Clinical Trial Protocol

Clinical Trial Protocol Number	EMR100070-004
Title	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
Short Trial Name	JAVELIN Lung 200
Phase	III
IND Number	IND CCI
EudraCT Number	2014-005060-15
Coordinating Investigator	PPD
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA Medical Responsible: PPD Tel: PPD Fax: PPD
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- [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
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
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)
C_{max}	Maximum plasma concentration observed postdose
C_{min}	Minimum postdose (trough) concentration
CR	Complete response
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
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQOL 5-dimensions questionnaire
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
IERC	Independent Endpoint Review Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice 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]
PK	Pharmacokinetic(s)
PR	Partial response
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RF	Rheumatoid factor
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
T4	Free thyroxine
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
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

Trial title	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
Trial number	EMR 100070-004
EudraCT number	2014-005060-15
Sponsor	For all countries except the United States: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany For sites in the United States: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA
Phase	III
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial centers/countries	The trial will be conducted at approximately 290 sites globally in North America, South America, Asia, Africa, and Europe.
Planned trial period (first enrollment-last subject out)	First subject in: Q1, 2015 Last subject out: Q1, 2018
Trial objectives	**Primary objective** To demonstrate superiority with regard to overall survival (OS) of avelumab versus docetaxel in subjects with programmed death ligand 1 (PD-L1) positive (+; as determined by a companion diagnostic test under development), non-small cell lung cancer (NSCLC) after failure of a platinum-based doublet **Secondary objectives** Secondary objectives are as follows: • To demonstrate superiority with regard to OS of avelumab versus docetaxel in the Full Analysis Set (FAS) • To demonstrate superiority with regard to the objective response rate (ORR) of avelumab versus docetaxel in PD-L1+ subjects

	• To demonstrate superiority with regard to progression free survival (PFS) of avelumab versus docetaxel in PD-L1+ subjects • To demonstrate superiority with regard to the ORR of avelumab versus docetaxel in the FAS • To demonstrate superiority with regard to PFS of avelumab versus docetaxel in the FAS • To compare the subject-reported outcomes / quality of life when treated with avelumab versus docetaxel using the EuroQOL 5-dimensions questionnaire (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-LC13 in the FAS • To determine the safety and tolerability of avelumab **Exploratory objectives** Exploratory objectives are as follows: CCI [redacted]
Trial design and plan	This is a multicenter, international, randomized, open-label, Phase III trial in subjects with locally advanced unresectable, metastatic, or recurrent NSCLC that has progressed after a platinum doublet.

	Approximately 750 subjects, among them approximately 522 PD-L1 assay positive subjects, will be randomized in a 1:1 ratio to receive either • avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks, or • docetaxel at a starting dose of 75 mg/m^2 (per label) by IV infusion once every 3 weeks. Subjects will be stratified according to PD-L1 assay status (positive versus negative expression in tumor cells) and NSCLC histology (squamous cell versus non-squamous cell). Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks from randomization until Week 55 (12 months) and then every 12 weeks thereafter to determine response to treatment. A central imaging laboratory will be used to read and interpret all CT / MRI data; however, treatment decisions will be made by the treating Investigator. Response will be evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. For subjects receiving avelumab, treatment may continue past the initial determination of disease progression per 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. Subjects receiving avelumab who have experienced a confirmed complete response (CR) should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and

	monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments. Patients assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis. Decisions regarding medical management of subjects will be made by the Investigator; however, the secondary endpoint determinations (response and disease progression) will be according to the central imaging assessment and review by a blinded Independent Endpoint Review Committee (IERC). Adverse events (AEs) will be assessed throughout 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 an Independent Data Monitoring Committee (IDMC) to ensure subject safety, the validity and scientific merit of the trial, and to evaluate efficacy at the 75% interim analysis.
Planned number of subjects	Approximately 750 subjects will be randomized. Accrual will proceed up to a target number of approximately 522 PD-L1+ subjects.
Schedule of visits and assessments	**Screening/Baseline Assessments (Day -28 to Randomization)** Subject enrollment will be randomized and managed by an interactive voice response system (IVRS). Screening procedures will include the following: • Signing of the informed consent and confirmation by the IVRS that the subject has not had disqualifying prior treatment • Collection of tumor tissue. Tumor tissue must be available within 10 calendar days after the subject has signed the Informed Consent Form (ICF) in order to establish the PD-L1 status of the tumor. Tumor tissue can be archival or resulting from a screening biopsy of the subject if no archival tissue is available (biopsies are only to be obtained from safely accessible tumor tissue / sites). **Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and**

	performed centrally (Investigators / trial site personnel will be blinded to the results of the PD-L1 expression determination) • Recording of the demographic information, complete medical history, and Baseline medical condition • A physical examination including vital signs, body weight, and height, 12-lead electrocardiogram (ECG), and a determination of the Eastern Cooperative Oncology Group Performance Status (ECOG PS) • With the use of a validated electronic tablet or validated site pad, subjects will complete subject-reported outcomes / quality of life questionnaires • AE and concomitant medication assessments • Safety laboratory assessments • Tumor evaluation by CT scan or MRI (a bone scan should be done at Screening as clinically indicated) • Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for females of childbearing potential • Blood samples for hepatitis B virus (HBV) and hepatitis C virus (HCV) testing (local laboratory) **Treatment period** Treatment period begins the day of randomization and ends when a decision is made to stop the trial drug by the Investigator or when consent is withdrawn by the subject. Once eligibility is established, (including when the Central Laboratory has confirmed that the PD-L1 status for the patient has been determined), subjects will be randomized in a 1:1 ratio using the IVRS to receive either avelumab or docetaxel. The treatment should start within 4 days after randomization. Visits will take place every 2 weeks (-3 / +1 days) for subjects assigned to avelumab and every 3 weeks (-3 / +1 days) for subjects assigned to receive docetaxel. All the laboratory samples and vital signs will be collected prior to each trial drug administration. Administration of trial drug will take place only after relevant results have been checked by a medically qualified person. Safety (including AEs and concomitant medications [weekly contact], laboratory values, ECOG PS, physical

examinations, and vital signs), PK, immunogenicity, and tumor response assessments will be conducted at designated times throughout the trial.

The main assessments are as follows:

- Tumor responses will be assessed every 6 weeks from randomization (within 5 days prior to the scheduled tumor assessment), per RECIST 1.1 until Week 55 (12 months) and then every 12 weeks thereafter while on trial.

	CCI [redacted] • With the use of a validated electronic tablet or validated site pad, subject-reported outcomes / quality of life questionnaires 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) at Week 1, Week 3 (treatment administration 2), Week 7 (treatment administration 4), and Week 13 (treatment administration 7) for subjects receiving avelumab and at Week 1, Week 4 (treatment administration 2), Week 7 (treatment administration 3), and Week 13 (treatment administration 5) for subjects receiving docetaxel and every 6 weeks thereafter while on treatment for all subjects • AEs and concomitant medications will be documented at each visit Trial treatment will be administered by IV infusion once every 2 weeks for avelumab and once every 3 weeks for docetaxel until disease progression, significant clinical deterioration (clinical progression), discontinuation for unacceptable toxicity, or withdrawal of consent. Note: For subjects receiving avelumab, treatment may continue past the initial determination of disease progression per 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 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. **Discontinuation visit** Any subject who experiences an AE that mandates discontinuation of trial treatment should have a Discontinuation visit within 7 days of the decision to discontinue trial treatment. **Follow-up phase** The Follow-up Phase starts when the decision has been made to stop trial drug treatment.

	Subjects will have • an End-of-Treatment visit at 28 days (± 5 days) after the last administration of trial treatment or before the start of any other antineoplastic therapy, and • a Safety Follow-up visit 12 weeks (± 2 weeks) after the last administration of trial treatment. During these two visits there will be a full assessment of safety parameters (including ECG at the Early Discontinuation / End-of-Treatment visit using a validated electronic tablet or validated site pad), subject-reported outcomes / quality of life (Discontinuation / End-of-Treatment visit), CCI [redacted] (End-of-Treatment visit only), and for subjects who were assigned to avelumab, CCI [redacted] After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration. Subjects with a serious AE (SAE) ongoing at the Safety follow-up visit must be followed up by the Investigator until stabilization or until outcome is known, unless the subject is documented as "lost to follow-up." Subjects who discontinue the trial treatment for reasons other than disease progression according to RECIST 1.1 will be followed up every 6 weeks (± 5 days) until Week 55 (12 months) and then every 12 weeks thereafter for radiographic assessment until disease progression, lost to follow-up, or withdrawal of informed consent. After the End-of-Treatment visit, subjects will be followed quarterly (that is, every 3 months ± 1 week) for survival (including assessment of any further tumor therapy). The survival follow-up will continue a maximum of 5 years after the last subject receives the last dose of avelumab. Subject-reported outcomes / quality of life questionnaires will be assessed at the Early Discontinuation / End-of-Treatment visit.
Diagnosis and main inclusion and exclusion criteria	**Inclusion criteria** 1. Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard patient management

	2. Male or female subjects aged ≥ 18 years 3. Availability of a formalin-fixed, paraffin-embedded block containing tumor tissue or 7 unstained tumor slides suitable for PD-L1 expression assessment 4. Tumor determined to be evaluable for PD-L1 expression per the evaluation of a central laboratory 5. Subjects with histologically confirmed Stage IIIb/IV or recurrent NSCLC who have experienced disease progression 6. Subjects must have progressed after an acceptable therapy defined as follows: a. Subjects must have progressed during or after a minimum of 2 cycles of 1 course of a platinum-based combination therapy administered for the treatment of a metastatic disease. A history of continuation (use of a non-platinum agent from initial combination) or switch (use of a different agent) maintenance therapy is permitted provided there was no progression after the initial combination. A switch of agents during treatment for the management of toxicities is also permitted provided there was no progression after the initial combination OR b. Subjects must have progressed within 6 months of completion of a platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for locally advanced disease 7. Subjects with non-squamous cell NSCLC of unknown epidermal growth factor receptor (EGFR) mutation status will require testing (local laboratory, or central laboratory if local testing is not available). Subjects with a tumor that harbors an activating EGFR mutation will not be eligible (see Exclusion Criterion 3) 8. ECOG PS of 0 to 1 at trial entry 9. Estimated life expectancy of more than 12 weeks

	10. Adequate hematological function defined by WBC count $\geq 2.5 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused) 11. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 2.5 \times$ ULN for all subjects 12. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method) 13. **Highly** effective contraception (that is, 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 study 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 28 days prior to first study treatment administration, for the duration of study treatment, and at least for 60 days after stopping study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately). All subjects who are randomized to the docetaxel arm are required to use effective contraception for up to 3 months after docetaxel treatment for women of childbearing potential and male subjects will be advised not to father a child during the 3 months after treatment with docetaxel. Male subjects will be requested to seek advice on conservation of sperm prior to treatment. **Exclusion criteria** 1. In the United States only, subjects with a squamous cell histology will be excluded 2. Systemic anticancer therapy administered after disease progression during or following a platinum-based combination

	3. Subjects with non-squamous cell NSCLC whose disease harbors EGFR mutation(s) and / or anaplastic lymphoma kinase (ALK) rearrangement will not be eligible for this trial. Subjects of unknown ALK and / or EGFR mutation status will require testing at screening (local laboratory, or central laboratory if local testing is not available) 4. Prior therapy with any antibody / drug targeting T-cell coregulatory proteins (immune checkpoints) such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4 (CTLA-4). 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 patients with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily). 8. All subjects with brain metastases, except those meeting the following criteria: a. Brain metastases have been treated locally, and b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable) 9. Previous malignant disease (other than NSCLC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (bladder, cervical, colorectal, breast) 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 • HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive) 12. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent: a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable 13. 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 14. 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) 15. History of hypersensitivity reaction to taxanes 16. History of hypersensitivity to Polysorbate 80 that led to unacceptable toxicity requiring treatment cessation 17. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03 (except neuropathy, see exclusion criterion #18) 18. Neuropathy ≥ Grade 3 19. Pregnancy or lactation 20. Known alcohol or drug abuse

	21. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication 22. All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment 23. Any psychiatric condition that would prohibit the understanding or rendering of informed consent 24. 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) 25. Legal incapacity or limited legal capacity
Investigational Medicinal Product: dose/mode of administration/dosing schedule	Avelumab will be administered as a 1-hour IV infusion at 10 mg/kg once every 2-week treatment cycle. In order to mitigate infusion-related reactions, 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) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). 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. Since this trial consists of the administration of recombinant antibodies to some subjects, there is the potential that a subset of subjects might experience infusion reactions that may require immediate medical attention; therefore, immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including IV epinephrine, corticosteroids, antihistamines, bronchodilators, and

	oxygen) must be in place for use in the treatment of potential infusion-related reactions. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or hypersensitivity reactions (according to NCI-CTCAE v 4.03). Following avelumab infusions, subjects must be observed for 2 hours post-infusion for potential infusion-related reactions. If the subject experiences an infusion-related reaction of Grade 2, the infusion rate of the subsequent administration of avelumab will be reduced by 50%. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab.
Reference therapy: dose/mode of administration/dosing schedule	Subjects randomized to docetaxel will be administered docetaxel according to the country-approved label at a starting dose of 75 mg/m^2 by IV infusion over 1 hour. Dose adjustments can be made according to label instructions and local institutional practices. Additionally, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, subjects will be administered dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion per docetaxel label instructions, or equivalent, per local institutional practice.
Planned treatment duration per subject	Subjects will receive trial treatment until progressive disease (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. For subjects receiving avelumab, treatment may continue past the initial determination of disease progression per 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 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. Subjects receiving avelumab who have experienced a CR should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a

	confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol. Patients assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis.
Primary endpoint	The primary endpoint for the trial is OS time, defined as the time (in months) from randomization to the date of death.
Secondary/exploratory endpoints	Secondary endpoints include • PFS time according to RECIST 1.1 and as adjudicated by the IERC, • Best overall response (BOR) according to RECIST 1.1 and as adjudicated by the IERC, • changes in subject-reported outcomes / quality of life as assessed by the EQ-5D and the EORTC QLQ-C30 and module QLQ-LC13 questionnaire, and • the safety profile of the trial drugs as measured by the incidence of AEs, SAEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS. Exploratory endpoints include CCI [redacted]

	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Statistical methods (includes sample size calculation)	The primary endpoint for the trial, OS time, will be analyzed using a stratified log-rank test taking the randomization strata into account. The primary analysis population will be the subjects with PD-L1+ tumors in the FAS. The final analysis will be performed after 337 events in PD-L1+ subjects have been observed. There will also be an interim analysis for efficacy after 75% of the events (253 deaths) in PD-L1+ subjects have been observed, using an O'Brien-Fleming stopping boundary. The nominal one-sided alpha levels are 0.0100 and 0.0219 for the interim and final analysis, respectively. The following assumptions are made for the sample size calculation: • Hazard ratio (HR) of 0.70 corresponding to an increase in median OS time from 8 months in the control arm to 11.43 months in the investigational arm • 1:1 randomization

	• Alpha = 0.025 (1-sided) • Power = 90% • Uniform accrual over a period of 10 months • A follow-up time of 11 months after randomization of the last subject • An expected drop-out rate of 5% • An interim analysis for efficacy after 75% of events (deaths) in PD-L1+ subjects have been observed, stopping for efficacy if the criteria are met A sample size of approximately 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. The total number of randomized subjects is expected to be approximately 750 subjects, based on an estimated prevalence of approximately 70% PD-L1+ subjects. The 75% interim analysis will be performed when 253 events have been observed. An IDMC will be convened to perform the evaluation at the interim analysis. In case the analysis of OS in the primary analysis population of PD-L1+ subjects demonstrates superiority of avelumab versus docetaxel at the interim or the final analysis, the following confirmatory analyses are planned, using a hierarchical test procedure with the following order to control the overall significance level at 0.025 one-sided: • OS in the PD-L1+ subset of the FAS; • OS in the FAS; • BOR in the PD-L1+ subset of the FAS; • PFS in the PD-L1+ subset of the FAS; • BOR in the FAS; • PFS in the FAS. Safety data will be summarized. Adverse events will be summarized by incidence, severity, seriousness and relationship to trial drug.

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.

This trial requires a significant logistic and administrative structure for its efficient execution. Details of such structures and associated procedures will be defined in a separate Manual of Operations (MOP). This will be prepared under the supervision of the clinical trial leader in close collaboration with the responsible units at the Sponsor.

2.1 Investigational Sites

The trial will be conducted at approximately 290 sites globally in North America (with approximately 30 sites in the USA), South America, Asia, Africa, and Europe.

2.2 Trial Coordination / Monitoring

The Sponsor will coordinate the trial and will provide the support of Contract Research Organizations (CRO) for some activities of the trial. Sponsor Global Clinical Operations will perform oversight of the activities performed by the CROs.

The Sponsor will supply the trial medication of avelumab. A CRO will distribute trial drug (avelumab and docetaxel) to the sites.

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

Subject enrollment will be randomized and managed by an interactive voice response system (IVRS).

Safety laboratory assessments will be performed locally by investigational sites. CCI [redacted] assessments will be performed under the responsibility and / or supervision of the Sponsor.

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

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

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

2.3 Review Committees

2.3.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will perform the evaluation at the interim analysis and 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 also periodically review safety data. The full membership, mandate, and processes of the IDMC will be detailed in the IDMC charter.

2.3.2 Central Reader and Independent Endpoint 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, see reference 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 Endpoint Review Committee (IERC) 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 IERC will be to review radiographic image findings for the determination of the time point overall response and date of disease progression according to RECIST 1.1 for each subject. The full membership, mandate, and processes of the IERC will be detailed in the IERC charter.

3 Background Information

3.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in men and women in the USA and results in more cancer deaths than breast cancer, prostate cancer, and colorectal cancer combined. The American Cancer Society estimated that in 2014 there would be 224,210 new cases of lung cancer in the USA alone, and 159,260 people would die from their lung cancers (2). In 2014 in the EU, 187,300 and 84,500 deaths are predicted from lung cancer for men and women, respectively (3). 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 (4). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer.

In NSCLC, results of standard therapy are poor except for the most localized cancers where surgery and / or combined modality therapy can provide cure in a small percentage of patients. In advanced-stage disease, chemotherapy offers modest benefit, though overall survival is poor (5,

6). There are 5 agents indicated for the treatment of advanced NSCLC in the second-line setting: docetaxel, pemetrexed, and the tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and crizotinib. These agents have an overall response rate of < 10% in an unselected patient population (7-10) and there is a growing body of evidence suggesting chemotherapy is preferable to erlotinib and gefitinib, especially in patients whose tumors do not harbor epidermal growth factor receptor (EGFR) activating mutations (11).

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 (12-15), 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 (14, 16).

In the clinical setting, treatment 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, with tolerable safety profiles (17-20). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients.

There are relatively few studies looking at PD-L1 expression in NSCLC and estimates of the proportion of patients with PD-L1 positive (PD-L1+) tumors vary widely from 25% to close to 60% (21, 22); however, treatment of unselected patient populations with NSCLC with antibodies directed against PD-1 or PD-L1 showed some clinical activity, with 30 responses recorded in 188 patients (18-20).

3.3 Avelumab

The Investigational Medicinal Product (IMP) for the present trial is avelumab (*avelumab is the proposed International Nonproprietary Name for the anti-PD-L1 monoclonal antibody 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 (23). For complete details of the in vitro and nonclinical studies, please refer to the Investigator's Brochure.

Avelumab is currently in clinical development with 2 ongoing Phase I studies in subjects with solid tumors and a Phase II trial in subjects with Merkel cell carcinoma:

- 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."

3.3.1 Trial EMR100070-001

This trial consists of 2 parts, a dose-escalation phase and an expansion phase, which is performed in selected tumor indications.

A maximum of 60 subjects with advanced malignancies with no established therapy available were planned to be enrolled in the dose-escalation phase of this trial. Avelumab was administered intravenously at the assigned dose level as a 1-hour intravenous (IV) infusion once every 2 weeks.

Dose escalation (3 + 3 design) was performed at the following dose levels:

- Dose level 1: 1.0 mg/kg (Cohort 1)
- Dose level 2: 3.0 mg/kg (Cohort 2)
- Dose level 3: 10.0 mg/kg (Cohort 3)
- Dose level 4: 20.0 mg/kg (Cohort 4)

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3.3.1.1 Safety Results

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Guidelines for the management of infusion-related reactions and severe hypersensitivity reaction according to the National Cancer Institute (NCI) are found in Sections 6.5.4.1 and 6.5.4.2, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf.

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3.3.2 Pharmacokinetic

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

3.3.2.1 Trial EMR100070-001

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 57 Caucasian subjects treated in the dose escalation and expansion cohort of the Phase 1 Trial EMR100070-001 by standard non-compartmental analysis based on rich serum concentration-time data obtained over a complete dosing interval of 2 weeks (= tau). The analysis of these data revealed that the exposure parameters maximum concentration observed postdose (C_{max}) and area under the concentration-time curve (AUC_{tau}) increased with the doses in a linear fashion.

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

Trough concentrations (C_{min}) were obtained for the majority of subjects enrolled in the trial. The median C_{min} at the end of the first cycle after administration of the 10 mg/kg dose was 20 µg/mL (n=256). This median C_{min} increased during the subsequent cycles to 24 µg/mL (second cycle; n=233), 26 µg/mL (third cycle; n=167), and remained between 24 and 37 µg/mL during the subsequent cycles (n=22 to 114) indicative for no significant accumulation with the biweekly dosing scheme. Median C_{min} after the 3 mg/kg dose were 3.7µg/mL after the first dose, 3.9 µg/mL after the second dose and 8.3 µg/mL after the third dose (n=7 to 12), though some trough values below 1 µg/mL were observed, as well as antidrug antibodies in at least one subject in this dose group on day 85 of the treatment period, accompanied by loss of quantifiable exposure. Median trough concentrations after the 20 mg/kg dose were 44, 70, and 77 µg/mL after the first, second, and third dose, respectively (n=14 to19).

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

3.3.2.2 Trial EMR100070-002

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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 eight 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 1b 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 two subjects.

Based on the observed avelumab serum concentrations in the EMR100070-001 Phase 1 clinical trial and the in vitro receptor occupancy data, trough concentrations were sufficient to achieve full target occupancy throughout the entire dosing interval in all of the subjects receiving the 10 mg/kg dose. After the 3 mg/kg dose, C_{min} were insufficient in 3 of the 13 subjects to assure full target occupancy; therefore, in order to achieve target saturation during the whole treatment period in all subjects, the dose of 10 mg/kg every two weeks was selected as the dose for further investigation in the Phase 1b expansion cohorts and for the subsequent clinical studies.

3.4 Rationale for the Current Clinical Trial

The evaluation of an anti-PD-L1 antibody as second-line therapy for the treatment of metastatic NSCLC is supported by

- the expression of PD-L1 by NSCLC tumor cells and by adjacent immune infiltrates,
- the clinical activity reported for avelumab and CCI [redacted]
- the existing need for better therapies that improve survival and maintain quality of life in patients with NSCLC no longer responding to platinum-based therapy.

3.5 Summary of the Overall Benefit and Risk

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

The primary known risks of exposure to avelumab include:

- infusion-related reactions and
- irAEs.

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

As noted above (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 (17-19), with response durations of 1 year or more for the majority of patients.

Furthermore, 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 13 weeks by the cut-off date of 15 October 2014) demonstrated an objective response rate (ORR) of 12.0% (22 of 184 subjects; 95% confidence interval [CI]: 7.6%, 17.5%), including 1 subject with complete response (CR) and 21 subjects with partial response (PR). There were also 70 subjects with stable disease (SD), 68 subjects with progressive disease (PD), and 24 subjects who were not evaluable. CCI [redacted]

[redacted]

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

4 Trial Objectives

Primary

The primary objective is to demonstrate superiority with regard to overall survival (OS) of avelumab versus docetaxel in subjects with PD-L1+ (as determined by a companion diagnostic test under development) NSCLC after failure of a platinum-based doublet.

Secondary

Secondary objectives are as follows:

- To demonstrate superiority with regard to OS of avelumab versus docetaxel in the Full Analysis Set (FAS)
- To demonstrate superiority with regard to the ORR of avelumab versus docetaxel in PD-L1+ subjects
- To demonstrate superiority with regard to progression-free survival (PFS) of avelumab versus docetaxel in PD-L1+ subjects
- To demonstrate superiority with regard to the ORR of avelumab versus docetaxel in the FAS

- To demonstrate superiority with regard to PFS of avelumab versus docetaxel in the FAS
- To compare the subject-reported outcomes / quality of life when treated with avelumab versus docetaxel using the EuroQOL 5-dimensions questionnaire (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-LC13 in the FAS
- To determine the safety and tolerability of avelumab

Exploratory objectives

Exploratory objectives are as follows:

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, international, randomized, open-label, Phase III trial in subjects with locally advanced unresectable, metastatic, or recurrent NSCLC that has progressed after a platinum doublet.

5.1.1 Overall Design

Approximately 750 subjects, among them approximately 522 PD-L1 assay positive subjects, are planned to be randomized in a 1:1 ratio to receive either avelumab at a dose of 10 mg/kg once every 2 weeks or docetaxel at a starting dose of 75 mg/m^2 once every 3 weeks. Subjects will be stratified according to PD-L1 assay status (positive versus negative expression in tumor cells) and NSCLC histology (squamous cell versus non-squamous cell).

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 from randomization until Week 55 (12 months) and then every 12 weeks thereafter to determine response to treatment. A central imaging laboratory will be used to read and interpret all CT / MRI data. Response will be evaluated using the RECIST 1.1 and as adjudicated by a blinded IERC. 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).

Subjects receiving avelumab who have experienced a CR should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

Subjects assigned to docetaxel will be treated until disease progression, unacceptable toxicity, or any of the criteria for withdrawal from trial treatment is fulfilled as above an in Section 5.5. Subjects assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis.

Assessments will be made by the Investigators for the purpose of subject management, but the disease response determinations will be supported by tumor assessments performed by an IERC (see Sections 2.3.2 and 7.3).

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

The primary endpoint for the trial will be OS time, defined as the time from randomization to death.

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

The final analysis will be conducted after 337 events (deaths) in PD-L1+ subjects have been observed An interim analysis for efficacy will be performed after 75% of events (253 deaths) in PD-L1+ subjects have been observed, stopping for efficacy if the criteria are met. An IDMC will be convened to perform the evaluation at the interim analysis (see Section 2.3.1 for committee details).

5.1.2 Trial Endpoints

5.1.2.1 Primary Endpoints

The primary endpoint for the trial will be OS time, defined as the time from randomization to death.

5.1.2.2 Secondary Endpoints and Exploratory Endpoints

Secondary endpoints include

- PFS time according to RECIST 1.1 and as adjudicated by the IERC (see Section 2.3.2),
- Best overall response (BOR) according to RECIST 1.1 and as adjudicated by the IERC (see Section 2.3.2),
- changes in subject-reported outcomes / quality of life as assessed by the EQ-5D, the EORTC QLQ-C30, and module QLQ-LC13 questionnaires, and
- safety and tolerability of the trial drugs as measured by the incidence of AEs, SAEs, deaths, and laboratory abnormalities.

Exploratory endpoints include

CCI [redacted]

5.1.3 Trial Medication Administration and Schedule

The trial Schedule of Assessments is illustrated in Appendix I.

5.1.3.1 Avelumab

Subjects randomized to the avelumab arm will receive IV infusion of avelumab (10 mg/kg over 1 hour) once every 2 weeks. In order to mitigate infusion-related reactions, subjects will receive pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to every avelumab infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent).

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

5.1.3.2 Docetaxel

Subjects randomized to the docetaxel arm will receive IV infusion of docetaxel (Hospira) according to the country approved label at a starting dose of 75 mg/m^2 by IV infusion over 1 hour once every 3 weeks until disease progression, unacceptable toxicity, or any of the criteria for withdrawal from trial treatment is fulfilled (Section 5.5).

Additionally, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, subjects will be administered dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion per docetaxel label instructions, or equivalent, per local institutional practice.

Patients assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis.

The formulation of docetaxel is provided in Section 6.1.2.

5.1.4 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

5.1.4.1 Dose Modification for Avelumab

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

Each subject will stay on the avelumab assigned dose of 10 mg/kg unless treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in Sections 5.1.4.2 and 6.5.4.1. There are to be no dose reductions.

5.1.4.2 Adverse Drug Reactions Requiring Avelumab Discontinuation or Modifications

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

Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Asymptomatic Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay or discontinuation. The study Medical Monitor should be consulted for such abnormalities.
- Infusion should not be given 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.

Any Grade 2 ADR should be managed as follows:

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

Treatment can be resumed according to original schedule once ADR resolved to Grade ≤ 1. Up to 2 subsequent study drug doses may be omitted. If more than two doses are skipped, treatment may be resumed after consultation with study Medical Monitor.

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

5.1.4.3 Dose Modification for Docetaxel

Dose modifications (dose delays and dose changes) for docetaxel should be made in accordance with labeling instructions and local institutional guidelines. Discontinuation of docetaxel due to ADRs should also be in accordance with the docetaxel label and local institutional practice.

5.2 Discussion of Trial Design

This is a Phase III, 2-arm, randomized, open-label trial to determine the efficacy and safety of avelumab compared with docetaxel in subjects with locally advanced unresectable or metastatic NSCLC that has progressed after a platinum doublet. Approximately 70% of subjects randomized in the trial are expected to be PD-L1+, reflecting the prevalence of PD-L1 positivity in the underlying patient population, and leading to a high proportion of potential avelumab-responsive subjects and minimizing avelumab exposure to potentially non-responsive subjects. The dosing regimen is based upon the current ongoing Phase I trials.

The primary endpoint of OS is usually the preferred endpoint (24) as it allows for a direct measure of patient benefit and is the most reliable cancer endpoint. An open-label design is appropriate for this trial given the different schedules of the administration of the trial drugs and premedication regimens. The endpoints of PFS and ORR will support the OS.

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment, despite initial evidence of PD (25); therefore, for subjects in 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).

Docetaxel was chosen as the comparator as it is an approved therapy for NSCLC in the second-line setting. Docetaxel remains a standard of care for patients experiencing progression after first-line therapy in NSCLC based on superior PFS, OS, and quality of life when compared with best supportive care or other chemotherapy agents (26). Docetaxel and pemetrexed show similar PFS (2.9 months) and overall survival (8 months) with pemetrexed showing a better side effect profile (27, 28); however, pemetrexed has shown particular efficacy in patients with non-squamous histology and is increasingly being used in first-line regimens (29). With this evolution of treatment paradigms, docetaxel remains the best option for patients with non-squamous histology who fail first-line therapy including maintenance and those with squamous histology where pemetrexed may not be as efficacious either as part of induction or maintenance. Erlotinib is another agent considered an option in the setting of progression after first-line therapy after demonstrating a PFS of 2.2 months and OS of 6.7 months (30). However, this was compared with placebo and by indirect comparison the clinical endpoints appear inferior to chemotherapy. Docetaxel remains the best option in this setting because of its broad applicability and demonstrated clinical benefit. Thus, it represents the ideal comparator for this trial.

5.2.1 Inclusion of Special Populations

Not applicable.

5.2.2 Rationale for Exclusion of Subjects with Epidermal Growth Factor Receptor Mutation

Emerging data from a randomized Phase III trial in patients with non-squamous NSCLC who failed prior platinum-based therapy suggests that subjects with EGFR mutations who receive anti-PD1 therapy may have different survival outcomes compared with patients with EGFR mutations who receive docetaxel. Data from the open-label CheckMate-057 trial that randomized 582 subjects with advanced nonsquamous NSCLC after the failure of platinum-based doublet chemotherapy to nivolumab (anti-PD1) or docetaxel was presented at the annual meeting of the American Society of Clinical Oncology in 2015. In the overall population, the median OS was 12.2 months with nivolumab versus 9.4 months with docetaxel (HR=0.73; 95% CI, 0.59-0.89; p=0.00155). In this nivolumab study, 15% of subjects in the nivolumab group and 13% in the docetaxel group were EGFR-positive. Among the 82 subjects who were EGFR mutation positive, the HR for OS in nivolumab treated subjects versus docetaxel was 1.18 (95% CI 0.69, 2.00), while in the 340 subjects who were not detected to have an EGFR mutation, the HR for OS in nivolumab versus docetaxel treated subjects was 0.66 (95% CI 0.51, 0.86, see reference 31). These randomized data suggest that subjects with EGFR mutation may have different survival outcomes compared with NSCLC subjects without an EGFR mutation when treated with anti-PD1.

The observation that subjects with EGFR mutation may have different clinical outcomes to immunotherapy with a checkpoint inhibitor is supported by emerging research regarding the potential correlation between mutational burden and response to immunotherapy. Data from the Cancer Genome Atlas Research Network have described NSCLC tumors with EGFR mutation to be associated with transversion low mutations and a lower mutational burden; whereas, transversion high mutations (often associated with smoking status) are associated with a higher mutation burden (32). In addition, Rizvi et al. have reported that in NSCLC, subjects with transversion high tumors respond better to pembrolizumab (anti-PD1) than subjects with transversion low tumors (ORR: 56% versus 17% [p=0.03]; PFS: median not reached versus 3.5 months, [p=0.0001], see reference 33).

As a result of these emerging data, the inclusion of NSCLC subjects with EGFR mutation might introduce unwanted heterogeneity to the current avelumab EMR 100070-004 study; therefore, one purpose of this amendment is to exclude further enrollment of NSCLC subjects with EGFR mutation to the study. For subjects with known EGFR mutation who have already been enrolled in the study, these subjects should consult with their physician and be informed when deciding whether or not to continue treatment based on this new information.

5.3 Selection of Trial Population

Subject enrollment will be randomized and managed by an IVRS (see Section 7.1.1). Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the

Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

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

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

2. Male or female subjects aged ≥ 18 years

3. Availability of a formalin-fixed, paraffin-embedded block containing tumor tissue or 7 unstained tumor slides suitable for PD-L1 expression assessment

4. Tumor determined to be evaluable for PD-L1 expression per the evaluation of a central laboratory

5. Subjects with histologically confirmed Stage IIIb/IV or recurrent NSCLC who have experienced disease progression

6. Subjects must have progressed after an acceptable therapy defined as follows:
   a. Subjects must have progressed during or after a minimum of 2 cycles of 1 course of a platinum-based combination therapy administered for the treatment of metastatic disease. A history of continuation (use of a non-platinum agent from initial combination) or switch (use of a different agent) maintenance therapy is permitted provided there was no progression after the initial combination. A switch of agents during treatment for the management of toxicities is also permitted provided there was no progression after the initial combination

      OR

   b. Subjects must have progressed within 6 months of completion of a platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for locally advanced disease
7. Subjects with non-squamous cell NSCLC of unknown EGFR mutation status will require testing (local laboratory, or central laboratory if local testing is not available). Subjects with a tumor that harbors an activating EGFR mutation will not be eligible (see Exclusion Criterion 3)

8. ECOG PS of 0 to 1 at trial entry

9. Estimated life expectancy of more than 12 weeks

10. 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, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

11. 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

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

13. **Highly** effective contraception (that is, 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 study 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 or as stipulated in national or local guidelines. **Highly** effective contraception must be used 28 days prior to first study treatment administration, for the duration of study treatment, and at least for 60 days after stopping study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately.)

    All subjects who are randomized to the docetaxel arm are required to use effective contraception for up to 3 months after docetaxel treatment for women of childbearing potential and male subjects will be advised not to father a child during the 3 months after treatment with docetaxel. Male subjects will be requested to seek advice on conservation of sperm prior to treatment.

5.3.2 Exclusion Criteria

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

1. In the USA only, subjects with a squamous cell histology will be excluded

2. Systemic anticancer therapy administered after disease progression during or following a platinum-based combination

3. Subjects with non-squamous cell NSCLC whose disease harbors EGFR mutation(s) and / or anaplastic lymphoma kinase (ALK) rearrangement will not be eligible for this trial. Subjects of unknown ALK and / or EGFR mutation status will require testing at screening (local laboratory, or central laboratory if local testing is not available)

4. Prior therapy with any antibody / drug targeting T-cell coregulatory proteins (immune checkpoints) such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4 (CTLA-4).

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).

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

    a. Brain metastases have been treated locally, and

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

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

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
    - Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)

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

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

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

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

13. 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

14. 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)

15. History of hypersensitivity reaction to taxanes

16. History of hypersensitivity to Polysorbate 80 that led to unacceptable toxicity requiring treatment cessation

17. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03 (except neuropathy, see exclusion criterion #18)

18. Neuropathy ≥ Grade 3

19. Pregnancy or lactation

20. Known alcohol or drug abuse

21. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication

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

23. Any psychiatric condition that would prohibit the understanding or rendering of informed consent

24. 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)

25. Legal incapacity or limited legal capacity

5.4 Criteria for Randomization / Initiation of Treatment with the Investigational Medicinal Product

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 criterion.

5.5 Criteria for Subject Withdrawal

5.5.1 Criteria for Withdrawal from Trial Treatment

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 as defined in Section 5.1.4.2
- 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 if considered necessary by the Investigator or Sponsor
- Noncompliance (see Section 6.9)

5.5.2 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

- 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, subject-reported outcomes / quality of life questionnaires, and subsequent anticancer therapy.

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

5.6 Premature Discontinuation of the Trial

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

- New information leading to unfavorable benefit-risk 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, or
  - 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 non-clinical 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
- After the interim analysis, the IDMC declares superior efficacy in the avelumab treatment arm compared with those randomized to receive docetaxel and recommends that the trial be stopped early

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

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

5.7 Definition of End of Trial

If the trial is not terminated for a reason given in Section 5.6, the survival follow-up will continue until 5 years after the last subject receives the last dose of avelumab.

The Sponsor may terminate the study at any time once access to IMP for subjects still benefitting is provisioned via a roll over study, expanded access, marketed product or another mechanism of access as appropriate.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term IMP refers to the investigational drug undergoing a clinical trial, as well as to any comparator drug or placebo (as applicable). In this trial, the investigational drug is avelumab and the comparator drug is docetaxel.

6.1 Description of 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 Docetaxel

Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}\cdot 3H_2O$ and a molecular weight of 861.9. Docetaxel is supplied commercially (Hospira, Lake Forest, Illinois) as 20 mg/2 mL and 160/16 mL in polysorbate 80/dehydrated alcohol suspension.

6.2 Dosage and Administration

6.2.1 Avelumab Dosage and Administration

Subjects will receive an IV infusion of avelumab at a dose of 10 mg/kg (over the duration of 1 hour) following pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to each avelumab infusion, once every 2 weeks (refer to Appendix I). Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). 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. Complete blood count and core chemistry samples must be drawn and results reviewed within 48 hours prior to dose administration. Subjects will receive avelumab once 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 trial drug
- 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).

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

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

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 (Appendix I).

For subjects who continue avelumab trial therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and / or the development of new measurable lesions. 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 volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Additionally, subjects receiving avelumab who have experienced a CR should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

6.2.2 Docetaxel Dosage and Administration

The starting dose of docetaxel for this trial is 75 mg/m^2 as per the country approved labeling instructions. Docetaxel should be administered at the clinic as a 1-hour IV infusion once every 3 weeks in accordance to the label instructions and per local administration guidelines.

Additionally, subjects will be administered dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion per docetaxel label instructions, or equivalent, per local institutional practice.

Dexamethasone will be prescribed locally according to local standards. Docetaxel will be provided to trial sites through IVRS.

Subjects assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis.

6.3 Assignment to Treatment Groups

Once the subject has provided a signed Informed Consent Form (ICF) and meets inclusion and exclusion criteria, the Investigator or delegate will request the trial treatment assignment using the IVRS. Qualified subjects will be randomized at a 1:1 ratio to receive either avelumab or docetaxel. The trial is fully controlled by the IVRS, 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.

Allocation of subjects will be stratified according to PD-L1 assay status (positive versus negative expression in tumor cells) and NSCLC histology (squamous cell versus non-squamous cell). This stratified randomization will be centrally allocated across all trial sites via the IVRS.

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 Other Drugs to be Used in the Trial

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) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This regimen may be modified based on local treatment standards and guidelines as appropriate.

Subjects randomized to receive docetaxel will receive pretreatment with dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion per docetaxel 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 ≥ 2 infusion-related, allergic, or anaphylactoid reactions. Following avelumab infusions, subjects must be observed for 2 hours post infusion for potential infusion-related reactions.

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

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity and flu-like symptoms according to the NCI are found in Sections 6.5.4.1 and 6.5.4.2, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. 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 for the subjects' welfare and will not interfere with the trial drug may be given at the Investigator's discretion.

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

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

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

Palliative bone-directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST 1.1 (1) and not based on the necessity for palliative bone directed-radiotherapy.

6.5.2 Nonpermitted Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody or concurrent anticancer treatment including:

- Cytoreductive therapy
- Radiotherapy [with the exception of palliative bone-directed radiotherapy, or radiotherapy administered on superficial lesions],
- Immune therapy, or
- Cytokine therapy except for erythropoietin,
- Concurrent systemic therapy with steroids or other immunosuppressive agents,
- 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 for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs is allowed)

  Note: The use of systemic corticosteroids for subjects randomized to receive docetaxel 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 docetaxel, 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/
- 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)

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 7.1.5.

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 docetaxel 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 Trial Considerations

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

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

6.5.4 Special Precautions

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

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

Investigators should also monitor subjects closely for potential irAEs, which may first manifest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like antinuclear antibodies (ANAs) or antineutrophil cytoplasmic antibodies (ANCAs). See Section 6.5.4.4 details on the management of irAEs.

6.5.4.1 Infusion-Related Reactions

A. Symptoms
   - Fever
   - Chills
   - Rigors
   - Diaphoresis
   - Headache

B. Management according to Table 6.1

Table 6.1 Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

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

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, 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 Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

A. Symptoms
- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension

- Pale / clammy skin
- Cyanosis

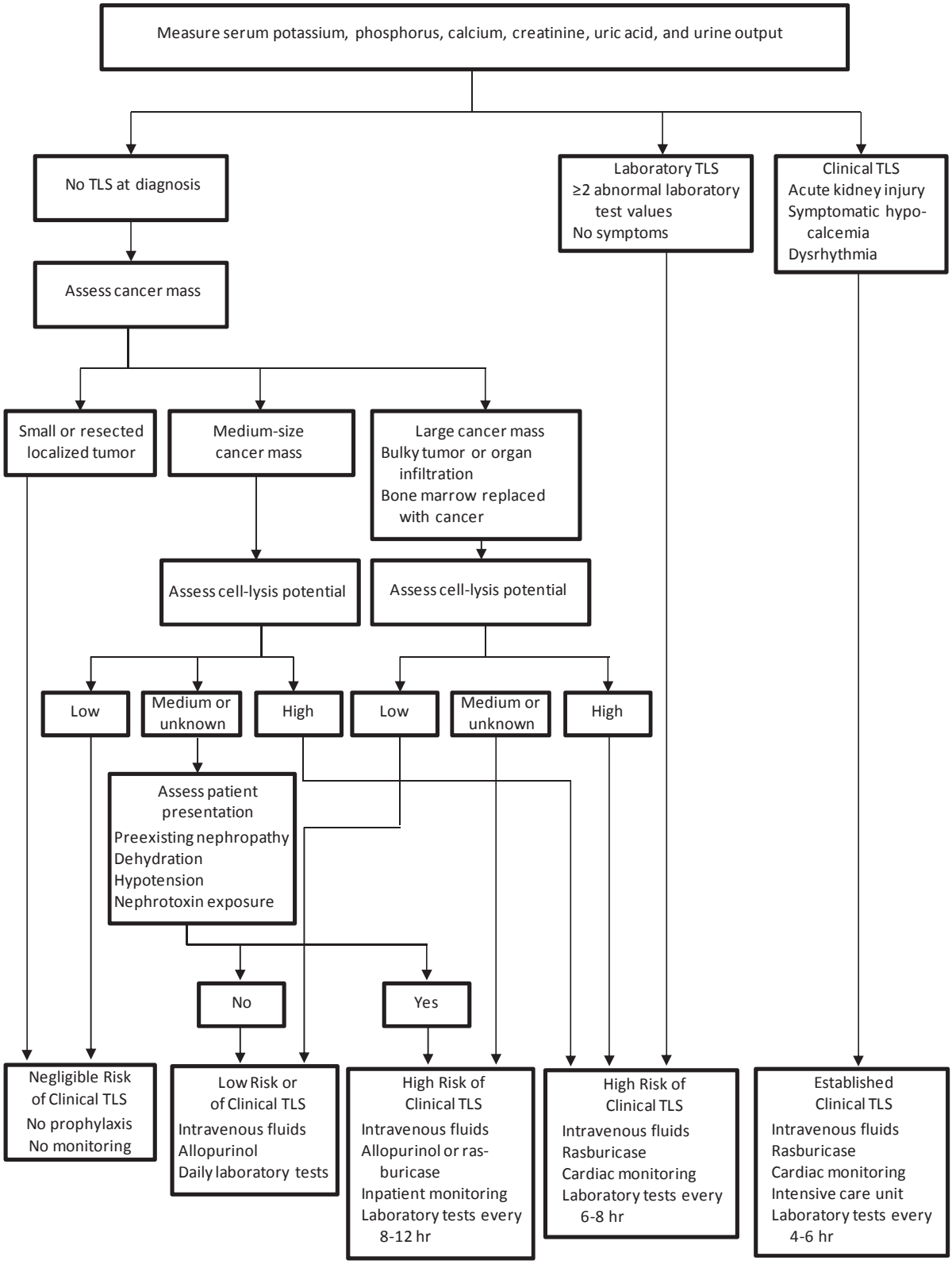
B. Management
- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert ICU for possible transfer if required

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

6.5.4.3 Tumor Lysis Syndrome

In addition, since avelumab can induce ADCC, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm (Figure 6.1) published by Howard et al (34).

Figure 6.1 Assessment and Initial Management of Tumor Lysis Syndrome



TLS=tumor lysis syndrome.

6.5.4.4 Immune-Related Adverse Events

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

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

Treatment of irAEs should follow guidelines set forth in Table 6.2.

Table 6.2 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; i.v. fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; i.v. fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone i.v. 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 If 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)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone i.v. or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone i.v. or i.v. equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone i.v. or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4

Grade of Pneumonitis (NCI-CTCAE v4)	Management	Follow-up
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone i.v. or i.v. equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, i.v. immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone i.v. or i.v. equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: 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

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, creatine kinase-MB, brain natriuretic peptide) or cardiac imaging abnormalities suggestive of myocarditis	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.[a] 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.[a] Methylprednisolone 1 to 2 mg/kg/day.	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).
a Local guidelines, or eg. European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan:	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections.

	Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone iv or by mouth equivalent Initiate appropriate hormone therapy Endocrinology consult to distinguish (differentiate) between primary from secondary dysfunction. No abnormal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month	Resume avelumab therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of i.v. steroids with mineralocorticoid activity i.v. fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography; irAE=immune-related adverse event, IV=intravenous, LFT=liver function test, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAID=nonsteroidal anti-inflammatory drugs, T4=free thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

6.6 Packaging and Labeling

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

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines. Avelumab will be packed in boxes each containing 1 vial. The information on the trial drug will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

6.7 Storage, Handling, and Preparation

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

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

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

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

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

Storage, handling, preparation, and disposal of docetaxel should be according to the package insert.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for trial drug (avelumab or docetaxel), 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 on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor's Medical Monitor at each monitoring visit.
- Trial drug accountability records will include:
  - confirmation of trial drug delivery to the trial site;
  - the inventory at the site of trial drug provided by the Sponsor and prepared at the site;
  - the use of each dose by each subject;
  - the return to the Sponsor or alternative disposition of unused trial drug; and
  - 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
  - that the subjects were provided the doses specified by the clinical trial protocol / amendment(s); and
  - 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 Sponsor's Monitor will periodically collect the trial drug accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.

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

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the Investigator / pharmacist.

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

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

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

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive trial treatment at the investigational site. Well-trained medical staff will monitor and perform the trial 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.

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 Method of Blinding

This is an open-label trial; thus, trial treatment is not blinded. However, Investigators and trial site personnel will be blinded to the results of the PD-L1 expression determination. Details of this blinding will be provided in the Study Manual.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose ≥ 10% than the planned calculated dose for that particular administration as described in this clinical trial protocol. 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 docetaxel, subjects should receive therapeutic granulocyte colony-stimulating factor per package insert as soon as possible after the overdose is discovered.

6.13 Medical Care of Subjects After End of Treatment

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 7.1.5.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments is provided in Appendix I.

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.

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). Criteria for determining the adequacy of tumor tissue are described in the Study Manual. Subjects who undergo a biopsy specifically as part of the Screening assessments for this protocol will be permitted to participate in the protocol provided they meet all other inclusion criteria and no exclusion criteria.

Randomization cannot occur until PD-L1 expression has been determined by a companion diagnostic test under development and performed centrally (Investigators and trial site personnel will be blinded to the results of the PD-L1 expression determination).

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

During Screening, subjects will undergo a physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS (Appendix II). With the use of a validated electronic tablet or validated site pad, subjects will also complete subject-reported outcomes/ quality of life questionnaires.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry (including core chemistry), and full urinalysis (dipstick plus microscopic evaluation). Adrenocorticotropic hormone (ACTH), ANA, ANCA, rheumatoid factor (RF), free thyroxine (T4), and thyroid-stimulating hormone (TSH) will also be assessed at Screening for all subjects. Additionally, HBV surface antigen and anti-HCV tests must be performed at screening to exclude hepatitis infection. If the anti-HCV antibody test is positive, infection should be confirmed by an HCV RNA test.

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of childbearing potential and blood hepatitis B virus and hepatitis C virus will be performed (local laboratory) for all Screening subjects as these conditions are trial entry exclusion criteria (see Section 5.3.2). Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who

have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be drawn at Screening.

The tumor evaluation (type and staging, etc) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory in all countries except Germany, in which case a MRI of the chest is allowed) or any other established methods (see Section 7.2.5 for details). A brain CT / MRI scan is required at Screening if not performed within 6 weeks prior to randomization. A bone scan should be done at Screening as clinically indicated.

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

Subject eligibility will need to be confirmed by the CRO before the first administration of the trial drug.

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 maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

The treatment should start within 4 days after randomization. While on trial treatment, subjects will be asked to visit the trial site either

- once every 2 weeks for subjects randomized to receive avelumab, or
- once every 3 weeks for subjects randomized to receive docetaxel.

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. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to the scheduled day (-5 days).

Subjects will receive either

- avelumab by IV infusion following pretreatment with H1 blockers (diphenhydramine 25 to 50 mg IV, or equivalent), and acetaminophen 500 to 650 mg (oral or IV), once every 2 weeks (see Section 6.2.1), or
- docetaxel by IV infusion following pretreatment with dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion (see Section 6.2.2).

During the treatment period, the following assessments will be performed (see Appendix I for the detailed schedule):

- With the use of a validated electronic tablet or validated site pad, subject-reported outcomes/ quality of life questionnaires 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) at
  - Week 1 (treatment administration 1), Week 3 (treatment administration 2), Week 7 (treatment administration 4), and Week 13 (treatment administration 7) for subjects receiving avelumab,
  - Week 1 (treatment administration 1), Week 4 (treatment administration 2), Week 7 (treatment administration 3), and Week 13 (treatment administration 5) for subjects receiving docetaxel, and
  - 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.
- Physical examinations will be performed at each visit until Week 13 and every 6 weeks thereafter.
- Vital signs and body weight will be assessed in each visit.
- The laboratory hematology, hemostaseology, and core serum chemistry tests will be assessed at each visit (complete blood count and core chemistry samples must be drawn and results reviewed within 48 hours prior to dose administration). Full serum chemistry (which includes core serum chemistry) will be assessed at Weeks 3, 5, and 13 for subjects randomized to avelumab, Weeks 4, 7, and 13 for subjects randomized to docetaxel, and then every 6 weeks thereafter for all subjects. 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 according to the Schedules of Assessments (Table 12.1 or Table 12.3 as appropriate) before administration of the trial drug for females of childbearing potential. Results of the most recent pregnancy test should be available prior to the next dosing of trial drug.
- Tumor evaluation for all subjects (see Section 7.3) will be performed every 6 weeks from randomization until Week 55 (12 months) and then every 12 weeks thereafter, with a tumor assessment visiting time window of 5 days prior to the scheduled tumor assessment day (-5 days).

[redacted]

- ACTH, ANA, ANCA, RF, T4, and TSH will be measured according to the Schedules of Assessments (Table 12.1 or Table 12.3 as appropriate) and if clinically indicated for all subjects.

[redacted]

7.1.3 End-of-Treatment

Discontinuation visit

Any subject who experiences an AE that mandates discontinuation of trial treatment should have a Discontinuation visit as soon as possible after the decision to discontinue trial treatment (at least within 7 days). For all these subjects, the Discontinuation visit will include the following (see Appendix I):

- Subject-reported outcomes / quality of life questionnaires will be completed with the use of a validated electronic tablet or validated site pad
- Documentation of AEs and concomitant medication
- Physical examination, including vital signs and body weight
- 12-lead ECGs
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis

- ECOG PS

Once the Discontinuation visit has been performed, subjects must return for the End-of-Treatment visit within 28 days (± 5 days) after discontinuation.

End-of-Treatment visit

The End-of-Treatment visit is scheduled 4 weeks (28 days ± 5 days) after the last administration of trial 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 (refer to Appendix I):

- Subject-reported outcomes / quality of life questionnaires will be completed with the use of a validated electronic tablet or validated site pad
- 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 plus 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)
- T4 and TSH levels

CCI [redacted]

7.1.4 Safety Follow-up

All subjects will have a subsequent visit scheduled 12 weeks (± 2 weeks) after the last administration of trial treatment. The visit will include the following full assessment of safety parameters (refer to Appendix I):

- After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit
- Concomitant medications will be documented, including further anticancer therapy
- Vital signs and body weight will be measured
- Physical examination will be performed
- ECOG PS will be assessed
- Laboratory testing consisting of the following will be assessed:

- Hematology, hemostaseology, core serum chemistry, and basic urinalysis (dipstick only)
- T4 and TSH levels
- CCI

- A urine or serum β-HCG pregnancy test (in females of childbearing potential) will be conducted

7.1.5 Long-term Follow-up

All SAEs ongoing at the Safety follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Any SAE assessed as related to the IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of the IMP.

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 [± 5 days] until Week 55 (12 months) after the first study drug administration, then every 12 weeks thereafter using the same procedures and review as while on treatment) until disease progression, lost to follow-up, or withdrawal of informed consent.

After the End-of-Treatment visit, subjects will be followed quarterly (that is, every 3 months ± 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.

7.1.6 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/day and 550 mL in an 8-week period for safety laboratory testing, pregnancy testing, CCI .

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

7.2.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier
- Date of birth
- Sex
- Race
- 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 CCI [redacted] t and performed centrally [Investigators and trial site personnel will be blinded to the results of the PD-L1 expression determination], 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 and chemotherapy, immunotherapy);
- any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy;
- smoking history;
- current cancer signs and symptoms and side effects from current and previous anticancer treatments; and
- current cancer disease status.

7.2.3 Medical History

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

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

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

7.2.4 Vital Signs and Physical Examination

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

A 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 (or chest MRI in Germany) 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 Early Discontinuation / 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 intervals, and possible arrhythmias.

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 enrolled 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 Assessment of Efficacy

Radiographic images and physical findings (physical assessments) used for the local determination of disease progression will be read centrally and reviewed by a blinded IERC. The IERC will make a determination as to whether the criteria for tumor response or progression according to RECIST 1.1 have been met.

For each subject, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory in all countries except Germany, in which case a MRI of the chest

is allowed) 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. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial must correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments (refer to Appendix I).

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

For efficacy determination, tumor responses to treatment will be assigned by the IERC based on the evaluation of the response of target, nontarget, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation, as described in RECIST 1.1 [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 assessment after the initial documentation of PR.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD. Subjects who withdraw from the trial for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

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 (refer to Appendix I).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of a 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.

In cases of 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 / intensity of each AE.

Investigators will reference the NCI-CTCAE v 4.03 (publication date: 14 June 2010). This is 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 referenced document, and specific event grades are also provided.

If a particular AE 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: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening

Grade 5: Death

According to the Sponsor's 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 respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

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

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

Related: Reasonably related to the trial treatment avelumab / docetaxel. The AE could medically (pharmacologically / clinically) be attributed to the trial treatment.

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)

Adverse drug reactions are defined in this trial as any AEs suspected to be related to trial treatment by the Investigator and / or Sponsor.

Serious Adverse Events (SAE)

A 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 prolongation of existing hospitalization,
- results in persistent or significant disability / incapacity,
- is a congenital anomaly / birth defect, or
- is otherwise considered as 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 a trial drug is also considered a SAE, as described in Section 7.4.1.4.

Events that do not meet the definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as 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.

AEs / SAEs observed in association with disease progression

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

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded, and reported as SAEs if meeting any seriousness criteria.

Predefined AEs of special interest for safety monitoring

Any AE that is suspicious to be a potential irAE will be considered AEs of special interest (AESI).

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit the subject will be queried on changes in his or her condition. During the reporting period of the trial 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 to be completed 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 through the trial's End-of-Treatment visit, defined as 28 days (± 5 days) after last trial drug administration. After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.

Any SAE suspected to be 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 (that is, within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Names, addresses, telephone, and fax numbers for SAE reporting will be included in the trial specific SAE report form.

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 or designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure a 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 by the responsible Clinical Trial Monitor, although in exceptional circumstances, the Global Drug Safety department may contact the Investigator directly 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 (and in particular deaths) involving his or her subjects to the IEC / IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor or 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 / IRB approval / favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (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 or the designee will provide appropriate Safety reports directly to the concerned lead IEC / IRB and will maintain records of these notifications. When direct reporting by the Sponsor 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 or 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.

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 End-of-Treatment visit. After the End-of-Treatment visit, only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.

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

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as 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 or designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

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

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

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

7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor or designee be provided with a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be taken from nonfasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the trial site and relevant results must be available and checked before administration of trial treatment (details to be provided in the Laboratory Manual).

The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the full safety tests listed in Table 7.1 will be taken from nonfasted subjects during the Screening phase (28 days prior to randomization), during the treatment period as specified in Table 7.1 and in Appendix I, at the End-of-Treatment visit, and at the Safety Follow-up visit. The ACTH, ANA, ANCA, RF, T4, TSH, and urinalysis will only be assessed at the time points defined in Table 7.1 and Appendix I. If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 7.1.1.

Table 7.1 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	Reticulocytes
Chloride	Phosphorus/Phosphates	MCH
Cholesterol	Magnesium	Mean corpuscular volume
Creatine kinase	Potassium	MCHC
Creatinine	Sodium	
CRP	Total bilirubin	
Glucose		**Hemostaseology**
LDH		aPTT
Lipase		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 plus 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		
Total protein		
Uric acid		CCI [redacted]
Triglycerides		
		ACTH, ANA, ANCA, RF, TSH, and T4 As indicated in the Schedules of Assessments (Table 12.1 and Table 12.3 as appropriate) and if clinically indicated.
Hormone		
FSH (yes / no if applicable)		

ACTH=adrenocorticotropic hormone, CCI [redacted] ALT=alanine aminotransferase, ANA=antinuclear antibody, ANC=absolute neutrophil count, ANCA=antineutrophil cytoplasmic antibody, 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, RF=rheumatoid factor; 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 Examinations, and Other Assessments

The ECOG PS will be assessed at Screening and at subsequent visits as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF.

Body weight will be measured at Screening and at subsequent visits as indicated in the Schedule of Assessments (Appendix I) 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 as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF (detailed description in Section 7.1). 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 (Appendix I).

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 according to the Schedules of Assessments (Table 12.1 or Table 12.3 as appropriate). Results of the most recent pregnancy test should be available prior to the next dosing of trial drug. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and FSH > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

Germline DNA will be investigated on DNA extracted from whole blood. For this purpose, an CCI [redacted]

[redacted]

[redacted]

[redacted]

7.7 Other Assessments

7.7.1 Subject-Reported Outcomes / Quality of Life

Subject-reported outcomes / quality of life will be assessed by the EQ-5D, EORTC QLQ-C30, and module QLQ-LC13. Questionnaires will be completed by the subject at Screening, Day 1 (Week 1), Weeks 3 and 7 prior to trial treatment administration and then every 6 weeks thereafter while on trial treatment for subjects randomized to receive avelumab and Day 1 (Week 1), Weeks 4 and 7 and then every 6 weeks thereafter while on trial treatment for subjects randomized to receive docetaxel. Subject-reported outcomes will also be assessed at the Early Discontinuation / End-of-Treatment visit (details will be provided in the Study Manual).

The subject-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.

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

8 Statistics

8.1 Sample Size

The following assumptions with regard to the primary endpoint of OS time in the PD-L1+ subjects are made for the sample size calculation:

- Hazard ratio (HR) of 0.70 corresponding to an increase in median OS time from 8 months in the control arm to 11.43 months in the investigational arm
- 1:1 randomization
- Alpha = 0.025 (1-sided)
- Power = 90%
- Uniform accrual over a period of 10 months
- A follow-up time of 11 months after randomization of the last subject
- An expected drop-out rate of 5%
- An interim analysis for efficacy after 75% of the planned events (deaths) PD-L1+ subjects have been observed, with an O'Brien-Fleming stopping boundary

A sample size of approximately 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. Calculations were performed using ADDPLAN V 6.01, Aptiv Solutions. The 75% interim analysis will be performed when 253 events have been observed. An IDMC (see Section 2.3.1) will be convened to perform the evaluation at the interim analysis in order to safeguard the Sponsor's personnel from unblinded trial results.

To ensure that the overall FAS is representative of the underlying patient population, the trial will enroll PD-L1 evaluable subjects without predetermining the ratio between PD-L1+ and PD-L1 negative subjects; therefore, the total number of subjects enrolled in the trial is unknown, but can be estimated based on a prevalence estimate of PD-L1+ subjects from the NSCLC expansion cohort of Trial EMR100070-001, which was conducted in a similar patient population. CCI

[redacted]

8.2 Randomization

Qualified subjects will be randomized at a 1:1 ratio to receive either avelumab or docetaxel using stratified permuted block randomization with variable block length via the IVRS. Randomization will be stratified according to PD-L1 assay status (positive versus negative expression in tumor cells) and NSCLC histology (squamous cell versus non-squamous cell). The purpose of stratification is to ensure balanced distribution of prognostic factors between treatment arms. Randomization will occur upon completion of the Screening procedures and determination of subject eligibility, using the IVRS as described in Section 6.3.

8.3 Endpoints

8.3.1 Primary Endpoint

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

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

8.3.2 Secondary Endpoints

8.3.2.1 Progression-Free Survival

The PFS will be determined according to RECIST 1.1 as adjudicated by an IERC (see Section 2.3.2). It is defined as the time from date of randomization until date of the first documentation of objective PD or death by any cause (whichever occurs first). The PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects who start new anticancer treatment prior to an event, or for subjects with an event after two or more consecutive 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.

The censoring and event date options to be considered for the PFS are presented in Table 8.1.

Table 8.1 General Censoring Rules for Progression-free Survival

Scenario	Date of event/censoring	Outcome
No baseline assessment	Start date	Censored [a]
PD or death ≤ 12 weeks after last tumor assessment or ≤ 12 weeks after start date	Date of PD or death	Event
PD or death > 12 weeks after the last adequate tumor assessment	Date of last adequate tumor assessment [b] documenting no PD before new anticancer therapy is given or missed assessments	Censored
No PD	Date of last adequate tumor assessment [b] documenting no PD before new anticancer therapy is given or missed assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anticancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anticancer therapy is given or missed assessments	Censored

PD=progressive disease.

[a] However if the patient dies ≤12 weeks after start date the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of randomization; if the criteria were met the censoring will be on the date of randomization.

The PFS time according to Investigator assessment will be derived in the same way as the PFS time according to the IERC.

8.3.2.2 Best Overall Response

The confirmed BOR will be determined according to RECIST 1.1 (1) and as adjudicated by an IERC (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. Details of determination of tumor response date at each time point will be provided in the IERC charter.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

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. Confirmation of PR or CR can be confirmed at an assessment later than the next assessment after the initial documentation of PR or CR, respectively.

A BOR of SD requires that a time point 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 IERC.

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

8.3.2.3 Changes in Subject-Reported Outcomes / Quality of Life

Changes in subject-reported outcomes / quality of life will be assessed by the EQ-5D, the EORTC QLQ-C30, and module QLQ-LC13 questionnaires.

The QLQ-LC13 comprises 13 questions incorporated into 1 multi-item scale designed to evaluate dyspnea and a series of single items assessing different types of pain, as well as, cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy. For each domain and item, a linear transformation was 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.

8.3.3 Safety Endpoints

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

8.3.4 Exploratory Endpoints

Exploratory endpoints include

[redacted]

8.4 Analysis Sets

Screening Analysis Set

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

Full Analysis Set / Intention-to-Treat (ITT) Analysis Set

The Full Analysis Set (FAS) / ITT analysis set will include all subjects who were randomly assigned to trial treatment. Analyses performed on the FAS will take into account subjects' allocation to treatment groups as randomized.

PD-L1+ FAS

The PD-L1+ FAS will include all PD-L1+ subjects who were randomly assigned to trial treatment. Analyses performed on the PD-L1+ FAS will take into account subjects' allocation to treatment groups as randomized.

The primary analysis population will be the subjects with PD-L1+ tumors in the FAS.

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.

PD-L1+ Safety Analysis Set

The PD-L1+ Safety analysis set will include all PD-L1+ subjects who were administered at least 1 dose of the trial medication. Analyses performed on the PD-L1+ 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.

Subject assignment per the IVRS will be used to determine the PD-L1+ subset.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

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

Baseline characteristics summary and the efficacy analysis will be performed on the PD-L1+ FAS and the FAS, with the primary analysis population being the PD-L1+ FAS. Analyses performed on the FAS 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.

A hierarchical testing strategy will be applied to perform confirmatory analysis of primary endpoint OS and the key secondary efficacy endpoints as follows:

1. OS in the PD-L1+ subset of the FAS;
2. OS in the FAS;
3. BOR in the PD-L1+ subset of the FAS;
4. PFS in the PD-L1+ subset of the FAS;
5. BOR in the FAS;
6. PFS in the FAS.

Statistical testing of each of the hypotheses 2 through 6 will be performed at the same nominal significance level as for hypothesis 1 (one-sided alpha of 0.0100 and 0.0219 at the interim and the final analysis, respectively) if, and only if, the preceding null hypothesis in terms of the hierarchical order was rejected.

All sensitivity analyses are regarded as purely exploratory; therefore, no formal adjustment for multiplicity will be undertaken for these sensitivity analyses.

For the safety analysis, Baseline is defined as the last measurement before the first trial drug administration. For the efficacy analysis, Baseline is defined as the last measurement prior to randomization. If such a value is missing, the last measurement prior to the first trial drug administration will be used as the baseline measurement for the efficacy analysis except for analyses of tumor assessments data where the baseline assessment would be considered missing.

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

8.5.2 Analysis of Primary Endpoint

Primary Analysis

The primary endpoint of this trial is OS. The primary analysis population will be the PD-L1+ FAS. It will compare the OS time between the two treatment groups, and will be performed using a one-sided stratified log rank test (overall $\alpha = 2.5\%$). The stratification factors are those used for randomization as captured via the IVRS (PD-L1 assay status: positive versus negative expression in tumor cells; and NSCLC histology: squamous cell versus non-squamous cell). For analysis purposes, the subjects in the previously used strata non-squamous cell EGFR normal and non-squamous cell EGFR activating mutations will be combined into the stratum non-squamous cell.

The final analysis will be conducted after 337 events (deaths) in PD-L1+ subjects have been observed. An interim analysis for efficacy will be performed after 75% of events (253 deaths) in PD-L1+ subjects have been observed, stopping for efficacy if the criteria are met.

The following null hypothesis will be tested:

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

where $\lambda(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in treatment groups A (avelumab) and B (docetaxel).

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the hazard ratio and its 95% CI. Each stratum will define a separate Baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

Based on the O'Brien-Fleming efficacy stopping boundary, α level will be 0.0100 (one-sided) at the 75% interim analysis, and 0.0219 (one-sided) at the final analysis.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median survival time with two-sided 95% CIs. In particular, the survival rate at 6 and 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) 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 (1980). The estimate of the standard error will be computed using Greenwood's formula.

The primary analysis performed as described above will be repeated on the FAS as part of the hierarchical testing strategy as described in Section 8.5.1.

Sensitivity Analyses

The following sensitivity analyses will be performed to explore the robustness of the primary confirmatory analysis. These analyses are regarded as purely exploratory. Additional sensitivity analyses may be specified in the trial SAP. The sensitivity analyses will include the following:

- The proportional hazards assumption for the primary analysis will be visually checked by plotting log(-log(survival)) versus log(time) by treatment arm
- An unstratified analysis will be performed to compare the OS time and to estimate the treatment effect
- The primary analysis will be repeated using strata according to eCRF instead of IVRS data
- The pattern of censoring with regard to OS time will be analyzed by treatment arm distinguishing between administrative censoring (that is, censoring imposed by the cut-off date) and censoring due to subjects being lost to follow-up.

Time of Follow-Up

A Kaplan-Meier plot will be created for both treatment groups to compare the duration of follow-up for overall survival using the following censoring rules (reversing the OS censoring and event indicators):

Table 8.2 Censoring Rules for Duration of Overall Survival Follow-up

	Date of Event / Censoring	Censoring
Subjects alive or lost to follow-up	Time from randomization to last date known to be alive	No
Subjects who died	Time from randomization to date of death	Yes

8.5.3 Analysis of Secondary Endpoints

Secondary efficacy analyses will be performed on the FAS set and the PD-L1+ FAS. Details will be provided in the trial SAP.

Based on the hierarchical testing strategy described in Section 8.5.1, if the one-sided p-value from the stratified log-rank test of the primary endpoint OS is below 0.0100 and 0.0219 at the interim and the final analysis, respectively, the secondary endpoints will be tested with the specified order within the hierarchical testing procedure at the same nominal significance level as the primary endpoint (one-sided alpha of 0.0100 and 0.0219 at the interim and the final analysis, respectively) if, and only if, the preceding null hypothesis within the specified hierarchical order was rejected.

For the secondary endpoint analysis of PFS time according to RECIST 1.1 and as adjudicated by the IERC, the statistical analysis will be the same as described for the primary analysis of OS time.

For the secondary endpoint analysis of BOR according to RECIST 1.1 and as adjudicated by the IERC, the ORR in terms of having a confirmed BOR of CR or PR will be calculated along with corresponding two-sided exact Clopper-Pearson 95% CIs for the 2 treatment groups. The Cochran-

Mantel-Haenszel test will be performed with the randomization strata taking into account to compare the ORR between the 2 treatment groups.

For PFS and BOR, the following sensitivity analyses will be performed to assess the robustness of the primary analysis results. These analyses are regarded as purely exploratory.

1. PFS and BOR according to Investigator assessment will be analyzed

2. An unstratified analysis will be performed

3. For PFS, the frequencies of event types and reasons for censoring will be assessed by treatment arm

4. For PFS time, all deaths will be considered events based on IERC assessment and counting all PD and deaths as events without considering the censoring rule for PD or death as described in Table 8.1;

5. PFS based on IERC assessment and initiation of subsequent anticancer therapies will not be used as a censoring reason for PFS

8.5.4 Analysis of Exploratory Endpoints

CCI [redacted]

CCI [redacted]

8.5.5 Safety Analyses

The extent of exposure to trial drugs (avelumab or docetaxel) will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg or mg/m^2), dose intensity (mg/kg/week or mg/m^2/week), relative dose intensity (actual dose given / planned dose), and number of dose delays.

Safety analyses will be performed on the Safety analysis set and the PD-L1+ 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. Summaries of laboratory results by visit will be provided. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from Baseline 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 (Appendix I) 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 endpoint and secondary efficacy endpoints with the subgroups, which will be specified in the SAP. Specifically, the subgroup analysis by PD-L1 status (positive versus negative expression in tumor cells) will be performed on the FAS for the primary and secondary efficacy endpoints. 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.

All the subgroup analyses will be exploratory; no adjustment for multiplicity will be performed. In the case of a low number of subjects within a category (< 25 subjects, which is about 5% of the randomized PD-L1+ population), the categories will be pooled.

8.6 Interim Analysis

An IDMC will be formed and will be responsible for periodic evaluations of the trial as well as the evaluation of the interim and the final analysis. For this trial there will be 1 interim analysis that

will be conducted after 75% of the events (deaths) in PD-L1+ subjects have been observed, that is, after 253 events have occurred. The primary endpoint, OS, key secondary endpoints analysis including PFS and BOR, and safety analysis will be conducted in this interim analysis. The interim analysis of efficacy endpoints will be conducted on the FAS, with the primary analysis population being the PD-L1+ subset of the FAS. The IDMC will also be presented with subject disposition, subject background, Baseline disease and demographic information, along with safety information. Details of the IDMC mission, composition, and operations will be provided in the IDMC charter.

An independent statistical provider will perform the interim analyses to support the IDMC. Results from the interim analyses will be transmitted from this group to the IDMC only and trial staff involved with the day to day management of the trial, as well as any Sponsor staff, will not have access to this interim information.

After 253 events have been observed in the PD-L1+ subjects, the independent statistical group will prepare the outputs in agreement with the IDMC charter and transmit the analyses, tabulations, and listings to the IDMC for the meeting. The independent support IDMC statistician will be available at the IDMC meeting should any questions from the IDMC members arise regarding the data and / or analyses.

The hierarchical testing strategy will be employed for the interim analysis. If the one-sided p-value from the stratified log-rank test of OS is below 0.0100, the treatment difference will be claimed as statistically significant and the secondary endpoints will be tested within the hierarchical testing strategy at the same nominal significance level. If, at the time of this interim analysis, the OS of avelumab assigned subjects is shown to be superior to that of those randomized to the docetaxel group with a p-value of < 0.0100 the IDMC may declare superior efficacy in the avelumab treatment arm compared with those randomized to receive docetaxel and recommend that the trial be stopped early. This interim analysis of OS will be performed in a manner identical to the final efficacy analysis.

An IDMC charter will provide details about the conduct of the IDMC meeting and decision making rules.

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.

In 1998, the USA FDA introduced a regulation (21 Code of Federal Regulations, Part 54) entitled "Financial Disclosure by Clinical Investigators." For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the trial drug (named "covered trials" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest

that they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his / her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. CCI [redacted]

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his / her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

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

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

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

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC / IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. 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 IVRS 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 enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

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

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

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

In cases where the Investigator is not available, Merck Serono / 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 shall be provided for each country participating in 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 ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

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 subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- 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)
- Tumor disease information
- Trial identification
- Date of subject's inclusion into the trial (that is, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from trial drug, if applicable

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must include at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per

ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

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

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

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

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

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC / IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could 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 according to ICH Topic E3 will be written by the Sponsor in consultation with the Coordinating Investigator.

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 Schedules of Assessments

Table 12.1 Avelumab Arm

Measure	Screening / Baseline Assessments	Treatment Phase[a]								Discontinuation (x) / End-of-Treatment Visit (X)	Safety Follow-up Visit	Long-term Follow-up[b]
	Day -28 to Randomization	V1 W1 D1	V2 W3 D15	V3 W5 D29	V4 W7 D43	V5 W9 D57	V6 W11 D71	V7 W13 D85	Until Progression	Up to 7 / 28 Days (± 5 days) after Last Treatment[c,d]	12 Weeks (± 2 weeks) after Last Treatment	Every 3 months[b] (± 1 week)
Written informed consent	X											
PD-L1 tumor expression level / Tumor tissue (biopsy)[e]	X											
Inclusion / exclusion criteria	X											
Medical history / smoking history[f]	X											
Demographic data	X											
HBV and HCV testing	X											
Subject-reported outcomes / quality of life assessments[g]	X	X	X		X			X	6-weekly	x/X		
Physical examination, including height at Screening	X	X	X	X	X	X	X	X	6-weekly	x/X	X	
Vital signs	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
Weight	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
ECOG PS	X[h]	X	X	X	X	X	X	X	2-weekly	x/X	X	
Enrollment (if eligible)[i]	X											
12-lead ECG[j]	X									x/X		
Hematology and hemostaseology	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
Core serum chemistry[k]		X			X	X	X		2-weekly		X	
Full serum chemistry[l]	X		X	X				X	6-weekly	x/X		
Urinalysis[m]	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
β-HCG pregnancy test[n]	X	X		X		X		X	4-weekly	- /X	X	

Measure	Screening / Baseline Assessments	Treatment Phase[a]								Discontinuation (x) / End-of-Treatment Visit (X)	Safety Follow-up Visit	Long-term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7				
		W1	W3	W5	W7	W9	W11	W13				
	Day -28 to Randomization	D1	D15	D29	D43	D57	D71	D85	Until Progression	Up to 7 / 28 Days (± 5 days) after Last Treatment[c,d]	12 Weeks (± 2 weeks) after Last Treatment	Every 3 months[b] (± 1 week)
Tumor evaluation / staging (CT Scan / MRI / other established methods)[o,p]	X				X			X	6 weekly up to 12 months then 12 weekly[o,p]	- /X		X
Documentation of AEs and concomitant medication[q]	X	X	X	X	X	X	X	X	2-weekly	x/X	X	X[b]
ACTH, ANA, ANCA, and RF	X	As clinically indicated										
T4 and TSH	X				X			X	6-weekly	- /X	X	
CCI												
Pretreatment and trial drug administration[r]		X	X	X	X	X	X	X	2-weekly			
CCI												

ACTH=adrenocorticotropic hormone, CCI, ADR=adverse drug reaction; AE=adverse events, ALT=alanine aminotransferase, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, AST=aspartate aminotransferase, β-HCG=β-human chorionic gonadotropin, BUN=blood urea nitrogen, CR= complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=Informed Consent Form, IV=intravenous, MRI=magnetic resonance imaging, NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1, CCI, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, RF=rheumatoid factor, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all trial procedures. Complete blood count and core chemistry samples must also be drawn and results reviewed within 48 hours prior to dose administration.

b Subjects with an SAE ongoing at the Safety follow-up 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [± 5 days]) until 12 months after the first study drug administration, then every 12 weeks. In addition, survival information (including assessment of any further anticancer therapy) will be collected

quarterly (that is, every 3 months ± 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).

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

d If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

CCI [redacted]

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

g The subject-reported outcomes / quality of life questionnaires (EQ-5D, EORTC QLQ-C30, and module QLQ-LC13) should be completed using a validated electronic tablet or validated site pad by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc.

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

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

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

k 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).

l Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 7.1. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

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

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

o In general, the tumor visit time window is 5 days prior to the scheduled tumor assessment. 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. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory in all countries except Germany, in which case a MRI of the chest is allowed).

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 Adverse events and concomitant medications will be documented at each trial visit. 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 through the trial's End of Treatment visit, defined as 28 days (± 5 days) after last trial drug administration. After the End of Treatment visit only treatment related AEs have to be documented until the Safety Follow up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.

r 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). Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent).

CCI [redacted]

Appendix I Schedule of Assessments

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[redacted]

Appendix I Schedule of Assessments

Table 12.3 Docetaxel Arm

Measure	Screening / Baseline Assessments	Treatment Phase[a]						Discontinuation (x) / End-of-Treatment Visit (X)	Safety Follow-up Visit	Long-term Follow-up[b]
		V1	V2	V3	V4	V5				
		W1	W4	W7	W10	W13				
	Day -28 to Randomization	D1	D22	D43	D64	D85	Until Progression	Up to 7 / 28 Days (± 5 days) after Last Treatment[c,d]	12 Weeks (± 2 weeks) after Last Treatment	Every 3 months[b] (± 1 week)
Written informed consent	X									
PD-L1 tumor expression level / Tumor tissue (biopsy)[e]	X									
Inclusion / exclusion criteria	X									
Medical history / smoking history[f]	X									
Demographic data	X									
HBV and HCV testing	X									
Subject-reported outcomes / quality of life[g]	X	X	X	X		X	6-weekly	x/X		
Physical examination, including height at Screening	X	X	X	X	X	X	6-weekly	x/X	X	
Vital signs	X	X	X	X	X	X	3-weekly	x/X	X	
Weight	X	X	X	X	X	X	3-weekly	x/X	X	
ECOG PS	X[h]	X	X	X	X	X	3-weekly	x/X	X	
Enrollment (if eligible)[i]	X									
ECG[j]	X							x/X		
Hematology and hemostaseology	X	X	X	X	X	X	3-weekly	x/X	X	
Core serum chemistry[k]		X			X		3-weekly		X	
Full serum chemistry[l]	X		X	X		X	6-weekly	x/X		
Urinalysis[m]	X	X	X	X	X	X	3-weekly	x/X	X	
β-HCG pregnancy test[n]	X	X	X	X	X	X	3-weekly	- /X	X	

Measure	Screening / Baseline Assessments	Treatment Phase[a]						Discontinuation (x) / End-of-Treatment Visit (X)	Safety Follow-up Visit	Long-term Follow-up[b]
		V1	V2	V3	V4	V5				
		W1	W4	W7	W10	W13				
	Day -28 to Randomization	D1	D22	D43	D64	D85	Until Progression	Up to 7 / 28 Days (± 5 days) after Last Treatment[c,d]	12 Weeks (± 2 weeks) after Last Treatment	Every 3 months[b] (± 1 week)
Tumor evaluation / staging (CT Scan / MRI / other established methods)[o,p]	X			X		X	6 weekly up to 12 months then 12 weekly[o,p]	- /X		X
Documentation of AEs and concomitant medication[q]	X	X	X	X	X	X	3-weekly	x/X	X	X[b]
Pretreatment and trial drug administration[r]		X	X	X	X	X	3-weekly			
ACTH, ANA, ANCA, and RF	X	As clinically indicated								
T4 and TSH[s]	X					X	Week 25 and as indicated	- /X	X	
CCI [redacted]										

ACTH=adrenocorticotropic hormone, ADR=adverse drug reaction; AE=adverse events, ALT=alanine aminotransferase, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, AST=aspartate aminotransferase, β-HCG=β-human chorionic gonadotropin, BUN=blood urea nitrogen, CR= complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=Informed Consent Form, IV=intravenous, MRI=magnetic resonance imaging, NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, RF=rheumatoid factor, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all trial procedures. Complete blood count and core chemistry samples must also be drawn and results reviewed within 48 hours prior to dose administration.

b Subjects with an SAE ongoing at the Safety follow-up 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. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [± 5 days]) until 12 months after the first study drug administration, then every 12 weeks. In addition, survival information (including assessment of any further anticancer therapy) will be collected quarterly (that is, every 3 months ± 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).

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

d If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

CCI [redacted]

f Medical history should include history of NSCLC, previous medications, smoking history, and Baseline medical condition.

g The subject-reported outcomes / quality of life assessments (EQ-5D, EORTC QLQ-C30, and module QLQ-LC13) should be completed using a validated electronic tablet or validated site pad by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc.

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

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

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

k 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).

l Full chemistry panel, which includes core serum chemistry, and other laboratory studies are detailed in Table 7.1. Follicle-stimulating hormone at Screening, if applicable (Section 7.1.1).

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

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

o In general, the tumor visit time window is 5 days prior to the scheduled tumor assessment. 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. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory in all countries except Germany, in which case a MRI of the chest is allowed).

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 Adverse events and concomitant medications will be documented at each trial visit. 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 through the trial's End of Treatment visit, defined as 28 days (± 5 days) after last trial drug administration. After the End of Treatment visit only treatment related AEs have to be documented until the Safety Follow up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.

r Subjects will be administered dexamethasone 8 mg orally at 12, 3, and 1 hour(s) prior to each docetaxel infusion per docetaxel label instructions, or equivalent, per local institutional practice.

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

CCI [redacted]

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. (38)

Appendix III Guidance on Contraception

Birth control methods considered as highly effective

Aligned with the Clinical Trials Facilitation Group (CTFG 2014) "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] Vasectomized 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. Abstinence needs to be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix IV Protocol Amendments and List of Changes

Previous Protocol Amendments

Amendment Number	Submission to Health Authority (Yes/No/ Notification only)	Date	Region or Country	Included in the current document (Y/N)
Amendment 0.1	No	18 December 2014	Japan	No
Amendment 1	Yes	5 May 2015	Global	Yes
Amendment 2	Yes	10 July 2015	Global	Yes
Amendment 2.1	No	10 July 2015	Japan	No
Amendment 2.2	No	04 August 2015	Czech Republic	No
Amendment 2.3	No	04 August 2015	Japan	No
Amendment 2.4	No	06 November 2015	Korea	Yes
Amendment 3	Yes	15 November 2016	Global	Yes
Amendment 4	FDA only	29 November 2016	Global	Yes

The purpose of this amendment (Protocol Version 6.0, Amendment 5, 10 January 2017) is to:

- Correct an administrative error in Table 6.2 that suggested for cardiac myocarditis that hospitalization was only required in the presence of life-threatening cardiac decompensation
- Add language clarifying that quality of life questionnaires are completed on a validated electronic tablet or validated site pad
- Make minor administrative changes for consistency throughout the protocol

This amendment is considered as non-substantial as only administrative changes were made.

List of Changes

Main changes to the clinical trial protocol text are presented in the table below (updates in minor typographical/grammatical errors are not noted).

Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison of Current version (Version 6.0) with Clinical Trial Protocol Version 5.0, Amendment 4, 29 November 2016

Change	Section	Pages	Previous Wording	New Wording	Rationale
Added "approximately" to the number of PD-L1+ subjects	Synopsis – Trial design and plan 5.1.1 Overall Design	15 46	Approximately 750 subjects, among them 522 PD-L1 assay positive subjects, ...	Approximately 750 subjects, among them **approximately** 522 PD-L1 assay positive subjects, ...	To provide some flexibility to avoid enrolling more subjects than necessary
Clarified that after 12 months from first administration, scans would be every 12 weeks	Synopsis – Trial design and plan 5.1.1 Overall Design	16 47	Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks from randomization to determine response to treatment.	Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks from randomization **until Week 55 (12 months) and then every 12 weeks thereafter** to determine response to treatment.	For clarification and internal consistency
Added "approximately" to the number of PD-L1+ subjects	Synopsis – Planned number of subjects	17	Approximately 750 subjects will be randomized. Accrual will proceed up to a target number of 522 PD-L1+ subjects.	Approximately 750 subjects will be randomized. Accrual will proceed up to a target number of **approximately** 522 PD-L1+ subjects.	To provide some flexibility to avoid enrolling more subjects than necessary
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	Synopsis – Schedule of visits and assessment (Screening / Baseline assessments)	18	• Subjects will complete subject-reported outcomes / quality of life questionnaires	• ~~Subjects~~ **With the use of a validated electronic tablet or validated site pad, subjects** will complete subject-reported outcomes / quality of life questionnaires	To provide additional guidance and clarity
Clarified that after 12 months from first administration, scans would be	Synopsis – Schedule of visits and assessments (Treatment period)	19	• Tumor responses will be assessed every 6 weeks from randomization (within 5 days prior to the scheduled tumor assessment), per RECIST 1.1 while on trial.	• Tumor responses will be assessed every 6 weeks from randomization (within 5 days prior to the scheduled tumor assessment), per RECIST 1.1 **until Week 55 (12 months) and then every**	For clarification and internal consistency

Change	Section	Pages	Previous Wording	New Wording	Rationale
every 12 weeks				**12 weeks thereafter** while on trial.	
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	Synopsis – Schedule visits and assessments (Treatment period)	20	• Subject-reported outcomes / quality of life questionnaires 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 ...	• ~~Subject~~ **With the use of a validated electronic tablet or validated site pad, subject**-reported outcomes / quality of life questionnaires 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 ...	To provide additional guidance and clarity
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	Synopsis – Schedule visits and assessment (Follow-up phase)	21	During these two visits there will be a full assessment of safety parameters (including ECG at the Early Discontinuation / End-of-Treatment visit), subject-reported outcomes / quality of life (Discontinuation / End-of-Treatment visit), CCI [redacted] (End-of-Treatment visit only) ...	During these two visits there will be a full assessment of safety parameters (including ECG at the Early Discontinuation / End-of-Treatment visit **using a validated electronic tablet or validated site pad**), subject-reported outcomes / quality of life (Discontinuation / End-of-Treatment visit), CCI [redacted] (End-of-Treatment visit only) ...	To provide additional guidance and clarity
Added the word "approximately" to the number PD-L1+ subjects and total number of subjects	Synopsis – Statistical methods (includes sample size calculation)	30	A sample size of 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. The total number of randomized subjects is expected to be 750 subjects, based on an estimated prevalence of approximately 70% PD-L1+ subjects.	A sample size of **approximately** 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. The total number of randomized subjects is expected to be **approximately** 750 subjects, based on an estimated prevalence of approximately 70% PD-L1+ subjects.	To provide some flexibility to avoid enrolling more subjects than necessary
Made correction in management of Cardiac irAEs (Myocarditis)	6.5.4.4 Immune-Related Adverse Events	71	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	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~~ **Hospitalize** **In** the presence of life threatening cardiac	To correct error that suggested to hospitalize only in the presence of life-threatening cardiac decompensation

Change	Section	Pages	Previous Wording	New Wording	Rationale
				decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management	
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	7.1.1 Screening and Baseline Procedures and Assessments	76	During Screening, subjects will undergo a physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS (Appendix II). Subject-reported outcomes/ quality of life questionnaires.	During Screening, subjects will undergo a physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS (Appendix II). ~~Subject~~ **With the use of a validated electronic tablet or validated site pad, subjects will also complete subject**-reported outcomes/ quality of life questionnaires.	To provide additional guidance and clarity
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	7.1.2 Treatment Period	78	• Subject-reported outcomes/ quality of life questionnaires 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) at ...	• ~~Subject~~ **With the use of a validated electronic tablet or validated site pad, subject**-reported outcomes/ quality of life questionnaires 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) at ...	To provide additional guidance and clarity
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	7.1.3 End-of-Treatment – Discontinuation visit End-of-Treatment visit	79 80	• Subject-reported outcomes / quality of life questionnaires will be completed	• Subject-reported outcomes / quality of life questionnaires **will be completed with the use of a validated electronic tablet or validated site pad**	To provide additional guidance and clarity
Added statement that subjects will use an electronic tablet or site pad to complete	7.7.1 Subject-Reported Outcomes / Quality of Life	96	The subject-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,	The subject-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,	To provide additional guidance and clarity

Change	Section	Pages	Previous Wording	New Wording	Rationale
subject-reported outcomes / quality of life questionnaires			blood draws, trial treatment administration, etc. Subjects may use a site pad to record their responses to these questionnaires.	blood draws, trial treatment administration, etc. Subjects ~~may use a~~ **will use a validated electronic tablet or validated** site pad to record their responses to these questionnaires. **In rare and extenuating circumstances when a validated electronic tablet or validated 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.**	
Added "approximately" to the number of PD-L1+ subjects	8.1 Sample Size	97	A sample size of 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. Calculations were performed using ADDPLAN V 6.01, Aptiv Solutions. The 75% interim analysis will be performed when 253 events have been observed. An IDMC (see Section 2.3.1) will be convened to perform the evaluation at the interim analysis in order to safeguard the Sponsor's personnel from unblinded trial results.	A sample size of **approximately** 522 PD-L1+ subjects is planned in order to observe 337 events (deaths) at the final analysis. Calculations were performed using ADDPLAN V 6.01, Aptiv Solutions. The 75% interim analysis will be performed when 253 events have been observed. An IDMC (see Section 2.3.1) will be convened to perform the evaluation at the interim analysis in order to safeguard the Sponsor's personnel from unblinded trial results.	To provide some flexibility to avoid enrolling more subjects than necessary
Added statement that subjects will use an electronic tablet or site pad to complete subject-reported outcomes / quality of life questionnaires	Appendix 1 – Table 12.1, footnote "g" Appendix 1 – Table 12.3, footnote "g"	120 125	g The subject-reported outcomes / quality of life assessments (EQ-5D, 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.	g The subject-reported outcomes / quality of life assessments (EQ-5D, EORTC QLQ-C30, and module QLQ-LC13) should be completed **using a validated electronic tablet or validated site pad** by all subjects prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc.	To provide additional guidance and clarity

Correction to Table 6.2

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
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~~ **Hospitalize.** **In** the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.[a] 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.

Appendix V Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Title	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
IND Number	IND CCI
EudraCT Number	2014-005060-15
Clinical Trial Protocol Date / Version	10 January 2017 / Version 6.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

PPD

Signature

PPD

Date of Signature

Name, academic degree	PPD
Function	PPD
Institution	Merck Serono SIA.
Address	23A Duntes street, Riga, LV-1005, Latvia
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Signature Page – Coordinating Investigator

Title	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
IND Number	IND CCI
EudraCT Number	2014-005060-15
Clinical Trial Protocol Date / Version:	10 January 2017 / 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

Signature PPD

PPD

Date of Signature

Name, academic degree PPD

Function PPD

Institution PPD

Address PPD

Telephone number PPD

Fax number PPD

E-mail address PPD

Signature Page – Principal Investigator

Title	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
IND Number	IND [redacted]
EudraCT Number	2014-005060-15
Clinical Trial Protocol Date / Version	10 January 2017 / 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:

Further Sponsor Responsible Persons

Name, academic degree	PPD
Function	Senior Expert Statistician, 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	PPD
Institution	EMD Serono Research & Development Institute, Inc.
Address	One Technology Place, Rockland, MA 02370, USA
Telephone number	PPD
Fax number	PPD
E-mail address	PPD