (TSH) will also be assessed at Screening for all subjects. The baseline CCI

During Screening, a serum β-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for females of childbearing potential (may be analyzed locally). HER2 testing (per local guidelines), blood HBV and HCV may be analyzed locally for all Screening subjects as these conditions are trial entry exclusion criteria (see Section 5.3.2). HBV surface antigen and anti-HCV tests must be performed at Screening to exclude subjects with hepatitis infection. If the anti-HCV

test is positive, the infection must be confirmed by an HCV RNA test. Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [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) as well as tumor markers or any other established methods (see Section 7.2.5 for details). A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to entering the Induction Phase. A bone scan should be done at Screening as clinically indicated.

Subjects are required to provide tumor tissue samples; see Section 7.6.1 for details. Tumor tissue collection will be done of a recently-obtained biopsy within 6 months from a non-irradiated area, FFPE block containing tumor tissue or a minimum number of 10 (preferably 25) unstained tumor slides suitable for PD-L1 expression assessment (cut within 1 week). 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 shall be permitted to participate in the protocol provided they meet all other inclusion criteria and no exclusion criteria. It is recommended that multiple biopsy samples should be collected, as feasible, for biomarker assessment to minimize inaccuracies in assessment due to tumor heterogeneity. The site pathologist shall review the Hematoxylin and Eosin stains when more than one FFPE block from a subject has been received. If from a resection specimen, the block that maximizes tumor content and tumor cell preservation should be tested by the central laboratory. If from biopsy specimen(s), all available tumor-containing blocks representing up to a maximum of 6 distinct biopsies, should be sent to the central laboratory as feasible.

The blood samples for baseline CCI [redacted], and CCI [redacted] as well as for CCI assessments (optional) will be collected before or on Day 1 before trial treatment starts for subjects randomly assigned to receive avelumab.

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7.1.2 Induction Phase Treatment Period

In this trial, the treatment will be given until PD, 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).

Treatment during the Induction Phase will consist of:

- 6 cycles of oxaliplatin (85 mg/m^2 IV on Day 1 every 2 weeks) + leucovorin (200 mg/m^2 IV on Day 1 every 2 weeks or equivalent levoleucovorin dose) followed by 5-FU (2600 mg/m^2 IV continuous infusion over 24 hours on Day 1 every 2 weeks,

OR

Oxaliplatin at 85 mg/m^2 IV on Day 1 with leucovorin 400 mg/m^2 IV on Day 1 (or equivalent levoleucovorin dose) followed by 5-FU at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Days 1 and 2) given every 2 weeks (for up to 12 weeks).

OR

- 4 cycles of Oxaliplatin (130 mg/m^2 IV on Day 1 every 3 weeks) + Capecitabine (1000 mg/m^2 PO twice daily on Days 1-14). Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

All the laboratory samples and vital signs will be collected prior to each drug administration. Administration of chemotherapy will take place only after relevant results have been checked by a medically qualified person and criteria for dosing have been met.

During the treatment period, the following assessments and procedures will be performed (see Table 1 and Table 2 for the detailed schedule):

- SAEs, AEs and concomitant medications and procedures will be documented at each trial visit.
- ECOG PS will be assessed at Day 1 of each treatment cycle (Screening ECOG PS may be used for Cycle 1 Day 1 if it was performed within 3 days prior to Day 1).
- Physical examinations will be performed on Day 1 of each treatment cycle. Such examinations will include a comprehensive skin examination for tumor.
- Vital signs and body weight will be assessed at each visit.
- Body weight will be assessed at Day 1 of each cycle.
- The laboratory hematology and hemostaseology, will be assessed on Day 1 of each cycle. Core serum chemistry tests will be assessed at Day 1 of each cycle. A full urinalysis will be performed at Screening and the End-of-treatment visit. Subjects should also return to the site as per local institutional practice for any additional routine assessments during chemotherapy.
- A urine or serum β-hCG pregnancy test will be performed every 4 weeks during the treatment cycle (before chemotherapy administration) for females of childbearing potential.

7.1.3 Randomization/Re-baseline

At the end of 12 weeks of Induction Phase, subjects enter a 10-day Re-baseline period and the following assessments and procedures will be performed (see Table 3 to Table 6 for detailed schedule):

- Review of eligibility criteria
- The subject-reported outcomes / QoL assessments will be completed by subjects prior to any other trial-related procedures.
- AEs and concomitant medications and procedures
- ECOG PS
- 12-lead ECG
- Physical examination, including a comprehensive skin examination for tumor
- Vital signs and body weight
- Laboratory hematology, hemostaseology, full serum chemistry (including core chemistry) and full urinalysis
- Urine or serum β-hCG pregnancy test for females of childbearing potential
- Free T_4 and TSH

CCI

- Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase.

Cardiac troponin levels will be evaluated centrally. Local laboratories may be used at the discretion of the Investigator as clinically needed for safety management/treatment decision of the subject. Measurement of cardiac troponin T (cTnT) is preferred, however cardiac troponin I (cTnI) may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured at the Re-baseline visit should be measured consistently throughout the study in each patient. At the Re-baseline visit, clinically significant positive results should be further assessed as per local SOC to rule-out concurrent cardiac conditions which would make the patient ineligible for the study as per exclusion criteria. During the study, clinically significant new elevations suggestive of myocarditis should be assessed as per Table 11. Additional tests should also be performed when clinically indicated.

Subjects who progress during the Induction Phase or who are determined to have PD during the Re-baseline period will be discontinued from the trial.

Subjects without PD will be randomly assigned to receive maintenance treatment with either avelumab or continuation of the same regimen of chemotherapy from the Induction Phase. Subjects who demonstrate a response during the Induction Phase that renders their measurable disease no longer measurable at the time of the Maintenance Phase can be randomized.

Subjects who discontinue treatment due to any reason during the Re-baseline period and before randomization will have an end of treatment (EOT) visit within 7 days of the decision to discontinue chemotherapy and a 30-day Safety Follow-up visit in accordance with the Induction Phase Schedule of Assessments.

7.1.4 Maintenance Phase Treatment Period

In the Maintenance Phase, subjects will receive trial treatment (avelumab or continuation of the regimen of chemotherapy from the Induction Phase) until PD, for the accepted maximal duration of the agent(s) selected, unacceptable toxicity, or any criterion for withdrawal from trial drug is fulfilled (see Section 5.5).

The CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1. Subjects receiving avelumab may continue treatment past the initial determination of disease progression according to RECIST v1.1 if they meet the criteria presented in Section 6.2.1 (Investigator-assessed benefit; tolerance of treatment; stable ECOG PS; and does not delay other imminent intervention).

The decision to continue avelumab treatment beyond progression should be discussed with the Medical Monitor and documented in the study records.

For subjects continuing avelumab after initial PD, 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, 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 restart, 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 3).

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

increase in tumor burden of 20% and ≥ 5 mm absolute increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions or the development of new measurable lesions.

Additionally, subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months or until disease progression or unacceptable toxicity, after confirmation of response. 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 after agreement with the Medical Monitor. In order to be eligible for retreatment, 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 follow the Schedule of Assessments until disease progression (see Table 3).

The treatment should start within 4 days after randomization. While on trial treatment, subjects will be asked to visit the trial site as specified in the Schedule of Assessments (see Table 3, Table 4, Table 5, and Table 6).

For both avelumab and maintenance chemotherapy, a time window of up to 4 days before or 2 day after the scheduled visit day (-4/ +2 days) will be permitted for all trial procedures. Subjects should return to the target date even if the previous visit was off schedule.

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 avelumab and maintenance chemotherapy.

Subjects will receive either:

- Avelumab by IV infusion following pretreatment (see Section 5.1.2.2.1) once every 2 weeks (see Section 6.2.1), or
- Maintenance chemotherapy following pretreatment as applicable prior to each infusion (see Section 6.2.2).

Assessments to be performed during the Maintenance Phase are presented in Table 3 to Table 6.

During the treatment period, the following assessments and procedures will be performed (see Table 3 to Table 6 for the detailed schedule):

- The subject-reported outcomes/QoL assessments will be completed by subjects prior to any trial-related procedures (time points outlined in Table 3 to Table 6) and then every 6 weeks thereafter.
- AEs and concomitant medications and procedures will be documented at each visit.
- ECOG PS will be assessed at each treatment visit.

- Physical examinations will be performed through Week 13 or while the subject is on-treatment. After Week 13, the physical examination will occur every 6 weeks. Such examinations will include a comprehensive skin examination for tumor.

- Vital signs and body weight will be assessed in each treatment visit.

- The laboratory hematology, hemostaseology will be assessed at each visit.

- Serum chemistry tests will be assessed as follows:

    - Full serum chemistry at Re-baseline for all subjects

    - Core serum chemistry:

        - Subjects on the avelumab arm: Week 1, Week 3, Week 5, Week 7, Week 9, Week 11, Week 13, and every 2 weeks thereafter.

        - Subjects on BSC-only with no active therapy: Week 1, Week 4, Week 7, Week 10, Week 13, and every 3 weeks thereafter.

        - Subjects on the chemotherapy doublet arm receiving oxaliplatin + capecitabine on Week 1, Week 4, Week 7, Week 10, Week 13 and every 3 weeks thereafter.

        - Subjects on the chemotherapy doublet arm receiving oxaliplatin + 5-FU on Week 1, Week 3, Week 5, Week 7, Week 9, Week 11, Week 13, and every 2 weeks thereafter.

- A basic urinalysis (dipstick) will be at Week 1, Week 7, Week 13, and every 12 weeks thereafter. If the basic urinalysis is abnormal, a full urinalysis should be performed.

- A urine or serum β-hCG pregnancy test will be performed at the visits indicated in the Assessment Schedules (for females of childbearing potential).

- Blood samples for PK determinations will be collected from all subjects in the avelumab arm on or before Day 1 (Week 1) prior to the first administration of study drug, within 2 hours prior to each trial drug administration at Weeks 3, 5, 7 (every 2 weeks), at Weeks 13, 19, and 25 (every 6 weeks), and then at 12-week intervals while on-treatment up to Week 109 (2 years from randomization). Post-trial drug administration samples will be collected at the end of infusion (within 15 minutes) at Weeks 1, 7, and 25. Samples will be collected at the End-of-Treatment visit and the 30-day Safety Follow-up visit, except for subjects still on trial treatment beyond Week 109.

[redacted]

- Trial drug infusion at each trial visit (once every 2 or 3 weeks).
- Premedication as described in Section 5.1.2.2.1
- Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase.

Cardiac troponin levels will be evaluated centrally. Local laboratories may be used at the discretion of the Investigator as clinically needed for safety management/treatment decision of the subject. Measurement of cTnT is preferred, however cTnI may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured at the Re-baseline visit should be measured consistently throughout the study in each patient. At the Re-baseline visit, clinically significant positive results should be further assessed as per local SOC to rule-out concurrent cardiac conditions which would make the patient ineligible for the study as per exclusion criteria. During the study, clinically significant new elevations suggestive of myocarditis should be assessed as per Table 11. Additional tests should also be performed when clinically indicated.

7.1.5 End of Treatment

Subjects must undergo an End-of-Treatment visit after discontinuation of IMP for any reason. 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. See Table 1 through Table 7 for the assessments to be performed.

All AEs will be collected up until the 30-Day Safety Follow-up visit.

At the End-of-Treatment visit, the following assessments will be performed:

- Documentation of AEs and concomitant medication and procedures
- Physical examination, including vital signs, and body weight
- 12-lead ECGs
- Laboratory hematology, hemostaseology, full serum chemistry, pregnancy test, and full urinalysis.
- T_4 and TSH
- ECOG PS

CCI

7.1.6 Safety Follow-up Visit

All subjects will have a subsequent visit scheduled 30 days (± 5 days) after the last administration of trial drug, and will be contacted by phone 90 days (± 1 week) after the last administration of trial drug.

The visit will include the following full assessment of safety parameters (see Table 3 to Table 6):

- The subject-reported outcomes / QoL assessments will be completed by subjects prior to any trial-related procedures
- Documentation of AEs and concomitant medication and procedures
- ECOG PS
- Physical examination including vital signs, body weight, and skin tumor extent
- The laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis (dipstick plus microscopic evaluation). If the basic urinalysis is abnormal, a full urinalysis should be performed.
- A urine β-hCG pregnancy test (in females of childbearing potential) will be conducted.
- T_4 and TSH levels

CCI

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 by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to

follow-up". 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. All subjects will be contacted by phone 90 days after the last administration of trial drug to collect information on new or ongoing SAEs and treatment-related non-serious AEs.

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

7.1.7 Long-term Follow-up

All SAEs ongoing at the 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."

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

Subjects without PD according to RECIST v1.1 at the End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±1 week], and after 12 months, every 12 weeks [±1 week] using the same procedures and review as while on-treatment) until PD.

Subjects will be followed quarterly (that is, every 12 weeks, ± 2 weeks) for survival (including assessment of any new tumor therapy). The survival follow-up of subjects will continue until 5 years after the last subject receives the last dose of avelumab. Under some circumstances, the subjects may not be followed for 5 years for survival in this study, eg, the subjects may be offered to enroll into a roll-over study, or the Sponsor may terminate the study early.

7.1.8 Blood Draws for Clinical Assessments

The overall amount of blood to be drawn from a single subject with a body weight ≥ 70 kg (154 lbs) must not exceed 60 mL/day and 200 mL in an 8-week period for safety laboratory testing, pregnancy testing, CCI [redacted]

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 (gender), race, and ethnicity.

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;
- Smoking history;
- Current cancer signs and symptoms and side effects from current and previous anticancer treatments; and
- 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 Vital Signs and Physical Examination

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, in general, appearance, dermatological, head/neck, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system, extremities, eyes [inspection and vision control], nose, throat, and neurologic status) will be performed and the results documented.

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).

Body weight and height will be recorded.

7.2.6 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 determination of disease progression will be evaluated per Investigator assessment, which will determine whether the criteria for tumor response or progression according to RECIST v1.1 have been met, as well as determine the time point overall response and date of disease progression according to RECIST v1.1 for each subject.

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 (except for brain scans, unless clinically indicated). 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.

A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to entering the Induction Phase. Brain CT / MRI scans should be performed after Screening, if clinically indicated by development of new specific symptoms. A bone scan should be done as clinically indicated at Screening and beyond. 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 Schedule of Assessments (see Table 1).

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

The CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1.

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

- To assess ORR, 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 non-target lesions as described in RECIST v1.1.

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, but no sooner than 4 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. 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 restart, 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 Schedule of Assessments (Table 1 and Table 5).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

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.

Adverse Drug Reaction

Adverse Drug Reactions are defined in this study as any AE suspected to be related to study treatment by the Investigator and/or Sponsor.

Serious Adverse Events

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.

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the patient's general condition is more severe than expected and/or unless the outcome is fatal within the adverse event reporting period (as defined in Section 7.4.1.3).

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. However, if adverse signs or symptoms occur in association with disease progression, then these should be recorded as 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.

Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE and infusion-related reactions 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 in Section 7.4.1.3) 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 study's Safety Follow-up Phone Call, defined as 90 days (±1 week) after the last IMP.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose-Limiting Toxicities

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum 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, a SAE Report Form 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. After this 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 (eg, 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 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 that are detailed in the Schedule of Assessments (see Table 1 to Table 7) must be collected, and sent to the central laboratory for analysis. Serum β-hCG pregnancy tests may be analyzed locally.

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

Urinalysis and urine pregnancy testing will be done locally.

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

In the case of liver function test (LFT) elevations (AST, ALT and/or total bilirubin) requiring additional lab draws (according to guidelines set forth in Table 11 Management of irAEs), an unscheduled lab draw should be sent to the central laboratory for analysis.

Cardiac troponin levels will be collected from Re-baseline up to 12 weeks in the Maintenance Phase. Cardiac troponin levels will be evaluated centrally. Local laboratories may be used at the discretion of the Investigator as clinically needed for safety management/treatment decision of the subject. Measurement of cTnT is preferred, however cTnI may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured at the Re-baseline visit should be measured consistently throughout the study in each patient. At the Re-baseline visit, clinically significant positive results should be further assessed as per local SOC to rule-out concurrent cardiac conditions which would make the patient ineligible for the study as per exclusion criteria. During the study, clinically significant new elevations suggestive of myocarditis should be assessed as per Table 11. Additional tests should also be performed when clinically indicated.

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 12 will be taken from nonfasted subjects during the Screening Phase (28 days prior to entering the Induction Phase); during the Treatment Phase as specified in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6; at the End-of-Treatment visit; and at the Safety Follow-up visit. The T_4, TSH, and urinalysis will only be assessed at the time points defined in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. If confirmation of a subject's postmenopausal status is necessary, an FSH level will also be performed at Screening, see Section 7.1.

Table 12 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	Reticulocytes
Chloride	Creatinine	MCH
Cholesterol	Glucose	Mean corpuscular volume
Creatine kinase	LDH	MCHC
Creatinine	Lipase	
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		

Full Chemistry	Core Chemistry[a]	Hematology
Total bilirubin		Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening, Re-baseline, and End of Treatment visits and a basic urinalysis prior to each administration of the trial treatment at Week 1, Week 7, Week 13, every 12 weeks thereafter, and at 30-day Safety Follow-up visit.
Total protein		
Uric acid		Totality of binding CCI
Triglycerides		
		TSH and T_4
Hormone		
FSH (yes/no if applicable)		

CCI , 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, T_4=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, 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 Schedule of Assessments and the results documented in the eCRF. 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 Schedule of Assessments and documented in the eCRF. Height will be measured at Screening only.

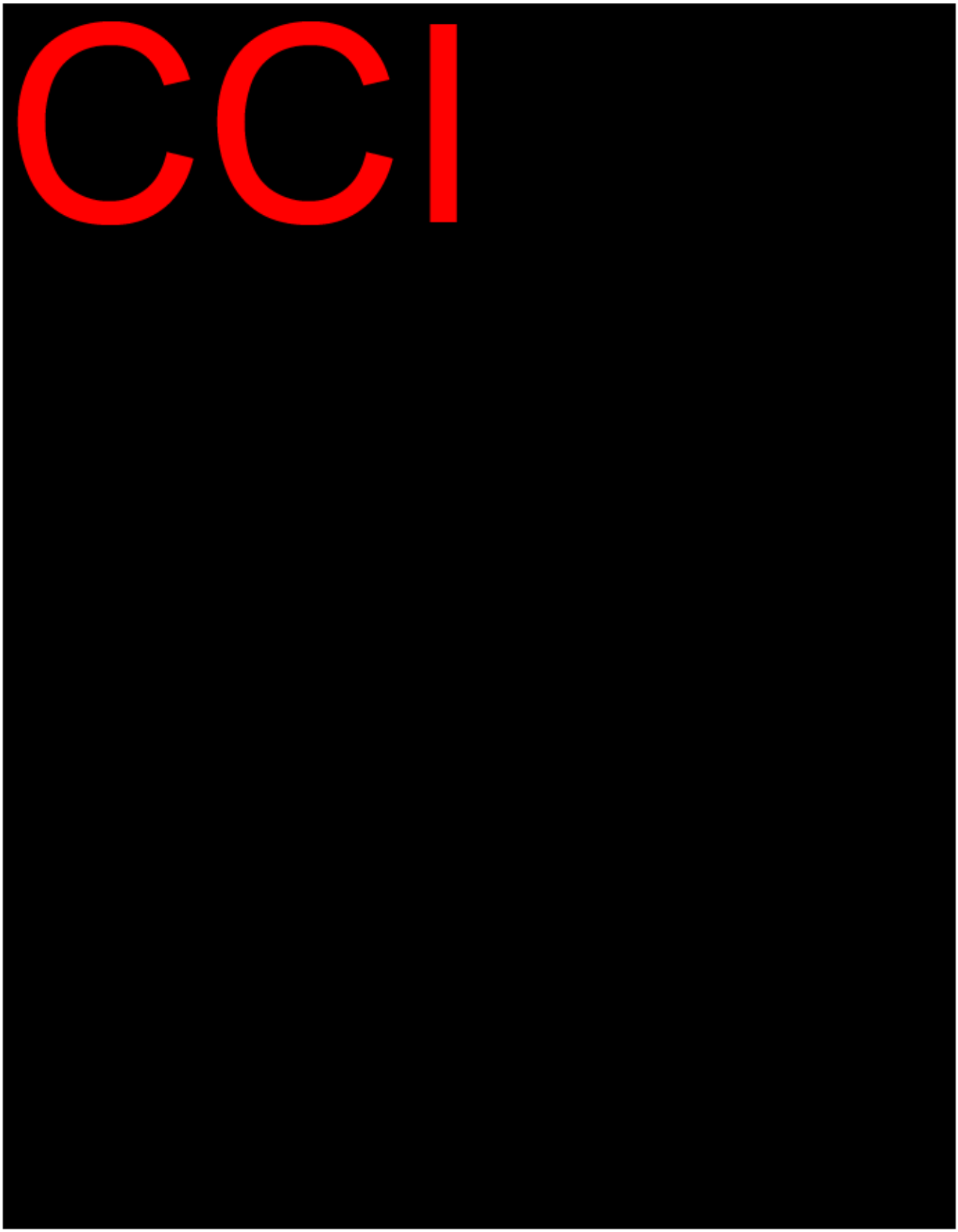
A 12-lead ECG will be recorded as indicated in the Schedule of Assessments.

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. A urine or serum β-hCG test will be performed at the visits as indicated in the Schedules of Assessments. Results of the most recent pregnancy test has to be available prior to the next dosing of trial treatment. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and FSH > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

7.5.1 Body Fluid(s)

Whole blood sufficient to provide 0.2 mL of serum will be collected for CCI [redacted]. Further details will be summarized in the Laboratory Manual.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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 Screening and as indicated while on trial treatment (see Table 1 to Table 6 for detailed schedule for each regimen). Subject-reported outcomes will also be assessed at the Discontinuation/End of Treatment visit and the Safety Follow-up visit (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 will use a validated electronic tablet or validated site pad to record their responses to these questionnaires. In rare and extenuating circumstances when an electronic tablet or site pad is not available or not working properly, collection on validated paper questionnaires may be allowed to ensure data are collected and not lost.

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 study is based on comparing maintenance therapy avelumab versus continuation of first-line chemotherapy in terms of the two primary hypotheses (for hierarchy of multiple testing procedure, see Section 8.5.1) of OS in all randomized subjects and in PD-L1+ subjects.

The study will be considered successful if at least one of the two null hypotheses for OS in either all randomized subjects or in PD-L1+ subjects, could be rejected as statistically significant. An imbalanced type I error allocation will be used for the two primary hypotheses and control overall family wise type I error rate at 2.5% (1-sided) with 0.5% (1-sided) allocated to PD-L1+ subjects and 2% (1-sided) allocated to all randomized subjects. The sample size for this study is driven by the following assumptions for the primary endpoint of OS:

- Exponential distribution of OS;
- 1:1 randomization;
- Drop-out rate = 5%;
- Uniform accrual over a period of 18 months;
- A follow-up time of 18 months after randomization of the last subject;

- For all randomized subjects receiving avelumab, median OS is 15 months;
- For PD-L1+ subjects receiving avelumab, the median OS is 19.3 months;
- For all randomized subjects and PD-L1+ subjects receiving first-line chemotherapy, the median OS is 10.5 months.

This corresponds to a hazard ratio (HR) of 0.7 for OS in all randomized subjects and 0.54 for OS in PD-L1+ subjects. At planning stage, it was assumed that the prevalence of PD-L1+ subjects in all randomized subjects is 35%. Due to a lower prevalence of PD-L1+ subjects in the study than initially expected, the targeted 112 OS events in PD-L1+ subjects for the primary analysis will not be reached during the study. The primary analysis of OS in PD-L1+ subjects will be conducted at the time of the primary analysis of OS in all randomized subjects with power less than 80%.

The assumed drop-out rate for OS is based on respective experience in previous clinical studies.

The actual number of subjects enrolled in the Induction Phase will be driven by the observed induction failure rates, and will be such to allow for approximately 466 subjects to be randomized into the treatment arm in the Maintenance Phase. At the time of this protocol amendment, subject enrollment into the Maintenance Phase is complete, with a total of 499 subjects randomized into the Maintenance Phase.

The data cut-off for the primary analysis will take place on a prospectively-determined date, upon which the target number of 356 OS events in all randomized subjects are projected to have been reached, and the last subject randomized in the Maintenance Phase has been followed for at least 18 months from randomization.

For OS in all randomized subjects, 356 OS events are required to achieve 90% power of the log-rank test at a 1-sided overall 2% alpha level. This calculation includes one interim efficacy analysis and assumes it will be performed after 75% of events have been observed. The interim and primary analyses will follow a sequential alpha spending function approach developed by Lan and DeMets, using an O'Brien and Fleming boundary function. Applying this approach with an assumed 267 and 356 observed events respectively, a 1-sided significance level of 0.0072 for the interim analysis and 0.0178 for the final analysis will preserve an overall type I error rate of 2% for the OS in all randomized subjects.

The simulations with the above assumptions have been performed to assess the overall power for the target number of OS events and timing of interim and primary analyses. The correlation between test statistics for OS in all randomized subjects and OS in PD-L1+ subjects (square root of prevalence $=\sqrt{0.35}$) has been considered. The complete multiple testing procedure for the two OS hypotheses (details of multiple testing procedure are in Section 8.5.1) using the interim test statistics for all randomized subjects and test statistics for all randomized subjects and PD-L1+ subjects at primary analysis have been applied in the simulations. If exactly 356 OS events in all randomized subjects and 112 OS events in PD-L1+ subjects are reached, the simulations showed a probability of rejection at least one hypothesis of 93.5%. The null hypothesis of OS in all randomized subjects is rejected in around 90.9% of the simulations, the null hypothesis of OS in PD-L1 + subjects is rejected in around 80.3% of the simulations.

Calculations were performed using EAST® version 6.3, Cytel Inc and R software.

8.2 Randomization

The study is a randomized, active-controlled, and open-label study. Eligible subjects will be randomly assigned into either the avelumab arm or control group in a 1:1 ratio after 12-week chemotherapy in the Induction Phase. The randomization will be stratified by region (Asia versus non-Asia). The purpose of the stratification is to ensure a balance of the treatment arms within each region. Randomization will occur using the IWRS as described in Section 2 upon completion of the Induction Phase 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.

The survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab. For subjects who are still alive at the time of data analysis or who are lost to follow-up, OS 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 randomized treatment administration, or date of last scan, whichever is the latest) as of the data cut-off date for the analysis.

8.3.2 Secondary Endpoints

The secondary endpoints, which correspond to the Maintenance Phase in this trial, are the following:

- PFS in all randomized subjects according to RECIST v1.1, per Investigator assessment
- BOR in all randomized subjects according to RECIST v1.1, per Investigator assessment
- Subject-reported outcomes / QoL
- Safety and tolerability in all subjects.

8.3.2.1 Progression-Free Survival

Progression-Free Survival, defined as the time (in months) from randomization to the date of the first documentation of objective PD or death due to any cause (whichever occurs first), is the first key secondary endpoint of the study. The date of the first documented objective PD will be determined according to RECIST v1.1 based on Investigator response assessment.

The 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 anticancer 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.

8.3.2.2 Best Overall Response

Best Overall Response in Maintenance Phase is the key secondary endpoint for the study. The confirmed BOR will be determined according to RECIST v1.1, per Investigator assessment, and statistically evaluated as the ORR. BOR is defined as the best response obtained among all tumor assessment visits after the date of randomization until documented disease progression.

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 but no sooner than 4 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 SD requires that an overall response of SD 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, as per Investigator assessment.

8.3.2.3 Subject-Reported Outcomes / Quality of Life

The following subject-reported outcomes are further secondary endpoints for maintenance therapy:

- EQ-5D-5L
- EORTC QLQ-C30
- EORTC Gastric Cancer Module QLQ-STO22.

8.3.3 Safety Endpoints

Safety endpoints include AEs, physical examinations, clinical laboratory assessments, concomitant medications, vital signs, ECG parameters, and ECOG PS.

[redacted]

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 randomly assigned to Maintenance Phase study treatment. Analyses performed on the ITT Analysis Set will be performed according to subjects' 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 clinically important protocol deviations. Clinically important protocol deviations will be specified in the trial SAP.

PD-L1+ Analysis Set

The PD-L1+ Analysis Set is a subset of the ITT Analysis Set consisting of all PD-L1+ subjects determined by the PD-L1 IHC 73-10 pharmDx companion diagnostic assay. Analyses performed on the PD-L1+ Analysis Set will be performed according to subjects' treatment arms as randomized. One of two primary hypotheses for OS subjects will be tested in the PD-L1+ Analysis Set.

Health-Related Quality of Life Analysis Set

The HRQoL Analysis Set is a subset of the ITT Analysis Set and includes all ITT subjects who meet both of the following criteria:

- Re-baseline HRQoL assessment completed
- At least one Maintenance Phase HRQoL assessment completed.

Re-baseline HRQoL assessment occurs following completion of Induction Phase chemotherapy treatment at the Re-baseline visit, which should occur within the 10-day Re-baseline period.

Maintenance Phase HRQoL assessment is defined as HRQoL questionnaires completed after the first dose of Maintenance Phase study treatment for subjects who received avelumab or continuation of Induction Phase chemotherapy treatment, and HRQoL questionnaires completed after date of randomization for subjects on BSC-only.

Safety for Induction Phase (Safety-Induction) Analysis Set

The Safety-Induction Analysis Set will include all subjects who were enrolled into the study (ie, signed informed consent) and received at least 1 dose of Induction Phase chemotherapy. Analysis for the Safety-Induction Analysis Set will be summarized for all subjects as one single group.

Safety for Maintenance Phase (Safety-Maintenance) Analysis Set

The Safety-Maintenance Analysis Set will include all subjects who received at least 1 dose of randomized treatment or who were assigned to receive BSC-only in the Maintenance Phase. Analyses performed on the Safety-Maintenance 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. The SAP may modify the plans outlined in the protocol; however, any major modifications of planned analyses will be reflected in a protocol amendment if it is modified before data unblinding. If, after the trial is unblinded, changes are made to the SAP, then these deviations to the plan will be documented in the Clinical Trial Report.

All safety and efficacy endpoints will be summarized by treatment arm with the exception of endpoints corresponding to the Induction Phase which will be summarized by total number of subjects.

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.

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, 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

For the Induction Phase, baseline is defined as the last measurement taken prior to the first dose of treatment during the Induction Phase. For the Maintenance Phase, baseline is defined as the last measurement taken prior to the first dose of randomized treatment for safety endpoints and the last measurement taken prior to randomization for efficacy endpoints. If such a value is missing, the last measurement prior to the first dose of randomized treatment will be used as the baseline measurement for the efficacy analysis except for analyses of tumor assessments data where the Baseline assessment would be considered missing. For subjects who received BSC-only, baseline is defined as the last measurement taken prior to randomization for both safety and efficacy

endpoints. Baseline for heart rate and QTc assessments will be derived from the visit where both heart rate and QT are not missing.

On-Treatment

For the Induction Phase, the on-treatment period is defined as the time from the first administration of chemotherapy to the last administration of chemotherapy + 30 days, the earliest date of subsequent anticancer drug therapy - 1 day, or the date of randomization into the Maintenance Phase - 1 day, whichever occurs first.

For subjects randomized to active Maintenance Phase study medication, the on-treatment period is defined as the time from the first study treatment administration to the last study treatment administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. For subjects who received BSC-only, study treatment is considered to start on the day of randomization and end on the earliest date from among the following: the date given on the End of Assessment and Study Termination eCRF pages, date of death.

Multiple Comparison Strategy

A hierarchical test strategy will be used to control the overall type I error rate for the primary endpoint OS and key secondary endpoints of PFS and BOR in the following hierarchical order:

1: OS in the ITT Analysis Set and the PD-L1+ Analysis Set in the Maintenance Phase

2: PFS in the ITT Analysis Set in the Maintenance Phase

3: BOR in the ITT Analysis Set in the Maintenance Phase

The overall 2.5% (1-sided) type I error will be split between OS in all randomized subjects and PD-L1+ subjects with 2.0% (1-sided) and 0.5% (1-sided), respectively. One interim analysis is planned for OS in all randomized subjects. OS in PD-L1+ subjects will be tested at the primary analysis only. A Lan-DeMets alpha spending function for O'Brien-Fleming boundaries will be used to control the overall type I error rate of OS in all randomized subjects at 2% between the interim and primary analysis (see Section 8.6).

For the primary endpoint, a closed testing procedure with weighted Bonferroni tests, described by Hommel 2007 will be used for determining significance of the dual hypothesis primary testing. The summary is briefly described as follows (detailed process is in the study SAP).

If any of the two null hypotheses of OS (evaluated in all randomized subjects and in PD-L1+ subjects) is rejected, the corresponding alpha level will be recycled between both populations. The alpha recycling approach is as follows:

1. If the null hypothesis of OS in all randomized subjects is rejected at either the interim or the primary analysis, the 2% (1-sided) alpha allocated to OS in all randomized subjects

will be recycled to OS in PD-L1+ subjects, then 2.5% (1-sided) alpha level will be used for OS in PD-L1+ subjects.

2. If the null hypothesis of OS in PD-L1+ subjects at the primary analysis is rejected, the 0.5% alpha allocated to OS in PD-L1+ subjects will be recycled to OS in all randomized subjects. In this case, the significance will be based on a local 2.5% (1-sided) alpha level for OS in all randomized subjects. Assuming the planned number of events are observed at each analysis, the 1-sided boundaries would then be 0.0233 for OS in all randomized subjects at primary analysis. This has been recalculated by keeping the alpha level of 0.0072 at interim analysis unchanged.

PFS, followed by BOR, will be tested if and only if both null hypotheses for OS in all randomized subjects and PD-L1+ subjects are rejected. In that case, PFS will be tested with full 2.5% (1-sided) type I error at the primary analysis. BOR will be tested with full 2.5% (1-sided) type I error at the primary analysis after the null hypothesis of PFS is rejected. All analyses including OS in PD-L1+ subjects, PFS and BOR will be exploratory if the study is stopped at interim based on rejection of null hypothesis of OS in all randomized subjects.

No formal adjustment for multiplicity will be undertaken for non-key secondary endpoints, sensitivity analyses, or exploratory analyses.

Statistical analyses will be performed using SAS® version 9.4 or higher.

8.5.2 Analysis of Primary Endpoint

Primary Analysis

The primary endpoint for maintenance therapy is OS. The two primary analysis sets will be the ITT Analysis Set and the PD-L1+ Analysis Set. The following analysis will be conducted in the same manner for both ITT and PD-L1+ Analysis sets. The difference between the two treatment arms will be compared using a stratified, 1-sided, log-rank test. The stratification factor will be region (Asia versus non-Asia). Control of type I error and statistical significance is discussed in Section 8.5.1. The following null hypothesis will be tested:

$$H_0: \lambda_A(t)/\lambda_B(t) \geq 1, \text{ versus } H_1: \lambda_A(t)/\lambda_B(t) < 1$$

where $\lambda(t)$ represents the hazard rate (corresponding to each endpoint) at time t for treatment arms A (avelumab) and B (continuation of the same chemotherapy regimen/BSC).

A stratified Cox proportional hazards model will be used to assess treatment effect between the two treatment arms and to explore the robustness of the primary endpoint confirmatory analysis. The natural parameter of this model is the log hazard ratio. Each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model. The hazard ratio of avelumab versus maintenance chemotherapy/BSC (with maintenance chemotherapy/BSC as reference) together with the corresponding Wald 2-sided 95% CIs will be presented.

Kaplan-Meier (ie, product-limit) estimates of median OS will be presented by treatment arm together with 2-sided 95% CIs calculated according to Brookmeyer and Crowley (1982). Finally, the number of subjects at risk vs. failed along with Kaplan-Meier estimates of survival probability (often referred to as "survival rate") at 3, 6, 9 and 12 months will be estimated with corresponding 2-sided 95% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (1980).

The number and percentage of subjects with observed OS events will be presented by treatment arm (avelumab or maintenance chemotherapy/BSC). In addition, frequency counts for censoring reason will be presented by treatment group.

Sensitivity Analyses

The following sensitivity analyses for OS will be performed to explore the robustness of the primary confirmatory analyses. These sensitivity analyses will be performed in the same manner for both ITT and PD-L1+ analysis sets. Additional sensitivity analyses may be specified in the trial SAP.

- The primary endpoint analysis will be repeated based on the PP Analysis Set if this analysis set includes less than 90% of subjects in the ITT Analysis Set.
- An unstratified analysis will be performed comparing OS between the treatment arms.
- If the actual number of events is 10% more than the planned number at the primary analysis, the primary analysis of OS will be repeated by using the date at which exactly 356 events in all randomized subjects were observed, or after a minimum follow-up of at least 18 months after randomization, whichever occurs last.

The following analyses will also be performed:

- The validity of the proportional hazards assumption will be assessed visually by plotting log(-log(survival)) versus log(time) by treatment arm.
- A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment arms by reversing the OS censoring and event indicators.

8.5.3 Analysis of Secondary Endpoints

Based on the hierarchical testing strategy described in Section 8.5.1, PFS and BOR will be tested at the primary analysis, if, and only if, both of hypotheses testing OS (in all randomized subjects and PD-L1+ subjects) reach statistical significance.

8.5.3.1 Key Secondary Endpoint – Progression-Free Survival

The statistical analysis of PFS per Investigator assessment will be the same as described for the primary analysis of OS.

In addition, the following sensitivity analyses of PFS will be performed:

- Events (PDs/deaths) after the start of new anticancer treatment will be considered as events
- Clinical progression will be considered as an event
- Counting all PD and deaths as events regardless of missing assessments or timing of the event.

8.5.3.2 Key Secondary Endpoint – Best Overall Response

For the analysis of BOR in the Maintenance Phase (see Section 8.5.3) according to RECIST v1.1 and per Investigator assessment, the ORR (defined as having a confirmed BOR of CR or PR) will be calculated along with corresponding 2-sided exact Clopper-Pearson 95% CIs for the two treatment arms. The Cochran-Mantel-Haenszel test will be stratified by region (Asia versus non-Asia) to compare the ORR between the two treatment arms. In case the assumptions of the Cochran-Mantel-Haenszel test are violated due to a small number of subjects in some strata, a Fisher's exact test will be used. This analysis will be based on the ITT Analysis Set.

8.5.3.3 Other Secondary Endpoints

8.5.3.3.1 European Quality of Life - 5 Dimensions - 5 Levels

Observed and change from baseline values for the EQ-5D-5L index score will be summarized descriptively at planned visits during the Maintenance Phase, the Discontinuation Visit, and End-of-Treatment Visit by treatment arm. This analysis will be based on the HRQoL Analysis Set. The EQ-5D-5L Visual Analog Scale scores will be presented by data listing only.

8.5.3.3.2 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 five QLQ-C30 functional scales (ie, Physical, Role, Emotional, Cognitive, and Social) will be summarized descriptively at planned visits during the Maintenance Phase, the Discontinuation Visit, 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 two treatment arms using a mixed-effects model repeated measures (MMRM) analysis to evaluate longitudinal change from baseline using region and baseline value as covariates. This analysis will be based on the HRQoL Analysis Set.

8.5.3.3.3 European Organization for Research and Treatment of Cancer Gastric Cancer Module QLQ-STO22

Observed and change from baseline values for each of the five QLQ-STO22 gastric cancer module symptom scales (ie, dysphagia, pain, reflux, eating, and anxiety) will be summarized descriptively at planned visits during the Maintenance Phase, the Discontinuation Visit, 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 two treatment arms using a MMRM analysis to evaluate longitudinal change from baseline using region and baseline value as covariates. This analysis will be based on the HRQoL Analysis Set.

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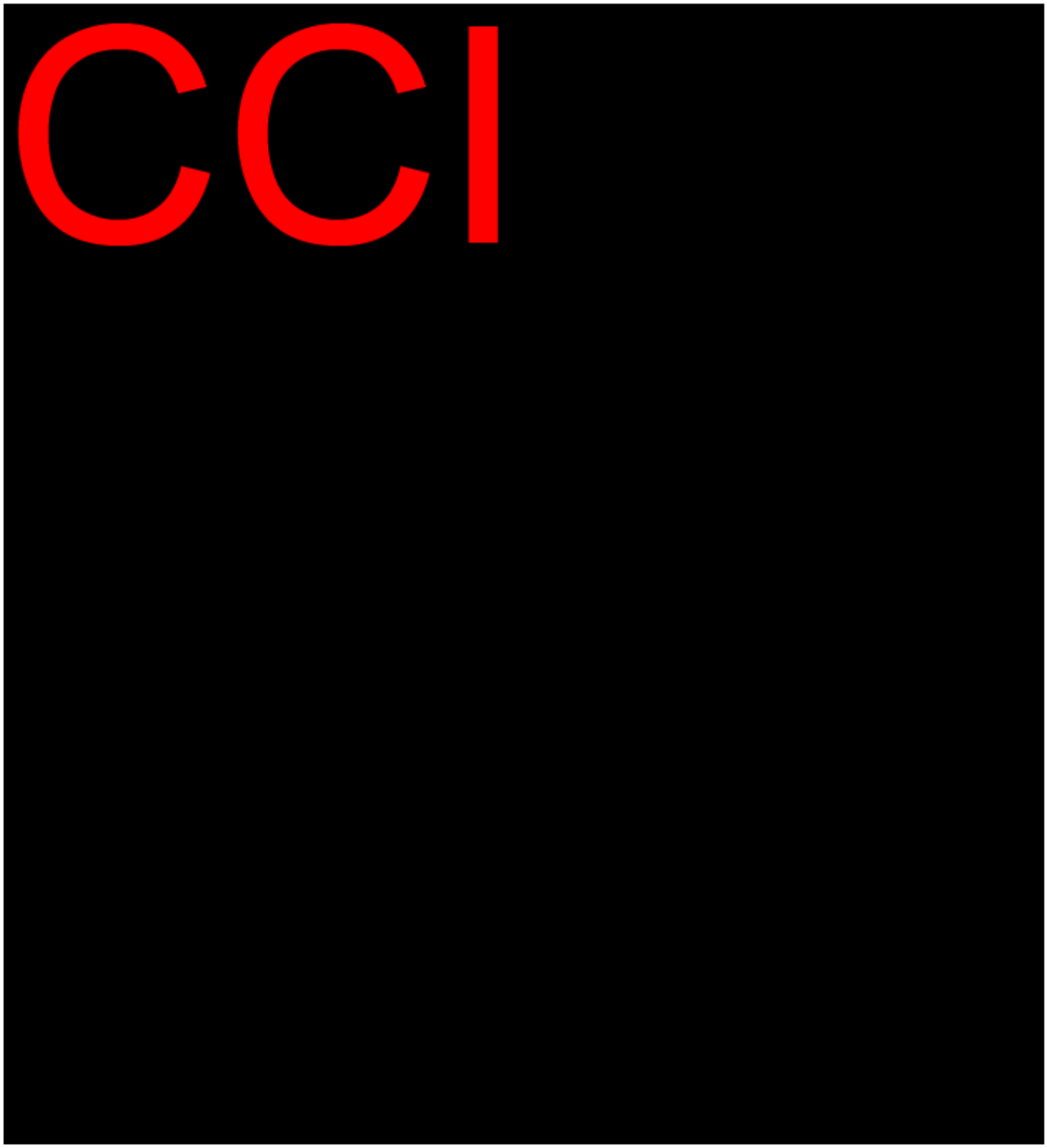

8.5.5 Analysis of Safety Endpoints

All Safety analyses will be performed on the Safety-Maintenance Analysis Set unless otherwise noted. Safety endpoints will be tabulated using descriptive statistics only.

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

Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 20.1). Severity of AEs will be graded using the NCI-CTCAE v 4.03 toxicity grading scale.

Treatment-emergent AEs (TEAEs) are defined as events with onset dates occurring on-treatment or events which worsen on-treatment (see Section 7.4.1.2). TEAEs are defined separately for the Induction and Maintenance Phases. Unless otherwise specified, summaries will be performed on Maintenance Phase TEAEs.

The incidence of TEAEs, regardless of relatedness to treatment, will be summarized by System Organ Class and Preferred Term for each treatment arm. Similar summaries will also be provided for treatment-emergent serious adverse events (TESAEs), TEAEs leading to permanent discontinuation of treatment, TEAEs by maximum severity, TEAEs by highest relationship to treatment, TEAEs with fatal outcome, and TEAEs of special interest (AESIs) such as irAEs.

The incidence of TEAEs and TESAEs during the Induction Phase will be summarized by system organ class/preferred term by total number of subjects.

Concomitant Medications and Procedures

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

Laboratory Values

Observed and change from baseline values during the Maintenance Phase will be summarized by visit, test, and treatment arm for chemistry and hematology laboratory results. Laboratory results will be classified by grade according to NCI-CTCAE. The worst on-treatment grades during the Maintenance Phase for chemistry and hematology laboratory results by treatment arm will be summarized. Shifts in toxicity grading from baseline to highest grade during the Maintenance Phase by treatment arm will be displayed. Results during the Maintenance Phase for laboratory tests that are not part of NCI-CTCAE will be presented categorically (eg, below, within, or above normal limits) by treatment arm. 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.

ECOG Performance Status

Shifts from Re-baseline (end of Induction Phase) in ECOG PS score will be presented at planned visits during the Maintenance Phase, the Discontinuation Visit, and End-of-Treatment Visit by number and percentage for each treatment arm. Shifts from Re-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 during the Maintenance Phase will be summarized by parameter (eg, body temperature, respiratory rate, heart rate, and blood pressure) using descriptive statistics by treatment arm. A similar summary will be provided for the Induction Phase by total number of subjects.

12-Lead ECGs

Observed and change from baseline values during the Maintenance Phase based on 12-lead ECGs will be summarized at the Discontinuation Visit and End-of-Treatment Visit by parameter (eg, Heart Rate, PR Interval, QRS Interval, RR Interval, QT Interval, QT corrected by Bazzett's formula [QTcB] Interval, or QT corrected by Fridericia's formula [QTcF] Interval) and treatment arm. In addition, shifts from baseline in ECG results (eg, normal, abnormal) will be presented at the Discontinuation Visit and 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

Pre-induction subject characteristics will be obtained during the Screening/Baseline procedures and will be summarized by total number of subjects 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. A similar summary of pre-maintenance Re-baseline characteristics will be provided by treatment arm and overall for the ITT Analysis Set.

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 (ie, stomach, GEJ), overall tumor response status (ie, CR, PR, or SD) following the Induction Phase, and PD-L1 assay status (ie, positive, negative).

Enrollment and Disposition

The number and percentage of subjects screened (number only), screen-failed (number only), discontinued during the Induction Phase (number only), randomized, randomized but not treated during the Maintenance Phase, treated during the Maintenance Phase, and prematurely discontinued during the Maintenance Phase will be summarized by treatment arm and overall. Primary reasons for screen-failure, randomization failure, and premature withdrawal during the Maintenance Phase will be summarized. The number and percentage of subjects in the 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 Safety-Maintenance Analysis Set. A similar summary will be provided by total subjects for the Safety-Induction Analysis Set.

Treatment Exposure and Compliance

The extent of exposure to treatment during the Induction Phase will be summarized for total number of subjects in the Safety-Induction Analysis Set.

The extent of exposure to randomized treatment (ie, avelumab or maintenance chemotherapy) will be characterized by duration (weeks), number of administrations, cumulative dose (eg, mg/kg or mg/m^2), dose intensity (mg/kg/week or mg/m^2/week), relative dose intensity (actual dose given / planned dose), number of dose delays, and number of infusion rate reductions (avelumab arm only), for the Safety-Maintenance Analysis Set. The number and percentage of non-compliant subjects (see Section 6.9) with regard to randomized treatment will be presented by treatment arm based on the Safety-Maintenance Analysis Set.

Prior Anti-Cancer Therapies and Procedures

Prior anti-cancer therapies (ie, anti-cancer medications other than trial treatment taken at any time prior to ICF signature) will be summarized using frequencies and percentages by drug class and preferred name within treatment arm and overall for the Safety-Induction Analysis Set and Safety-Maintenance Analysis Set. A similar summary will be provided by drug class, preferred name, and total subjects for the Safety-Induction Analysis Set. Prior anti-cancer procedures (ie, procedures undertaken at any time prior to ICF signature) will be listed only.

8.6 Interim and Additional Planned Analyses

No interim analysis is planned for OS in PD-L1+ subjects. There is one interim analysis planned for overwhelming efficacy of OS in all randomized subjects when approximately 75% of OS events, ie, 267 OS events have been observed. A Lan-DeMets alpha spending function for O'Brien-Fleming boundaries will be used to control the overall type I error rate of 2% (1-sided) for OS. The boundaries for declaring superiority for the interim analysis and the final analysis of

OS in all randomized subjects will be updated based on the actual number of events observed at the time of the data cut for each analysis. If the planned number of events are observed at each analysis, 1-sided boundaries of 0.0072 and 0.0178, respectively will be used for evaluating statistical significance. Since formal efficacy boundaries will be used at the interim analysis for the statistical testing of OS in all randomized subjects, a statistically significant finding at the interim will be intended to claim the superiority. If OS in all randomized subjects is statistically significant at the interim analysis, only descriptive analysis of OS in PD-L1+ subjects will be performed at this interim analysis time point. If the study proceeds to the final analysis and null hypothesis of OS in PD-L1+ is rejected at alpha level 0.005 then the boundary for the final hypothesis of OS in randomized subjects will be based on a local significance level of 0.025. Assuming the planned number of events are observed at each analysis, the 1-sided boundaries would then be 0.0233 for OS in all randomized subjects at primary analysis. This has been recalculated by keeping the alpha level of 0.0072 at interim analysis unchanged.

The Table 13 summarizes the operating characteristics and efficacy boundaries, in the case that planned number of events are observed for OS in randomized subjects in both analyses. The O'Brien-Fleming efficacy boundaries based on a Lan-DeMets spending function will be updated prior to the time of analysis of OS based on the actual number of events and the information fraction for type I error control. Information fraction at the interim analysis will be calculated assuming the planned 356 events will be observed at the time of the primary analysis. At the primary analysis, the boundaries will be updated based on the true number of events observed and information fraction used at each analysis.

Table 13 Planned Lan-DeMets (O'Brien-Fleming) Efficacy Boundaries of OS in All Randomized Subjects

Look	Info Fraction	Approx. Cum. Events of OS	Cumulative Type I Error (1-sided)	Efficacy Boundaries	
				Z-scale	P-scale (1-sided)
Interim	~75%	267	0.0072	2.45	0.0072
Final	100%	356	0.0200	2.10	0.0178

OS = Overall Survival.
Lan-DeMets alpha spending function for O'Brien-Fleming boundaries
The overall type I error rate = 0.020 (1-sided) for primary endpoint of OS in all randomized subjects.
The exact efficacy boundaries may be updated prior to the time of analysis based on the actual number of events and the information fraction.

Further details regarding the interim analysis will be provided in the trial SAP.

An IDMC will be formed and will be responsible for periodic evaluations of the trial as well as the evaluation of the interim analysis. The IDMC (see Section 2.3.1) will convene to perform the evaluation at the interim analysis in order to safeguard the Sponsor's personnel from unblinded trial results. The primary endpoint of OS, the key secondary endpoints of PFS, BOR, and other

secondary efficacy endpoint (reported outcomes / QoL assessed by the EQ-5D-5L, EORTC QLQ-C30, and EORTC module QLQ-STO22 questionnaires) analyses will be conducted in this interim analysis. See Sections 8.5.1 and 8.5.3 for details regarding the hierarchical testing strategy to be used. If at the time of this interim analysis, the analysis is performed with exactly 267 deaths observed (75% planned information fraction), the OS in all randomized subjects of avelumab-assigned subjects is shown to be superior to that of subjects randomly assigned to the maintenance chemotherapy/BSC arm with a p-value of < 0.0072 the IDMC may declare superior efficacy in the avelumab treatment arm compared with the maintenance chemotherapy/BSC arm and recommend that the trial be stopped early. The IDMC will also be presented with subject disposition, demographic information, baseline disease characteristics, and safety information. An independent statistical provider will perform the interim analyses to support the IDMC. Details will be documented in a separate SAP or IDMC charter. Results from the interim analyses will be transmitted from this group to the IDMC only. Trial staff involved with the day to day management of the trial as well as any Sponsor staff will not have access to this interim information. Details of the IDMC mission, composition, and operations will be provided in the IDMC charter.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his / her site. He / she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their 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 FDA 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 FDA), the Investigator and all subinvestigators 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 a subject's participation in the trial is his / her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. CCI [redacted]

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance

with the Note for Guidance on GCP (ICH Topic E6, 1996) 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 his / her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally 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 by the Investigator 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 the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC / IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating, which will be documented. Sufficient time will be provided to subjects to read the information and the opportunity to ask questions and to request additional information and clarification about the changes. The Investigator will explain the changes to the previous version.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion by the IWRS system, 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.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Clinical Trial Monitor, audits, and Health Authority inspections will be kept strictly confidential.

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 (see Section 7.6). Details regarding subjects' right to privacy will be described in the ICF.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care

providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

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, she or he will answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, Merck KGaA / EMD Serono R&D or designee will provide the appropriate means to contact a Sponsor 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 and to provide support for the subject concerned.

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 at 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 (eg, IMP Dossier, Subject Information, and the 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

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data entry guidelines. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs and to sign the case report forms. Please refer to the Manual of Operations for eCRF handling guidelines.

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 CRO will be responsible for data review and processing, in accordance with the CRO's data management procedures. Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed. Copies 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, ie, 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).
- It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must

include at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or 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.

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 Note for Guidance on GCP (ICH Topic E6, 1996). The Clinical Trial Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the trial drug, and the subjects' original medical records / files.

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.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) 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 (see 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 be a publication of the results of the analysis of the primary endpoints that 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 presubmission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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CCI

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12 Appendices

Appendix I Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction
IND Number:	CCI [redacted]
EudraCT Number:	2015-003300-23
Clinical Trial Protocol Date / Version:	17 July 2019/Version 7.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821-3936, USA
Telephone number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Trial Title	A Phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction
IND Number	CCI
EudraCT Number	2015-003300-23
Clinical Trial Protocol Date / Version	17 July 2019/Version 7.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD PPD

Signature Date of Signature

Name, academic degree: PPD

Institution: PPD

Address: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	A Phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction
IND Number	CCI [redacted]
EudraCT Number	2015-003300-23
Clinical Trial Protocol Date / Version	17 July 2019/Version 7.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Healthcare KGaA Darmstadt, Germany, an affiliate of Merck KGaA, Darmstadt, Germany.
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PPD
E-mail address:	PPD

Appendix II Guidance on Contraception

BIRTH CONTROL METHODS CONSIDERED AS HIGHLY EFFECTIVE

According to the 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.

Appendix III Protocol Amendments and List of Changes

Protocol Version 1.0 (14 August 2015) was the original protocol. The protocol was revised to include feedback from the FDA, PMDA, and EMA, and Version 2.0 (Amendment 1) was issued on 23 September 2015. Version 3.0 (Amendment 2) was issued on 06 January 2016 and included feedback from Voluntary Harmonisation Procedure (VHP). Version 3.1 (Japan Only Addendum) was issued on 06 April 2016 and included modifications for the Pharmaceuticals and Medical Devices Agency. Version 3.2 (France Only Addendum) was issued on 01 April 2016 and included modifications for the French National Agency for Medicines and Healthcare Products Safety (ANSM) and French Central Ethics Committee requests. Protocol Version 4.0 (Amendment 3) was issued on 25 January 2017 and includes program-wide changes and corrected an administrative error in the version numbering of the protocol. Protocol Version 5.0 (Amendment 4) was issued on 28 August 2017 and includes program-wide changes considered as non-substantial as only administrative changes were made. Protocol Version 6.0 (Amendment 5) was issued on 21 June 2018 and included changes to the study primary and secondary endpoints/objectives considered as substantial. Version 6.1 (Japan only addendum) was issued on 11 July 2018 and Version 6.2 (France only addendum) was issued on 07 August 2018 and included Amendment 5.

Protocol Version 7.0 Summary of Changes

The key reasons for Amendment 6, Protocol version 7.0, are summarized below:

Rationale for Changes

Study EMR100070-007 was amended in June 2018 to change the primary objective to include OS in PD-L1+ subjects, in addition to OS in all randomized subjects, where PD-L1 status was defined based on a 1% cut-off for tumor cells (reference protocol EMR100070-007 Amendment 5, Version 6). At that time, the prevalence of PD-L1+ subjects was assumed to be 35% (based on the prevalence of PD-L1+ tumors in patients with gastric cancer (GC) in the non-progressed GC cohort of study EMR100070-001). As such, 112 events in the PD-L1+ subgroup were projected to occur to the 356 OS events required for the primary analysis in all randomized subjects, and the primary analysis in both analysis sets was planned at a common timepoint when both conditions are met.

At the time of release of Protocol Version 6, the PD-L1 assay utilized was an investigational use only (IUO) assay for CCI [redacted] testing. Because the amended primary endpoint of OS in the PD-L1+ analysis set would require testing by validated assay, validation of the proposed PD-L1 IHC 73-10 pharmDx kit for testing of GC samples at 1% cut-off for tumor cells was initiated in September 2018.

Results of the PD-L1 scoring with validated assay became available in June 2019. From 499 randomized subjects, 438 samples were available for PD-L1 scoring with the validated assay. Less than 15% of the samples were scored as PD-L1 positive, which is considerably less than the previously assumed prevalence during Protocol Versions 1-6. Based on this prevalence, the number of previously projected events (Protocol Version 6) in the PD-L1+ subjects will not be reached. Thus, the condition of meeting the pre-specified number of PD-L1+ events for the Final Analysis data cut-off

has been removed as a trigger for the Final Analysis in the Protocol Version 7. The Final Analysis will be triggered by the events in the ITT population as well as a minimum follow-up time of 18 months for primary analysis which is expected to ensure sufficiently mature data for OS in PD-L1+ subjects. The primary analysis of OS in PD-L1+ subjects will be conducted at the same time as OS in all randomized subjects with substantially reduced power, according to the endpoint definition as in Protocol Version 6.

The sampling for PK and CCI analysis was limited to 2 years from randomization, as further sampling will not add value to pharmacokinetic and CCI evaluation. Therefore, the last sampling point will be at Week 109. This will avoid unnecessary burden to the subjects.

The above-mentioned changes are considered substantial based on the 'Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)'.

Protocol Version 7.0 Detailed List of Changes

Changes to the clinical trial protocol text with the exception of minor editorial changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. Deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 6.0, 21 June 2018 (Amendment 5)

Change	Section	Page	Previous Wording	New Wording	Rationale
Sponsor Medical responsible person changed from Ilaria Conti to Hong Zhang	Title Page and Signature Page- Protocol Lead	1, 135	PPD	PPD	Study Personnel updated
Last subject out date changed from Q4 to Q3	Synopsis Planned Trial Period	11	Last subject out: Q4, 2019	Last subject out: Q3, 2019	Updated as the date on which data collection is completed for all the primary analysis is 13 Sep 2019
As the prevalence of PD-L1+ subjects	Synopsis	18	The data cut-off for the primary analysis will take place on a prospectively-determined date,	The data cut-off for the primary analysis will take place on a prospectively-determined date, upon	As per the results of the PD-L1 scoring

is lower than initial forecasted 35%. From current enrolled number of subjects, it is impossible to ever reach 112 events anticipated for primary analysis in PD-L1 positive subjects.			upon which the target number of 356 OS events in all randomized subjects and 112 OS events in PD-L1+ subjects are projected to have been reached, and the last subject randomized in the study has been followed for at least 18 months from randomization. [….] For OS in PD-L1+ subjects, a prevalence rate of 35% in all randomized subjects is assumed, and a median OS of 19.3 months in the avelumab arm corresponding to a hazard ratio of 0.54.	which the target number of 356 OS events in all randomized subjects ~~and 112 OS events in PD-L1+ subjects~~ are projected to have been reached, and the last subject randomized in the study has been followed for at least 18 months from randomization. [….] For OS in PD-L1+ subjects, **at planning stage** a prevalence rate of 35% in all randomized subjects **was** ~~is~~ assumed, and a median OS of 19.3 months in the avelumab arm corresponding to a hazard ratio of 0.54.	with validated assay available in June 2019, the number of previously projected events (Protocol Version 6) in the PD-L1+ subjects will not be reached. Thus, the condition of meeting the pre-specified number of PD-L1+ events for the Final Analysis data cut-off has been removed as a trigger for the Final Analysis. The Final Analysis will be triggered by the events in the ITT population as well as a minimum follow-up time of 18 months for primary analysis which is expected to ensure sufficiently mature data for OS in PD-L1+ subjects. The primary analysis of OS in PD-L1+ subjects will be conducted at the same time as OS in all randomized subjects with substantially reduced power.


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					be at Week 109 to avoid unnecessary burden to the subjects, except for subjects still on treatment beyond Week 109.
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