Clinical Trial Protocol

Clinical Trial Protocol Number	EMR100070-005
Title	A Phase III, open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line treatment of recurrent or Stage IV PD-L1+ non–small-cell lung cancer
Short Trial Name	JAVELIN Lung 100
Phase	III
IND Number	CCI [redacted]
EudraCT Number	2015-001537-24
Coordinating Investigator	PPD [redacted] Tel: PPD [redacted]
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA Medical Responsible: PPD [redacted] 45A Middlesex Turnpike Billerica, MA 01821, USA Tel: PPD [redacted] Fax: PPD [redacted]
Clinical Trial Protocol Version	03 January 2019 / Version 6.0
Replaces Version	21 February 2018 / Version 5.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	13-Jul-2015
2.0	Amendment 1.0	25-Aug-2015
3.0	Amendment 2.0	14-Oct-2015
4.0	Amendment 3.0	21-Nov-2016
5.0	Amendment 4.0	21-Feb-2018
6.0	Amendment 5.0	03-Jan-2019

Protocol Version [6.0] (03-January-2019)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The scheduling of the study interim and primary analyses for both endpoints (progression-free survival [PFS] and overall survival [OS]) have been reconfigured based on updated assessments of the expected PFS events drop-out rate. The adjustment of statistical assumptions has been prompted by standard monitoring of the number of PFS events performed in a blinded fashion by the Sponsor.

Based on the above available information, the current estimate of PFS drop-out rate in Study EMR100070-005 is considerably higher than the original assumption of 15% which would lead to a much later anticipated timepoint to reach the number of 171 PFS events required for the primary analysis in subjects with high expression PD-L1 status in the modified Full Analysis Set. Based on the new assumption of PFS drop-out rate and blinded monitoring of PFS and OS events, it is expected the required number of events for the primary analysis of both endpoints will be reached at a similar time. Consequently, it is reasonable to decouple the OS interim analysis from the PFS final analysis, and to perform interim and primary analyses for both endpoints at the same time and therefore, the analyses have been reconfigured accordingly. While efficacy objectives of the study will not change, there will be a change in protocol-defined main analyses affecting the timing of the interim and final analyses as well as the information fraction triggering the analyses.

Section # and Name	Description of Change	Brief Rationale
Synopsis (Statistical Methods), Section 5.1.1 Overall design, Section 8.1 Sample Size, Section 8.5.1 General Considerations, Section 8.5.2 Analysis of Primary Endpoints, Section 8.6 Interim Analysis	Assumptions on PFS drop-out rate have been revised. The scheduling of interim and primary analysis of PFS and OS has been changed to have interim and primary analysis of both endpoints at the same time determined by the number of OS events and minimum-follow-up time	Monitoring of the number of PFS events led to a revised assumption of the drop-out rate and to a revised estimation when the required number for the interim and primary analysis of PFS will be met.
CCI [redacted]		

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ADA	Anti-drug Antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
CCI	[redacted]
ANC	Absolute neutrophil count
ANCA	Antineutrophil cytoplasmic antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{tau}	Area under the concentration-time curve
β-hCG	β-human chorionic gonadotropin
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval(s)
CBC	Complete blood count
C_{max}	Maximum plasma concentration observed postdose
C_{min}	Minimum postdose (trough) concentration
CR	Complete response
CRA	Clinical Research Associate

CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CYP3A4	Cytochrome P450 3A4
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality Of Life 5-dimensions 5-level questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMP	Good Manufacturing Practice
H1	Histamine H1 receptor
HAHA	Human antihuman antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPMP	Integrated Project Management Plan
IRC	Independent Review Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Operations
MRI	Magnetic resonance imaging

NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
PD-L1+	PD-L1 positive
PD-L2	Programmed death-ligand 2
PFS	Progression free survival
CCI	[redacted]
CCI	[redacted]
PP	Per-protocol
PR	Partial response
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
T4	Free thyroxine
TEAE	Treatment-emergent adverse event

TLS	Tumor lysis syndrome
t_{max}	Time to reach maximum concentration
TO	Target occupancy
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
USA	United States
WBC	White blood cell

1 Synopsis

Clinical Trial Protocol Number	EMR100070-005
Title	A Phase III, open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line treatment of recurrent or Stage IV PD-L1+ non-small cell lung cancer
Trial Phase	III
IND Number	CCI [redacted]
FDA covered trial	Yes
EudraCT Number	2015-001537-24
Coordinating Investigator	PPD [redacted]
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA
Trial centers/countries	The trial will be conducted at up to 386 sites globally in North America (approximately 27 in the USA), South America, Asia, Africa, and Europe.
Planned trial period (first subject in-last subject out)	First subject in: Q3, 2015 Last subject out: Q2, 2020
Trial Registry	ClinTrials.gov

Objectives:

Primary objective

The primary objective is to demonstrate superiority with regard to overall survival (OS) or progression free survival (PFS) of avelumab versus platinum-based doublet, based on an independent review committee assessment as per RECIST 1.1, in NSCLC subjects with high expression PD-L1+ tumors.

Secondary objectives

Secondary objectives are as follows:

- To demonstrate superiority with regard to OS or PFS based on an independent review committee assessment per RECIST 1.1 in NSCLC subjects with moderate and high expression PD-L1+ tumors
- To demonstrate superiority with regard to OS in NSCLC subjects with any expression PD-L1+ tumors
- To comparatively assess the objective response rate (ORR) by RECIST 1.1 of avelumab versus chemotherapy in high, moderate and high, and any expression PD-L1+ tumors
- To determine duration of response (DOR) of avelumab versus chemotherapy
- To compare the patient-reported outcomes / quality of life when treated with avelumab versus chemotherapy using the European Quality of Life (EuroQOL) 5-dimensions 5-level questionnaire (EQ-5D-5L), and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-LC13
- To determine the safety and tolerability of avelumab

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Methodology: This is a multicenter, international, randomized, open-label, Phase III trial in chemotherapy-naïve (first line) metastatic or recurrent (Stage IV) NSCLC subjects comparing avelumab to first-line platinum-based doublet chemotherapy. The trial consists of a 28-day screening period, followed by the treatment phase (within 4 days after randomization).

To achieve the target enrollment of 484 subjects randomized with high expression PD-L1+ tumors, approximately 1131 eligible subjects will be randomized with any expression PD-L1+ tumors and approximately 3100 subjects will be screened for study participation.

Subjects will be randomly allocated into the 3 study arms as follows:

- Arm A: Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities, or
- Arm B: Investigator's choice platinum-containing chemotherapy regimen to be administered in 3-week cycles up to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities consisting of one of the following:
    - for subjects whose tumor is of non-squamous histology:
        - pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2 administered on Day 1 of each cycle), or pemetrexed (500 mg/m^2) in combination with carboplatin (AUC 6 mg/mL × min administered on Day 1 of each cycle).
    - for subjects whose tumor is of squamous histology:
        - paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL × min administered on Day 1 of each cycle); or
        - gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2); or
        - gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL × min)
- Arm C: Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) intravenous (IV) infusion every week for 12 consecutive weeks, followed by avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.

Subjects will be randomly allocated to one of the 3 treatment arms, initially into Arm A and Arm B in a 1:1 ratio. The allocation ratio will change to 1:2:2 (Arm A: Arm B: Arm C) once the IDMC recommends the avelumab once a week dosing regimen may be included in the randomization scheme after the initial safety evaluation of avelumab 10 mg/kg every week in a cohort of 6 subjects.

NSCLC histology (squamous versus non-squamous cell) will be used as stratification factors for randomization. The PD-L1 tumor expression level at Baseline (low expression versus moderate expression versus high expression) will be supplemented as randomization strata for the 1:2:2 randomization scheme.

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. Response will be evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Treatment with avelumab will continue until disease progression or unacceptable toxicity. Subjects receiving avelumab who have experienced a complete response (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, one re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the medical monitor.

Treatment with chemotherapy will continue until disease progression, unacceptable toxicity, or after the completion of up to 6 cycles of chemotherapy. Subjects with non-squamous histology are authorized to continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease has not progressed, or in accordance with the pemetrexed local label. No other maintenance therapy is permitted.

Decisions regarding medical management of subjects will be made by the Investigator; however, the primary and secondary endpoint determinations (response and progressive disease [PD]) will be according to the central imaging assessment and review by a blinded Independent Review Committee (IRC).

Adverse events (AEs) will be assessed throughout the trial and evaluated using the National Cancer Institute (NCI) Common Technology Criteria version for Adverse Events version 4.03 (CTCAE v 4.03).

Periodic evaluations of the trial data will be conducted by the IDMC to ensure subject safety, and the validity and scientific merit of the trial.

- **End-of-Treatment visit**: within 7 days from the decision to discontinue, or before the start of any other antineoplastic therapy including a full safety evaluation for subjects that have discontinued treatment due to an AE, and
- **Follow-up phase:** Safety Follow-up visit 30 days (± 5 days) after the last administration of trial treatment, followed by a 90-day telephone Safety Follow-up (± 1 week), and Long-term Follow-up every 12 weeks (± 1 week).

Planned number of subjects: Approximately 3100 subjects will be screened. Accrual will proceed up to a target number of approximately 1131 subjects randomized with any expression PD-L1+ tumors in order to obtain at least 484 subjects randomized with high expression PD-L1+ tumors. This is based on the estimation that among subjects with any expression PD-L1+ tumors, approximately 45% of them will have high expression PD-L1 tumors.

Primary endpoints: The primary endpoints for the trial are PFS and OS. Progression free survival is defined as the time from date of randomization until date of the first documentation of PD as determined by the independent review committee (per RECIST 1.1) or death due to any cause in the absence of documented PD, whichever occurs first. Overall survival is defined as the time from randomization to the date of death, regardless of the actual cause of the subject's death.

Secondary endpoints

The secondary endpoints include**:**

- BOR according to RECIST 1.1 and as adjudicated by the IRC
- Duration of response according to RECIST 1.1
- Patient-reported outcomes/quality of life (assessed by the EQ-5D-5L, and the EORTC QLQ-C30, and module QLQ-LC13 questionnaires)
- Safety endpoints (including AEs, clinical laboratory assessments, vital signs, physical examination, electrocardiogram [ECG] parameters, and ECOG PS).

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Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria:

Male or female subjects ≥ 18 years, with an ECOG PS of 0 to 1 at trial entry, with the availability of a formalin-fixed, paraffin-embedded block containing tumor tissue or 10 (preferably 25) unstained tumor slides with PD-L1+, at least 1 measurable tumor lesion, and with histologically confirmed metastatic or recurrent (Stage IV) NSCLC. Subjects must not have received any treatment for systemic lung cancer, and have an estimated life expectancy of more than 12 weeks.

Key exclusion criteria:

Subjects whose disease harbors an EGFR mutation or an anaplastic lymphoma kinase (ALK) rearrangement are not eligible. Other exclusion criteria include prior therapy with any antibody or drug targeting T-cell coregulatory proteins, concurrent anticancer treatment, or immunosuppressive agents, known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma), and persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03. Subjects with brain metastases are excluded, except those meeting the following criteria: brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to randomization, subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent), and do not have ongoing neurological symptoms that are related to the brain localization of the disease.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule: Avelumab will be administered as a 1-hour (-10/+20 minutes) IV infusion at 10 mg/kg once every 2 weeks or once a week for 12 consecutive weeks followed by once every 2 weeks, depending on randomization, until progressive disease or unacceptable toxicity. In order to mitigate infusion-related reactions, all subjects will receive pretreatment with histamine H1 receptor (H1) blockers and acetaminophen 30 to 60 minutes prior to every avelumab infusion.

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

Reference therapy: dose/mode of administration/dosing schedule: Subjects randomized to chemotherapy will be administered the Investigator-chosen chemotherapy regimen according to the protocol in 3-week cycles up to a maximum of 6 cycles or until progressive disease or unacceptable toxicities. Dose adjustments can be made according to label instructions and local institutional practices.

Planned trial and treatment duration per subject: In this trial, treatment with avelumab will continue until disease progression or unacceptable toxicity. 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. Chemotherapy will be administered until disease progression or unacceptable toxicity or for a maximum of 6 cycles of chemotherapy.

Statistical methods: The aim of the study is to demonstrate superiority of either avelumab regimen versus standard of care (SOC) in terms of PFS or OS time.

The OS or PFS time will serve as primary endpoints to test the superiority of each investigational treatment arm (Arm A, Arm C) versus SOC (Arm B).

Statistical testing will consider hierarchically ordered hypothesis with respect to tumor PD-L1 expression status at Baseline, starting with high PD-L1 expression, followed by moderate and high PD-L1 expression for both endpoints of OS and PFS. Any PD-L1 expression will be tested only for OS.

Multiplicity adjustments will follow closed testing procedures with weighted Bonferroni tests including allocation of local significance levels to the next step of hypothesis testing in case of statistically significant results. Overall significance level of 0.025 (one-sided) will be split to local significance levels due to primary PFS or OS endpoints and two treatment group comparisons against control arm.

The OS and PFS time will be analyzed based on as-randomized principle using a one-sided stratified log-rank test. An interim analysis is planned after recruitment has been completed based on required events for the high expression PD-L1+ population. The interim analysis for PFS and OS is scheduled after approximately 130 OS events for the Arm C versus B comparison have been reached representing a 75% information fraction. Interim analyses for PFS and OS will be conducted, considering Lan-DeMets α-spending with O'Brien-Fleming-like boundaries given the local significance levels at the first hierarchy step. No futility analysis is planned.

The primary statistical comparisons of Arm A vs Arm B will include all subjects who were randomized to trial treatment. The primary statistical comparison of Arm C vs Arm B will consider all randomized subjects after the first subject is randomly assigned according to

Amendment 3 (1:2:2 allocation ratio) to ensure a randomized comparison of treatment arms that is not impacted by the time of randomization.

The total sample size will depend on the target to randomize at least 484 subjects with high expression PD-L1+ tumors. Assuming a prevalence ratio of approximately 7/3 (70% prevalence rate for any PD-L1+ and 30% with high expression PD-L1+) the randomized allocation to treatment groups will proceed up to a target number of approximately 1131 subjects with any expression PD-L1+ tumors. Further assumptions are given below:

- Similar efficacy boundaries for treatment group comparisons i.e. for each endpoint determination of superiority of avelumab vs control a similar treatment effect is considered for both avelumab regimens.
- HR=0.6 for Arm A or C versus Arm B for high expression PD-L1 populations, eg, median PFS prolongation from 6 to 10 months and median OS prolongation from 12 to 20 months under an exponential model assumption.
- Subjects will initially be randomized in a 1:1 (Arm A: Arm B) allocation ratio. After this amendment, subjects will be randomized in a 1:2:2 (Arm A: Arm B: Arm C) allocation ratio.
- PFS drop-out rate of approximately 25% and OS drop-out rate of approximately 5%
- Overall, accrual time up to 24 months and 70% prevalence of any PD-L1 expression (accrual time up to 14 months after Amendment 3)
- Minimum follow-up time of 10 months for interim analysis after randomization of the last subject
- Minimum follow-up time of 20 months for final analysis after randomization of the last subject
- Overall significance level of 0.025 (one-sided) split to local significance levels due to primary PFS and OS endpoints (2:1 ratio) and 2 treatment group comparisons against control (3:1 ratio), ie, α_{PFS}=0.0125 (=0.025 × 6/12) and α_{OS}=0.00625 (=0.025 × 3/12) for Arm C versus Arm B local comparisons and α_{PFS}=0.00417 (=0.025 × 2/12) and α_{OS}=0.00208 (=0.025 × 1/12) for Arm A versus Arm B local comparisons for high and moderate expression PD-L1+ subsets.
- Actual significant levels might differ according to multiple testing procedures.
- Local power > 80%.
- Randomization into the 3rd treatment arm (Arm C) will start after approximately 154 subjects with high PD-L1+ expression have been randomized to Arm A and B initially under the 1:1 randomization schema.

The data cut-off for the primary PFS and OS analyses will occur after the target number of 173 OS events for Arm C versus B comparison of the randomized subjects with high expression PD-L1+ tumors has been reached and at least 20 months follow-up after the randomization of the last subject in the study.

The PD-L1 IHC assay and the scoring algorithm to determine low, moderate, and high PD-L1 expression status will be defined prior to conducting any statistical analyses. Details will be specified in laboratory manual and statistical analysis plan.

Study procedures will be established to maintain data integrity in this open-label trial and to limit biased assessment of endpoints, e.g. by establishing an independent and blinded review of tumor images; by ensuring adequate blindness of the PD-L1+ status through regulating the flow of PD-L1 expression data between the laboratory site; by IWRS vendor for the stratification; and by IDMC during study conduct.

Safety data will be summarized, and AEs will be summarized by incidence, severity, seriousness, and relationship to trial drug according to the as-treated principle.

Table 1 Schedule of Assessments- Avelumab Dosed Once Every 2 Weeks (Arm A)

	Screening/ Baseline	Treatment Phase[b]								End of Treatment	Follow-up[c]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Random-ization[a]	W 1 Day 1	W 3 Day 15	W 5 Day 29	W 7 Day 43	W 9 Day 57	W 11 Day 71	W 13 Day 85	Until progression [t]	Within 7 Days of Decision to Discontinue Treatment[d,e]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
Study Procedures													
Written informed consent	X												
PD-L1 tumor expression/Tumor tissue [f]	X												
Inclusion/exclusion criteria	X												
Medical history/smoking history[g]	X												
Demographic data	X												
HBV and HCV testing	X												
Patient-reported outcomes/quality of life assessments[h]	X[h]				X			X	6 weeks	X	X		
Physical examination[i]	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	X	X	X	X	X	X	X	X	2 weeks	X	X		

	Screening/ Baseline	Treatment Phase[b]								End of Treatment	Follow-up[c]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W 1 Day 1	W 3 Day 15	W 5 Day 29	W 7 Day 43	W 9 Day 57	W 11 Day 71	W 13 Day 85	Until progression[t]	Within 7 Days of Decision to Discontinue Treatment[d,e]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
ECOG PS	X[j]	X	X	X	X	X	X	X	2 weeks	X	X		
12-lead ECG[k]	X									X			
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit												
Further antitumor therapy											X	X	X
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[c]											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 Phone Call will be followed up[c]											X	
Samples and Laboratory Assessments													
Hematology and hemostaseology	X	X	X	X	X	X	X	X	2 weeks	X	X		
Full serum chemistry[l]	X		X	X				X	6 weeks	X			
Core serum chemistry[m]		X[m]			X	X	X		2 weeks		X		
Urinalysis[n]	X				X			X	6 weeks	X	X		
β-HCG pregnancy test[o]	X	X		X		X		X	4 weeks	X	X		

	Screening/ Baseline	Treatment Phase[b]								End of Treatment	Follow-up[c]		
		V1	V2	V3	V4	V5	V6	V7		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W 1 Day 1	W 3 Day 15	W 5 Day 29	W 7 Day 43	W 9 Day 57	W 11 Day 71	W 13 Day 85	Until progression[t]	Within 7 Days of Decision to Discontinue Treatment[d,e]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
ACTH[p]	X												
T_4 and TSH[p]	X				X			X	6 weeks	X	X		
Response Assessments													
Tumor evaluation/staging (CT scan/MRI/Other established methods)[q,r]	X				X			X	6 weeks for the first 12 months, Every 12 weeks Thereafter	X			
Dosing													
Pretreatment[s]		X	X	X	X	X	X	X	2 weeks				
Avelumab		X	X	X	X	X	X	X	2 weeks				
Optional Tumor Biopsy										After progression			

ACTH: adrenocorticotropic hormone; AE: adverse events; β-HCG: β-human chorionic gonadotropin; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D-5L: European Quality Of Life 5-dimensions 5-level questionnaire; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: Informed Consent Form; IV: intravenous; MRI: magnetic resonance imaging; PD-L1: programmed death-ligand 1; PR: partial response; T4: free thyroxine; TSH: thyroid-stimulating hormone; V: visit; W: Week.

[a] Randomization will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

[b] A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures; however the bi-weekly 14-day schedule for avelumab dosing should be strictly adhered to, returning to the target date even if the previous visit was off schedule. The calculation of the dose of avelumab will be based on the weight of the subject determined within 72 hours prior to the day of drug administration (see Section 5.1.3.1).

[c] Subjects with an AE will be documented until the Safety Follow-up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up phone call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed 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 IMP (see Section 7.1.5 for details). In addition, survival information (including assessment of any further anticancer therapy) will be collected every 12 weeks (± 1 week). The survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab (see Section 7.1.6 for details). Adverse events and concomitant medications will be documented at each trial visit.

[d] Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. The subject may stay on a 6 week schedule if they continue tumor evaluations in the absence of progression and there is no start of further anticancer therapy.

[e] If another antineoplastic therapy is administered before the end of this 7 day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy. The End-of-Treatment visit should occur within 7 days of the decision to discontinue.

[f] Tumor tissue must be available within 10 calendar days after the subject has signed the ICF in order to establish the PD-L1 status of the tumor. A biopsy should be collected unless tissue from an archival specimen is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Preferably, archived samples, if needed should be less than 6 months old. Samples can be provided as block or slides (see Section 7.6 for details). Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and performed centrally.

[g] Medical history should include history of NSCLC, previous and ongoing medications, smoking history, and baseline medical conditions.

[h] The patient-reported outcomes/quality of life assessments (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-LC13) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The pretreatment assessment should be conducted at Screening; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

[i] If the Screening physical examination was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1. A full physical examination should be performed at Screening and the EOT visit. Physical examinations at all other visits should be directed towards signs and symptoms.

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

[k] 12-lead ECG should be assessed during screening and at the End-of-Treatment visit. ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline detected during the physical examination and/or vital signs measurements performed prior to avelumab treatment. The avelumab administration should not be withheld in the isolated situation of an increased heart rate, unless the overall evaluation, including the ECG, is suggestive of myocarditis, in which case the protocol guidelines (as outlined in Table 10) should be followed.

[l] Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

[m] Core serum chemistry includes liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If Screening full chemistry was performed within 3 days prior to Day 1, core serum chemistry does not have to be completed at Visit 1.

[n] Full urinalysis (dipstick and microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

[o] β-hCG should be determined from serum at Screening and from urine or serum thereafter. Results of the pregnancy test should be available prior to dosing of trial drug.

[p] ACTH will be collected only at Baseline. T4 and TSH will be collected at Screening/Baseline, and every 6 weeks during the treatment phase, at the End-of-Treatment visit and the 30-day Safety Follow-up visit.

[q] On study imaging will be performed every 6 weeks (±1 week) calculated from the randomization date and as clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. 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 every 12 weeks after 12 months) until PD is assessed by the Investigators according to RECIST 1.1 or start of new cancer therapy. In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1, 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 scheduled assessment after the initial documentation of PR. After progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. In case of avelumab treatment beyond progression, additional images should be collected in accordance with imaging schedule as long as the subject continues on avelumab therapy. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory).

[r] A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.

[s] Subjects must receive pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to infusion of avelumab (10 mg/kg IV over 1 hour [-10/+20 minutes]). Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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.

[t] If avelumab treatment is terminated before disease progression and no new cancer treatments are initiated and the subject is stable, all assessments (including tumor imaging) will continue on a 6-week schedule until disease progression (except pretreatment and avelumab administration).

Table 2 **Schedule of Assessments: Chemotherapy (Arm B) for Subjects Receiving Pemetrexed, Cisplatin, Carboplatin, or Paclitaxel**

	Screening/ Baseline	Chemotherapy Treatment Phase[b]							End of Treatment	Follow-up[d]		
		V1	V2	V3	V4	V5	V6		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1 Day 1	W4 Day 22	W7 Day 43	W10 Day 64	W13 Day 85	W16 Day 106	Until progression[c]	Within 7 Days of Decision to Discontinue Treatment[e,f]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
Study Procedures												
Written informed consent	X											
PD-L1 tumor expression/Tumor tissue [g]	X											
Inclusion/exclusion criteria	X											
Medical history/smoking history[h]	X											
Demographic data	X											
HBV and HCV testing	X											
Patient-reported outcomes/quality of life assessments[i]	X[i]			X		X		6 weeks	X	X		
Physical examination[j]	X	X[j]	X	X	X	X		6 weeks	X	X		
Vital signs	X	X	X	X	X	X	X	3 weeks	X	X		
Weight	X	X	X	X	X	X	X	3 weeks	X	X		

	Screening/ Baseline	Chemotherapy Treatment Phase[b]							End of Treatment	Follow-up[d]		
		V1	V2	V3	V4	V5	V6		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1 Day 1	W4 Day 22	W7 Day 43	W10 Day 64	W13 Day 85	W16 Day 106	Until progression[c]	Within 7 Days of Decision to Discontinue Treatment[e, f]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
ECOG PS[k]	X	X	X	X	X	X	X	3 weeks	X	X		
12-lead ECG[l]	X								X			
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit											
Further antitumor therapy										X	X	X
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[d]										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 Phone Call will be followed up[d]										X	
Samples and Laboratory Assessments												
Hematology and hemostaseology	X	X	X	X	X	X	X	3 weeks	X	X		
Full serum chemistry[m]	X		X	X		X		6 weeks	X			
Core serum chemistry[n]		X[n]			X		X	3 weeks		X		
Urinalysis[o]	X			X		X		6 weeks	X	X		
β-HCG pregnancy test[p]	X	X	X	X	X	X	X	3 weeks	X	X		
ACTH[q]	X											
T_4 and TSH[q]	X			X		X		6 weeks	X	X		

	Screening/ Baseline	Chemotherapy Treatment Phase[b]							End of Treatment	Follow-up[d]		
		V1	V2	V3	V4	V5	V6		End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1 Day 1	W4 Day 22	W7 Day 43	W10 Day 64	W13 Day 85	W16 Day 106	Until progression[c]	Within 7 Days of Decision to Discontinue Treatment[e,f]	Visit 30 Days after Last Treatment (± 5 days)	Phone Call 90 Days after Last Treatment (± 1 week)	Every 12 Weeks (± 1 week)
CCI [redacted]												
Response Assessments												
Tumor evaluation/staging (CT scan/MRI/Other established methods)[s,t]	X			X		X		6 weeks for the first 12 months, Every 12 weeks Thereafter	X			
Dosing												
Pretreatment[u]		X	X	X	X	X	X	X	3 weeks				
Chemotherapy		X	X	X	X	X	X	X	3 weeks				

ACTH: adrenocorticotropic hormone; AE: adverse events; β-HCG: β-human chorionic gonadotropin; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D-5L: European Quality Of Life 5-dimensions 5-level questionnaire; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: Informed Consent Form; IV: intravenous; MRI: magnetic resonance imaging; PD-L1: programmed death-ligand 1; PR: partial response; T4: free thyroxine; TSH: thyroid-stimulating hormone; V: visit, W: Week.

[a] Randomization will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

[b] A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. The tri-weekly 21-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule.

[c] Chemotherapy to be administered to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities. Pemetrexed may be continued as maintenance therapy, after 4 cycles of platinum-based chemotherapy in the absence of disease progression, or in accordance with pemetrexed local label. No other maintenance therapy is permitted. If chemotherapy treatment is terminated before disease progression and no new cancer treatments are initiated and the subject is stable, all assessments (including tumor imaging) will continue on a 6-week schedule until disease progression.

[d] Subjects with an AE will be documented until the Safety Follow-up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up phone call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed 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 IMP. In addition, survival information (including assessment of any further anticancer therapy) will be collected every 12 weeks (± 1 week). The survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab (see Section 7.1.5 for details). Adverse events and concomitant medications will be documented at each trial visit.

[e] Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. The subject may stay on a 6 week schedule if they continue tumor evaluations in the absence of progression and there is no start of further anticancer therapy.

[f] If another antineoplastic therapy is administered before the end of this 7 day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy. The End-of-Treatment visit should occur within 7 days of the decision to discontinue.

[g] Tumor tissue must be available within 10 calendar days after the subject has signed the ICF in order to establish the PD-L1 status of the tumor. A biopsy should be collected unless tissue from an archival specimen is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details). Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and performed centrally.

[h] Medical history should include history of NSCLC, previous medications, smoking history, and Baseline medical condition.

[i] The patient-reported outcomes/quality of life assessments (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-LC13) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The pre-treatment assessment should be conducted at Screening; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

[j] If the Screening physical examination was performed within 3 days prior to Day 1, it does not have to repeated at Visit 1. A full physical examination should be performed at Screening and the EoT visit. Physical examinations at all other visits should be directed towards signs and symptoms.

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

[l] 12-lead ECG should be assessed during screening and at the End-of-Treatment visit. ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline detected during the physical examination and/or vital signs measurements performed prior to study treatment. The treatment administration should not be withheld in the isolated situation of an increased heart rate, unless the overall evaluation, including the ECG, is suggestive of myocarditis, in which case the protocol guidelines (as outlined in Table 10) should be followed

[m] Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

[n] Core serum chemistry includes liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If Screening full chemistry was performed within 3 days prior to Day 1, core serum chemistry does not have to be completed at Visit 1.

[o] Full urinalysis (dipstick and microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

[p] β-hCG should be determined from serum at Screening and from urine or serum thereafter. Results of the most recent pregnancy test should be available prior to next dosing of trial drug.

[q] ACTH will be collected only at Baseline. T4 and TSH will be collected at Screening/Baseline and every 6 weeks during the treatment phase, and continue thereafter until progression if progression does not occur at treatment termination at the End-of-Treatment visit, and the 30-day Safety Follow-up visit.

CCI [redacted]

[s] On study imaging will be performed every 6 weeks (±1 week) calculated from the randomization date and as clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. 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 every 12 weeks after 12 months) until PD is assessed by the Investigators according to RECIST 1.1. In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1, 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. After progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory).

[t] A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.

[u] Subjects will be administered pretreatment prior to each chemotherapy infusion per chemotherapy label instructions, or equivalent per local institutional practice. As the premedication for pemetrexed (oral folic acid, vitamin B12 intramuscular injection) will need to be delivered in the week before the first dose of chemotherapy, this premedication is permitted to be initiated in all subjects with non-squamous histology after signing the informed consent and prior to randomization (Section 5.1.2.2).

Table 3 Schedule of Assessments for Chemotherapy (Arm B) for Subjects Receiving Gemcitabine

	Screening/ Baseline Assessments	Chemotherapy Treatment Phase (Gemcitabine only)[b]												End of Treatment	Follow-up[c]		
		V1		V2		V3		V4		V5		V6			End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1	W2	W4	W5	W7	W8	W 10	W 11	W 13	W 14	W 16	W 17	Until progression[d]	Within 7 Days of Decision to Discontinue Treatment[e, f]	Visit 30 Days after Last Treatment (±5 days)	Phone Call 90 Days after Last Treatment (±1 week)	Every 12 Weeks (±1 week)
	Day	1	8	22	29	43	50	64	71	85	92	106	113					
Study Procedures																		
Written informed consent	X																	
PD-L1 tumor expression/Tumor tissue [g]	X																	
Inclusion/exclusion criteria	X																	
Medical history/smoking history[h]	X																	
Demographic data	X																	
HBV and HCV testing	X																	
Patient-reported outcomes/quality of life assessments[i]	X					X				X				6 weeks	X	X		
Physical examination[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	6 weeks	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	3 weeks	X	X		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	3 weeks	X	X		
ECOG PS[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	3 weeks	X	X		

	Screening/ Baseline Assessments	Chemotherapy Treatment Phase (Gemcitabine only)[b]													End of Treatment	Follow-up[o]		
		V1		V2		V3		V4		V5		V6			End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1	W2	W4	W5	W7	W8	W 10	W 11	W 13	W 14	W 16	W 17	Until progression[d]	Within 7 Days of Decision to Discontinue Treatment[e, f]	Visit 30 Days after Last Treatment (±5 days)	Phone Call 90 Days after Last Treatment (±1 week)	Every 12 Weeks (±1 week)
	Day	1	8	22	29	43	50	64	71	85	92	106	113					
12-lead ECG[l]	X														X			
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit																	
Further antitumor therapy																X	X	X
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[c]																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 Phone Call will be followed up[c]																X	
Samples and Laboratory Assessments																		
Hematology[m] and hemostaseology	X	X	X	X	X	X	X	X	X	X		X		3 weeks	X	X		
Full serum chemistry[n]	X			X		X				X				6 weeks	X			
Core serum chemistry[o]		X	X		X		X	X	X		X		X	3 weeks		X		
Urinalysis[p]	X					X				X				6 weeks	X	X		
β-HCG pregnancy test[q]	X	X		X		X		X		X		X		3 weeks	X	X		
ACTH[r]	X																	
T_4 and TSH[r]	X					X				X				6 weeks	X	X		
CCI																		

	Screening/ Baseline Assessments	Chemotherapy Treatment Phase (Gemcitabine only)[b]												End of Treatment	Follow-up[c]		
		V1		V2		V3		V4		V5		V6			End-of-Treatment Visit	Safety Follow-up Visit		Survival Long-term Follow-up
	Day -28 to Randomization[a]	W1	W2	W4	W5	W7	W8	W 10	W 11	W 13	W 14	W 16	W 17	Until progression[d]	Within 7 Days of Decision to Discontinue Treatment[e, f]	Visit 30 Days after Last Treatment (±5 days)	Phone Call 90 Days after Last Treatment (±1 week)	Every 12 Weeks (±1 week)
	Day	1	8	22	29	43	50	64	71	85	92	106	113					
CCI [redacted]																		
Response Assessments																		
Tumor evaluation/staging (CT scan/MRI/Other established methods)[t, u]	X					X				X				6 weeks for the first 12 months, every 12 weeks thereafter	X			
Dosing																		
Pretreatment[v]		X	X	X	X	X	X	X	X	X	X	X	X	3 weeks				
Chemotherapy		X	X	X	X	X	X	X	X	X	X	X	X	3 weeks				

ACTH: adrenocorticotropic hormone; AE: adverse events; β-HCG: β-human chorionic gonadotropin; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D-5L: European Quality Of Life 5-dimensions 5-level questionnaire; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: Informed Consent Form; IV: intravenous; MRI: magnetic resonance imaging; PD-L1: programmed death-ligand 1; PR: partial response; T4: free thyroxine; TSH: thyroid-stimulating hormone; V: visit, W: Week.

[a] Randomization will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

[b] A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures. The tri-weekly 21-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. While each treatment cycle is performed every 21 days, treatment visits at the site should be completed on Day 1 and Day 8 in accordance with the gemcitabine administration label.

[c] Subjects with an AE will be documented until the Safety Follow-up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up phone call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed 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 IMP. In addition, survival information (including assessment of any further anticancer therapy) will be collected every 12 weeks (± 1 week). The survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab (see Section 7.1.5 for details). Adverse events and concomitant medications will be documented at each trial visit.

[d] If chemotherapy treatment is terminated before disease progression and no new cancer treatments are initiated and the subject is stable, all assessments (including tumor imaging) will continue on a 6-week schedule until disease progression.

[e] Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. The subject may stay on a 6 week schedule if they continue tumor evaluations in the absence of progression and there is no start of further anticancer therapy.

[f] If another antineoplastic therapy is administered before the end of this 7 day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy. The End-of-Treatment visit should occur within 7 days of the decision to discontinue.

[g] Tumor tissue must be available within 10 calendar days after the subject has signed the ICF in order to establish the PD-L1 status of the tumor. A biopsy should be collected unless tissue from an archival specimen is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details). Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and performed centrally.

[h] Medical history should include history of NSCLC, previous medications, smoking history, and Baseline medical condition.

[i] The patient-reported outcomes/quality of life assessments (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-LC13) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The pre-treatment assessment should be conducted at Screening; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

[j] If the Screening physical examination was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1. A full physical examination should be performed at Screening and the EoT visit. Physical examinations at all other visits should be directed towards signs and symptoms.

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

[l] 12-lead ECG should be assessed during screening and at the End-of-Treatment visit. ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline detected during the physical examination and/or vital signs measurements performed prior to avelumab treatment.

[m] Hemasteology is NOT performed at Day 8 of each cycle.

[n] Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

[o] Core serum chemistry includes liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If the Screening full chemistry was performed within 3 days prior to Day 1, core serum chemistry does not have to be completed at Visit 1.

[p] Full urinalysis (dipstick and microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

[q] β-hCG should be determined from serum at Screening and from urine or serum thereafter. Results of the most recent pregnancy test should be available prior to next dosing of trial drug.

[r] ACTH will be collected only at Baseline. T4 and TSH will be collected at Screening/Baseline and every 6 weeks during the treatment phase, and continue thereafter until progression if progression does not occur at treatment termination at the End-of-Treatment visit, and the 30-day Safety Follow-up visit.

CCI [redacted]

[t] On study imaging will be performed every 6 weeks (±1 week) calculated from the randomization date and as clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. 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 every 12 weeks after 12 months) until PD. In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1, 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. After progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory).

[u] A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.

[v] Subjects will be administered pretreatment prior to each chemotherapy infusion per chemotherapy label instructions, or equivalent per local institutional practice.

Table 4 Schedule of Assessments - Avelumab Dosed Once a Week (Arm C)

	Screening/ Baseline Assessments	Treatment Phase[b]												
		V1		V2		V3		V4		V5		V6		V7 (Roll-over into Once-every-2 weeks dosing)
	Day -28 to Randomization[a]	W1 Day 1	W2 Day 8	W3 Day 15	W4 Day 22	W5 Day 29	W6 Day 36	W7 Day 43	W8 Day 50	W9 Day 57	W10 Day 64	W11 Day 71	W12 Day 78	W13 Day 85 (Follow Table 1 after V7/W13)
Study Procedures														
Written informed consent	X													
PD-L1 tumor expression/Tumor tissue [c]	X													
Inclusion/exclusion criteria	X													
Medical history/smoking history[d]	X													
Demographic data	X													
HBV and HCV testing	X													
Patient-reported outcomes/quality of life assessments[e]	X[e]							X						X
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X		X		X		X		X		X		X
ECOG PS	X[g]	X		X		X		X		X		X		X
12-lead ECG[h]	X													

	Screening/ Baseline Assessments	Treatment Phase[b]												
		V1		V2		V3		V4		V5		V6		V7 (Roll-over into Once-every-2 weeks dosing)
	Day -28 to Randomization[a]	W1 Day 1	W2 Day 8	W3 Day 15	W4 Day 22	W5 Day 29	W6 Day 36	W7 Day 43	W8 Day 50	W9 Day 57	W10 Day 64	W11 Day 71	W12 Day 78	W13 Day 85 (Follow Table 1 after V7/W13)
Concomitant medications and procedures	Collected through the 30-day Safety Follow-up Visit													
Further antitumor therapy	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													
SAE collection	All SAEs are documented until the 90-day Safety Follow-up Phone Call, Ongoing SAEs at the 90-day Safety Follow-up Phone Call will be followed up													
Samples and Laboratory Assessments														
Hematology and hemostaseology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full serum chemistry[i]	X		X		X		X		X		X		X	X
Core serum chemistry[j]		X[j]		X		X		X		X		X		
Urinalysis[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
β-HCG pregnancy test[l]	X	X				X				X				X
ACTH[m]	X													
T_4 and TSH[n]	X							X						X
Response Assessments														
Tumor evaluation/staging (CT scan/MRI/Other	X							X						X

	Screening/ Baseline Assessments	Treatment Phase[b]												
		V1		V2		V3		V4		V5		V6		V7 (Roll-over into Once-every-2 weeks dosing)
	Day -28 to Randomization[a]	W1 Day 1	W2 Day 8	W3 Day 15	W4 Day 22	W5 Day 29	W6 Day 36	W7 Day 43	W8 Day 50	W9 Day 57	W10 Day 64	W11 Day 71	W12 Day 78	W13 Day 85 (Follow Table 1 after V7/W13)
established methods)[o,p]														
Dosing														
Pretreatment[q]		X	X	X	X	X	X	X	X	X	X	X	X	X
Avelumab		X	X	X	X	X	X	X	X	X	X	X	X	X

ACTH: adrenocorticotropic hormone; AE: adverse events; β-HCG: β-human chorionic gonadotropin; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D-5L: European Quality Of Life 5-dimensions 5-level questionnaire; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: Informed Consent Form; IV: intravenous; MRI: magnetic resonance imaging; PD-L1: programmed death-ligand 1; PR: partial response; T4: free thyroxine; TSH: thyroid-stimulating hormone; V: visit; W: Week.

[a] Randomization will be done after the confirmation of fulfilling all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

[b] A time window of 1 day before or 1 day after the scheduled visit day (-1/+1 days) will be permitted for all trial procedures while subjects receive avelumab once weekly. A time window up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures while subjects receive avelumab once every two weeks; however the weekly 7-day schedule for avelumab dosing should be strictly adhered to, returning to the target date even if the previous visit was off schedule. The calculation of the dose of avelumab will be based on the weight of the subject determined within 72 hours prior to the day of drug administration (see Section 5.1.3.1).

[c] Tumor tissue must be available within 10 calendar days after the subject has signed the ICF in order to establish the PD-L1 status of the tumor. A biopsy should be collected unless tissue from an archival specimen is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). Samples can be provided as block or slides (see Section 7.6 for details). Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and performed centrally.

[d] Medical history should include history of NSCLC, previous and ongoing medications, smoking history, and Baseline medical condition.

[e] The patient-reported outcomes/quality of life assessments (EQ-5D-5L, EORTC QLQ-C30, and module QLQ-LC13) should be completed by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. The pretreatment assessment should be conducted at Screening; in the event that this doesn't occur, it can be done at Visit 1 (Day 1) prior to treatment.

[f] If the Screening physical examination was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1. A full physical examination should be performed at Screening and the EOT visit. Physical examinations at all other visits should be directed towards signs and symptoms.

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

	Screening/ Baseline Assessments	Treatment Phase[b]												
		V1		V2		V3		V4		V5		V6		V7 (Roll-over into Once-every-2 weeks dosing)
	Day -28 to Randomization[a]	W1 Day 1	W2 Day 8	W3 Day 15	W4 Day 22	W5 Day 29	W6 Day 36	W7 Day 43	W8 Day 50	W9 Day 57	W10 Day 64	W11 Day 71	W12 Day 78	W13 Day 85 (Follow Table 1 after V7/W13)

[h] 12-lead ECG should be assessed during screening and at the End-of-Treatment visit. ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline detected during the physical examination and/or vital signs measurements performed prior to avelumab treatment. The avelumab administration should not be withheld in the isolated situation of an increased heart rate, unless the overall evaluation, including the ECG, is suggestive of myocarditis, in which case the protocol guidelines (as outlined in Table 10) should be followed

[i] Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 11. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

[j] Core serum chemistry includes liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If Screening full chemistry was performed within 3 days prior to Day 1, core serum chemistry does not have to be completed at Visit 1.

[k] Full urinalysis (dipstick and microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

[l] β-hCG should be determined from serum at Screening and from urine or serum thereafter. Results of the pregnancy test should be available prior to dosing of trial drug.

[m] ACTH will be collected only at Baseline.

[n] T4 and TSH will be collected at Screening/Baseline, and every 6 weeks during the treatment phase, and continue thereafter until progression if progression does not occur at treatment termination at the End-of-Treatment visit and the 30-day Safety Follow-up visit.

[o] On study imaging will be performed every 6 weeks (±1 week) calculated from the randomization date and as clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1, 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 scheduled assessment after the initial documentation of PR. After progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. In case of avelumab treatment beyond progression, additional images should be collected in accordance with imaging schedule as long as the subject continues on avelumab therapy. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory).

[p] A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.

[q] Subjects must receive pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to infusion of avelumab (10 mg/kg IV over 1 hour [-10/+20 minutes]). Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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.

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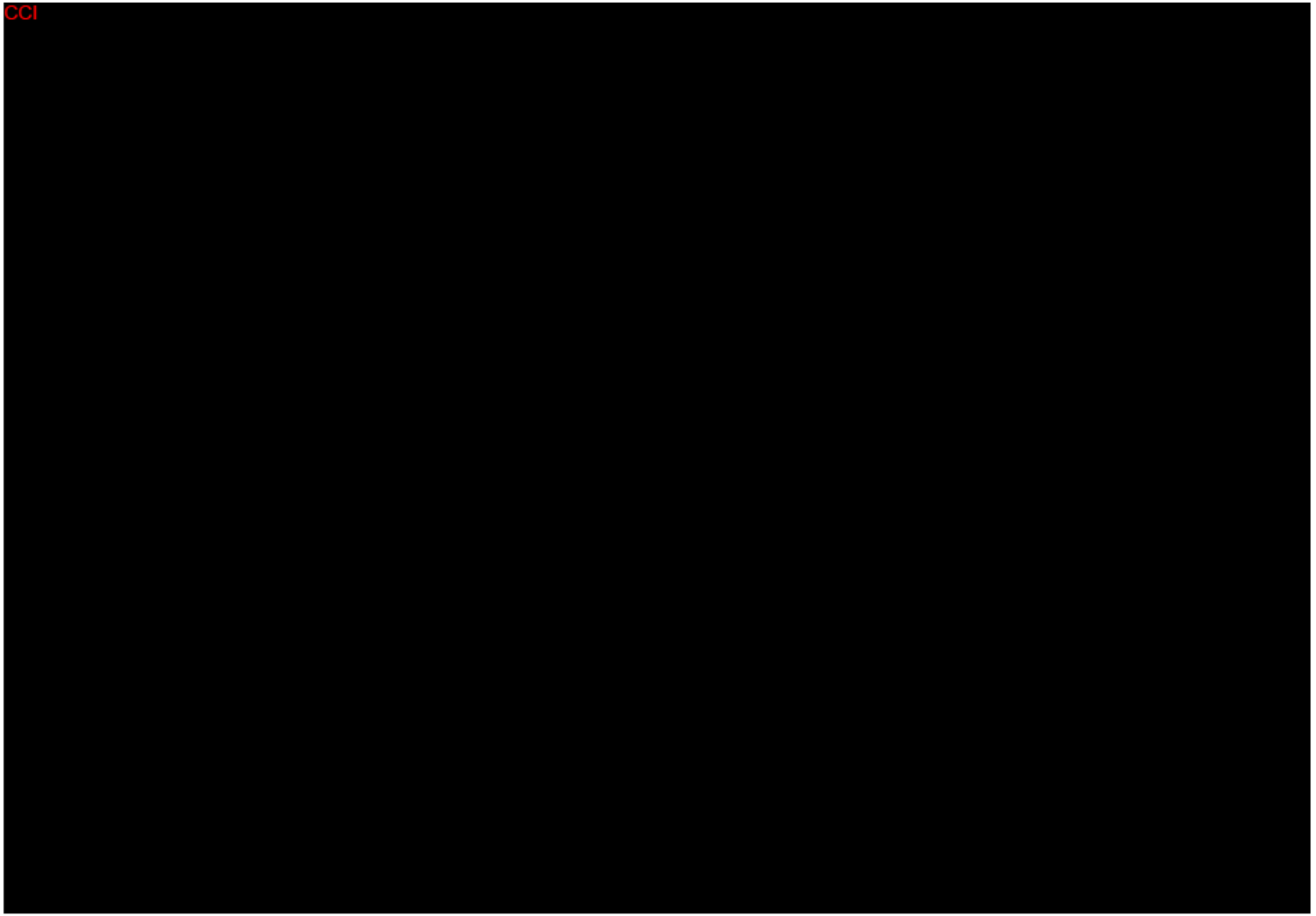

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[redacted]

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 (USA), and Merck KGaA, Darmstadt, Germany, in rest of world.

A contract research organization (CRO), PPD , 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 up to 386 sites globally in North America (approximately 27 in the USA), South America, Asia, Africa, and Europe.

2.2 Trial Coordination/Monitoring

The Sponsor will coordinate the trial and will use 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 randomization will be managed by an interactive web response system (IWRS).

Protocol required 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. Urinalysis and urine pregnancy testing will be performed locally.

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

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses), which will be outsourced to a CRO.

2.3 Review Committees

2.3.1 Independent Data Monitoring Committee

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

2.3.2 Independent Review Committee

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

The Independent Review Committee (IRC) will perform a blinded determination as to whether the criteria for tumor response or progression according to RECIST 1.1 have been met. The role of the IRC will be to review radiographic image findings for the determination of the time point overall response according to RECIST 1.1 for each subject. The IRC membership, assessment criteria details, mandate, and processes of the IRC are provided in the IRC charter.

3 Background Information

3.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer is the leading cause of cancer-related death in men and women in the USA and in the EU, resulting in more cancer related deaths than breast cancer, prostate cancer, and colorectal cancer combined. Worldwide, an estimated 1.8 million new cases of lung cancer were diagnosed in 2012, approximately 13% of the total of all new cancers diagnosed (2). In 2014, an estimated 224,210 new cases (116,000 in men and 108, 210 in women) of lung and bronchial cancer will be diagnosed, and 149, 260 deaths (86, 930 in men and 72, 330 in women) are estimated to occur because of the disease. Only 16.6% of all lung cancer patients are alive 5 or more years after diagnosis (3).

In patients with NSCLC, outcomes from standard therapy are poor except for the most localized cancers where surgery and / or combined modality therapy can provide a cure in a small percentage of patients. In patients with advanced or metastatic NSCLC, chemotherapy offers modest benefit, though overall survival (OS) remains poor (4, 5). Despite treatment with platinum-based regimens with third generational agents, patients with metastatic NSCLC have a median survival of approximately 10 to 12 months, and a 5-year survival rate of approximately 15% (6).

Recently, personalized therapy for patients with tumors with specific genetic alternations, such as tyrosine kinase inhibitors for tumors with activating EGFR mutations, has resulted in better OS outcomes in these biologically selected subgroups. However, these patients represent only 10-15% of patients and new treatment options are still needed to improve the prognosis for patients with lung cancer. Novel agents that harness the immune system, such as vaccines and antibodies that modulate T-cell activity, offers an alternative treatment approach that could help improve outcomes. Improvements in OS in randomized Phase III clinical trials have led to the approval of ipilimumab (anti-CTLA4) for melanoma, and sipuleucel-T for prostate cancer, and generated a renewed interest in immunotherapy for solid tumors. In fact, while immunotherapy for lung cancer has not been successful in the past, nivolumab (anti-PD1) was recently approved by the FDA for the treatment of patients with metastatic squamous cell NSCLC based on a statistically significant improvement in OS in a randomized Phase III clinical trial. In light of these recent data validating the clinical importance of blocking the PD-1/PD-L1 pathway in metastatic NSCLC, avelumab, which is an anti-PD-L1 monoclonal antibody, is being investigated in late stage clinical trials in patients with various advanced solid tumors, including NSCLC.

Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the Investigator.

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 (7-10), potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate antitumor activity in nonclinical animal models (8,11).

In the clinical setting, treatment with antibodies that block the PD-1 – anti-PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles (8,10,11). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients.

In 2015, pembrolizumab and nivolumab (anti-PD-1 antibodies) were approved by the US FDA for the treatment of patients with NSCLC who had progressed following platinum-based therapy. While nivolumab was approved for patients with NSCLC regardless of PD-L1 expression, approval of pembrolizumab was restricted to patients whose tumors expressed PD-L1.

In first line treatment setting of NSCLC, extensive studies are ongoing to evaluate anti-PD1/PD-L1 agents based on various PD-L1 expression cutoffs. Preliminary and emerging clinical data suggest that PD-1/PD-L1inhibitors are active in patients whose tumors exhibit tumor cell PD-L1 expression. While better clinical outcome in terms of ORR, PFS and OS has recently been reported in patients with increased levels of PD-L1 expression, its role in patients whose tumors express lower levels of PD-1 expression needs to be further characterized.

In light of these recent data demonstrating the clinical efficacy of an anti-PD1 antibody in metastatic NSCLC and considering the clinical importance of PD-L1 expression by NSCLC tumor cells, avelumab (an anti-PD-L1 monoclonal antibody) is being developed in advanced NSCLC.

3.3 Avelumab

The investigational medicinal product (IMP) for the present trial is avelumab (formerly designated MSB0010718C), a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono R&D, Billerica, MA, USA.

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 therefore, is 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 (15). For complete details of the in vitro and nonclinical studies, please refer to the IB.

Avelumab is currently being investigated in the following ongoing clinical studies:

- Trial EMR100070-001 is a "Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, 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, pharmacokinetics, 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."
- Trial EMR100070-003 is a "Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma." This trial is ongoing and no data are available.
- Trial EMR100070-004 is a "Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet." This trial is ongoing and no data are available.
- Trial EMR100070-007 is 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". This trial is ongoing and no data are available.
- Trial EMR100070-008 is a "Phase III open-label, multicenter trial of avelumab (MSB0010718C) as a third-line treatment of unresectable, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma". This trial is ongoing and no data are available.
- Trial B9991002 is a "Phase Ib open-label, dose-finding study to evaluate safety, PK and PD of avelumab (MSB0010718C) in combination with Axitinib (AG-013736) in patients with previously untreated advanced renal cell cancer." This trial is ongoing and no data are available.

- Trial B9991005 is a "Phase Ib and Phase II open-label dose-finding study to evaluate safety and efficacy, PK and PD of avelumab in NSCLC in combination with crizotinib in ALK negative disease or PF-06463922 in ALK-positive disease. Objective for Phase Ib: to determine the MTD and RP2D." This trial is ongoing and no data are available.
- Trial B9991007 is a "Phase I, open-label study to evaluate the PK and PD of avelumab in subjects with previously treated advanced stage classical Hodgkins Lymphoma to characterize the PK of different dosing regimens and its relation to target occupancy in peripheral blood." This trial is ongoing and no data are available.
- Trial B9991009 is a "Phase III Randomized, open-label study of avelumab (MSB0010718C) alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer." This trial is ongoing and no data are available.
- Trial B9991001 is a "Phase III multicenter, multinational, open-label randomized parallel-arm study of avelumab plus BSC vs BSC alone as maintenance treatment in subjects with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of 1L platinum-containing chemotherapy to demonstrate benefit in overall survival in PD-L1 positive subjects." This trial is ongoing and no data are available.
- Trial B9991010 is a "Randomized, open-label, multicenter, Phase 3 study to evaluate the efficacy and safety of avelumab (MSB0010718C) in combination with and/or following chemotherapy in patients with previously untreated epithelial ovarian cancer." This trial is ongoing and no data are available.

3.3.1 Phase I Data from Trial EMR100070-001

Available safety and efficacy data for the avelumab program are discussed in the IB and establish a positive benefit-risk profile for conducting Phase III studies with 10 mg/kg (the dose used in this trial). Highlights relevant to developing this protocol are provided below. As of the safety cutoff

date of 05 November 2015, 1353 subjects had received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg administered once every 2 weeks (IB). In the dose escalation portion of the Phase I study a total of 53 subjects were treated, including 21 subjects who received 20 mg/kg, and there was no evidence of differences in the safety profile across all administered dose levels. The MTD was not reached. Subsequently, 1300 subjects received 10 mg/kg administered once every 2 weeks in the pooled expansion cohort).

The 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 MoAB blocking the PD-1/PD-L1 axis.

Infusion-related reactions, including hypersensitivity reactions and immune-mediated adverse reactions (eg, hypothyroidism, pneumonitis, hyperthyroidism, adrenal insufficiency, autoimmune hepatitis, colitis, thyroiditis, or myositis) have been identified as important risks for avelumab (see IB for details).

Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this one (please see Sections 3.5, 5.1.2.1, 6.2.1, and 6.5.4).

3.3.2 Pharmacokinetics

Pharmacokinetic assessments have been performed in ongoing studies EMR100070-001 and EMR100070-002. The PK results based on the data available as of 20 November 2015 are presented under the individual trial headings.

3.3.2.1 Trial EMR100070-001

The pharmacokinetics of avelumab has been examined at 1, 3, 10, and 20 mg/kg doses during the dose escalation phase and at 10 mg/kg dose during an expansion phase for selected indications, following iv infusion once every 2 weeks. As of the data cutoff date of 20 November 2015, a total of 53 subjects were enrolled and received at least 1 dose of study drug in the dose-escalation phase of the study and 1436 subjects across 16 expansion cohorts were enrolled and received at least 1 dose of study drug in the expansion phase of the study (NDA 2.7.2). Frequent blood samples for the analysis of serum concentrations of avelumab were drawn from subjects in the dose escalation phase and 2 expansion cohorts. Sparse PK samples were collected and analyzed from all subjects.

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized by standard non-compartmental analysis (NCA) based on the rich serum concentration-time data using recorded times obtained over a complete 2-week dosing interval. The dose-normalized exposure parameters, maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}336hr}$) after first dose appeared flat across 3 to 20 mg/kg, suggesting the exposure increased in an approximately dose-proportional manner between 3 to 20 mg/kg. The concentration at the end of dose interval, C_{trough}, increased proportionally with doses between 10 to 20 mg/kg, but more than proportionally for doses between 1 to 10 mg/kg, likely due to the presence of target mediated drug disposition (TMDD) at these

lower dose levels. The $t_{1/2}$ after the first dose increased with the dose for the 1 and 3 mg/kg dose groups. However, the geometric mean values for $t_{1/2}$ were similar for 10 mg/kg and 20 mg/kg dose levels, 94.6 hours (3.9 days) and 99.1 hours (4.1 days), respectively. The geometric mean clearance was estimated to be 0.362 mL/hr/kg (0.0264 L/hr for a subject who weighs 73 kg) for the 10 mg/kg dose.

Following repeated 10 mg/kg once every 2 weeks dosing, the concentrations at the end of infusion (C_{EOI}) reached the steady state approximately between the second and the third dosing with a minimal accumulation. The C_{trough} values were similar across subjects with different tumor types indicating that there is no meaningful difference in avelumab PK in subjects with different solid tumor types.

3.3.2.2 Trial EMR100070-002

Study EMR100070-002 is an ongoing Phase I dose escalation study with consecutive expansion to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors. In the dose escalation part subjects received 3, 10, and 20 mg/kg of avelumab given as a 1-hour infusion. The expansion part is being performed in Asian subjects with gastric cancer and who receive the 10 mg/kg of avelumab once every 2 weeks until confirmed progression, unacceptable toxicity, or withdrawal from the study or study drug occurred. As of the data cut-off date of 20 November 2015, a total of 17 subjects had been enrolled in the dose-escalation part of the study and 34 subjects had been enrolled in the expansion part of the study.

Pharmacokinetic data were obtained from 5 Japanese subjects treated with 3 mg/kg, 6 Japanese subjects treated with 10 mg/kg and 6 Japanese subjects treated with 20 mg/kg of avelumab as a 1-hour IV infusion once every 2 weeks in the dose escalation part of the study.

After the first dose, the exposure parameters C_{max} and $AUC_{0\text{-}336hr}$ after appeared to increase dose-proportionally between 3 to 20 mg/kg dose levels. C_{trough} increased proportionally with dose between 10 to 20 mg/kg, but more than proportionally for between dose levels 3 to 10 mg/kg, likely due to the presence of TMDD at these lower dose levels. The geometric mean clearance was calculated to be 0.471 mL/hr/kg (0.0344 L/hr for a subject who weighs 73 kg) at the 10 mg/kg dose. The $t_{1/2}$ increased with the dose. However, the geometric mean values were 122 hours (5.1 days) and 112 hours (4.7 days) for 10 and 20 mg/kg doses, respectively, similar between the 2 dose cohorts.

Following repeated 10 mg/kg once every 2 weeks dosing, C_{EOI} values appeared stable over the treatment period at the 10 mg/kg dose level and moderate variability was observed, probably due to small sample size. The mean C_{EOI} at 10 mg/kg on Day 15 and Day 1 was 207 µg/mL and 174 µg/mL, respectively, and the ratio between them was 1.19. The extent of accumulation of serum concentration during the treatment period was mild, which is in line with the estimated $t_{1/2}$ from the first administration and once every 2 weeks dosing frequency.

3.3.3 Clinical Pharmacodynamics

Receptor occupancy was measured in vitro by flow cytometry on peripheral blood CD3+ T-cells after spiking of human whole blood samples from 8 healthy volunteers with avelumab over a concentration range of 0.003 to 10 µg/mL. In this assay, free receptors were measured in samples spiked over this range and compared with the amount of free receptors in the unspiked sample. A 50% receptor occupancy was observed at a drug concentration of 0.122 µg/mL ± 0.042 µg/mL (standard deviation) and a plateau indicating at least 95% receptor occupancy was reached in all donor blood samples at 1 µg/mL.

These in vitro data combined with PK data were confirmed in ex vivo samples taken at C_{min} after the first dose (Day 15) in a small number of subjects during the initial dose-escalation part of the Phase Ib Trial EMR100070-001 (n=9). For doses of 10 mg/kg, target occupancy (TO) was greater than 90% for these 4 subjects, at trough serum levels ranging between 12.69 to 26.87 µg/mL. Also, for doses of 3 mg/kg, available TO data for 2 subjects with trough levels ranging from 4.56 to 6.99 µg/mL, showed greater than 90% TO at trough exposure levels. At dose level 1 mg/kg, 2 out of 3 subjects displayed less than 90% TO at trough serum concentrations. Avelumab serum concentrations were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Based on the observed avelumab serum concentrations in the EMR100070-001 Phase I clinical trial and the in vitro receptor occupancy data, trough concentrations were sufficient to achieve full target occupancy throughout the entire dosing interval in all of the subjects receiving the 10 mg/kg dose, while after the 3 mg/kg dose, C_{trough} values were insufficient in 3 of the 13 subjects to assure full target occupancy.

3.4 Rationale for the Current Clinical Trial

The rationale to include NSCLC subjects who have not received a systemic treatment for their metastatic disease and to administer avelumab is supported by the following:

- The expression of PD-L1 by NSCLC tumor cells and by adjacent immune infiltrates
- The results from studies that used an anti-PD-1 antibody to block the interaction between PD-L1 and PD-1
- The interim data of the first 184 subjects with NSCLC (post platinum doublet) treated with avelumab, who were enrolled in the current EMR100070-001 Phase I study and were followed up for at least 13 weeks.
- The interim data of the 156 subjects with NSCLC without prior systemic chemotherapy treatment for locally advanced or metastatic disease were treated with avelumab in the current EMR100070-001 Phase I study. Of these subjects, 75 subjects were followed for at least 13 weeks at the time of interim analysis (17). Key results are described below.
- The data from other Phase 1 checkpoint inhibitor studies that exhibit clinical activity (ORR, OS, PFS) in an advanced metastatic NSCLC, first line setting (16,18,19).

- These data suggest that the blockade of the PD-1/PD-L1 axis results in response rates that compares favorably against the existing standard of care, ie, platinum-based doublets chemotherapy.

Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. 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, Billerica, MA.

In the avelumab Phase 1 Study EMR100070-001, 156 patients with advanced NSCLC have been treated with avelumab 10 mg/kg intravenous (IV) once every 2 weeks until progression, unacceptable toxicity, or withdrawal. These patients had not been treated previously with systematic chemotherapy for metastatic or recurrent (Stage IV) disease and had not been selected for PD-L1 expression. An interim analysis for 75 patients with ≥ 3 months follow-up was conducted in October 2015 (ASCO 2016; abstract 9036). Objective response rate (ORR; unconfirmed) was 18.7% (95% CI: 10.6, 29.3) regardless of PD-L1 expression. Of the 14 - responses, 12 were still ongoing at the time of the interim analysis. PD-L1 expression was evaluable in 45 of 75 patients. Based on a ≥ 1% cutoff for tumor cell staining, 35 of 45 patients (77.8%) were PD-L1+ and the ORR in this subgroup was 20.0% (7 of 35 patients; CI: 8.4, 36.9) vs 0 of 10 patients (CI: 0.0, 30.8) in patients with PD-L1– tumors. Median PFS was 11.6 weeks (95% CI: 6.7, 17.9) for all patients. Subsequent follow-up of this cohort continues to demonstrate similar response rates and PFS. The majority of responses occurred within the first 12 weeks of treatment, appear durable, and the rates increased with higher expression PD-L1 (Section 5.2.6). Similarly, PFS also appeared to improve in patients with higher levels of PD-L1 expression.

3.5 Summary of the Overall Benefit and Risk

Based on the nonclinical and Phase I data available to date, the dose and dose regimen of avelumab as specified in this clinical trial protocol are justified. An IDMC (see Section 2.3.1) will assess patient safety 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 event (irAEs)

As of 05 November 2014, two Grade 4 infusion reactions have been reported in 480 subjects (0.4%) treated with avelumab (see IB); therefore, already implemented risk mitigation measures for infusion-related reactions / hypersensitivity have been extended by a mandatory premedication with H1 receptor blockers and acetaminophen for all subjects prior to any infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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.

As noted in Section 3.2, trials with antibodies that block the PD-1 – PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors (16-21), with response durations of 1 year or more for the majority of patients.

Furthermore, a recent snapshot in Trial EMR100070-001 of subjects with NSCLC who had progressed after platinum-containing therapy (n=184 treated subjects with a minimum follow-up time of at least 6 months by the cut-off date of 15 January 2015) demonstrated an objective response rate (ORR) of 14.1% (26 of 184 subjects 95% CI: 9.4, 20.5%), including 1 subject with CR. There were also 66 subjects with SD, 69 subjects with PD, and 23 subjects who were not evaluable. Twenty (76.9%) out of the 26 responses were still ongoing at the cut-off date for this analysis (duration of response: range, 1 to 54.1 weeks; median not reached) including 3 subjects who continue to respond off-treatment. The onset of response was rapid, with 11 of 22 (50.0%) subjects having their first documented response by Week 7.

Close safety monitoring will be performed throughout the study by the IDMC (details in Section 5.1.1).

Given the suboptimal treatment options for patients with recurrent or metastatic NSCLC and the safety profile of avelumab as currently demonstrated by ongoing Phase I trials, the risk-benefit ratio of treatment with avelumab in the targeted trial population is considered positive. Overall, these data support the development of avelumab in subjects with metastatic or recurrent (Stage IV) NSCLC who have not yet received systemic treatment for their metastatic disease. This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and the applicable national regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objective is to demonstrate superiority with regard to overall survival (OS) or progression free survival (PFS) of avelumab versus platinum-based doublet, based on an independent review committee assessment as per RECIST 1.1, in NSCLC subjects with high expression PD-L1+ tumors.

4.2 Secondary Objectives

Secondary objectives are as follows:

- To demonstrate superiority with regard to OS or PFS based on an independent review committee assessment per RECIST 1.1 in NSCLC subjects with moderate and high expression PD-L1+ tumors
- To demonstrate superiority with regard to OS in NSCLC subjects with any expression PD-L1+ tumors

- To comparatively assess the objective response rate (ORR) by RECIST 1.1 of avelumab versus chemotherapy in high, moderate and high, and any expression PD-L1+ tumors
- To determine duration of response of avelumab versus chemotherapy
- To compare the patient-reported outcomes / quality of life when treated with avelumab versus chemotherapy using the European Quality of Life (EuroQOL) 5-dimensions 5-level questionnaire (EQ-5D-5L), and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-LC13
- To determine the safety and tolerability of avelumab.

CCI

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, international, randomized, open-label, Phase III trial in chemotherapy-naïve (first line) metastatic or recurrent (Stage IV) NSCLC subjects comparing avelumab to first-line platinum-based doublet chemotherapy.

5.1.1 Overall Design

To achieve the target enrollment of 484 subjects randomized with high expression PD-L1+ tumors, approximately 1131 eligible subjects will be randomized with any expression PD-L1+ tumors and approximately 3100 subjects will be screened for study participation.

Subjects will be randomly allocated into the 3 study arms as follows:

- Arm A: Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities, or
- Arm B: Investigator's choice platinum-containing chemotherapy regimen to be administered in 3-week cycles up to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities consisting of one of the following:

  For subjects whose tumor is of non-squamous histology:

  pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2 administered on Day 1 of each cycle), or pemetrexed (500 mg/m^2) in combination with carboplatin (AUC 6 mg/mL × min administered on Day 1 of each cycle).

  For subjects whose tumor is of squamous histology:

  paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL × min administered on Day 1 of each cycle); or
  gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2) or
  gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL × min).

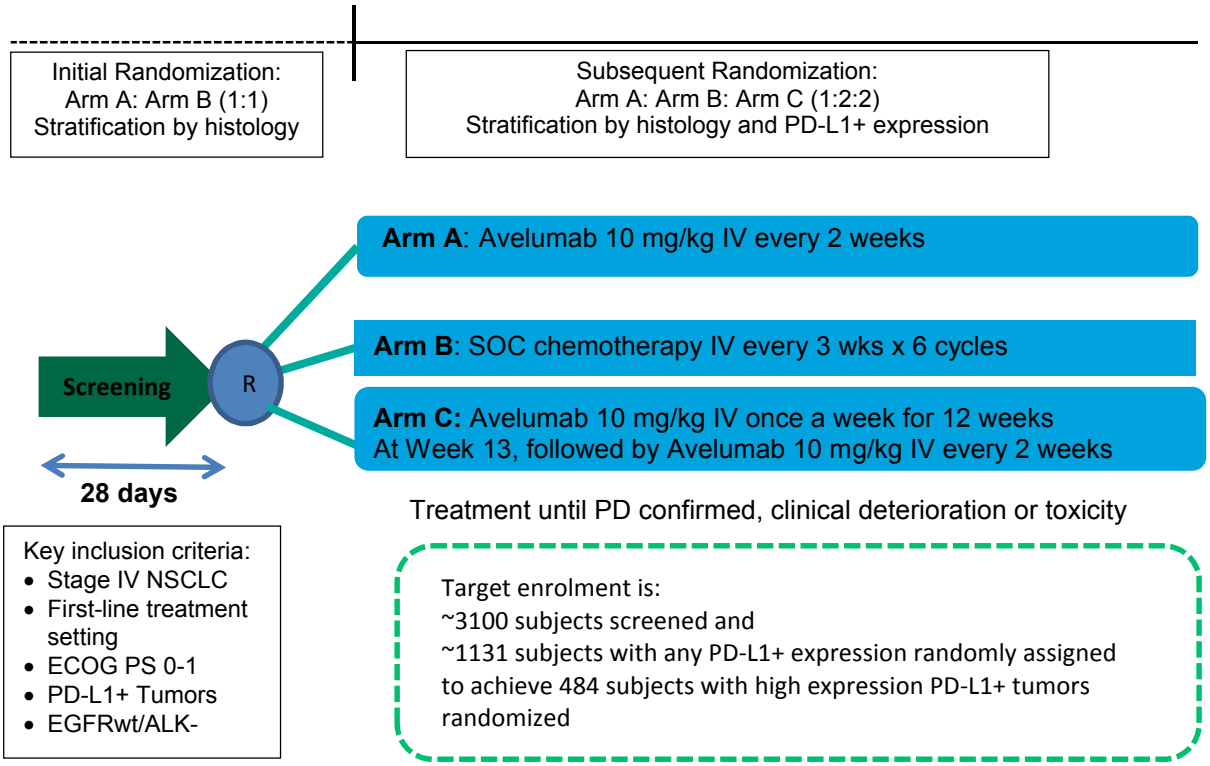
Arm C: Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) intravenous (IV) infusion every week for 12 consecutive weeks, and then at Week 13, transition to avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.

The NSCLC histology (squamous cell versus non-squamous cell) and PD-L1 tumor expression level at baseline (low versus moderate versus high) will be used as stratification factors for randomization (Figure 1).

The trial will initially randomly allocate subjects into Arm A and Arm B in a 1:1 ratio. A randomization ratio of 1:2:2 (Arm A: Arm B: Arm C) will start after the initial safety evaluation of avelumab 10 mg/kg every week in a cohort of 6 subjects. The IDMC will evaluate the safety data from this cohort once all of these 6 subjects have completed a minimum observation period of 4 weeks. The subjects treated with avelumab 10 mg/kg every week will receive a maximum of 12 doses and, at Week 13, will transition to receive avelumab 10 mg/kg every 2 weeks (see Section 5.1.3 for dosing requirements).

The trial design schematic is presented in Figure 1.

Figure 1 **Trial Design**



ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD: progressive disease; PD-L1+: programmed death-ligand 1 positive; SOC: standard of care.

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 and/or assessment of disease progression. The CT/MRI scans will be collected until disease progression is assessed by the Investigators according to RECIST 1.1. For all subjects and if clinically feasible, a subsequent scan at least 4 weeks after the initial assessment of progressive disease should be collected to confirm progression.

Assessments will be made by the Investigator for the purpose of subject management. The disease response endpoint determinations including PD assessments associated with the trial endpoints will be supported by tumor assessments performed by an IRC (see Section 7.3). The central imaging laboratory will read and interpret all CT / MRI data. Response will be evaluated using the RECIST 1.1 and as adjudicated by the blinded IRC.

The subject's treatment will continue until:

- Disease progression (see Section 5.5.1),
- Significant clinical deterioration (clinical progression, see Section 5.5.1),
- Unacceptable toxicity, or

- Any criterion for withdrawal from the trial or trial drug is fulfilled (see Section 5.5).

For subjects receiving avelumab, treatment may continue past the initial determination of disease progression according to RECIST 1.1 if the subject's performance status has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol, that is, no new symptoms or worsening of existing symptoms and no decrease in performance score (see Section 6.2.1).

These subjects will be evaluated for further tumor response as per the protocol schedule. For these subjects, further progression is defined as an additional increase in tumor burden of 20% and ≥ 5 mm absolute increase from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

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 nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden 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). Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months and/or disease progression or unacceptable toxicity, after confirmation of response. In case a subject with a confirmed CR relapses after stopping treatment, during long term follow-up, one re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol from Visit 1 and the "until progression" schedule in the Schedule of Assessments (see Table 1 for bi-weekly schedule or Table 4 for weekly schedule).

Subjects assigned to chemotherapy will be treated until disease progression, unacceptable toxicity, or after the completion of up to 6 cycles of chemotherapy. Subjects with non-squamous histology will be authorized to continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease has not progressed, or in accordance with pemetrexed local label. No other maintenance therapy is allowed.

Subject management will be based on clinical assessments made by the Investigators.

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

Safety endpoints include AEs, assessed throughout the trial and evaluated using the NCI-CTCAE v 4.03 (CTCAE v 4.03), clinical laboratory assessments, vital signs, and electrocardiogram (ECG) parameters.

The initial safety evaluation of Arm C, avelumab 10 mg/kg every week for 12 consecutive weeks, followed by avelumab at a dose of 10 mg/kg once every 2 weeks will be performed during the study as follows: prior to randomization into the 3 arms of the study, 6 subjects will be enrolled at

selected sites to receive avelumab 10 mg/kg every week for 12 weeks followed by avelumab 10 mg/kg every 2 weeks. After all of these 6 subjects have completed a minimum safety observation period of 4 weeks, the IDMC will evaluate all available safety data.

If there are no safety concerns precluding inclusion of the Arm C dose schedule, the enrollment and the 1:2:2 randomization in the 3 study arms will proceed (Arm A: Arm B: Arm C). Other options may be recommended by the IDMC, such as termination of this regimen or enrollment of 6 additional subjects on this dose regimen prior to allowing randomization into Arm C including an additional IDMC safety evaluation after all of these 6 subjects have completed a minimum safety observation period of 4 weeks. Once randomization to Arm C is initiated, a second safety evaluation will be performed by the IDMC when an additional 20 subjects in Arm C have been followed for at least 4 weeks, without a subject enrollment hold in any arm. The frequency of subsequent IDMC meetings for the entire study will be determined by the IDMC at the time of this second safety evaluation, which includes the additional 20 subjects' safety information from Arm C.

If safety data for 6 evaluable subjects treated with avelumab at 10 mg/kg once a week is available from the EMR100070-001 study, the IDMC may review the safety data after all of these 6 subjects have completed a minimum safety observation period of 4 weeks. The IDMC may determine the safety information as satisfactory and recommend that the initial safety evaluation of 6 subjects at 10 mg/kg once a week in this study may not be performed. Alternatively, the IDMC may also recommend that the safety data from the safety evaluation periods from subjects in both Studies EMR100070-001 and EMR100070-005 may be combined, for up to 6-12 evaluable subjects, for further assessment by the IDMC.

The safety evaluation period refers to the first 4 weeks of trial drug treatment for all subjects with data used by the IDMC to evaluate the safety. The additional 20 subjects randomized in Arm C of study EMR100070-005 will have the secondary safety evaluation by IDMC which will be based on safety data collected for a minimum of 4 weeks for all subjects.

The data cut-off for the primary PFS and OS analyses will occur after the target number of 173 OS events for Arm C versus B comparison of the randomized subjects with high PD-L1 has been reached and at least 20 months follow-up after the randomization of the last subject in the study.

5.1.2 Trial Medication Administration and Schedule

The trial Schedule of Assessments is presented in Table 1 to Table 4.

5.1.2.1 Avelumab

Subjects randomized to avelumab will receive IV infusion of avelumab (10 mg/kg over 1 hour [-10/+20 minutes]) either once every 2 weeks (Arm A) for the full study, or once every week for 12 consecutive weeks, followed by once every 2 weeks, starting Week 13 (Arm C). Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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.

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

5.1.2.2 Chemotherapy

Subjects randomized to the chemotherapy arm will receive IV infusion of chosen chemotherapy regimen according to the country-approved label and local institutional practice by IV infusion once every 3 weeks until disease progression, unacceptable toxicity, or any of the criteria for withdrawal from trial treatment is fulfilled (Section 5.5) or to a maximum of 6 cycles.

Additionally, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, subjects will be administered pre-treatment prior to each chemotherapy infusion per chemotherapy label instructions, or equivalent, per local institutional practice. As the premedication for pemetrexed (oral folic acid, vitamin B12 intramuscular injection) will need to be delivered in the week before first dose of chemotherapy, this premedication is permitted to be initiated in all subjects with non-squamous histology after signing the informed consent and prior to randomization. In the event that a subject is subsequently randomized to avelumab or is screen failed, vitamin B12 and the folic acid may be discontinued.

The formulation of the chemotherapy regimens is provided in Section 6.1.2.

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 subject's weight is 10% or less than the weight used for the last dose calculation. If the weight change is ≥ 10%, the intended dose should be recalculated.

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 due to adverse drug reactions (ADRs), infusion-related reactions and immune-related reactions are described in Sections 5.1.3.2, 6.5.4.1, and 6.5.4.2, respectively. There will be no dose reductions.

Treatment with avelumab can be skipped for a delay of up to 4 weeks from the previous dose for any non-related AEs, laboratory abnormalities, or intercurrent illness, which in the judgment of the Investigator warrants delaying the dose of study medication. If dosing is delayed more than 4 weeks, treatment may be resumed only after consultation with the study Medical Monitor. Any delay in dosing in excess of 6 weeks is not permitted.

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: permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.

Any Grade 3 ADRs:

- Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate.
- Permanently discontinue avelumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks is not permitted.

- Infusion should not be given if ECOG PS is ≥ 3 on the day of trial treatment administration. Treatment should be discontinued if ECOG PS has not improved to ≤ 2 by the next scheduled treatment administration.

Dermatological irAEs Grade 3 and Grade 4 should be handled according to guidelines in Table 10.

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 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 a 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).
- If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 6 weeks is not permitted.
- 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, and irAEs should be handled according to guidelines in Sections 6.5.4.1, and 6.5.4.2, respectively.

5.1.3.3 Dose Modification for Chemotherapy

After the starting dose, dose modifications (dose delays and dose changes) for toxicity should be made in accordance with labeling instructions and local institutional guidelines. Discontinuation of chemotherapy due to AEs should also be in accordance with the chemotherapy label and local institutional practice (see Table 7).

Table 7 Dose Modification Schedule for Chemotherapy

Dose Level	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Starting dose	1250 mg/m^2 (with cisplatin) or 1000 mg/m^2 (with carboplatin)	500 mg/m^2	75 mg/m^2	AUC 6 mg/mL × min (with pemetrexed or paclitaxel) or AUC 5 mg/mL × min with gemcitabine	200 mg/m^2
First dose reduction	950 mg/m^2 (with cisplatin) or 750 mg/m^2 (with carboplatin)	375 mg/m^2	56 mg/m^2	AUC 5 mg/mL × min (with pemetrexed or paclitaxel) or AUC 4 mg/mL × min with gemcitabine	150 mg/m^2
Second dose reduction	625 mg/m^2 (with cisplatin) or 500 mg/m^2 (with carboplatin)	250 mg/m^2	38 mg/m^2	AUC 4 mg/mL × min (with pemetrexed or paclitaxel) or AUC 3 mg/mL × min with gemcitabine	100 mg/m^2
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

AUC: area under the concentration-time curve.

5.2 Rationale for Trial Design

This is a Phase III, 3-arm, randomized, open-label trial to determine the efficacy and safety of avelumab compared with first-line platinum-containing chemotherapy in chemotherapy-naïve subjects with metastatic or recurrent (Stage IV) NSCLC.

The following sections present the rationale for this trial design including the PD-L1 disease status, chemotherapy doublet comparator, open-label design, stratification by histology and PD-L1 tumor expression level at baseline (low versus moderate versus high), PFS and OS as primary endpoints, dose selection, and the exclusion/inclusion of special populations.

5.2.1 Requirement of PD-L1+ Disease Status

All subjects randomized in the trial are expected to be PD-L1+ as determined by a companion diagnostic test under development. The rationale to restrict subject eligibility to those with tumors that are PD-L1+ is based on the prevalence of PD-L1 positivity in the NSCLC cohort from EMR100070-001 and the decision to target subjects who may have a greater chance to respond to an anti-PD-L1 therapy while at the same time minimizing avelumab exposure and toxicity in subjects who may be less likely to benefit.

5.2.2 Chemotherapy Doublet Comparator

Several platinum doublet chemotherapy regimens with similar efficacy are approved for first-line treatment of advanced NSCLC, although some agents have indications that are histology-specific. For example, pemetrexed is approved in first-line in combination with cisplatin for locally advanced or metastatic non-squamous NSCLC. Pemetrexed has also been approved as continuation maintenance therapy in non-squamous subjects who have not progressed after four cycles of a first-line pemetrexed/platinum regimen. In contrast, gemcitabine in combination with cisplatin has been demonstrated to yield improved overall survival compared to pemetrexed/cisplatin in subjects with squamous NSCLC. Although some but not all meta-analyses and randomized studies have demonstrated that cisplatin-based regimens may produce improved survival compared to carboplatin-based regimens, many subjects are not ideal candidates for cisplatin due to its higher toxicity (29).

5.2.3 Open-label Design

This study will use an open-label design. Due to the multiple options available for Investigator's choice chemotherapy (described in Section 5.1.2.2), the different schedules and durations of therapy in the treatment arms, different dose modification rules for safety management, and different premedication requirements according to the Investigator's choice chemotherapy, an open-label design is appropriate. An open-label design will also help ensure that immune-related toxicities in subjects receiving avelumab are promptly identified and managed. Because this study will be open label, a blinded IRC will be used to review tumor assessments in all randomized subjects to determine all response-related endpoints, including PFS.

5.2.4 Stratification by Histology and PD-L1 Tumor Expression

Among the different histologies of NSCLC, squamous histology typically represents 25% of all lung cancer cases (25). Most studies involving first-line and second-line therapy did not specifically separate subjects by histology, although this was recorded in all of the pivotal trials (26-29). The first study that showed a difference in histology involved the comparison of gemcitabine and cisplatin to pemetrexed and cisplatin. In this study, subjects with squamous cell

NSCLC had a median survival time of 10.8 months with the gemcitabine combination while it was only 9.4 months with pemetrexed. This is compared with the median survival time of 10.9 months with gemcitabine versus 12.6 months with pemetrexed in adenocarcinoma and 6.7 months with gemcitabine versus 10.4 months with pemetrexed in large cell lung cancer (26). A subanalysis of the pemetrexed non-inferiority study in second-line therapy, showed a statistically significant improvement in the combined non-squamous histologies when compared with docetaxel (9.3 months vs. 8.0 months [HR 0.778]), but not in squamous (6.2 months vs. 7.4 months [HR 1.563]) (30). Additional data has shown that there is a poorer prognosis among subjects with squamous cell NSCLC due to comorbidities related to smoking history, larger tumors with lymphatic and vascular invasion, and the presence of more poorly differentiated tumors. As a result of the potential differences in prognosis, outcome, and treatment for subjects with non-squamous and squamous histology, although the risk of disease recurrence after initial treatment is the same between adenocarcinoma and squamous cell (31).

Currently there are no data available to support potential differences in the prognosis of subjects in relation to the level of PD-L1 tumor expression. However, PD-L1 expression level may be a predictive factor for the treatment outcome in first line monotherapy setting with checkpoint inhibitors as demonstrated by recent data from studies in subjects with advanced NSCLC. Study KEYNOTE-024 evaluated pembrolizumab in subjects with advanced NSCLC, PD-L1 tumor proportion score (TPS) $\geq$ 50%. Reported data have shown superior PFS and OS over platinum doublet chemotherapy in this patient population. Study CheckMate 026 evaluated nivolumab in the same setting in subjects with PD-L1 tumor expression $\geq$ 1%. Reported data have not demonstrated superior PFS over chemotherapy.

5.2.5 PFS and OS as the Primary Endpoints

FDA guidance for industry on clinical trial endpoints for NSCLC drugs recommends OS to be the standard clinical benefit endpoint. However, the guidance also comments that other endpoints can be considered for regulatory decisions based on population and the risk benefit profile of the drug. Per the FDA guidance, PFS can be considered as a primary endpoint for demonstration of efficacy for drug approval based on magnitude of effect and risk benefit profile of the drug.

In this trial, efficacy of avelumab versus chemotherapy will be assessed based on various expression levels of PD-L1 and based on exposure to avelumab. Based on data from the first-line NSCLC cohort of EMR100070-001, it is anticipated that both PFS and OS will be improved for subjects with high or moderate to high expression of PD-L1, and OS will be improved for subjects with any PD-L1 expression. Since checkpoint inhibitors may already be available for subjects in the second line treatment setting, OS results may be confounded by such therapies. Thus, simultaneous assessment of PFS and OS will allow the analysis of treatment-effect in this population.

5.2.6 Dose Selection

In this trial, avelumab will be evaluated in 2 dose regimens: 10 mg/kg once every 2 weeks (Arm A) and 10 mg/kg once a week for 12 weeks, followed by transition to once every 2 weeks at Week 13

for the remainder of the study (Arm C) and compared to the platinum-containing chemotherapy regimen (Arm B).

In Arm A, the 10 mg/kg given by IV infusion once every 2 weeks dose is selected based on manageable safety profiles in Study EMR100070-001, EMR100070-002, and EMR100070-003 and based on the preliminary efficacy data in 1L NSCLC cohort in Study EMR100070-001.

Avelumab has been studied in over 1600 subjects with advanced solid tumors, including 27 subjects treated with 20 mg/kg once every 2 weeks and more than 1450 subjects treated with 10 mg/kg once every 2 weeks (Studies EMR100070-001, EMR100070-002 and EMR100070-003). This dose provides a high and sustained receptor occupancy in the blood throughout the dosing interval. The MTD was not reached in the dose escalation phase of Study EMR100070-001. For the safety profile, see the Investigator Brochure.

The preliminary efficacy analysis for 1L NSCLC cohort in Study EMR100070-001 (n=156) indicated clinical benefit to NSCLC subjects (Section 3.4).

Preliminary exposure-efficacy relationship in 1L NSCLC subjects suggests that an increase in exposure compared with the 10 mg/kg once every 2 weeks regimen may improve the efficacy with marginal if any impact on the safety profile, as demonstrated by the exposure safety evaluation.

- An exposure-efficacy response relationship was observed in NSCLC subjects treated with 10 mg/kg once every 2 weeks. For 1L NSCLC cohort of Study EMR100070-001 (n=156), a relationship between predicted $C_{trough,ss}$ and BOR was observed and supported by logistic regression (univariate analysis): the response rate was higher in subjects with higher PK exposure (5%, 10%, 23%, and 36% objective response rate in 1st, 2nd, 3rd, and 4th exposure quartiles, respectively) regardless of PD-L1 expression. Similarly for PFS and OS endpoints in NSCLC subjects, exposure-response relationship was suggested by COX models, though high uncertainty exists in these analyses.
- Population PK analysis and simulation showed that 10 mg/kg once every week regimen will increase the exposure, such that more than 90% of the subjects dosed with 10 mg/kg once every week will have a predicted $C_{trough,ss}$ higher than the lower bound of the 4th exposure quartile for the 10 mg/kg once every 2 weeks. Specifically, the median (CI) $C_{trough,ss}$ is predicted to increase from 22.9 µg/mL (4.2-74.5 µg/mL) in the once-every-2-weeks regimen to 83.3 µg/mL (28.6-204 µg/mL) in the once-a-week regimen (data on file), potentially enhancing efficacy as suggested by the exposure-efficacy analyses described above.
- For Arm C, the 12-week duration for avelumab once a week administration, followed by once every 2 weeks, was selected for this study based on preliminary observations from the 1L NSCLC cohort of EMR100070-001 dosed with 10 mg/kg avelumab once every 2 weeks, which showed that:
    - Approximately 80% of responses occurred within 12 weeks of treatment initiation, and
    - Majority of responses appeared to be durable.

It is not expected that the exposure at 10 mg/kg once every week would substantially impact the manageable safety profile currently observed with 10 mg/kg once every 2 weeks dosing:

- The exposure-irAE relationship curve appeared to be flat or shallow for shorter treatment durations (≤ 18 weeks) based on dataset that included > 1450 subjects from studies EMR100070-001, EMR100070-002, and EMR100070-003 (refer to exposure-safety report). For all other AEs analyzed, AE incidence appeared to not increase with increasing exposure.
- Based on population PK modeling, median exposures are not expected to exceed those for previously administered regimens: $C_{max,ss}$ is similar to that for 10 mg/kg once every 2 weeks regimen, while AUC_{ss} is similar to that for 20 mg/kg once every 2 weeks regimen (data on file).
- Avelumab has shown adequate safety profile in 27 subjects treated with 20 mg/kg once every 2 weeks and more than 1450 subjects treated with 10 mg/kg once every 2 weeks. The MTD was not reached in the dose escalation phase of Study EMR100070-001.

In summary, the dosing regimen of 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks is supported by the exposure-efficacy relationship, CCI, and an acceptable benefit-risk profile, as described above. This regimen also allows the evaluation of clinical outcomes in subjects with higher exposure and high expression of PD-L1 (See Section 3.4).

5.2.7 Exclusion of Subjects with EGFR Mutations and ALK Translocation

For subjects with EGFR mutations and ALK translocations, the current standard of care for initial therapy is targeted agents rather than chemotherapy. In addition, subjects with EGFR mutations have a better prognosis, even in the absence of EGFR inhibitor therapy (22) and may have an improved response to chemotherapy compared to subjects without EGFR mutations (23). Subjects with ALK translocations, who are treated with chemotherapy, appear to have similar PFS compared to subjects without ALK translocations who are treated with chemotherapy (24). As a result, subjects known to have these abnormalities will be excluded from this study. Furthermore, excluding subjects with EGFR mutation and ALK translocation will help to reduce the potentially confounding effects of these abnormalities on the study endpoints.

Subjects with unknown ALK and EGFR status and those with either non-squamous histology or those who are never-smokers will require testing (local laboratory, or central laboratory if local testing is not available) and must be determined to be wild type to be eligible for this trial. If an Investigator deems it important to conduct EGFR/ALK tests in subjects other than those with non-squamous histology or never-smokers, (eg, ex-smokers, tumor with mixed histology) in order to offer EGFR/ALK targeted therapy, such testing may be conducted.

5.2.8 Exclusion of Bevacizumab as a Comparator Therapy

Bevacizumab was approved in 2006 by the FDA for subjects with unresectable locally advanced recurrent or metastatic non-squamous NSCLC. Bevacizumab in combination with chemotherapy is indicated in PS 0-1 subjects with advanced or recurrent non-squamous NSCLC. However, only select NSCLC subjects may be appropriate for bevacizumab therapy. For example, subjects who have active cardiovascular disease or who have a recent history of hemoptysis should not receive bevacizumab given the association between bevacizumab and thrombocytopenia and bleeding

events. Due to these restrictions, bevacizumab has not been widely adopted as standard of care therapy in clinical practice and therefore it is not included as one of the physician choice therapeutic options for this trial.

5.2.9 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Subject randomization will be managed by an IWRS (see Section 7.1.1). Only persons meeting all inclusion criteria and no exclusion criteria may be randomized into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

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

1. Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard subject management
2. Male or female subjects aged ≥ 18 years
3. Availability of a recently-obtained, formalin-fixed, paraffin-embedded (FFPE) tissue sample containing tumor (biopsy from a non-irradiated area preferably within 6 months) or a minimum number of 10 (preferably 25) unstained tumor slides cut within 1 week, and suitable for PD-L1 expression assessment
4. Tumor determined to be positive for any PD-L1 expression per the evaluation of a central laboratory
5. At least 1 measurable lesion per RECIST 1.1 criteria. A lesion that has been irradiated can be used as a measurable lesion providing that disease has progressed at that site
6. Subjects with histologically-confirmed Stage IV metastatic or recurrent (Stage IV) NSCLC as per the 7th International Association for the Study of Lung Cancer and the American Joint Committee on Cancer classifications
7. Subjects must not have received any treatment for systemic lung cancer, including EGFR inhibitors or anaplastic lymphoma kinase (ALK) inhibitors
8. Subjects could have received neoadjuvant/adjuvant chemotherapy or loco-regional treatment that included chemotherapy for locally advanced disease, as long as disease recurrence occurred at least 6 months after the completion of the last administration of chemotherapy treatment. Subjects who received thoracic radiation therapy of >30 Gy within 2 months of the first dose of trial treatment are not eligible.
9. ECOG PS of 0 to 1 at trial entry
10. Estimated life expectancy of more than 12 weeks
11. Adequate hematological function defined by white blood cell (WBC) count ≥ 2.5×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

12. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN for all subjects, or for subjects with documented metastatic disease to the liver and AST and ALT levels ≤ 5 x ULN. Subjects with documented Gilbert disease are allowed if total bilirubin is less than 3 x ULN.
13. Adequate renal function defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
14. Negative blood pregnancy test at screening for women of childbearing potential. For the purposes of this trial, women of childbearing potential are defined as: "All female subjects after puberty unless they are post-menopausal or not sexually active." Females are considered postmenopausal if they have age-related amenorrhea ≥ 12 consecutive months or if they have undergone hysterectomy or bilateral oophorectomy. If necessary to confirm postmenopausal status, follicle-stimulating hormone (FSH) may be drawn at Screening with documented increased FSH > 40 mIU/mL.
15. 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 III or as stipulated in national or local guidelines. Highly effective contraception must be used for the duration of trial treatment, and at least for 60 days after stopping trial treatment. 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). For subjects randomized to the avelumab arm of the study, highly effective contraception is required at least 30 days prior and 60 days after avelumab treatment. All female subjects of childbearing potential who are randomized to the chemotherapy arm are required to use highly effective contraception for up to 6 months after chemotherapy treatment, and male subjects will be advised not to father a child during the 6 months after treatment with chemotherapy.

5.3.2 Exclusion Criteria

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

1. Subjects whose disease harbors an EGFR mutation. Subjects with non-squamous histology of unknown EGFR status will require testing for EGFR mutations (local laboratory, or central laboratory if local testing is not available) and must be determined to be EGFR wild-type to be eligible for this trial
2. Subjects with non-squamous cell NSCLC whose disease harbors an ALK rearrangement. Subjects with non-squamous histology of unknown ALK status will require testing for ALK rearrangement (local laboratory, or central laboratory if local testing is not available) and must be determined to be ALK wild-type to be eligible for this trial. Subjects with indeterminate ALK status may be enrolled, unless they are non-smokers and < 40 years old with tumors of adenocarcinoma histology.
3. Subjects with tumors known to harbor molecular alterations for which a targeted therapy is approved.
4. Prior therapy with any antibody or drug targeting T-cell coregulatory proteins, concurrent anticancer treatment, or immunosuppressive agents.

5. Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin)
6. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of randomization and / or if the subject has not fully recovered from the surgery within 4 weeks of randomization
7. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment (with the exception of subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily).
   Note: Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be ≤ 10 mg per day of equivalent prednisone
8. All subjects with brain metastases, except those meeting the following criteria:
   - Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to randomization
   - 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)
   - Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)
9. Previous malignant disease (other than NSCLC) with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ (bladder, cervical, colorectal, breast or prostate) is an exclusion unless a complete remission without further recurrence was achieved at least 2 years prior to study entry, and the subject was deemed to have been cured with no additional therapy required or anticipated to be required.
10. Prior organ transplantation, including allogeneic stem-cell transplantation
11. Significant acute or chronic infections including, among others:
    - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
    - Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive)
12. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
    - Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
    - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day
    - Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable
13. 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)
14. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03
15. Pregnancy or lactation

16. Known alcohol or drug abuse
17. The subject has uncontrolled intercurrent illness including not limited to:
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mm Hg or lower)
    - or, uncontrolled active infection,
    - or, uncontrolled diabetes (eg, HgbA1c ≥ 8%)
18. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to randomization), myocardial infarction (< 6 months prior to randomization), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication
19. All other significant diseases (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment. Cisplatin should not be employed in subjects with hearing impairment.
20. Any psychiatric condition that would prohibit the understanding or rendering of informed consent
21. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines)
22. Legal incapacity or limited legal capacity.

5.4 Criteria for Initiation of Trial Treatment

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

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

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

- PD per RECIST 1.1 (subjects receiving avelumab treatment may continue past the initial determination of disease progression if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment, see Section 6.2.1)
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms
- Unacceptable toxicity
- Withdrawal of consent
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Therapeutic failure requiring urgent additional drug (if applicable)

- Occurrence of any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.1.3.2
- Occurrence of AEs resulting in the discontinuation of the trial 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).

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.

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

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

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

In case of withdrawal from the trial, the assessments scheduled for the last visit (End-of-Treatment visit) should be performed (see Section 7.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate End-of-Treatment electronic case report form (eCRF) visit 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, patient-reported outcomes/quality of life questionnaires, and subsequent anticancer therapy. For subjects withdrawing from trial-related procedures, collection of survival data will be pursued as permitted by local regulations. This may include accessing public records such as survival registries, and obituaries.

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 nonclinical examinations, for example, toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's trial drug.

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 or within this Section, the survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab. Under some circumstances, the subject may not be followed for 5 years for survival in this study, for example, the subjects may be offered to enter into a roll-over study or the Sponsor may terminate the study early.

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 first-line platinum-containing chemotherapy regimen (based on Investigator's discretion).

6.1 Description of the Investigational Medicinal Product

6.1.1 Avelumab

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

6.1.2 Chemotherapy

Subjects will receive the physician's choice of chemotherapy among the following treatments:

6.1.2.1 Carboplatin

Carboplatin is a platinum-based drug that is used in NSCLC. Carboplatin is administered intravenously at a dose of AUC 6 mg/mL × min (per Calvert formula) over 15 to 30 minutes after the use of paclitaxel (33) or pemetrexed (34). Carboplatin may also be given at a dose of AUC

5 mg/mL × min (per Calvert formula) with gemcitabine (35). Subjects who are receiving carboplatin must be monitored for myelosuppression and anaphylaxis. Dose modifications according to toxicities are noted in Section 5.1.3.3. For preparation and storage, please consult the local prescribing information for carboplatin or the Summary of Product Characteristics (SMPC) (36).

6.1.2.2 Cisplatin

Cisplatin is a platinum-based drug that is used in NSCLC. Cisplatin is administered intravenously at a dose of 75 mg/m² over 30 minutes after gemcitabine or pemetrexed. Subjects who are receiving cisplatin must be monitored for nephrotoxicity, ototoxicity, and neuropathy in addition to myelosuppression. Cisplatin should not be employed in subjects with hearing impairment. Caution must be observed in the case of nausea, vomiting, and dehydration. Dose modifications according to toxicities are noted in Section 5.1.3.3. For preparation and storage, please consult the local prescribing information for cisplatin or the SMPC (37).

6.1.2.3 Gemcitabine

Gemcitabine is indicated in combination with cisplatin in first-line treatment of inoperable, locally advanced (Stages IIIA or IIIB) or metastatic (Stage IV) NSCLC. Using the 3-week schedule, gemcitabine is administered intravenously at a dose of 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin should be administered 30 minutes after gemcitabine on Day 1 only at a dose of 75 mg/m². Gemcitabine may also be given at a dose of 1000 mg/m² over 30 minutes on Days 1 and 8 or each 21-day cycle, in combination with carboplatin at AUC 5 mg/mL × min (per Calvert formula), as first-line treatment of advanced NSCLC. Dose adjustments for hematology toxicity may be required for gemcitabine and cisplatin (individually). Gemcitabine dosage adjustment for hematologic toxicities based upon the granulocyte and platelet counts on the day of treatment. Subjects receiving gemcitabine should be monitored prior to each dose using complete blood counts (CBC). If marrow suppression is noted, dose modifications are noted in Section 5.1.3.3. For non-hematologic toxicities, other than alopecia and nausea, dose modifications should be considered for both gemcitabine and cisplatin. For preparation and storage, please consult the local prescribing information for gemcitabine or the SMPC (38).

6.1.2.4 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor indicated as initial treatment for locally advanced or metastatic non-squamous NSCLC in combination with cisplatin. Pemetrexed is also indicated as maintenance treatment for locally advanced or metastatic non-squamous NSCLC subjects whose disease has not progressed after platinum-based first-line chemotherapy. Pemetrexed is administered intravenously at a dose of 500 mg/m² on Day 1 of each 21-day cycle. Cisplatin should be administered 30 minutes after pemetrexed at a dose of 75 mg/m². The premedication regimen for pemetrexed includes folic acid and vitamin B12 as well as dexamethasone or equivalent to reduce cutaneous reactions. Subjects receiving pemetrexed should be monitored prior to each dose using CBC and renal function tests. If marrow suppression is noted, dose modifications are noted in Section 5.1.3.3. For renal toxicity, pemetrexed should be held when the CrCl < 45 mL/minute. Caution should be used among subjects who are receiving non-steroidal

anti- inflammatory drugs (NSAIDs) and who have mild to moderate renal insufficiency (CrCl between 45 and 79 mL/minute). Caution should also be used when nephrotoxic drugs are administered with pemetrexed. For preparation and storage, please consult the local prescribing information for pemetrexed or the SMPC (39).

6.1.2.5 Paclitaxel

Paclitaxel is a taxane that is indicated in combination with cisplatin in first-line treatment for inoperable, locally advanced (Stages IIIA and IIIB) or metastatic (Stage IV) NSCLC. Paclitaxel is administered intravenously at 200 mg/m^2 over 3 hours, and premedication using diphenhydramine (or equivalent) and dexamethasone (or equivalent) is required. Subjects must be observed for hypersensitivity reactions, myelosuppression, and neuropathy. Dose modifications according to toxicities are noted in Section 5.1.3.3. For preparation and storage, please consult the local prescribing information for paclitaxel or the SMPC (40).

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 [-10/+20 minutes]) following pretreatment with histamine H1 blockers and acetaminophen 30 to 60 minutes prior to each avelumab infusion, either once a week (for 12 weeks followed by once every 2 weeks, starting at Week 13 [see Table 4]) or every 2 weeks (see Table 1). Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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. 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 of weight used for the last dose calculation.

Subjects will receive avelumab either once a week (for 12 weeks) or every 2 weeks until the criteria in Sections 5.5 through 5.7 are met.

For subjects receiving avelumab, treatment may continue past the initial determination of disease progression per RECIST 1.1 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).

In addition, if disease progression is due to brain metastasis, subjects may continue avelumab treatment after the local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab
- There are 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)
- Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)
- In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) which in the opinion of the investigator may be surgically removed or treated with palliative radiation therapy, subjects may continue avelumab treatment after the local treatment of such a lesion provided that:
    - It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the subject has fully recovered from the surgery.
    - It has been at least 2 weeks since the subject's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to < Grade 2.

The decision to continue treatment post disease progression should be discussed with the medical monitor and documented in the trial records.

Subjects in Arm C for whom there is a decision to continue treatment post disease progression and who are on every two week treatment administration may re-initiate treatment with weekly treatment administration for a duration of up to 12 weeks. This alternative should be considered by the treating physician taking into consideration the subject general status and the comparison of subject's treatment toxicities reported during the prior weekly versus every two week treatment administration.

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.

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

For subjects who continue avelumab trial therapy beyond progression, they will be evaluated for further tumor response as per the protocol schedule. For these subjects, further progression is defined as an additional increase in tumor burden of 20% and ≥ 5 mm absolute increase from time of initial PD. For subjects who underwent treatment for progression (brain metastasis or metastatic lesion [nodal or visceral]), the evaluation of further progression will be based on increase in tumor burden from the time of post treatment of progression. This includes an increase in the sum of all

target lesions and/or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

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 nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden 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 at the discretion of the Investigator. In case a subject with a confirmed CR relapses after stopping treatment, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the medical monitor. To be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Table 1 for bi-weekly schedule or Table 4 for weekly schedule).

6.2.2 Chemotherapy Dosage and Administration

The standard of care for chemotherapy-naïve (first line) patients with metastatic NSCLC is to receive a platinum-based chemotherapy regimen (see Table 2 and Table 3). Chemotherapy should be administered at the clinic in accordance to the label instructions and per local administration guidelines for a maximum of 6 cycles. The choice of the chemotherapy administered will depend on histology and clinical judgment of the Investigator.

In order to accommodate subjects with both squamous and non-squamous histology in this study, squamous subjects randomized to the comparator arm may receive the Investigator's choice of any of the following platinum-based chemotherapy regimens:

- Gemcitabine/cisplatin (up to 6 cycles)
- Gemcitabine/carboplatin (up to 6 cycles)
- Paclitaxel/carboplatin (up to 6 cycles)

Subjects with non-squamous histology who are randomized to the comparator arm (Arm B) may receive Investigator's choice of any of the following pemetrexed/platinum regimens, including the option for continuation of pemetrexed as maintenance therapy:

- Pemetrexed/cisplatin (up to 6 cycles)
- Pemetrexed/carboplatin (up to 6 cycles)
- Pemetrexed/cisplatin (up to 4 cycles), followed by pemetrexed maintenance (and/or, in accordance to the local label instructions)
- Pemetrexed/carboplatin (up to 4 cycles), followed by pemetrexed maintenance (and/or, in accordance to the local label instructions)

Subjects with non-squamous histology who have been assigned to receive pemetrexed might, based on Investigator judgment, continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease has not progressed, or in accordance with pemetrexed local label. No other maintenance therapy is permitted. In addition, if there is toxicity to a given platinum agent (cisplatin or carboplatin) for which its administration should be discontinued, the platinum agent may, at the Investigator's discretion, be either discontinued or switched to another platinum agent (cisplatin or carboplatin) and treatment continued for up to 6 cycles in total, provided that there was no disease progression.

Subjects will receive trial treatment until PD per RECIST 1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled, or for a maximum of 6 cycles.

Table 8 Allowed Chemotherapy Regimens

Product Description	Dosage Form	Potency	Dose	Dosing Frequency
Carboplatin	Solution for infusion	150 mg/vial (10 mg/mL)	AUC 5 with gemcitabine/AUC 6 with paclitaxel/pemetrexed	Day 1 of each cycle
Cisplatin	Solution for infusion	50 mg/vial (1 mg/mL)	75 mg/m^2	Day 1 of each cycle
Gemcitabine	Solution for infusion	1000 mg/vial	1250 mg/m^2 with cisplatin/1000 mg/m^2 with carboplatin	Day 1 and Day 8 of each cycle
Pemetrexed	Powder for infusion solution	500 mg/vial	500 mg/m^2	Day 1 of each cycle
Paclitaxel	Solution for infusion	100 mg/vial (6 mg/mL)	200 mg/m^2	Day 1 of each cycle

6.3 Assignment to Treatment Groups

Once the subject has provided a signed Informed Consent Form (ICF) and has been determined to meet inclusion and exclusion criteria, the Investigator or delegate will request the trial treatment assignment using the IWRS. The trial is fully controlled by the IWRS, which assigns treatment individual (unique) vial numbers for each subject. The vial number is linked via the Good Manufacturing Practice (GMP) qualified system to the corresponding treatment as well as to the subject.

Qualified subjects will be randomized overall to receive avelumab once a week, avelumab once every 2 weeks, or chemotherapy using stratified permuted block randomization via the IWRS.

Subjects will be randomly allocated to one of the 3 treatment arms, initially into Arm A and Arm B in a 1:1 ratio. The allocation ratio will change to 1:2:2 (Arm A: Arm B: Arm C) once the IDMC recommends the avelumab once a week dosing regimen may be included in the randomization scheme after the initial safety evaluation of avelumab 10 mg/kg every week in a cohort of 6 subjects.

NSCLC histology (squamous versus non-squamous cell) will be used as stratification factors for randomization. The PD-L1 tumor expression level at baseline (low expression versus moderate expression versus high expression) will be supplemented as randomization strata for the 1:2:2 randomization scheme. This stratified randomization will be centrally allocated across all trial sites via the IWRS.

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

6.4 Noninvestigational Medicinal Products to be Used

Subjects randomized to receive avelumab will receive pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to each avelumab infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. 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.

Subjects randomized to receive chemotherapy will receive pretreatment prior to each chemotherapy infusion per chemotherapy label instructions, or equivalent, per local institutional practice.

Immediate access to an intensive care unit (ICU) 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 $\geq$ 2 infusion-related, allergic, or anaphylactoid reactions. Following avelumab infusions, subjects must be observed for 1 hour post infusion, for the first 4 infusions, for potential infusion-related reactions.

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

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions according to the NCI is found in Section 6.5.4.1. 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/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

6.5 Concomitant Medications and Therapies

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 medication may be given at the Investigator's discretion.

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 1.1 (1) and not based on the necessity for palliative bone directed-radiotherapy.

Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, inhalation, or local steroid injections [eg, intra-articular injections]) are acceptable.

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.

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

6.5.2 Prohibited Medicines

Prohibited medicines are listed in the exclusion criteria (see Section 5.3.2).

The following treatments must not be administered during the trial:

- cytoreductive therapy,
- radiotherapy (with the exception of palliative bone-directed radiotherapy, or radiotherapy administered on superficial lesions) as long as there is no identified soft tissue component which has been selected as target lesion,
- cytokine therapy except for erythropoietin (only for subjects randomized to avelumab),
- use of any investigational drug within 28 days before randomization.

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

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids) except:
    - When required for treatment of allergic reactions or for the treatment of irAEs or infusion related reactions/hypersensitivity
    - Systemic corticosteroids for management of patients with allergy to CT IV Radiographic Contrast Media.
    - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent

Note: The use of systemic corticosteroids for subjects randomized to receive chemotherapy is per Investigator's discretion and is to be based on local and institutional guidelines.

- Growth factors for subjects randomized to receive avelumab (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the Investigator's discretion
- For subjects randomized to receive paclitaxel, use of concomitant strong cytochrome P450 3A4 (CYP3A4) inhibitors should be avoided (for example, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). For more information on CYP3A4 substrates, Investigators are directed to the following URL: http://medicine.iupui.edu/clinpharm/ddis/.

If the administration of a nonpermitted 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 7.1.3) 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 chemotherapy as required. These might include analgesics, antinausea medications, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

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

6.5.3 Other Interventions

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

- Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment. For any other surgical interventions planned during the study, study treatment should be delayed to allow subject's recovery, for up to a maximum of 4 weeks.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)

- Subjects should not abuse alcohol or other drugs during the trial.

6.5.4 Special Precautions

As a routine precaution, subjects randomized to the avelumab arm must be observed for 1 hour post infusion, for the first 4 infusions, in an area with resuscitation equipment and emergency agents. At all times during avelumab or 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, according to the NCI are as outlined in Section 6.5.4.1.

Investigators should also monitor subjects closely for potential irAEs, which may first become 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 (ANAs) or antineutrophil cytoplasmic antibodies (ANCAs). See Section 6.5.4.2 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 9.

Table 9 Treatment Modification for Symptoms of Infusion-related Reactions Associated With Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
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.	• Temporarily discontinue 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.	• 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.

• Grade 4: Life-threatening consequences; urgent intervention indicated.	

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 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 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 10.

Table 10 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 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.

Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; 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 31.0 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**
Grades 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisolone 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 image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4

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

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 **Creatinine increased > ULN to 1.5 x ULN**	Continue avelumab therapy	Continue renal function monitoring If worsens: **Treat as Grade 2 to 3 or 4.**
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 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 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy **Nephrology consult**	If returns to Grade ≤ 1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**

New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management Cardiology consult to establish etiology and ruleout immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: **http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001**		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • 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 re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.

Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; 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 Events; PRL=prolactin;; T4: free thyroxine; TSH: thyroid-stimulating hormone; ULN: upper limit of normal.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

The management of irAEs is described in Section 6.5.4.2.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by the Sponsor in single use glass vials, CCI [redacted]

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and GMP Guidelines. Avelumab will be packed in boxes by using a suitable packaging design. The information on the trial drug will be in accordance with approved submission documents.

Avelumab will be shipped in transport CCI [redacted] (CCI [redacted]) that are monitored with temperature control devices.

Pemetrexed, cisplatin, carboplatin, paclitaxel, and gemcitabine 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 drug product must be stored at CCI [redacted] 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 drug product stored at room temperature (CCI [redacted]) or at elevated temperatures (CCI [redacted]) 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 drug product must be diluted with CCI [redacted] CCI [redacted] Alternatively, a CCI [redacted] can be used if needed. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration are outlined in the MOP, and included in the pharmacy manual which will be shared with sites.

Avelumab must not be used for any purpose other than the trial. The administration of avelumab to subjects who have not been randomized 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 chemotherapy should be according to the package insert.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for avelumab or chemotherapy, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of trial drug, 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 File.
- The dispensing of the trial drug will be carefully recorded in the IWRS system. The IWRS system will also be used to document drug accountability and an accurate accounting will be available for verification by the clinical research associate (CRA) at each monitoring visit.
- Trial drug accountability records will include:
    1. Confirmation of trial drug delivery to the trial site
    2. The inventory at the site of trial drug provided by the Sponsor and prepared at the site
    3. The use of each dose by each subject
    4. The return to the Sponsor or alternative disposition of unused trial drug
    5. Dates, quantities, batch numbers, expiry dates and (for trial drug 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 drug provided by the Sponsor was fully reconciled.

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

The CRA will periodically collect the trial drug accountability forms (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 Trial

- Date of destruction(s)
- Name and signature of the Investigator/pharmacist.

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

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

This is to be closely monitored by the CRA.

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 drug administration. The information of each trial drug administration including the date, time, and dose of trial drug 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.

For the once every week dosing regimen, noncompliance is defined as a subject missing > 2 infusion of trial treatment for nonmedical reasons (see Section 5.5.1). If 2 infusions are missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

For the every 2 weeks dosing regimen, noncompliance is defined as a subject missing > 1 infusion of trial treatment for nonmedical reasons (see Section 5.5.1). If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

6.10 Blinding

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

Study procedures will be established to maintain data integrity in this open-label trial and to limit biased assessment of endpoints by:

- Establishing an independent and blinded review of tumor images (IRC) (see Section 5.2.3), and
- Regulating the flow of PD-L1 expression data between the laboratory site, the IWRS vendor for the stratification, and the IDMC during study conduct.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose ≥ 10% over the intended dose for that particular administration as described in this clinical trial protocol (Section 5.1.3.1). Any overdose must be recorded in the trial drug 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 drug.

In the case of an overdose of chemotherapy, subjects should receive therapeutic granulocyte colony-stimulating factor per package insert or equivalent as soon as possible after the overdose is discovered.

6.13 Medical Care of Subjects after End of Trial

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

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

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments is provided in Table 1 to Table 6.

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

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 before randomization. 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 within 6 weeks of signing the ICF. In this case, a new ICF will be required to be signed by the subject. A new subject number will be assigned by the IWRS. Procedures from Screening (Table 1, Table 2, Table 3, and Table 4) will need to be repeated to ensure that the subject is

eligible, excluding PD-L1 tumor expression, ECG, HBV, HCV, urinalysis, adrenocorticotropic hormone (ACTH), free thyroxine (T4), and thyroid-stimulating hormone (TSH), and the tumor evaluation scans if the scans performed during the prior screening period will be within the protocol-specified randomization window of 28 days.

Potential exceptions for the 6-week rescreening window must be discussed with the study Medical Monitor.

Tumor tissue must be available within 10 calendar days after the subject has signed the ICF in order to establish the PD-L1 status of the tumor. Tumor tissue can be archival tissue or resulting from a screening biopsy of the subject if no archival tissue is available (see Section 7.6 for details). Preferably, archived samples, if needed, should be less than 6 months old. Criteria for determining the adequacy of tumor tissue are described in the Study Manual. Subjects who undergo a biopsy specifically as part of the Screening assessments for this protocol will be permitted to participate in the protocol provided they meet all other inclusion criteria and if no exclusion criteria.

Randomization cannot occur until PD-L1 expression has been determined by an Investigational Use Only PD-L1 IHC pharmDx companion diagnostic test by Dako (IDE No. G150051 S 001) to be evaluated centrally.

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 disease history (NSCLC), previous and ongoing medications with administration started before the informed consent signature), baseline medical condition. The AE reporting period for safety surveillance and a concomitant medication recording period begins when the subject first signs an informed consent. Moreover, an Emergency Medical Support card will be handed out at the Baseline assessments visit.

During Screening, subjects will undergo a complete physical examination, vital signs including recording of body height and weight, 12-lead ECG, and a determination of the ECOG PS (Appendix II). Subjects will also complete patient-reported outcomes / quality of life assessments.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry (including Full serum chemistry and core chemistry), and full urinalysis (dipstick and microscopic evaluation). Adrenocorticotropic hormone (ACTH), T4, and TSH will also be assessed at Screening for all subjects.

During Screening, a serum β-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for females of childbearing potential (local and central laboratory) and blood hepatitis B virus and hepatitis C virus will be performed (central laboratory) for all Screening subjects as these conditions are trial entry exclusion criteria (see Section 5.3.2). Females who are postmenopausal are exempt from pregnancy testing. Females are considered postmenopausal if they have age-related amenorrhea ≥ 12 consecutive months or if they have undergone hysterectomy or bilateral oophorectomy. If necessary to confirm/assess postmenopausal status, FSH may be drawn at Screening with documented increased FSH > 40 mIU/mL).

The tumor evaluation (type and staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory) or any other established methods (see Section 7.2.5 for details). A brain CT / MRI scan is required at Baseline. A bone scan should be done at Screening as clinically indicated.

CCI [redacted]

7.1.2 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 drug is fulfilled (see Section 5.5.1). For subjects receiving avelumab, treatment may continue past the initial determination of disease progression according to RECIST 1.1 if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment (see Section 6.2.1). Additionally, subjects receiving avelumab 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, during long term follow-up, one re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the medical monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol from Visit 1, and the "until progression" schedule in the Schedule of Assessments (see Table 1 to Table 3).

The treatment should start within 4 days after randomization. As the premedication for pemetrexed (oral folic acid, vitamin B12 intramuscular injection) will need to be delivered in the week before first dose of chemotherapy, this premedication is permitted to be initiated in all subjects with non-squamous histology after signing the informed consent and prior to randomization. In the event that a subject is subsequently randomized to avelumab or is screen failed, vitamin B12 and the folic acid may be discontinued. While on trial treatment, subjects will be asked to visit the trial site either:

- Once every week or once every 2 weeks for subjects randomized to receive avelumab (see Table 1 and Table 4).
- Once every 3 weeks for subjects randomized to receive chemotherapy, except for gemcitabine, which is to be administered on Day 1 and Day 8 of each 3-week cycle (see Table 2 and Table 3).

If the study treatment is terminated before disease progression, all assessments will continue on a 6-week schedule until disease progression if no new cancer treatment is initiated and subjects are stable.

A time window up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures for subjects enrolled in Arm A, Arm B and for subjects in Arm C while receiving avelumab once every two weeks. A time window of 1 day before or 1 day after

the scheduled visit day (-1/ +1 days) will be permitted for all trial procedures for subjects enrolled in Arm C while receiving avelumab once weekly.

Subjects will receive either:

- Avelumab by IV infusion following premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose, once every week or once every 2 weeks, depending on randomization (see Section 6.2.1), or
- Chemotherapy by IV infusion following pretreatment as applicable prior to each chemotherapy infusion (see Section 6.2.2).

During the treatment period, the following assessments will be performed (see Table 1, Table 2, Table 3, and Table 4 for the detailed schedules):

- Patient-reported outcomes / quality of life assessments will be completed by the subject after randomization (before the first administration of the trial treatment) then prior to administration of trial treatment and before any trial-related procedures (including collection of biological samples)
    - Week 1 (treatment administration 1), Week 7 (treatment administration 4), and Week 13 (treatment administration 7) for subjects receiving avelumab,
    - Week 1 (treatment administration 1), Week 7 (treatment administration 3), and Week 13 (treatment administration 5) for subjects receiving chemotherapy (pemetrexed, paclitaxel, cisplatin, carboplatin, gemcitabine)
    - Every 6 weeks thereafter while on treatment for all subjects.
- AEs and concomitant medications will be documented at each trial visit.
- ECOG PS will be assessed at Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and at each trial visit thereafter for Arm A and B, and at every other visit (ie, every 2 weeks) for Arm C.
- Physical examinations will be performed at each visit until Week 13 and every 6 weeks thereafter. A full physical examination should be performed at Screening and the EoT visit. Physical examinations at all other visits should be directed towards signs and symptoms.
- Vital signs will be assessed at each visit until Week 13 (Week 16 or Week 17 [regimens containing gemcitabine only] in Arm B) and every 2 or 3 weeks (chemotherapy arm) thereafter
- Body weight will be assessed every 2 weeks until Week 13 in Arms A and C and Week 16 or Week 17 (regimens containing gemcitabine only) in Arm B as indicated in the Schedule of Assessments and every 2 or 3 weeks (chemotherapy arm) thereafter.
- ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline detected during the physical examination and/or vital signs measurements performed prior to avelumab treatment.

- The avelumab administration should not be withheld in the isolated situation of an increased heart rate, unless the overall evaluation, including the ECG, is suggestive of myocarditis, in which case the protocol guidelines (as outlined in Table 10) should be followed.
- Hematology and hemostaseology (except for Arm B on Day 8 of each cycle: only hematology is to be performed) tests will be assessed at each visit up to Week 13 and every 2 or 3 weeks (chemotherapy arm) thereafter.
- Full serum chemistry will be assessed at Weeks 3, 5, and 13 for subjects randomized to avelumab in Arm A and at Weeks 2, 4, 6, 8, 10, 12 and 13 for subjects randomized to avelumab in Arm C; at Weeks 4, 7, and 13 for subjects randomized to chemotherapy; and then every 6 weeks thereafter for all subjects.
- Core serum chemistry will be assessed at:
    - Weeks 1, 7, 9, and 11, and then every 2 weeks (when full serum chemistry is not scheduled to be done) thereafter for subjects receiving avelumab in Arm A;
    - Weeks 1, 3, 5, 7, 9, and 11, and then every 2 weeks (when full serum chemistry is not scheduled to be done) thereafter for subjects receiving avelumab in Arm C;
    - Weeks 1, 10, and then every 3 weeks (when full serum chemistry is not scheduled to be done) thereafter for subjects receiving pemetrexed, cisplatin, carboplatin, or paclitaxel;
    - Weeks 1, 2, 5, 8, 10, 11, 14, and every 3 weeks (when full serum chemistry is not scheduled to be done) thereafter for subjects receiving gemcitabine.
- Full urinalysis (dipstick and microscopic evaluation) at the Screening and End-of-Treatment Visits and a basic urinalysis (dipstick) will be performed at each treatment visit. If the basic urinalysis is abnormal, a full urinalysis should be performed.
- A urine or serum β-hCG pregnancy test will be performed before the administration of the trial drug every 4 weeks for subjects receiving avelumab, or every 3 weeks for subjects receiving chemotherapy for females of childbearing potential. Results of the most recent pregnancy test should be available prior to the next dosing of trial drug. The pregnancy test may be done by a local laboratory.
- Tumor evaluation for all subjects (see Section 7.3) will be performed at Week 7 and then once every 6 weeks and every 12 weeks after 12 months, until disease progression. The subject may stay on a 6 week schedule if they continue tumor evaluations in the absence of progression and there is no start of further anticancer therapy.

CCI [redacted]

- ACTH will be collected only at the Baseline visit. T4 and TSH will be collected at Screening/Baseline, every 6 weeks thereafter during the treatment phase.

CCI [redacted]

CCI

[redacted]

7.1.3 End of Treatment

7.1.3.1 End-of-Treatment Visit

Subjects must undergo 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 therapy is started, if possible, whichever occurs earlier. The End-of-Treatment visit will comprise a full assessment for safety, immunogenicity, and tumor response as appropriate, and will include the following (see Table 1 to Table 6):

- Patient-reported outcomes / quality of life assessments
- AEs, concomitant medications, and ECOG PS
- Physical examination including vital signs and body weight
- 12-lead ECGs
- Laboratory hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick and microscopic evaluation)
- Urine or serum β-hCG pregnancy test (in females of childbearing potential)
- Tumor evaluation (only to be performed if no disease progression was documented previously)
- Optional tumor biopsy
- T4, and TSH levels

CCI

[redacted]

- Blood samples for plasma biomarkers for subjects receiving avelumab.

7.1.4 Safety Follow-up

All subjects will have a subsequent visit scheduled 30 days (±5 days) after the last administration of trial treatment, followed by a 90-day telephone Safety Follow-up. The 30-day Safety Follow-up visit will include the following assessments of safety parameters:

- Patient-reported outcomes/quality of life assessments
- Any SAEs and non-serious AEs will be documented.
- Ongoing SAEs will be followed.
- Concomitant medications and procedures will be reported.
- Physical examination
- Vital signs measurements
- Body weight
- ECOG PS
- Hematology and hemostaseology
- Core serum chemistry
- Urinalysis
- β-HCG pregnancy test
- T4 and TSH levels

CCI [redacted]

7.1.5 Safety Follow-up Phone Call

At 90 days (± 1 week) after the last dose of IMP, 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 study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study treatment. Subjects will also be asked about any antitumor therapy.

7.1.6 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 outcome is known, unless the subject is documented as "lost to follow-up." Any SAE assessed as related to the IMP must be reported whenever it occurs, irrespective of the time elapsed since the last trial drug administration.

Subjects without PD according to RECIST 1.1 at the End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [± 1 week] during the first 12 months of the study, and then every 12 weeks using the same procedures and review as while on treatment) up to PD. Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. The subject may stay on a 6 week schedule if they continue tumor evaluations in the absence of progression and there is no start of further anticancer therapy.

After the End-of-Treatment visit, subjects will be followed up on every 12 weeks (± 1 week) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab. Under some circumstances, the subject may not be followed for 5 years for survival in this study, for eg, the subjects may be offered to enter into a roll-over study, or the Sponsor may terminate the study early.

7.1.7 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 120 mL in a single day and 550 mL over 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 the Screening Visit, the following demographic data will be collected: date of birth, sex (gender), race, and ethnicity.

7.2.2 Diagnosis of Non-Small Cell Lung 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 (including documentation of PD-L1 expression as determined by a companion diagnostic test under development and performed centrally, Section 7.6 for details), 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, chemotherapy, and 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 (Screening only) will be recorded.

7.2.5 CT or MRI Scans for Tumor Assessment at Baseline

Baseline imaging will be performed within 28 days prior to randomization in order to establish baseline disease status of target and nontarget lesions according to RECIST 1.1. Acceptable modalities include CT scans (chest, abdomen, and pelvis), CT chest with contrast together with MRI of the abdomen and pelvis, or positron emission tomography/CT scans. The use of IV contrast is preferred unless there is a history of allergy or other risk in the opinion of the Investigator (chest X-ray is not acceptable and other imaging modalities may be performed at the discretion of the Investigator and as clinically indicated). Bone scans should be performed if clinically indicated. Baseline tumor burden should be determined as outlined in Section 7.3. A brain CT/MRI scan is required at Screening if one has not been performed within 6 weeks prior to randomization. In general, lesions detected at Screening/Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening and at the End-of-Treatment visit after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR and QT duration, and possible arrhythmias. ECGs are to be performed as clinically indicated in case of abnormalities such as increased heart rate above the subject's baseline, detected during the physical examination and/or vital signs measurements performed prior to avelumab treatment.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the Baseline values for subsequent safety clinical laboratory evaluations during the trial, but will also help to make sure that each randomized subject fulfills all the trial entry criteria and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

On study imaging will be performed every 6 weeks (±1 week) calculated from the randomization date and as clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. The CT/MRI scans will be performed and collected until disease progression is assessed by the Investigators according to RECIST 1.1. For all subjects and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progressive disease should be collected to confirm progression.

NOTE: Subjects who discontinue treatment for reasons other than radiological progression assessed according to RECIST 1.1, will continue to have efficacy assessments (CT/MRI scans) according to the protocol schedule until disease progression.

In case of avelumab treatment beyond progression, additional images should be collected in accordance with imaging schedule as long as the subject continues on avelumab therapy.

Radiographic images and physical findings (physical assessments) will be used by the Investigators for the local determination of disease progression and subject treatment decisions. Images will also be read centrally and reviewed by a blinded IRC. The IRC will make a determination for tumor response and/or progression of disease according to RECIST 1.1.

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 randomization. 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 and submitted for central radiological review. 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 randomization. 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 (tumor response and disease progression). Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v1.1.

For the study objectives of efficacy determination, tumor responses to treatment will be assigned by the IRC based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1.

To assess objective response, the tumor burden at Baseline will be estimated and used for comparison with subsequent measurements. At Baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST 1.1 (1).

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

Any CR or PR should be confirmed, preferably at the scheduled 6-week interval, 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 scheduled 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 or for adverse events 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. After radiological progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. If radiological progression is not confirmed, and there was no new anticancer therapy initiated, then the subject may resume or continue trial treatment and have their next scan according to the study schedule.

There will also be an optional biopsy for avelumab subjects only. A de novo (ie, fresh biopsy) tumor sample should be collected at End of Treatment, unless clinically contraindicated, or after

disease progression (if EOT occurred before progression). If after disease progression, the biopsy should be collected before the start of any new therapy.

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 (see Table 1, Table 2, Table 3, and Table 4).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Events

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, v 4.03 (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 trial treatment avelumab/chemotherapy. 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 trial treatment avelumab/chemotherapy. 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 (ADR)

ADRs are defined in this study as any AEs 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 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 chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

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 suspicious to be a potential irAE including infusion related reactions will be considered AEs of special interest (AESIs).

7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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

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

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

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

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, 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" or 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, all SAEs and all treatment-related non-serious AEs need to be documented through the study's Safety Follow-up Phone Call, defined at 90 days (± 1 week) after the last IMP administration. 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

Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately. Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the paper 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 Adverse Event 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 medication 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 4) must be collected, and sent to the central laboratory for analysis.

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 collected in the eCRFs as per eCRF completion guidelines, however, central laboratory samples must be collected in addition.

In the case of LFT elevations (AST, ALT and/or total bilirubin) requiring additional lab draws (according to guidelines set forth in Table 10 Management of irAEs), an unscheduled lab draw should be sent to the central laboratory for analysis.

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 11 will be taken from nonfasted subjects during the Screening phase (28 days prior to randomization), during the treatment phase as specified in Table 11, Table 1 to Table 4, at the End-of-Treatment visit, and at the Safety Follow-up visit. The ACTH, T4, TSH, and urinalysis will only be assessed at the time points defined in Table 11, Table 1, Table 2, and Table 3. If confirmation of a subject's postmenopausal status is necessary, an FSH level will also be performed at Screening, see Section 7.1.1.

Table 11 Required Full Laboratory Safety Tests

Full Chemistry	Core Chemistry[a]	Hematology
Albumin	Alkaline phosphatase	Absolute lymphocyte count
Alkaline phosphatase	ALT	ANC
ALT	AST	Hematocrit
Amylase	BUN/total urea	Hemoglobin
AST	Calcium	Platelet count
GGT	Chloride	RBC count
BUN / total urea	Creatinine	WBC count and differential count
Calcium	Glucose	RBC morphology
Chloride	Phosphorus / Phosphates	Reticulocytes
Cholesterol	Magnesium	MCH
Creatine kinase	Potassium	Mean corpuscular volume
Creatinine	Sodium	MCHC
CRP	Total bilirubin	
Glucose	Amylase	**Hemostaseology**
LDH	Lipase	aPTT
Lipase	Creatine kinase	Prothrombin time / INR
Phosphorus / Phosphates		
Magnesium		**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick and microscopic evaluation) to be performed only at the Screening and End-of-Treatment visits and a basic urinalysis prior to each administration of the trial drug.
Potassium		
Sodium		
Total bilirubin		

Full Chemistry	Core Chemistry[a]	Hematology
Total protein		
Uric acid		Totality of binding ADAs
Triglycerides		
		ACTH (only at Baseline), TSH, and T4 To be assessed - according to schedule of assessments in Table 1, Table 2, Table 3, and Table 4.
Hormone		
FSH (yes / no if applicable)		

ACTH: adrenocorticotropic hormone; ADA: Anti-drug antibody; ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; FSH: follicle-stimulating hormone; GGT: gamma-glutamyltransferase; INR: international normalized ratio; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RBC: red blood cell; TSH: thyroid-stimulating hormone; T4: free thyroxine; WBC: white blood cell.

[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 Examination and Other Assessments

The ECOG PS will be assessed at Screening and at subsequent visits as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and documented in the eCRF.

Body weight will be measured at Screening and at subsequent visits as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and documented in the eCRF. Body height will be measured at Screening only.

A physical examination will be conducted at Screening and at subsequent visits if indicated as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and documented in the eCRF (detailed description in Section 7.2.4). Results of the physical examination, including any abnormalities, will be documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

A 12-lead ECG will be recorded as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). 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.

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 before administration of trial drug (every 4 weeks for the avelumab arm or every 3 weeks for the comparator arm) during the treatment phase and at the End-of-Treatment visit. Results of the most recent pregnancy test

should be available prior to the next dosing of trial drug. Subjects who are postmenopausal are exempt from pregnancy testing. Females are considered postmenopausal if they have age-related amenorrhea ≥ 12 consecutive months or if they have undergone hysterectomy or bilateral oophorectomy. If necessary to confirm/assess postmenopausal status, FSH may be drawn at Screening with documented increased FSH > 40 mIU/mL.

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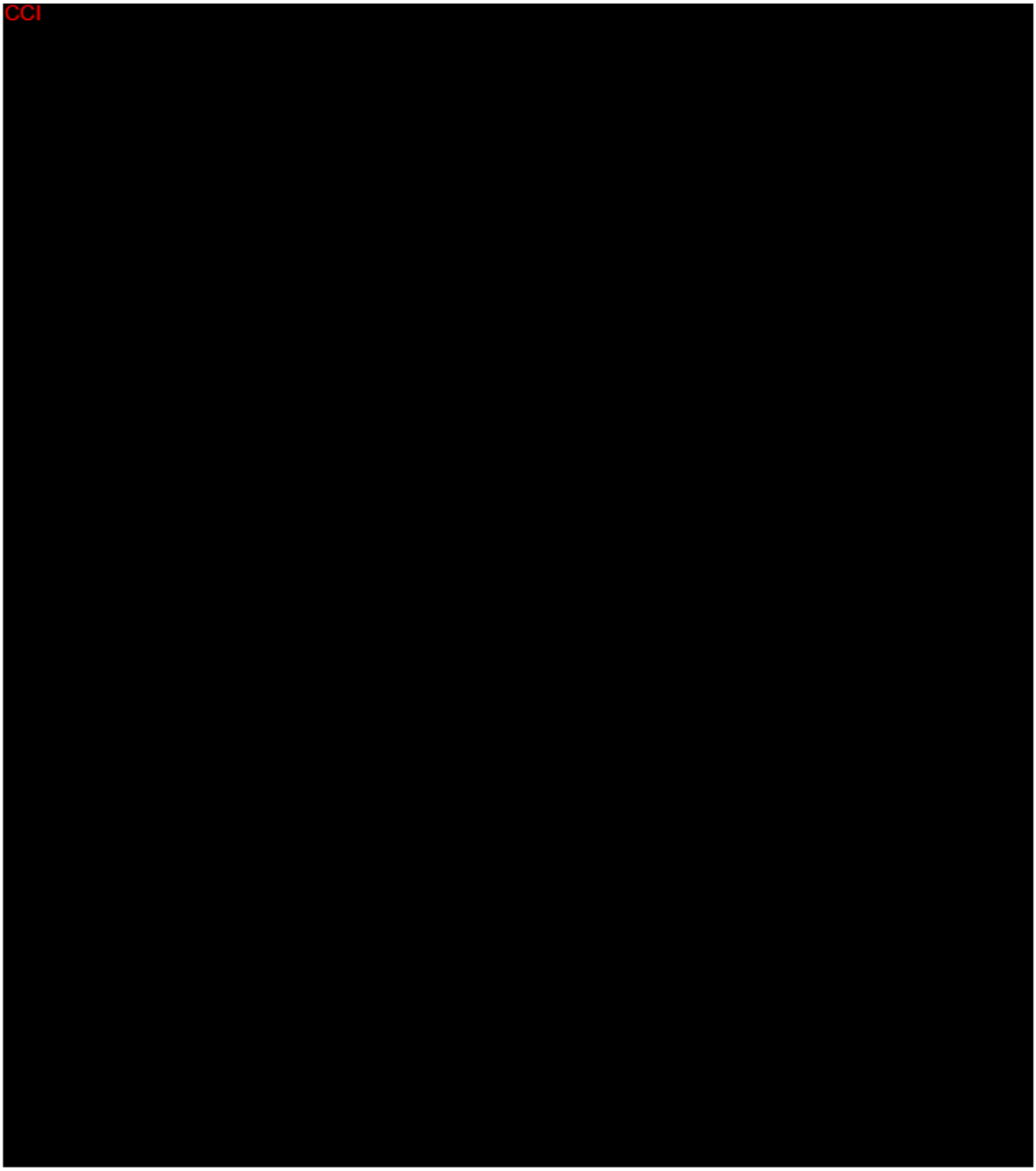

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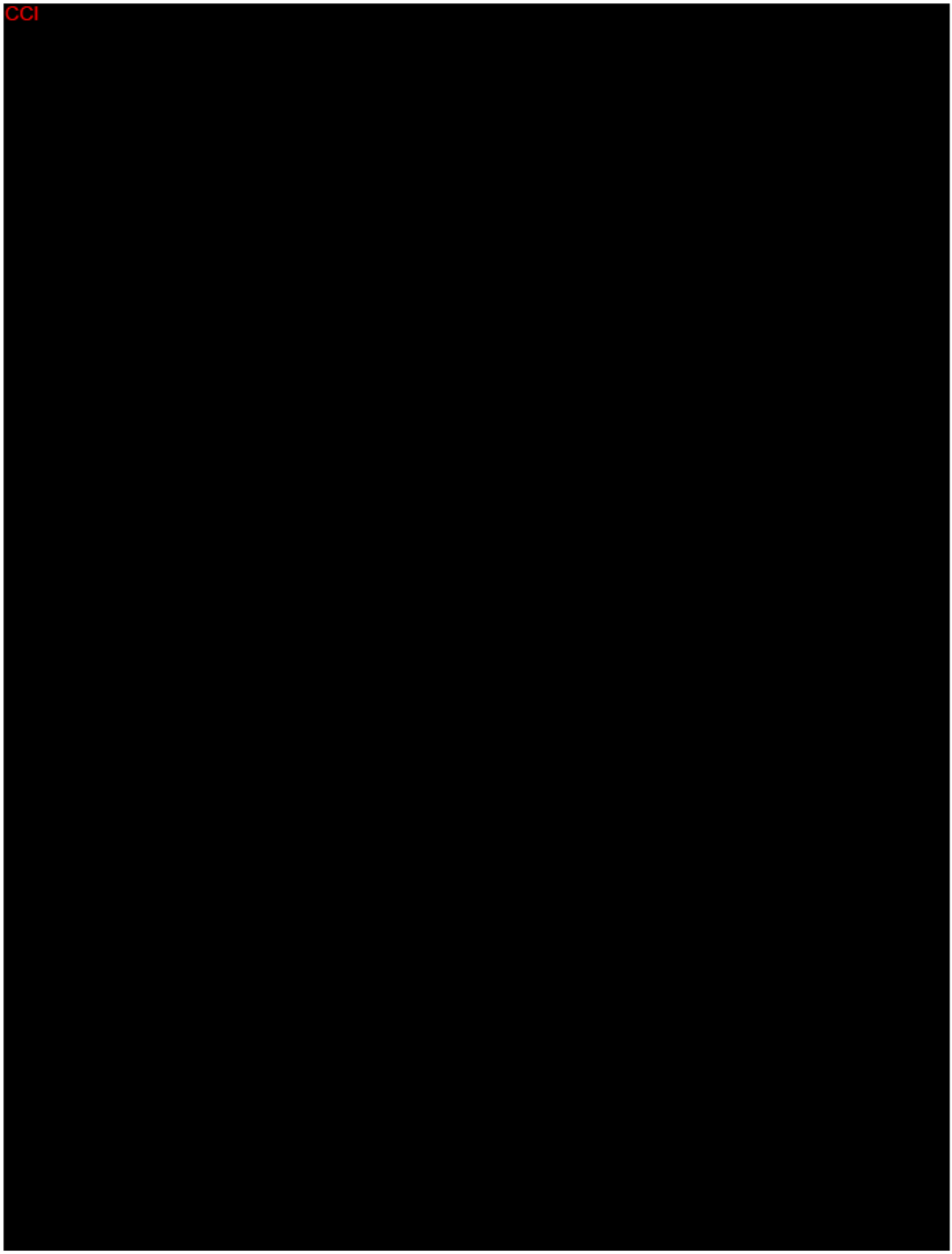

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7.7 Other Assessments

7.7.1 Patient-reported Outcomes/Quality of Life

Patient-reported outcomes / quality of life will be assessed by the EQ-5D-5L, EORTC QLQ-C30, and module QLQ-LC13. Questionnaires will be completed by the subject at Screening (or on Day 1, if not done at Screening), Week 7, Week 13 prior to trial treatment administration, and then every 6 weeks thereafter while on trial treatment for subjects randomized to receive avelumab; and Screening (or on Day 1, if not done at Screening), Week 7, Week 13, and then every 6 weeks thereafter while on trial treatment for subjects randomized to receive chemotherapy. Patient-reported outcomes will also be assessed at the End-of-Treatment visit (details will be provided in the Study Manual) and Safety Follow-up Visit 30 Days after Last Treatment.

The patient-reported outcomes / quality of life 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.

The EQ-5D-5L comprises 5 questions and a visual analogue scale. The questionnaire is used to calculate the utility index, used in economic evaluations. The 5 items are mobility, self-care, usual activities of daily living, pain/discomfort, anxiety/depression with 5 descriptive levels ranging from “no problem to…” to “extreme…/unable to do….” The visual analogue scale ranges from 0-100 where 0 is “the worst health you can imagine” and 100 is “the best health you can imagine.” The recall period is defined as “today.”

EORTC QLQ-C30 accesses the quality of life of cancer patients with 30 questions including the dimensions of activities of daily living, pain, fatigue, shortness of breath, appetite loss, nausea, vomiting, sleeping disturbances, diarrhea, difficulties to concentrate, anxiety and depression, memory loss, social activities, financial burden, impression of overall health and impression of overall quality of life. Questions 1-28 are measured in a range from 1-4 where 1 represents “Not at All” and 4 represents “Very Much”, and questions 29-30 are measured in a range from 1-7 where 1 represents “Very poor” and 7 represents Excellent. The recall period is defined as “during the past week.”

The QLQ-LC13 comprises 13 questions incorporated into 1 multi-item scale designed to evaluate lung cancer symptoms such as dyspnea, different types of pain, cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy. For each domain and item, a linear transformation is applied to standardize the raw score to a range from 0 to 100, with 100 representing the best possible function / quality of life, and highest burden of symptoms for symptom domains and single items. The recall period is defined as “during the past week.”

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

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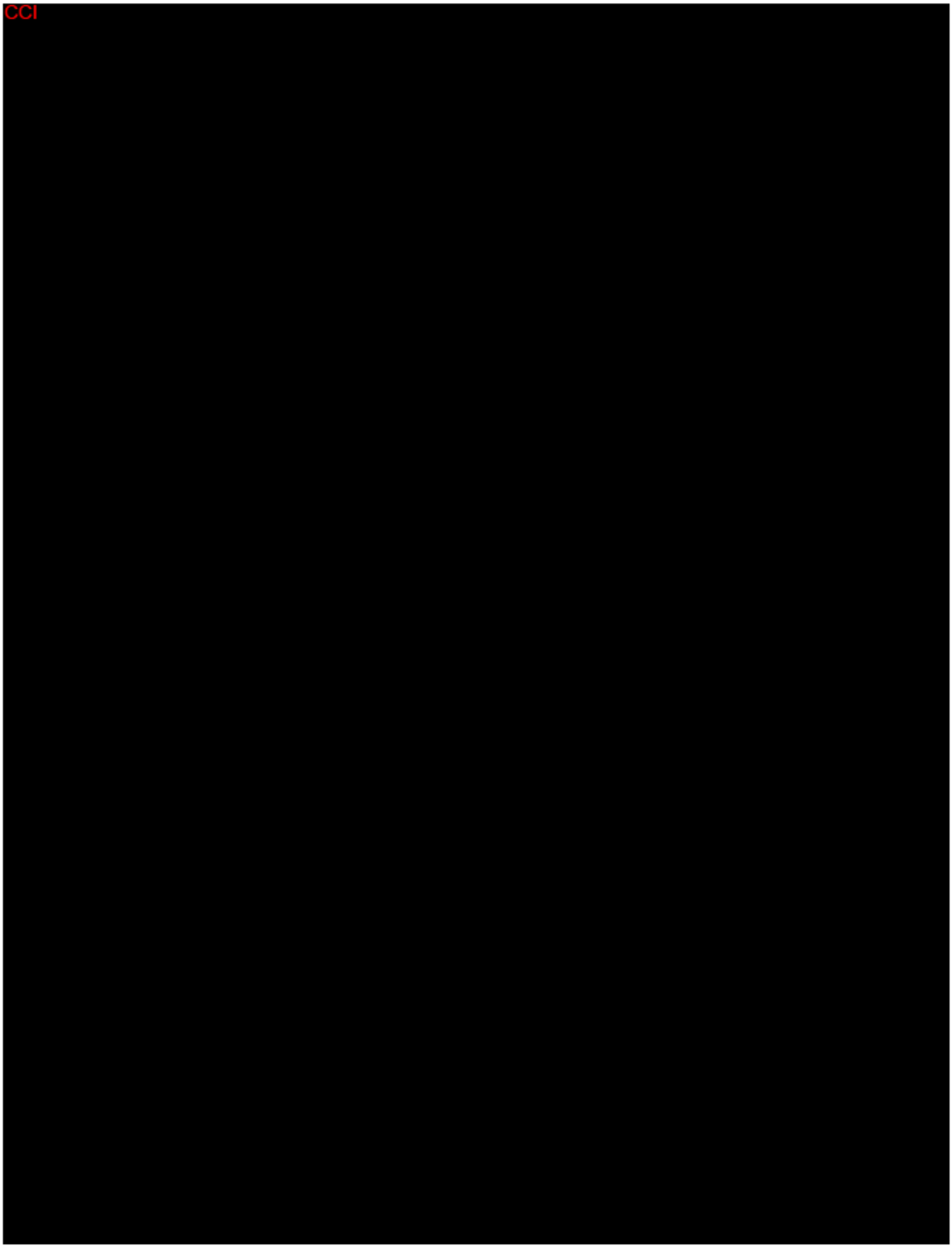
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8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints of the trial are the PFS time or OS time. The trial will be considered to have met its objective if either or both of the primary endpoints are positive.

PFS is defined as the time from date of randomization until date of the first documentation of PD or death due to any cause in the absence of documented PD, whichever occurs first.

The PFS will be defined according to RECIST 1.1 and as adjudicated by an IRC (see Section 2.3.2). Details on determination of the first disease progression date will be specified in the IRC charter.

For the primary analysis PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects who start new anticancer treatment prior to an event, or for subjects with an event after two 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.

Some subjects may start new anticancer therapy prior to documented disease progression. For such subjects, the protocol requires tumor assessments to be continued per schedule of assessments

through documented disease progression or death to enable conduct of a supportive analysis for PFS that will ignore (that is, not censor subjects at) start of new anticancer treatment.

The OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subject's death.

For subjects who are still alive at the time of data analysis or who are lost to follow-up, OS time will be censored at the last recorded date that the subject is known to be alive (specified in the SAP) as of the data cut-off date for the analysis.

8.3.2 Secondary Endpoints

8.3.2.1 Best Overall Response

The BOR will be determined according to RECIST 1.1 (1) and as adjudicated by an IRC (see Section 2.3.2). It is defined as the best response obtained among all tumor assessment visits after the date of randomization until documented disease progression or start of subsequent new anti-cancer therapy. Details of determination of tumor response date at each time point will be provided in the IRC charter.

For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 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. 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 1.1 and as adjudicated by the IRC.

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

8.3.2.2 Duration of Response

The duration of response according to RECIST 1.1, defined for each subject with a confirmed response as the time from the date of the first assessment demonstrating a CR or PR to date of the first assessment demonstrating PD or death within 12 weeks after the last tumor assessment, whichever occurs first.

8.3.2.3 Patient-reported Outcomes/Quality of Life (QoL) assessment

Changes in patient-reported outcomes / quality of life will be assessed by the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 questionnaires, as defined in the SAP.

8.3.3 Safety Endpoints

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

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8.4 Analysis Sets

Screening Analysis Set

The screening analysis set includes all subjects who signed the ICF.

Full Analysis Set (FAS)

The FAS will include all subjects who were randomized to trial treatment. Analyses performed on the FAS will take into account subjects' allocation to treatment groups as randomized.

Modified Full Analysis Set (mFAS)

The modified FAS is defined as the FAS restricted to subjects who were randomly assigned to treatment according to CTP version 4.0 or later, after Arm C is activated in the treatment allocation.

PD-L1 Positive

The inclusion criteria for positive PD-L1 is determined by a Dako PD-L1 immunohistochemistry (IHC) pharmDx companion diagnostic test, developed for the purpose of this trial. The PD-L1 IHC assay and the scoring algorithm to determine any, moderate, and high PD-L1 expression status will be defined prior to conducting any statistical analyses. Details will be specified in laboratory manual and SAP.

The any PD-L1+ analysis set will include all subjects with any expression PD-L1+ tumors at any staining intensity who were randomized to trial treatment.

The moderate and high expression PD-L1+ analysis set will include all subjects with moderate expression and high expression PD-L1+ tumors at any staining intensity (in tumor cells) who were randomized to trial treatment.

The high expression PD-L1+ analysis set will include all subjects with high expression PD-L1+ tumors at any staining intensity (in tumor cells) who were randomized to trial treatment.

Safety Analysis Set

The Safety analysis set will include all subjects who were administered at least 1 dose of the trial medication. Analyses performed on the Safety analysis set will consider subjects as treated.

Subgroup Analysis Sets

Analysis of efficacy variables will also be performed on subgroups of interest, which will be specified in the SAP.

Pharmacokinetic Analysis Set

The PK Analysis Set will include subjects who were administered at least 1 dose of the trial medication and at least 1 quantifiable serum concentration at a scheduled PK time point post dose.

Immunogenicity (ADA) Analysis Set

All subjects who complete at least 1 administration of avelumab and who have at least 1 valid ADA result.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

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

Primary analysis population

The primary analysis population will be:

- The FAS population for Arm A (avelumab once every 2 weeks) and Arm B (SOC chemotherapy) comparisons.
- The mFAS population for Arm C (avelumab once a week for 12 weeks followed by avelumab once every 2 weeks) and Arm B (SOC chemotherapies) comparisons.

Significance level

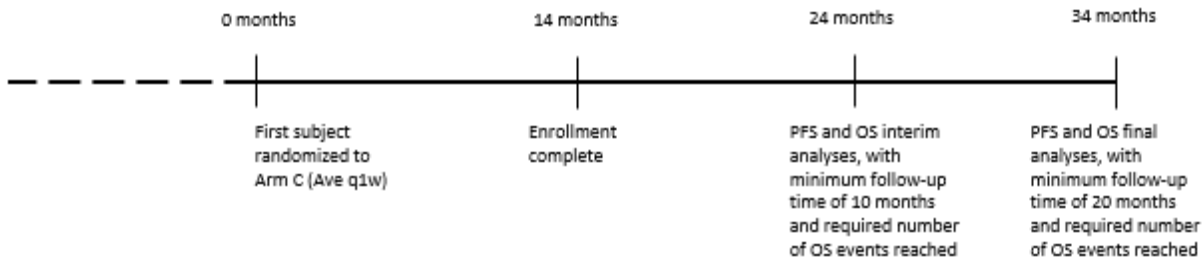
The overall significance level is 2.5% one-sided. Confirmatory statistical tests are described in Section 8.5.2 along with procedures for controlling the family wise error rate in the strong sense. CCI [redacted] All statistical tests comparing

treatment arms will be performed one-sided. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified.

Sequence of Analyses

The planned sequence of analysis is displayed in Figure 2. Dates are exemplary cut-off dates.

Figure 2 Sequence of Analyses



OS: overall survival; PFS: progression free survival.

The data cut-off for the primary OS and PFS analysis will occur after the target number of 173 OS events for Arm C versus B comparison of the randomized subjects with high PD-L1 has been reached and at least 20 months follow-up after the randomization of the last subject in the study. Lan-de-Mets alpha spending with O'Brien-Fleming-like boundaries will be adopted for the currently observed event size at cut-off date for each treatment group comparison (see Section 8.5.2).

The PD-L1 IHC assay and the scoring algorithm to determine low, moderate, and high PD-L1 expression status will be defined prior to conducting any statistical analyses. Details will be specified in laboratory manual and statistical analysis plan.

Further details concerning interim analysis are included in Section 8.6.

General Conventions

Baseline characteristics summary and the efficacy analysis will be performed on the FAS and mFAS population considering treatment Arms A, B and C. Analyses performed on the FAS and mFAS will take into account subjects' allocation to treatment groups as randomized. Analyses performed on the safety population will consider subjects as treated.

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

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, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

In general, the last measurement prior to randomization will serve as the baseline measurement. If such a value is missing, the last measurement prior to the first trial drug administration will be used as the baseline measurement.

Statistical analyses will be performed using SAS® version 9.3 or higher.

8.5.2 Analysis of Primary Endpoints

Primary Analysis

The primary statistical comparisons of Arm A vs Arm B will be performed with the FAS. The primary statistical comparison of Arm C vs Arm B will be performed with the mFAS to ensure a randomized comparison of treatment arms that is not impacted by the time of randomization.

The primary endpoints of this trial are PFS and OS. The primary analysis will compare the PFS and OS time between the 2 investigational treatment groups (Arm A, Arm C) vs the control group (Arm B) independently, and will be performed using a one-sided stratified log rank test at the global $\alpha = 0.025$ (one-sided). The stratification factors are those used for randomization as captured via the IWRS (NSCLC histology: squamous versus non-squamous cell, and PD-L1 tumor expression: low expression versus moderate versus high expression). Missing PD-L1 expression classification for subjects enrolled prior to Amendment 3 will be imputed from the results of the Dako PD-L1 immunohistochemistry (IHC) pharmDx companion diagnostic test.

A hierarchical testing strategy will be applied to test superiority of either avelumab regimen vs SOC chemotherapy for the primary endpoints PFS and OS. The FAS will be used for the comparisons of Arm A and Arm B and mFAS will be used for the comparison of Arm C and Arm B:

Hierarchy Step 1: PFS and OS in the high expression PD-L1+ population

Hierarchy Step 2: PFS and OS in the moderate and high expression PD-L1+ population (including high expression PD-L1+ population)

Hierarchy Step 3: OS in the any expression PD-L1+ population

A closed testing procedure will be used with weighted Bonferroni tests according to Hommel, Bretz, Maurer 2007 to account for multiplicity. For the closure test, it holds: an intersection hypothesis H_i can only be rejected if all intersection hypotheses implying H_I can also be rejected by their local tests.

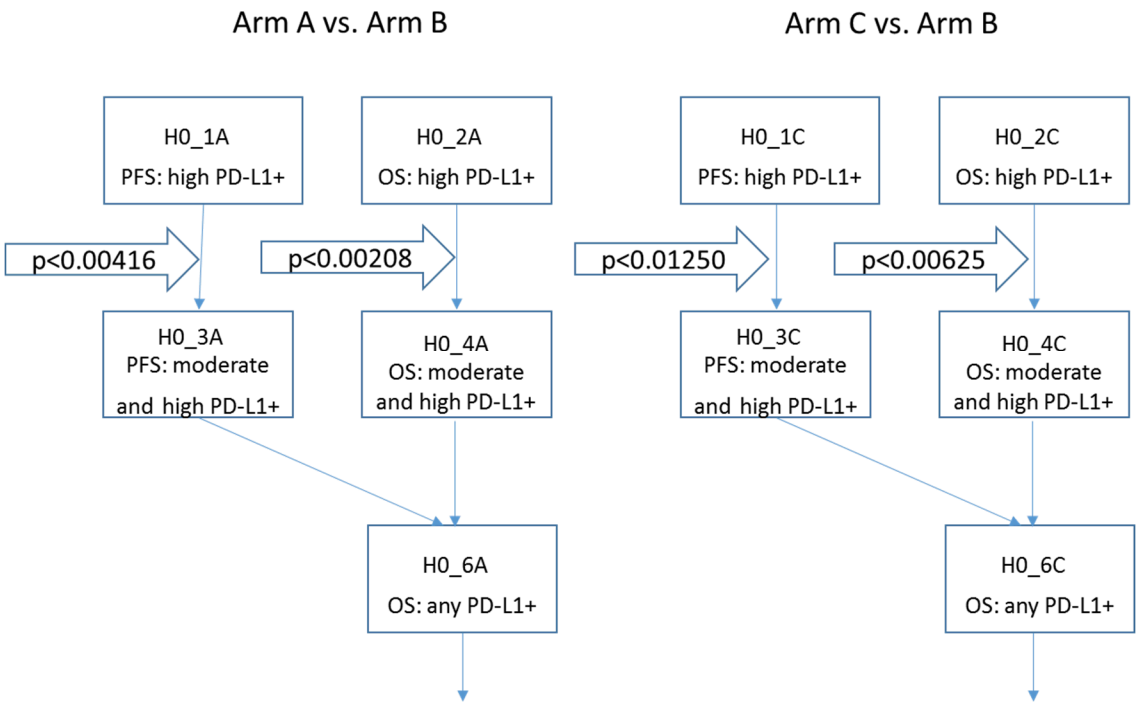
The following procedure is used:

- All hypotheses comparing Arm C vs Arm B get three times the weight of the hypotheses comparing Arm A vs Arm B, ie, weight ¾ and ¼. Corresponding hypotheses for PFS and OS get different weights, ie, 2/3 for PFS and 1/3 for OS.

- Exception: as long as an hypothesis with PD-L1 high expression (H0_1A,H0_2A,H0_1C,H0_2C) is included in an intersection hypothesis the corresponding hypotheses for PD-L1 moderate and high expression (H0_3A,H0_4A,H0_3C,H0_4C) and all hypotheses for any PD-L1+ (H0_6A,H0_6C) get weight 0, as long as both hypotheses (PFS and OS) with PD-L1 moderate expression (H0_3A,H0_4A and H0_3C,H0_4C) is included in an intersection hypothesis the corresponding OS hypotheses for any PD-L1+ (H0_6A and H0_6C) get weight 0.
- For hypotheses with interim analyses the corresponding significance levels at interim and final analysis are defined based on α-spending approaches using local significance levels according to 1 and 2.
- Sum of the weights for each intersection hypothesis is 1.

The following figure provides an exemplary overview of the statistical testing procedure.

Figure 3 **Exemplary Inferential Testing Procedure**



OS: overall survival; PFS: progression free survival.
Note: Arm A vs Arm B should read p<0.00417

The statistical hypotheses are described below. The significance levels noted are the minimum significance levels that can to be used for the corresponding hypothesis. Depending on the already rejected hypothesis according to closed testing procedure above the local significance level might increase.

Hierarchy Step 1: Comparisons for high expression PD-L1+ population

PFS for high expression PD-L1+ in the FAS: Arm A versus B comparison at $\alpha = 0.00417$ or above according to closed testing procedure

$$H_{0\_1A}: \lambda_{1A}(t) = \theta_{1h}\lambda_{1B}(t), \theta_{1h} \geq 1, \text{ versus } H_{1\_1A}: \lambda_{1B}(t)=\theta_{h}\lambda_{1C}(t), \theta_{1h} < 1,$$

OS for high expression PD-L1+ in the FAS: Arm A versus B comparison at $\alpha = 0.00208$ or above according to closed testing procedure

$$H_{0\_2A}: \lambda_{2A}(t) = \theta_{2h}\lambda_{2B}(t), \theta_{2h} \geq 1, \text{ versus } H_{1\_2A}: \lambda_{2A}(t)=\theta_{2h}\lambda_{2B}(t), \theta_{2h} < 1,$$

PFS for high expression PD-L1+ in the mFAS: Arm C versus B comparison at $\alpha = 0.0125$ or above according to closed testing procedure

$$H_{0\_1C}: \lambda_{1C}(t) = \theta_{1h}\lambda_{1B}(t), \theta_{1h} \geq 1, \text{ versus } H_{1\_1C}: \lambda_{1B}(t)=\theta_{1h}\lambda_{1B}(t), \theta_{1h} < 1,$$

OS for high expression PD-L1+ in the mFAS: Arm C versus B comparison at $\alpha = 0.00625$ or above according to closed testing procedure

$$H_{0\_2C}: \lambda_{2C}(t) = \theta_{2h}\lambda_{2B}(t), \theta_{2h} \geq 1, \text{ versus } H_{1\_2C}: \lambda_{2C}(t)=\theta_{2h}\lambda_{2B}(t), \theta_{2h} < 1,$$

If local significant results are obtained in Hierarchy Step 1, inferential testing will proceed to corresponding hypotheses in Hierarchy Step 2.

Hierarchy Step 2: Comparisons for moderate and high expression PD-L1+ population

PFS for moderate and high expression PD-L1+ in the FAS: Arm A versus B comparison at $\alpha = 0.00417$ or above according to closed testing procedure

$$H_{0\_3A}: \lambda_{3A}(t) = \theta_{3m}\lambda_{3B}(t), \theta_{3m} \geq 1, \text{ versus } H_{1\_3A}: \lambda_{3A}(t)=\theta_{3m}\lambda_{3B}(t), \theta_{3m} < 1,$$

OS for moderate and high expression PD-L1+ in the FAS: Arm A versus B comparison at $\alpha = 0.00208$ or above according to closed testing procedure

$$H_{0\_4A}: \lambda_{4A}(t) = \theta_{4m}\lambda_{4B}(t), \theta_{4m} \geq 1, \text{ versus } H_{1\_4A}: \lambda_{2A}(t)=\theta_{4m}\lambda_{4B}(t), \theta_{4m} < 1,$$

PFS for moderate and high expression PD-L1+ in the mFAS: Arm C versus B comparison at $\alpha = 0.00125$ or above according to closed testing procedure

$$H_{0\_3C}: \lambda_{3C}(t) = \theta_{3m}\lambda_{3B}(t), \theta_{3m} \geq 1, \text{ versus } H_{1\_3C}: \lambda_{3C}(t)=\theta_{3m}\lambda_{3B}(t), \theta_{3m} < 1,$$

OS for moderate and high expression PD-L1+ in the mFAS: Arm C vs B comparison at $\alpha = 0.00625$ or above according to closed testing procedure

$$H_{0\_4C}: \lambda_{4C}(t) = \theta_{4m}\lambda_{4B}(t), \theta_{4m} \geq 1, \text{ versus } H_{1\_4C}: \lambda_{4C}(t)=\theta_{4m}\lambda_{4B}(t), \theta_{4m} < 1,$$

If local significant results are obtained for Hierarchy 2, inferential testing will proceed to corresponding hypotheses in Hierarchy 3.

Hierarchy Step 3: Comparisons for low expression PD-L1+ population:

OS for low expression PD-L1+ in the FAS: Arm A versus B comparison at $\alpha = 0.00208$ or above according to closed testing procedure

$$H_{0\_6A}: \lambda_{6A}(t) = \theta_{6l}\lambda_{6B}(t), \theta_{6l} \geq 1, \text{ versus } H_{1\_6A}: \lambda_{6A}(t)=\theta_{6l}\lambda_{6B}(t), \theta_{6l} < 1,$$

OS for any expression PD-L1+ in the mFAS: Arm C vs B comparison at $\alpha = 0.00625$ or above according to closed testing procedure

$$H_{0\_6C}: \lambda_{6C}(t) = \theta_{6l}\lambda_{6B}(t), \theta_{6l} \geq 1, \text{ versus } H_{1\_6C}: \lambda_{6C}(t)=\theta_{6l}\lambda_{6B}(t), \theta_{6l} < 1,$$

Interim analyses are planned for PFS and OS based on required OS events and minimum follow-up time of 10 months for the high expression PD-L1+ population. Interim and final analysis for PFS and OS will be conducted at the same time. Alpha will be spent according to Lan-DeMets with O'Brien-Fleming-like boundaries with the local significance level at the first hierarchy step. Further details are given in Section 8.6.

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the HR and its CI with a confidence level in line with the local significance level. In addition 95% CIs will be provided. Each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS and OS time with two-sided 95% CIs. In particular, the PFS rate at 6, 9, 12 and 15 months and OS rate at 12, 18, 24 and 30 months will be estimated with corresponding CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (41) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (42). The estimate of the standard error will be computed using Greenwood's formula.

The proportional hazards assumption for the primary analysis will be visually checked by plotting log(-log[survival]) versus log(time) by treatment arm. The frequencies of event types and reasons for censoring will be assessed by treatment arm in terms of descriptive statistics.

Sensitivity analyses will be detailed in the SAP.

Time of Follow-Up for PFS

A Kaplan-Meier plot will be created for both treatment groups to compare the duration of follow-up for PFS using the following censoring rules.

Table 14 Censoring Rules for Duration of Progression Free Survival Follow-up

	Date of Event / Censoring	Censoring
Subjects alive and without disease progression	Time from randomization to last date known to be progression free (according to IRC)	No
Subjects who progressed or died	Time from randomization to date of PD or death	Yes

IRC: Independent Review Committee; PD: progressive disease.

8.5.3 Analysis of Secondary Endpoints

Other secondary efficacy analyses on BOR will be performed on the FAS and mFAS analysis set respectively for the PD-L1 analysis sets. Details will be provided in the trial SAP.

Time of follow-up will be calculated from the randomization date and the date the subject was last known to be alive. For subjects who died, time of follow-up will be censored on the date of death. A Kaplan-Meier plot will be created for both treatment groups to compare the duration of follow-up.

For the secondary endpoint analysis of BOR according to RECIST 1.1 and as adjudicated by the IRC, the ORR in terms of having a confirmed BOR of CR or PR will be calculated along with corresponding two-sided exact Clopper-Pearson CIs according to local significance level and 95% CI for the 2 treatment groups. The Cochran-Mantel-Haenszel test will be performed with the randomization strata taken into account to compare the ORR between the 2 treatment groups.

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8.5.5 Analysis of Safety Endpoints

The extent of exposure to trial drugs (avelumab or chemotherapy) will be characterized by duration (weeks), number of administrations, cumulative dose, dose intensity, relative dose intensity (actual dose given / planned dose), and number of dose delays.

Safety analyses will be performed on the Safety analysis set. The safety endpoints will be tabulated using descriptive statistics.

Safety assessments will be based on review of the incidence of AEs including AESIs, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology and serum chemistry).

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

AEs

All AEs will be coded according to the MedDRA. Severity of AEs will be graded using the NCI-CTCAE v 4.03 toxicity grading scale.

The incidence of TEAEs, regardless of attribution, and TEAEs defined as possibly related to trial treatment will be summarized by Preferred Term and System Organ Class for each treatment arm, and described in terms of intensity and relationship to trial treatment. Treatment-emergent AEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

All premature terminations will be summarized by primary reason for treatment discontinuation / withdrawal.

Laboratory variables

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from randomization to highest grade during the on-treatment period will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal

limits. Only subjects with post-Baseline laboratory values will be included in these analyses. Further details of analyses for all the laboratory parameters will be provided in the SAP.

Physical examination (including vital signs and 12-lead ECGs)

Physical examination data, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and 12-lead ECGs recorded according to the Schedule of Assessments (Table 1 to Table 4) will be presented.

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

8.5.6 Subgroup Analyses

Subgroup analyses will be performed on the primary endpoints and secondary efficacy endpoints with the subgroups, which will be specified in the SAP. For PFS and OS analyses, the HR and its corresponding 95% CI will be computed per subgroup level. To assess the heterogeneity of treatment effects across the subgroup levels, a Cox regression model will be fitted with the event time as the dependent variable; subgroup, treatment, and with and without the treatment-by-subgroup interaction as explanatory variables. A p-value for the interaction test (Likelihood Ratio test) will be provided together with the HR and corresponding 95% CI of the interaction model parameter. For the secondary endpoint of BOR, analogous analyses will be performed using a logistic regression model.

Subgroup analysis to explore the effect size between Arm A and Arm B will be performed with the FAS, and mFAS for Arm C and Arm B.

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8.6 Interim Analysis

Interim analyses are planned after recruitment have been completed for PFS and OS based on required events for the high expression PD-L1 population. Interim analysis for PFS and OS will be conducted based on required number of events for Arm B and C in the high expression PD-L1+ population. Lan-DeMets α-spending with O'Brien-Fleming-like boundaries will be considered given the local significance levels at the first hierarchy step. The exact timing and the event size will be confirmed in the SAP. No futility analysis is planned.

The interim analysis will test the hypotheses for PFS: H_{0_1A}, H_{0_1C}, H_{0_3A}, H_{0_3C} and the hypotheses for OS: H_{0_2A}, H_{0_2C}, H_{0_4A}, H_{0_4C}, H_{0_6A}, H_{0_6C} after the required number of OS events for the interim analysis for Arm C+B have been reached and 10 months have elapsed from the last subject randomized for the high expression PD-L1 analysis set in mFAS (see Table 16).

Primary PFS and OS analyses will be conducted after the required number of OS events for Arm C+B have been reached and at least 20 months have been elapsed from last subject randomized for the high expression PD-L1 analysis set in mFAS. The current plan considers

- 130 OS events for Arm C and B and a minimum follow-up of 10 months to determine the cut-off date for the interim PFS and OS analyses.
- 173 OS events and a minimum follow-up of 20 months for the final PFS and OS analyses.

Table 16 describes the expected number of events, information fraction, the associated cumulative alpha spending and the corresponding expected efficacy boundaries, under proportional hazard assumptions. The actual numbers in particular for the Arm A and B could vary as the event size at the planned cut-off dates is unknown. The alpha levels are however fixed according to Lan-DeMets α-spending with O'Brien-Fleming-like boundaries. Details will be confirmed in the SAP.

Table 16 Interim Analyses

Primary Inferential Analyses (high expression PD-L1)	Expected number of events	Information fraction	Cumulative alpha spent	Efficacy boundary HR
IA – PFS				
Arm A vs. B (FAS)	228	91%	0.0026994	0.69
Arm C vs. B (mFAS)	146	84%	0.0063969	0.66
Final PFS				
Arm A vs. B (FAS)	250	100%	0.004170	0.71
Arm C vs. B (mFAS)	174	100%	0.012500	0.70
IA – OS				
Arm A vs. B (FAS)	214	83%	0.0007241	0.64
Arm C vs. B (mFAS)	130	75%	0.001609	0.60
Final OS				
Arm A vs. B (FAS)	258	100%	0.002080	0.69
Arm C vs. B (mFAS)	173	100%	0.006250	0.68

FAS: full analysis set, HR: hazard ratio, IA: interim analysis, mFAS: modified full analysis set, OS: overall survival, PFS: progression free survival.

An IDMC will be formed and will be responsible for periodic evaluations of the trial including interim analyses and PFS and OS event monitoring. 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 Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the 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. A separate specific CCI ICF will be provided to subjects who are willing to participate in this optional procedure, which refers to the extraction and analysis of germline DNA from blood in order to better understand how gene(s) may affect the efficacy of avelumab.

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. 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.

9.4 Emergency Medical Support and Subject Card

Subjects randomized into 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, the clinical trial protocol will be submitted together with its associated documents (such as the ICF) to the responsible IEC / IRB for its

favorable opinion / approval. The written favorable opinion / approval of the IEC / IRB will be filed in the Investigator Site File, and a copy will be filed with the CRO.

The trial must not start at a site before the Sponsor or designee has obtained written confirmation of favorable opinion / approval from the concerned IEC / IRB. The IEC / IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion / approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion / 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 the clinical trial will also be submitted to the concerned IEC / IRB before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC / IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) 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.

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, race, height, weight
- Medical history and concomitant diseases

- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

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 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 have an impact on the subject's agreement to participate in the trial requires the subject's 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 endpoint(s) 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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12 Appendices

Appendix I: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Title	A Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line of treatment of recurrent or Stage IV PD-L1+ non-small cell lung cancer
IND Number	CCI [redacted]
EudraCT Number	2015-001537-24
Clinical Trial Protocol Date / Version	03 January 2019 / Version 6.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD [redacted] _____ PPD [redacted] _____

Signature Date of Signature

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

Signature Page – Coordinating Investigator

Trial Title	A Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line of treatment of recurrent or Stage IV PD-L1+ non-small cell lung cancer
IND Number	CCI [redacted]
EudraCT Number	2015-001537-24
Clinical Trial Protocol Date / Version	03 January 2019 / Version 6.0

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 [redacted] PPD [redacted]

Signature Date of Signature

PPD [redacted]

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – Principal Investigator

Trial Title	A Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line of treatment of recurrent or Stage IV PD-L1+ non-small cell lung cancer
IND Number	CCI [redacted]
EudraCT Number	2015-001537-24
Clinical Trial Protocol Date / Version	03 January 2019 / Version 6.0
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:	Merck KGaA
Address:	Frankfurter Str. 250 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	Principal Clinical Trial Lead
Institution:	Merck KGaA
Address:	Frankfurter Str. 250 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix II: Eastern Cooperative Oncology Group Performance Status

ECOG PS[a]	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5: 649-55.

Appendix III: Guidance on contraception

Birth control methods considered as highly effective.

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

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

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

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

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

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

Appendix IV: Protocol Amendments History

The information for the current amendment is on the title page.

Amendment 4.0

This is the fourth amendment to the original protocol.

The key reasons (major and administrative changes) for this amendment are summarized below:

- To update the number of sites where the study will be conducted and planned trial period
- Move in Secondary Objectives with related change in Secondary Endpoints to Exploratory Objectives and Endpoints:
  - Secondary Objectives: To characterize pharmacokinetics (PK) of avelumab and individual drug exposures based on sparse PK sampling and to characterize the immunogenicity of avelumab.
  - The secondary endpoints for the trial: PK of avelumab and immunogenicity of avelumab.

CCI [redacted]

- To update the CCI [redacted] for the study
- To update the PD-L1 tumor expression level from any to low
- To remove reference to co-primary endpoints and update to primary endpoints
- To clarify that premedication for avelumab is mandatory for the first 4 infusions only
- To update the schedules of assessment to match the body of the protocol
- To clarify the timing of SAE collection
- To include collection of further antitumor therapy at Follow-up
- To clarify the nature of physical examination assessments
- To update the requirements on ECG assessments
- To clarify the collection of T4 and TSH
- To clarify that blood CCI [redacted] samples will not be collected at sites in China
- To update the name of the CRO from Quintiles to PPD
- To update the information on packaging, distribution and supply of clinical supplies
- To remove the determination of date of disease progression by the IRC

- To update ongoing clinical studies in avelumab
- To update the management of adverse drug reactions
- To update inclusion criterion 8 to include neoadjuvant chemotherapy and clarification on prior thoracic radiation therapy
- To update exclusion criterion 9 for clarity
- To clarify in exclusion criterion 18 that cardiac arrhythmia may be serious and uncontrolled
- To update text on management for disease progression due to brain metastasis
- To clarify tumor evaluation for subjects who continue avelumab therapy beyond progression
- To allow local steroid injections as permitted medications
- To update prohibited medicines to clarify targeted bone lesions
- To include details on immunotherapy as prohibited medicines
- To update treatment modifications for symptoms of infusion-related reactions
- To remove severe hypersensitivity reactions, flu-like symptoms and tumor lysis syndrome as they are no longer applicable for this protocol
- To update the management of immune-related adverse events
- To update the protocol text and schedule of assessments for consistency
- To include information on the mandatory use of tablets

CCI [redacted]

- To update the biostatistician responsible for the study
- To correct minor grammatical errors, administrative changes, and correct inconsistencies between protocol sections.

Rationale for Major Changes

- After implementation of Protocol Version 4.0, 36 subjects were erroneously randomized according to Protocol Version 3.0 (Arm A and Arm B in a 1:1 ratio instead of Arm A, Arm B and Arm C in a 1:2:2 ratio). Of these, 15 subjects are expected to belong to the high PD-L1 expression group. In order to reach the required numbers of events in due time, these 36 subjects will be replaced. This increases the number of subjects to be randomized from originally 1095 to 1131 (to achieve 484 high PD-L1 expression subjects instead of 469). The expected number of screened subjects increased to up to 3100.
- The number of sites and trial duration were updated based on current enrollment.
- Management of ADRs was updated to adhere to the current guidelines in the IB.

CCI [redacted]

- To update protocol text to avoid ambiguity on tumor assessments for subjects until disease progression with or without treatment.
- To clarify management of disease progression due to brain metastases.

Additional changes were incorporated into the protocol based on the results of current avelumab studies and to update protocol sections based on inconsistencies between text and schedules of assessments.

Amendment 3.0

This is the third amendment to the original protocol.

The key reasons (major and administrative changes) for this amendment are summarized below:

- Addition of a new study arm (ARM C): Avelumab 10 mg/kg administered once weekly (Q1W) for 12 consecutive weeks, followed by avelumab of 10 mg/kg once every 2 weeks (Q2W).
- Change in Primary Objective with related change in Primary Endpoints:
    - Primary Objective: To demonstrate superiority with regard to overall survival (OS) or progression free survival (PFS) of avelumab versus platinum-based doublet, based on an independent review committee assessment as per RECIST 1.1, in NSCLC subjects with high expression PD-L1+ tumors.
    - The primary co-endpoints for the trial: PFS or OS in subjects with high expression on PD-L1+ tumors.
- Changes to secondary endpoints
    - To demonstrate superiority with regard to OS in NSCLC subjects with moderate-to-high expression PD-L1+ tumors; OS in NSCLC subjects with any expression PD-L1+ tumors; PFS in NSCLC subjects with moderate-to-high expression PD-L1+ tumors.
- Increased CCI [redacted] for the additional arm
- Added an initial safety evaluation period for avelumab 10 mg/kg administered every week
- To update the medical lead responsible for the study
- To update the approximate number of sites in the USA
- To update the planned trial period of the study
- To clarify the timing of the End-of-Treatment, Safety Follow-up and Long-term Follow-up visits
- To update Safety Follow-up to include a 30-day Follow-up visit and a 90-day Follow-up phone call
- To reduce the frequency of assessment of vital signs, weight, pregnancy testing, tumor evaluation, and ACTH assessments

- To update the Schedule of Assessments and relevant sections in the protocol to remove ANA, ANCA, RF, and CCI [redacted]
- To update the Schedule of Assessments and relevant sections in the protocol for CCI samples and ADA samples calculated for the new arm, Arm C
- To include the collection of CCI [redacted] samples
- To update inclusion criterion 3 to clarify type and number of tumor tissue slides collected
- To update inclusion criterion 6 to clarify the stage of metastatic cancer
- To update inclusion criterion 15 to update information on highly effective contraception methods
- To clarify the definition of survival follow-up
- To update the information on radiographic confirmation of disease progression
- To clarify laboratory for collection of serum for pregnancy testing
- To update allowed chemotherapy regimens
- To use randomization within the protocol text and remove enrollment for consistency and clarity
- To correct minor grammatical errors, administrative changes, and correct inconsistencies between protocol sections.

Rationale for Changes

- A new study arm (Arm C) was added to test weekly administration of avelumab, which is hypothesized to improve efficacy with marginal impact on safety.
    - In order to assess, if higher exposure to avelumab offers the ability to improve the clinical outcomes for subjects with recurrent/metastatic NSCLC, a 3rd arm was proposed to the ongoing two arms of the trial. The addition of Avelumab 10 mg/kg IV once a week for 12 weeks followed by avelumab 10 mg/kg IV every two weeks thereafter provides the ability in a randomized controlled setting to assess if this schedule is more efficacious and yet safer for subjects with PD-L1 positive NSCLC versus a platinum based doublet standard of care chemotherapy.
    - In addition the continuation of the ongoing two arms will continue to evaluate if avelumab 10 mg/kg IV every 2 weeks is also more efficacious and yet safer than the standard of care platinum based doublet chemotherapy in subjects with PD-L1 positive recurrent/metastatic NSCLC.
- The primary analysis patient population was changed from subjects with any expression of PD-L1+ tumors to those with high expression of PD-L1+ tumors because subjects with increased expression of PD-L1+ tumors have demonstrated improved clinical outcomes with avelumab treatment compared with subjects with lower expression of PD-L1+ tumors.
- The co-primary endpoint of overall survival (OS) was added to progression free survival (PFS) to evaluate the long term impact of avelumab on patient survival.

- Secondary endpoints will be evaluated by different levels of PD-L1 expression because of its effect on clinical outcomes that has been hypothesized and shown in previous studies.
- The sample size was modified to include Arm C and support the enrollment of the necessary number of subjects with high expression of PD-L1 under the study statistical assumptions and population prevalence of approximately 7/3.
- An initial safety evaluation was included in a cohort of 6 subjects to evaluate the safety of weekly administration prior to enrolling subjects in Arm C. A second safety evaluation will be performed once 20 subjects have completed at least 4 weeks of treatment in Arm C.

Amendment 2.0

This is the second amendment to the original protocol.

The key reasons (major and administrative changes) for this amendment are summarized below:

- For protocol clarification, adding text to the Schedule of Assessments and Sections 7.1.4, 7.4.1.3, 7.4.1.6, and 7.4.1.6, indicating that all SAEs and all non-serious treatment-related AEs need to be documented.
- To change inclusion criteria 15, indicating that male subjects are advised not to father a child during the 6 months after treatment with chemotherapy.
- To specify in exclusion criteria 18, that cisplatin should not be used in patients with hearing impairment.

Amendment 1.0

- To ensure consistency of safety assessments throughout the avelumab program.
- To streamline Section 3.3.1 and refer the Investigator to the IB for the most current safety information from prior clinical studies.
- For protocol clarification, to add Day 8 assessments (i.e., physical examination, vital signs measurements, weight measurement, ECOG, hematology, core chemistry, urine β-HCG pregnancy test) for each cycle of treatment for subjects receiving gemcitabine in the chemotherapy arm. A separate Schedule of Assessments table was created for these subjects (Table 3).
- To specify that eligible subjects for the chemotherapy arm use effective contraception for at least 6 months after ceasing participation in the trial, to be consistent with the SmPCs for chemotherapy-treated patients. This differs from the original protocol, in which subjects in both treatment arms were to use effective contraception 30 days prior and 2 months after trial participation.
- To inform the investigators that subjects who have a CR while receiving avelumab may be treated (after confirmation of response and at the discretion of the Investigator) for a minimum of 12 months and/or until disease progression or unacceptable toxicity.

- To change the time points for assessment of ACTH, ANA, ANCA, RF, TSH, and T4 from Week 13, Week 25, and if clinically indicated to Screening, End-of-Treatment, and Safety Follow-up visits, for consistency with other avelumab protocols.
- To remove the requirement for collection of AEs and concomitant medications between visits by weekly telephone contact, as this may not be feasible.