Clinical Trial Protocol

Clinical Trial Protocol Number	EMR100070-001
Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
Short Trial Name	JAVELIN Solid Tumor
Trial Phase	Phase I/Ib
IND Number	CCI [redacted]
EudraCT Number	2013-002834-19
Coordinating Investigator	PPD [redacted]
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250, Darmstadt, Germany For sites in the USA: EMD Serono, Inc One Technology Place, Rockland, MA 02370, USA Medical Responsible: PPD [redacted] PPD [redacted] 45A Middlesex Turnpike Billerica, MA 01821, USA Tel: PPD [redacted] Fax: PPD [redacted]
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[redacted]

Table of Contents

Table of Contents 3
Table of In-Text Tables 7
Table of In-Text Figures 8
List of Abbreviations 9
1 Synopsis 15
2 Sponsor, Investigators and Trial Administrative Structure 40
2.1 Investigational Sites 40
2.2 Trial Coordination / Monitoring 40
2.2.1 Safety Monitoring Committee 40
2.2.2 Central Reader and Independent Endpoint Review Committee 41
3 Background Information 41
3.1 Investigational Medicinal Product 41
3.2 Non-Clinical Findings for Avelumab 42
3.2.1 In vitro and in vivo Pharmacology Findings 42
3.2.2 Toxicology 43
3.3 Pharmacokinetics / Immunogenicity Findings 44
3.4 Safety 45
3.4.1 Clinical Pharmacodynamics 52
3.5 Rationale for the Clinical Trial 52
3.5.1 Rationale for 10 mg/kg Once Weekly Dose-Escalation Cohort 54
3.5.2 Rationale for Expansion Cohorts 56
3.5.3 Rationale for New Expansion Cohorts / Expanding Initial Expansion Secondary Cohorts 56
3.5.4 Rationale for Adding First-Line NSCLC Cohort 59
3.5.5 Rationale for Additional Efficacy Expansion Cohorts 61
3.6 Rationale for Expanding Inclusion Criteria for Gastric / GEJ Cohort 64
3.7 Summary of the Overall Benefit and Risk 64
4 Trial Objectives 67
5 Investigational Plan 68
5.1 Overall Trial Design and Plan 68
5.1.1 Overall Design 68

5.1.2 Trial Endpoints 72
5.1.3 Trial Medication Administration and Schedule....73
5.1.4 Avelumab Dose Escalation....74
5.1.5 Planned Number of Subjects 80
5.1.6 Planned Treatment Duration....80
5.1.7 Dose Modification and ADRs Requiring Treatment Discontinuation....81
5.1.8 Analysis Cut-Off Dates....82
5.2 Discussion of Trial Design 83
5.2.1 Inclusion of Special Populations 84
5.3 Selection of Trial Population....84
5.3.1 Inclusion Criteria 84
5.3.2 Exclusion Criteria (applicable to all subjects, including all expansion cohorts)....89
5.4 Criteria for Initiation of Treatment with the Investigational Medicinal Product....90
5.5 Criteria for Subject Withdrawal....91
5.5.1 Withdrawal From the Trial 91
5.5.2 Withdrawal From the Investigational Medicinal Product 91
5.6 Premature Discontinuation of the Trial 92
5.7 Definition of End of Trial 92
6 Investigational Medicinal Product and Other Drugs Used in the Trial....92
6.1 Description of Investigational Medicinal Product(s)....93
6.2 Dosage and Administration 93
6.3 Assignment to Treatment Cohorts....94
6.4 Other Drugs to be Used in the Trial....94
6.5 Concomitant Medications and Therapies 95
6.5.1 Permitted Medicines and Therapies....95
6.5.2 Non-Permitted Medicines and Therapies 95
6.5.3 Other Trial Considerations 96
6.5.4 Special Precautions....96
6.6 Packaging and Labeling....105

6.7 Preparation, Handling and Storage 105
6.8 Investigational Medicinal Product Accountability 106
6.9 Assessment of Investigational Medicinal Product Compliance 107
6.10 Method of Blinding 107
6.11 Emergency Unblinding 108
6.12 Treatment of Overdose 108
6.13 Medical Care of Subjects After End of Trial 108
7 Trial Procedures and Assessments 108
7.1 Schedule of Assessments 108
7.1.1 Screening and Baseline Procedures and Assessments 108
7.1.2 Treatment Period 110
7.1.3 End of Treatment 115
7.1.4 Post-Treatment Safety Follow-Up 116
7.1.5 Blood Consumption for Clinical Assessments 116
7.2 Demographic and Other Baseline Characteristics 117
7.2.1 Demographic Data 117
7.2.2 Diagnosis of Tumor 117
7.2.3 Medical History 117
7.2.4 Vital Signs and Physical Examination 118
7.2.5 CT or MRI Scans for Tumor Assessment at Baseline 118
7.2.6 Cardiac Assessments 118
7.2.7 Clinical Laboratory Tests 119
7.3 Assessment of Efficacy 119
7.4 Assessment of Safety 123
7.4.1 Adverse Events 123
7.4.2 Pregnancy and In Utero Drug Exposure 128
7.4.3 Laboratory Assessments 129
7.4.4 Vital Signs, Physical Examinations, and Other Assessments 131
7.5 Pharmacokinetics 131
7.5.1 Dose Escalation Phase 131
7.5.2 Expansion Phase 132
7.5.3 Body Fluid 133

7.6 Biomarkers and CCI [redacted] 133
7.6.1 Biomarker Investigation in Dose Escalation Cohorts....134
7.6.2 Biomarkers Investigation in Expansion Cohorts 134
CCI [redacted]
7.7 Other Assessments....138
7.7.1 ADA Analysis....138
CCI [redacted]
8 Statistics....138
8.1 Sample Size 138
8.2 Randomization....141
8.3 Endpoints 141
8.3.1 Primary Endpoints 141
8.3.2 Secondary Endpoints 141
8.3.3 Safety Endpoints....142
8.4 Analysis Sets....142
8.5 Description of Statistical Analyses....143
8.5.1 General Considerations....143
8.5.2 Analysis of Primary Endpoints....144
8.5.3 Analysis of Secondary Endpoints....145
8.5.4 Safety Analyses 147
8.6 Interim Analysis....148
9 Ethical and Regulatory Aspects....150
9.1 Responsibilities of the Investigator 150
9.2 Subject Information and Informed Consent 151
9.3 Subject Identification and Privacy....151
9.4 Emergency Medical Support and Subject Card....152
9.5 Clinical Trial Insurance and Compensation to Subjects....152
9.6 Independent Ethics Committee or Institutional Review Board 152
9.7 Health Authorities....153
10 Trial Management....153
10.1 Case Report Form Handling 153
10.2 Source Data and Subject Files 153

10.3 Investigator Site File and Archiving....154
10.4 Monitoring, Quality Assurance and Inspection by Health Authorities....155
10.5 Changes to the Clinical Trial Protocol....155
10.6 Clinical Trial Report and Publication Policy....155
10.6.1 Clinical Trial Report....155
10.6.2 Publication....155
11 References....157
12 Appendices....163
Appendix I Schedule of Assessments....164
Appendix II ECOG Performance Status....180
Appendix III Guidance on Contraception....181
Appendix IV Protocol Amendments and List of Changes....182
Appendix V Signature Pages and Responsible Persons for the Trial....186
Signature Page – Protocol Lead....187
Signature Page – Coordinating Investigator....188
Signature Page – Principal Investigator....189

Table of In-Text Tables

Table 3.1 Most Frequently Reported TEAEs During Dose Expansion (≥ 10% of Subjects)....46
Table 3.2 Most Frequently Reported TEAEs ≥ Grade 3 During Dose Expansion (> 1.5% of Subjects)....47
Table 3.3 Most Frequently Reported Treatment-related TEAEs During Dose Expansion (≥ 5% of Subjects)....48
Table 5.1 Modification of Dose Escalation Based on DLT Observations at Dose Levels Below 10.0 mg/kg....76
Table 6.1 Treatment Modification for Symptoms of Infusion-related Reactions Caused by Avelumab....98
Table 6.2 Management of Immune-Related Adverse Events....101
Table 7.1 Overall Responses Derived from Changes in Index, Non-Index, and New Lesions....122
Table 7.2 Required Laboratory Panel Tests....130
Table 8.1 95% Confidence Intervals of Estimated Response Rates....140

Table 8.2 Probability of Observing a Response Rate of Less Than 5% in Interim Analysis....149

Table of In-Text Figures

Figure 5.1 Schematic of Trial Design 72
Figure 5.2 Dose Escalation Algorithm for Doses up to 10 mg/kg 75
Figure 5.3 Dose Escalation Algorithm for 15 and 20 mg/kg 78
Figure 6.1 Assessment and Initial Management of Tumor Lysis Syndrome (TLS)....100

List of Abbreviations

5-FU	5-fluorouracil
ACC	adrenocortical carcinomas
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
$AUC_{0-\infty}$	area under the curve from the time of dosing extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from the time of dosing to the time of the last observation
AUC_{tau}	area under the concentration-time curve
β-HCG	β-human chorionic gonadotropin
BOR	best overall response
bpm	beats per minute
BSC	best supportive care

CA-125	cancer antigen 125
CI	confidence interval
C_{max}	maximum plasma concentration observed post-dose
C_{min}	trough concentration
CNS	central nervous system
CPT	Cell Preparation Tube™
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DQA	Development Quality Assurance
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISPOT	enzyme-linked immunosorbent spot
EMA	European Medicines Agency
FACS	fluorescence-activated cell sorter

FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics
FOLFOX	Oxaliplatin, 5-FU, and folinic acid
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
H1	histamine H1 receptor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
IASLC	International Association for the Study of Lung Cancer
ICF	Informed Consent Form
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IHC	immunohistochemistry
IMP	Investigational Medicinal Product

irAE	immune-related adverse event
irBOR	immune-related best overall response
irPFS	immune-related progression-free survival
irRC	Immune-Related Response Criteria
IRB	Institutional Review Board
i.v.	intravenous
LDH	lactate dehydrogenase
MBC	metastatic breast cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mIU/mL	milli international units per milliliter
MoA	mechanism of action
MOP	Manual of Operations
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NBF	neutral-buffered formalin
NCI	National Cancer Institute
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OS	overall survival

PAD	pharmacologically active dose
PBL	peripheral blood leukocytes
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD	pharmacodynamic(s)
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
CCI	[redacted]
PK	pharmacokinetic(s)
PR	partial response
QS	quantum satis
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RF	rheumatoid factor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	stable disease
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T4	free thyroxine
t_{max}	time to reach maximum concentration
TEAE	treatment-emergent adverse event

TNM	Tumor Node Metastasis Classification of Malignant Tumors (UICC)
TO	total occupancy
TSH	thyroid-stimulating hormone
TGF	transforming growth factor
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VEGFR-2	vascular endothelial growth factor receptor-2
WBC	white blood cell
λz	terminal elimination rate constant

1 Synopsis

Trial title	A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
Trial number	EMR 100070-001
EudraCT number	2013-002834-19
Sponsor	For all countries except the United States: Merck KGaA, Frankfurter Str. 250, Darmstadt, Germany For sites in the United States: EMD Serono, Inc One Technology Place, Rockland, MA 02730, USA
Phase	I/Ib
IND Number	CCI [redacted]
FDA "covered trial"	Yes
Trial centers/country	Up to 8 enrolling centers for dose escalation and up to approximately 160 enrolling centers for treatment expansion. The trial will be performed in the USA, Asia, and Europe.
Planned trial period (first enrollment-last subject out)	First subject in: Q1, 2013. Last subject out (dose escalation): Q2, 2018. Last subject out (after expansion and follow-up): Q2, 2019.
Trial objectives	**Primary objective** • To assess the safety and tolerability of avelumab and to determine the maximum tolerated dose (MTD) of avelumab in subjects with metastatic or locally advanced solid tumors. • To assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the efficacy expansion cohorts (ovarian cancer, platinum refractory and prior liposomal doxorubicin; urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy; gastric and gastroesophageal junction [GEJ] cancer, third-line; head and neck squamous cell

	carcinoma [HNSCC], platinum ineligible or progressed after at least 1 line of platinum-based therapy). **Secondary objectives** • To characterize the pharmacokinetic (PK) profile of avelumab and to correlate exposure with target occupancy. • To evaluate the immunogenicity of avelumab and to correlate it to exposure and biological activity. • To assess the best overall response (BOR) and progression-free survival time (PFS) according to RECIST 1.1. • To assess the immune-related BOR (irBOR) and immune-related PFS (irPFS) using the modified Immune-Related Response Criteria (irRC), derived from RECIST 1.1. • To assess overall survival time (OS). • To evaluate biological responses to avelumab in blood/ serum. • To evaluate the association between tumor programmed death ligand 1 (PD-L1) expression and BOR. • To characterize changes in soluble factors (e.g., cytokine profiles, soluble programmed death 1 [PD-1] and soluble PD-L1) and immune cell profiling (e.g., natural killer [NK] cells, neutrophils, lymphocytes). **Exploratory objectives (efficacy expansion cohort only)** • CCI [redacted]
Trial design and plan	This is a Phase I, open-label, dose-escalation trial with consecutive parallel group expansion in non-small cell lung cancer (NSCLC), gastric and GEJ cancer, metastatic breast cancer (MBC), colorectal cancer (CRC), castrate-resistant prostate cancer (CRPC), melanoma, ovarian cancer, HNSCC, adrenocortical carcinoma (ACC), mesothelioma, and urothelial carcinoma. Subjects in the 10mg/kg once weekly cohort, NSCLC (post platinum doublet), CRC and CRPC cohorts will be enrolled in the USA only. **Dose escalation phase** Cohorts of 3 subjects with metastatic or locally advanced solid tumors will receive avelumab at escalating dose levels. At each dose level, subjects will receive avelumab intravenously as a 1-hour intravenous infusion once every

	2 weeks until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or the investigational medicinal product (IMP) occurs (see Section 5.5). An additional cohort of 6 subjects will receive avelumab once weekly at a dose of 10 mg/kg for 12 consecutive weeks (10 mg/kg once weekly cohort) and then once every 2 weeks thereafter (this cohort will not be subject to DLT as a primary endpoint and will not be subject to SMC review after the first 3 subjects). Subjects 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. Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Appendix I). **Dose escalation (3+3 design) will be performed at the following dose levels** • 1.0 mg/kg, once every 2 weeks • 3.0 mg/kg, once every 2 weeks • 10.0 mg/kg, once every 2 weeks Once 1 subject has experienced dose-limiting toxicity (DLT) at a dose below 10.0 mg/kg, dose escalation will be reduced as described in Section 5.1.4.2. The first subject of each cohort should be observed for 16 days (i.e., 48 hours after the second dose) for the occurrence of DLT before the second subject is administered the trial medication. Thereafter, within each cohort of the dose escalation phase, subjects may only be consecutively dosed with an interval of at least 48 hours. However, after 3 subjects have been treated at 10 mg/kg and no DLT has been observed, the other 3 subjects required to complete this cohort can be enrolled without sequential dosing (i.e., not required to wait until 48 hours). If no more than 1 DLT has been observed in these 6 subjects, the safety of 10 mg/kg will have been established. Each subject will stay on the dose level assigned at trial entry (only adaptations for weight changes are needed as described in Section 5.1.7.1). The decision to escalate to the next dose level will be based on safety assessments after all subjects of a cohort have

	reached Day 21 (DLT evaluation period). In order to assess the safety of avelumab, a safety monitoring committee (SMC), responsible for dose escalation decisions, will be established. Once the MTD (see Section 5.1.4.2) or maximum dose to be investigated is reached, the respective dose level cohort will be filled to a total of 6 subjects. Once the dose of 10 mg/kg is established as safe, 10 additional subjects at 3 mg/kg and 10 mg/kg each may be enrolled, for the purpose of generating additional safety, PK and receptor occupancy data, if agreed with the SMC. Once 6 subjects treated at 10 mg/kg have completed the DLT observation period and the safety of 10 mg/kg is established, a dose level of 15 mg/kg (if 1 DLT was observed) or 20 mg/kg (if no DLT was observed) dosing every 2 weeks will be initiated. In this 20 mg/kg dose level, the safety, PK, receptor occupancy, and PD activity of the IMP will be evaluated using the methodology that was used for the other cohorts. Accrual in these dose levels will be completed using a "3+3" method, the same methodology that was used for the completion of the previous dose levels. Once the safety of the 15 and/or 20 mg dose level has been established (i.e., no more than 1 DLT out of 6 subjects treated), up to 15 additional subjects will be enrolled at 15 or 20 mg/kg without sequential dosing (i.e., not required to wait until 48 hours between 2 subjects). This additional cohort will have the purpose of generating safety data, PK data and receptor occupancy data at a dose of the respective dose. With the safety of the 10 mg/kg and 20 mg/kg once every 2 weeks established, a new cohort of 10 mg/kg administered once weekly is being initiated in 6 evaluable subjects to assess safety of a more frequent dosing at 10 mg/kg every week for 12 weeks followed by 10 mg/kg every 2 weeks. Subjects in this cohort of 6 evaluable subjects will receive avelumab at 10 mg/kg once weekly for the first 12 weeks. Starting Week 13, dosing with 10 mg/kg will be once every 2 weeks. Subjects in this cohort will be enrolled in selected sites in the USA only. **Definition of DLT** With some exceptions discussed in Section 5.1.4.2.2, a DLT is defined as a Grade ≥ 3 adverse drug reaction (ADR) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0, occurring in the DLT evaluation period confirmed by the SMC to be relevant for the study drug treatment. Any DLT

	will immediately lead to permanent withdrawal of avelumab. ADRs requiring treatment discontinuation are defined in Section 5.1.7.2. **Expansion phase** After determination of the avelumab dose and regimen for further investigation, enrollment in several expansion cohorts will be opened in selected tumor indications to determine the safety and clinical activity of avelumab. Subject eligibility will need to be confirmed by the contract research organization (CRO) / Sponsor before the first administration of the study drug during the expansion phase. Based on data generated in the dose escalation phase, the dose of avelumab to be used in the expansion phase was determined to be 10 mg/kg. In addition, with the emergence of promising efficacy data, expansion cohorts have been expanded and divided into: • 4 primary cohorts (N=150 subjects each) of: 1. NSCLC, post platinum doublet; 2. NSCLC, first-line, does not carry an epidermal growth factor receptor (EGFR) activating mutation or anaplastic lymphoma kinase (ALK) re-arrangements (non-squamous cell histologies require testing if status is unknown); 3. Gastric and GEJ junction cancer; and 4. MBC. • 8 secondary cohorts: 1. CRC (N=20), 2. CRPC (N=20), 3. ACC (N=50), 4. Melanoma (N=50), 5. Mesothelioma (N=50), 6. Urothelial carcinoma (N=50; note: enrollment is being stopped [N=44] due to the opening of a urothelial efficacy expansion cohort), 7. Ovarian cancer (N=120), and 8. Renal cell carcinoma (RCC), second-line, (N=20 with expansion of 60 first-line). • 4 efficacy expansion cohorts with the primary objective to assess BOR according to RECIST 1.1: 1. Ovarian cancer, platinum refractory, prior liposomal doxorubicin (N=100);

	2. Urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy (N=200); 3. Gastric and GEJ cancer, third line (N=150); 4. HNSCC, platinum ineligible or progressed after at least 1 line of platinum-based therapy (N=150); Subjects in the NSCLC (post platinum doublet), CRC, and CRPC cohorts will be enrolled in the USA only. During enrollment of the expansion part, the SMC will monitor all safety information of the participating subjects on an ongoing basis (i.e., when 40, 120, 200, 290, 380, 480, 600, 740, 900, 1080, and 1300 subjects have been enrolled and treated for at least 4 weeks and on a quarterly basis thereafter until end of enrolment). The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the trial. For subjects enrolled in the efficacy expansion cohorts and the secondary urothelial carcinoma cohort, an 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. Subjects will receive avelumab intravenously as a 1-hour infusion once every 2 weeks until confirmed progression, unacceptable toxicity, or any reason for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a confirmed 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. Subjects who experienced a CR and have already stopped can resume treatment with avelumab at the same dose and schedule. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Appendix I). For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy.

	Prior to re-initiation of the study treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments. In the case of study termination, subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).
Planned number of subjects	Dose escalation phase: 18 up to 66 subjects. Expansion phase: Up to approximately 1640 subjects. The final sample size, however, may vary, depending on the total number of dose levels to be tested, subject replacement for DLT evaluation if applicable, and the number of expanded cohorts.
Schedule of visits and assessments for dose escalation cohorts	**Washout (Day -28 to first treatment)/Screening/ Baseline Assessments (Day -18 to first treatment)** Screening will include the informed consent, recording of the demographic information, the complete medical history, and baseline medical condition; a complete physical examination including vital signs, body weight, and height, 12-lead electrocardiogram (ECG) and a determination of the Eastern Cooperative Oncology Group (ECOG) performance status; AE and concomitant medication assessments; safety laboratory assessments; the tumor evaluation by computed tomography (CT) scan or magnetic resonance imaging (MRI) as well as tumor markers; tumor tissue (biopsy or surgical specimen prepared as blocks or slides [optional]); bone scan (as clinically indicated); serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of child bearing potential; blood hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) testing. Adrenocorticotropic hormone, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, free thyroxine, and thyroid-stimulating hormone will also be assessed at screening. Following completion of the above screening assessments, baseline samples for human anti-drug antibody (ADA),

	CCI [redacted] assessments will be collected prior to the first administration of avelumab, i.e., either during the screening period or pre-dose on Day 1. **Treatment phase** Visits will take place on Days 1, 2, 3, 15, 29, 43, and every 2 weeks thereafter. For the 10 mg/kg once weekly cohort only, visits will take place every week up to and including Week 12 and then every 2 weeks thereafter starting at Week 13. Safety (including AEs and concomitant medications, laboratory values, ECOG performance status, physical examinations, vital signs, and 12-lead ECGs), PK, immunogenicity, and tumor response assessments will be conducted as outlined in Appendix I. The schedule of the biological response assessment comprising immunomonitoring on tumor biopsies and blood, measurement of soluble factors, and tumor tissue evaluation are displayed in Appendix I. **Discontinuation visit, end-of-treatment visit, safety follow-up visit, and survival follow-up** All subjects who discontinue trial treatment prematurely for an AE should have a full safety evaluation at the time of discontinuation of trial treatment (discontinuation visit). The discontinuation visit will consist of documentation of AEs and concomitant medication, physical examination (including vital signs and body weight), 12-lead ECG, laboratory evaluations (hematology, hemostaseology, full serum chemistry, and full urinalysis) and ECOG performance status. In addition, all subjects will have an end-of-treatment visit scheduled 4 weeks after the last administration of avelumab. The end-of-treatment visit is scheduled 4 weeks after the last administration of avelumab but before any new therapy is started, if possible. The visit will comprise a full assessment of safety parameters, immunogenicity assessment, and tumor response assessment as appropriate. **Post-treatment Follow-up** All subjects will have a subsequent visit scheduled 10 weeks after the last administration of avelumab. The visit will include a full assessment of safety parameters. Adverse events will be documented until the end of treatment visit. After the end of treatment visit only

	treatment related AEs have to be documented until the post-treatment safety follow-up visit. Subjects with a serious AE ongoing at the post-treatment 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". Subjects without progressive disease at the end-of-treatment visit will be followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year. In addition, subjects will be followed for any AE suspected to be related to trial treatment, especially for the occurrence of new autoimmune events up to 3 months after the last dose of avelumab. After the end-of-treatment visit, subjects will be followed quarterly for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab.
Schedule of visits and assessments for expansion cohorts	**Washout (Day -28 to first treatment)/Screening/ Baseline Assessments (Day -18 to first treatment)** Subjects in all expansion cohorts will be enrolled after the dose and regimen of avelumab has been determined. Visits will be conducted every 2 weeks and the main assessments are the same as those for dose escalation cohorts with the following exceptions: • Subjects with liver metastases at baseline will have visits every week, up to Week 7. • PK samples will be collected prior to each IMP administration in all subjects in the expansion phase. In addition, expanded PK sampling will be collected in all expansion subjects in the CRC and CRPC secondary cohorts (20 subjects in each). For subjects in the first-line NSCLC cohort, samples for PK analysis will be collected within 2 hours prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, 99, and 169. Post-study drug administration samples will also be collected at the end of the infusion and also 2 to 8 hours after the end of infusion (later is better depending on how long the subject will stay in the clinic), on Days 1, 43, 85, and 169. Samples will also be collected at the 10-week safety follow-up visit. For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, samples for PK determination will be collected prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, and 169. Post-study drug administration

	samples will be collected at the end of infusion and 2 to 8 hours after the end of infusion (later is better, depending on how long the subject will stay in the clinic) at Days 1, 43, 85, and 169. Exact sampling times will be recorded. Samples will be collected at the 10-week Safety Follow-up visit. • Samples for ADA analysis will be collected before start of infusion on Days 1, 15, 29, 43, 57, 71, 85 (every 2 weeks) and on Days 127, and 169 (every 6 weeks), and at the end-of-treatment visit. • Immunomonitoring samples will be collected before start of infusion on Days 1, 15, 43, 85 and at the end-of-treatment visit in all subjects enrolled in secondary expansion cohorts, except for the RCC cohort. In addition a sample may be collected at Day 3, but is optional. • Soluble factors samples will be collected for all subjects in the primary and secondary expansion cohorts, except for the RCC cohort, before start of first infusion (Day 1), Day 43, and at the end-of-treatment visit. In addition, except for the RCC cohort, subjects in the secondary expansion cohorts will have samples collected on Day 3 (optional). For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, CCI [redacted] • For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, blood samples for CCI [redacted] profiling will be collected before the start of infusion on Days 1, 15, 29, and 43 and the end-of-treatment visit. • Samples will be collected for receptor occupancy in the CRC and CRPC cohorts only. • For subjects in the HNSCC cohort only, human papillomavirus status should be determined. • Collection of tumor tissue (the most recent biopsy or surgical specimen provided as block or slides) is required for all subjects. o For subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration.

	○ For subjects in the melanoma and mesothelioma cohorts only, if an optional fresh biopsy is obtained prior to the first dose of trial treatment, archival tumor material is not required. Fresh biopsies may also be collected on Day 43 and at the end-of-treatment visit. These biopsies are optional. ○ For subjects in the efficacy expansion cohorts and the first-line NSCLC primary expansion cohort, fresh biopsies may also be collected on Days 43 and at the end-of-treatment visit. These biopsies are optional.
Diagnosis and inclusion and exclusion criteria	**Inclusion criteria for dose escalation, including the 10 mg/kg once weekly cohort:** 1. Signed written informed consent. 2. Male or female subjects aged ≥ 18 years. 3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no standard therapy exists or standard therapy has failed. Availability of tumor archival material or fresh biopsies is optional for subjects in dose escalation. 4. ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months. 5. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1, except for subjects with metastatic CRPC or MBC who may be enrolled with objective evidence of disease without a measureable lesion. 6. Adequate hematological function defined by white blood cell (WBC) count ≥ 3 × 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). For subjects with gastric cancer only, the acceptable parameters for WBC, ANC, and lymphocytes are as follows: WBC ≥ 2 × 10^9/L, ANC ≥ 1.0 × 10^9/L, and lymphocyte count ≥ 0.5 × 10^9/L. 7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal range (ULN), an aspartate aminotransferase (AST), level ≤ 2.5 × ULN, and an alanine aminotransferase (ALT) level ≤ 2.5 × ULN or, for subjects with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN.

	8. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula. 9. **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.) **Inclusion criteria for expansion phase:** 1. Signed written informed consent. 2. Male or female subjects aged ≥ 18 years. 3. Subjects must have relapsed, refractory, or progressive disease following last line of treatment (with the exception of the NSCLC first-line and gastric and GEJ cancer primary cohorts, which do not require progression). Availability of tumor archival material or fresh biopsies (excluding bone biopsies) is mandatory for eligibility in the expansion cohorts. For subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration. Specifically, the following will be required: **Primary expansion cohorts** o **NSCLC post platinum doublet:** Histologically or cytologically confirmed stage IIIB or stage IV NSCLC that has progressed after 1 line of platinum-containing doublet chemotherapy. Subjects should have received only 1 line of platinum-containing treatment for metastatic disease (i.e., adjuvant treatment with a platinum-containing regimen is not sufficient for eligibility because not received in the context of a metastatic disease). Subjects in the NSCLC cohort will only be enrolled in the USA.

	○ **NSCLC first line:** Stage IV (per 7th International Association for the Study of Lung Cancer [IASLC] classification) or recurrent NSCLC that is histologically proven. Subjects must not have received treatment for their metastatic or recurrent disease. No activating EGFR mutation nor ALK translocation / re-arrangement (non-squamous cell histologies require testing if status is unknown). ○ **Gastric and GEJ cancer**: Histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the gastric and GEJ, treated with first-line chemotherapy combination in metastatic setting with or without disease progression. Subjects should have received no more than 1 line of treatment for metastatic disease. Subjects should not have been treated with trastuzumab (but can be Human Epidermal growth factor Receptor 2 [HER2] positive). Subjects who received any platinum containing doublet or triplet as a neoadjuvant chemotherapy strategy, but are not ultimately candidates for surgery will also be eligible. In addition, subjects with gastric cancer can enter in the study if their WBC is $\geq 2 \times 10^9$/L with ANC $\geq 1.0 \times 10^9$/L and lymphocyte count $\geq 0.5 \times 10^9$/L. ○ **MBC**: Subjects must have histologically confirmed locally advanced or MBC and have tumor that is refractory to or progressive after standard of care therapy. Subjects must have received no more than 3 prior lines of cytotoxic therapy for metastatic disease. Subjects must have received a taxane and an anthracycline, unless contra-indicated. **Secondary expansion cohorts** ○ **CRC**: Histologically or cytologically confirmed recurrent or refractory metastatic CRC (according to AJCC/UICC TNM Staging System seventh edition) after failure of prior therapy containing oxaliplatin/ fluoropyrimidine and/or irinotecan/ fluoropyrimidine and, if eligible, cetuximab (Erbitux®) and bevacizumab (Avastin®). These subjects will be enrolled in sites located in the USA only. ○ **CRPC**: Histologically or cytologically confirmed asymptomatic or minimally symptomatic metastatic CRPC (according to AJCC/UICC TNM Staging System seventh edition) with objective evidence of

	disease (non measureable or measurable lesion) with stable, ongoing adequate testosterone suppression proven by castrate levels of testosterone (≤ 50 ng/dL), except for subjects with prior orchiectomy. Minimally symptomatic is defined as patients who do not require consistent treatment with opiates over the last month (less than 7 days of opiates in the last 28 days, and no opiates administered 3 days in a row), for the treatment of their prostate cancer. Additional androgen blockade or treatment with an anti-androgen receptor is acceptable. These subjects will be enrolled in sites located in the USA only. ○ **Melanoma**: Histologically or cytologically confirmed stage IIIc or IV unresectable melanoma, (according to AJCC/UICC TNM Staging System seventh edition) after failure of at least 1 prior standard therapy for metastatic disease. All subjects with metastatic melanoma will be required to undergo screening with a MRI or CT scan (either, with contrast preferred) to rule out brain metastases, unless imaging has previously been performed within 28 days prior to screening. ○ **Ovarian cancer**: Histologically or cytologically confirmed recurrent or refractory (progression within 6 months of platinum-based therapy or progression after subsequent therapy in previously relapsed subjects), stage III-IV epithelial ovarian, fallopian tube or peritoneal cancer subjects (according to AJCC/UICC TNM and International Federation of Gynecology and Obstetrics (FIGO) Staging System seventh edition) who have progressed following adjuvant therapy or therapy for metastatic disease. ○ **ACC:** Histologically or cytologically confirmed metastatic ACC. Subjects must have previously received at least 1 line of systemic therapy for metastatic disease, of which at least 1 must be platinum-based. Subjects receiving mitotane may continue to receive mitotane at enrolment and on study. ○ **Mesothelioma:** Histologically or cytologically confirmed mesothelioma (pleural or peritoneal) with unresectable disease. Subjects must have received and progressed after either a platinum-pemetrexed

	containing regimen or a platinum-containing regimen followed by pemetrexed (or vice versa) after disease progression. Subjects must present with at least 1 measurable lesion that has not been irradiated. ○ **Urothelial carcinoma:** Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra). A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Subjects can be either: ineligible for cisplatin-based chemotherapy or have progressed after treatment with at least one platinum-containing regimen (e.g., platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade ≥ 2 peripheral neuropathy. ○ **Renal cell carcinoma, second-line with first-line expansion:** Histologically or cytologically documented RCC with a component of clear cell subtype, with metastasis. A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Eligible subjects must have measureable disease. Subjects must have failed 1 prior systemic first-line regimen for metastatic RCC (except for subjects enrolled in first-line expansion). **Efficacy expansion cohorts:** ○ **Gastric and GEJ cancer, third line:** Histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the gastric and GEJ, treated with both a first-line chemotherapy combination and followed by ramucirumab (alone or in combination). Subjects must have progressed during or after ramucirumab therapy. Subjects with gastric cancer can enter into the study if their WBC is $\geq 2 \times 10^9$/L with ANC $\geq 1.0 \times 10^9$/L and lymphocyte count $\geq 0.5 \times 10^9$/L. ○ **Ovarian cancer, platinum refractory and prior liposomal doxorubicin:** Histologically or cytologically confirmed, platinum-refractory (progression within 6 months of platinum-based

	therapy), Stage III-IV epithelial ovarian, fallopian tube, or peritoneal cancer subjects (according to AJCC/UICC TNM and FIGO Staging System, 7th edition). Subjects must have received at least 1 line of prior platinum-based chemotherapy regimen, as well as prior liposomal doxorubicin (monotherapy or combination), in order to be considered eligible for this study. Subjects may have received any additional number of prior systemic therapies for metastatic disease. ○ **Urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy:** Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra). A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Subjects can be either: ineligible for cisplatin based chemotherapy or have progressed after treatment with at least 1 platinum-containing regimen (e.g., platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade ≥ 2 peripheral neuropathy. Subjects may have received any number of prior systemic therapies for metastatic disease. ○ **Head and neck, platinum ineligible or progressed after at least 1 line of platinum-based therapy:** Histologically or cytologically documented recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx. Subjects must have experienced tumor progression or recurrence within 6 months of the last dose of any number of platinum-based chemotherapy regimens given in the adjuvant, primary, recurrent, or metastatic setting. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade ≥ 2 peripheral neuropathy. A tumor sample (1 tumor block or at

	least 7 unstained slides) must be available. Subjects may have received any number of prior systemic therapies for metastatic disease. Except for subjects who are platinum ineligible, subjects must have received at least 1 line of platinum-based chemotherapy. 4. ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months. 5. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1, except for subjects with metastatic CRPC who may be enrolled with objective evidence of disease without a measureable lesion. 6. Adequate hematological function defined by WBC $\geq 3 \times 10^9$/L with 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). For subjects with gastric cancer only the acceptable parameters for WBC, ANC, and lymphocytes are as follows: WBC $\geq 2 \times 10^9$/L, ANC $\geq 1.0 \times 10^9$/L, and lymphocyte count $\geq 0.5 \times 10^9$/L. 7. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ ULN and an AST level $\leq 2.5 \times$ ULN and an ALT level $\leq 2.5 \times$ ULN for all subjects. 8. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula or measured 24-hour creatinine clearance (or local institutional standard method). 9. **Highly** effective contraception for both male and female subjects if the risk of conception exists. (See Section 5.3.1 for additional details.) **Exclusion criteria (applicable to all subjects, including all expansion cohorts):** 1. Concurrent treatment with a non-permitted drug (see Section 6.5.2). 2. Prior therapy with any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody. For subjects with metastatic melanoma, prior treatment with a CTLA-4 antibody is not an exclusion. 3. Concurrent anticancer treatment within 28 days before the start of trial treatment (e.g., cytoreductive therapy,

	radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin); major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy); use of hormonal agents within 7 days before the start of trial treatment, except for subjects in the CRPC cohort who may remain on treatment with luteinizing hormone-releasing hormone agonists or antagonists; or use of any investigational drug within 28 days before the start of trial treatment. Subjects in the gastric and GEJ cohort who have not progressed on first-line chemotherapy may be enrolled within the 28-day period following prior treatment provided all toxicity from prior therapy has resolved to Grade ≤ 1. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the study treatment (with the exception of patients with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily). Steroids with no or minimal systemic effect (topical, inhalation) are allowed. 4. Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ. 5. Rapidly progressive disease (e.g., tumor lysis syndrome). 6. Active or history of central nervous system (CNS) metastases. 7. Receipt of any organ transplantation including allogeneic stem-cell transplantation. 8. Significant acute or chronic infections including, among others: • Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive). 9. Active or history of any autoimmune disease (subjects with diabetes Type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive

	treatment are eligible) or immunodeficiencies. 10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.0), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of partly controlled asthma). 11. Persisting toxicity related to prior therapy Grade > 1 NCI-CTCAE v4.0, however sensory neuropathy ≤ Grade 2 is acceptable. 12. Pregnancy or breast feeding. 13. Known alcohol or drug abuse. 14. Clinically significant (i.e., 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. 15. All other significant diseases (e.g., inflammatory bowel disease), which, in the opinion of the investigator, might impair the subject's tolerance of trial treatment. 16. Any psychiatric condition that would prohibit the understanding or rendering of informed consent. 17. Legal incapacity or limited legal capacity. 18. Vaccination within 4 weeks of the first dose of avelumab and while on study is prohibited except for administration of inactivated vaccines (e.g. inactivated influenza vaccines).
Investigational Medicinal Product: dose/mode of administration/ dosing schedule	Avelumab will be administered as a 1-hour (-10 minutes / +20 minutes, i.e., 50-80 minutes) intravenous (i.v.) infusion. Subjects will receive avelumab once every 2 weeks until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). For the 10 mg/kg once weekly cohort only, subjects will receive avelumab once weekly for 12 consecutive weeks and then starting at Week 13, once every 2 weeks thereafter. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

	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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate. Immediate access to intensive care unit or equivalent environment and appropriate medical therapy (including i.v. 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 anaphylactic reactions (according to NCI-CTCAE v4.0). Following avelumab infusions, subjects must be observed for 2 hours post infusion for potential infusion-related reactions. Relevant clinical laboratory results essential for patient management decisions (hematology, biochemistry, liver function tests) must be available and reviewed before administration of avelumab.
Reference therapy: dose/mode of administration/dosing schedule	Not applicable.
Planned treatment duration per subject	The planned treatment duration is until unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs. Subjects who have experienced a confirmed 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. Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to

	the protocol and the "until progression" schedule in the Schedule of Assessments.
Primary endpoints	Occurrence of DLTs during the first 3 weeks of treatment in the dose escalation part (excluding 10 mg/kg once weekly cohort). The confirmed BOR, per RECIST 1.1, as adjudicated by an Independent Endpoint Review Committee (IERC) for subjects enrolled in the efficacy expansion cohorts only.

Secondary endpoints	• Number, severity, and duration of treatment-emergent adverse events (TEAEs) for all dose groups / indications according to the NCI-CTCAE v4.0.
	• Number, severity, and duration of treatment-related AEs according to NCI-CTCAE v4.0.
	• PK profile.
	• irBOR and BOR according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
	• The confirmed BOR, per RECIST 1.1, as adjudicated by an IERC, for subjects enrolled in the secondary urothelial carcinoma cohort.
	• irPFS time and PFS time according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
	• OS time.
	• Pharmacodynamic (PD) profile
	• Serum titers of ADAs.
	• Expression of PD-L1 on tumor tissue.
	• For the primary expansion cohorts only: Unconfirmed response at Week 13 according to RECIST 1.1.
	• Duration of response according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
	• For the efficacy expansion cohorts only:
	  ○ PFS time, according to RECIST 1.1, per IERC
	  ○ Duration of response according to RECIST 1.1, per IERC.

Pharmacokinetics/Receptor occupancy	PK parameters are described in Section 7.5. Receptor occupancy (Pharmacodynamics): avelumab binding to PD-L1 molecules on circulating peripheral blood leukocytes (PBLs) will be investigated by flow cytometry on serially collected blood samples as described in Section 7.6.1.1.

Biomarkers CCI [redacted]	**In the dose escalation part,** biological activities such as circulating cellular markers monitoring (e.g., lymphocyte, NK cells activation and regulatory markers by flow cytometry), soluble factors (e.g., cytokines profile, soluble PD-1, soluble PD-L1), predictive biomarker candidates (i.e., level of PD-L1 tumor expression), and optionally mechanisms related to antibody-dependent cell-mediated cytotoxicity (ADCC) (e.g., in vitro ADCC assay) and cellular composition of tumor microenvironment will be investigated on blood and plasma / serum samples as described in Section 7.6.1.2. **In the expansion part (including efficacy expansion cohorts),** a similar immunomonitoring approach (e.g., cellular and soluble markers monitoring and optional intratumoral cellular monitoring) to the escalation part will be considered as follow-up in all subjects in the secondary expansion cohorts. Additional analyses such as antigen specific immune responses (e.g., enzyme-linked immunosorbent spot, profile of tumor infiltrated cells, intra-tumoral immune response profiling) may be investigated as retrospective analyses according to indication. For the RCC secondary cohort, the primary cohorts, and the efficacy expansion cohorts, immunomonitoring will be limited to soluble factors analyses. Predictive biomarker candidates will be investigated in all indications (for example, level of PD-L1 tumor expression). CCI [redacted]
Statistical methods (includes sample size calculation)	The total sample size at the end of the trial (based on the dose escalation part and all expansion cohorts) is expected to be approximately 1706 treated subjects. The dose escalation part of the trial follows a well established current methodology (3 + 3 cohort design) of dose-finding studies in oncology. The sample size of 150 for expansion in the primary cohorts (NSCLC [first-line and post platinum doublet cohorts], gastric and GEJ cancer, and MBC) and 2 efficacy expansion cohorts (gastric and GEJ cancer [third-line] and HNSCC) has been chosen based on knowledge that PD-L1 is clinically active in NSCLC and that PD-L1 is also expressed in MBC, gastric cancer, and HNSCC microenvironment. Published data have linked the expression of PD-L1 by

	tumor cells and clinical activity of agents blocking the PD-1 / PD-L1 pathway. Enrollment of 150 subjects will allow for a robust assessment of safety and efficacy endpoints in these indications, including a precise determination of response rates. In addition, data from these cohorts will be used to investigate the association between the pattern of expression of membrane PD-L1 and clinical response to PD-L1 blockade, and to determine whether accrual in future studies should be restricted based on PD-L1 expression status. The sample size of 20 for each of the 4 original secondary expansion cohorts (CRC, CRPC, ovarian, and melanoma) was chosen primarily to further explore the safety and efficacy of avelumab in specific indications and to provide preliminary data to aid in future study design. Following completion of dose escalation in this trial and in the broader context of ongoing research with PD-L1 inhibition, it is considered appropriate to add 4 new secondary cohorts (ACC, mesothelioma, urothelial carcinoma, and RCC) to the expansion phase of this trial and to increase subject enrollment in 2 of the initial secondary cohorts (melanoma and ovarian cancer). The primary endpoint of the efficacy expansion cohorts is the confirmed BOR according to RECIST 1.1, as adjudicated by an IERC. For each of these cohorts, the primary analysis will aim to reject the null hypothesis of an ORR ≤10% by means of an exact binomial test at the 1-sided alpha level of 0.025. Analyses are considered positive if the lower limit of the 95% confidence interval of the confirmed BOR exceed 10%. Confidence intervals will be constructed using the Clopper-Pearson method. For the gastric, ovarian, and head and neck cancer cohorts, the primary analysis is planned 6 months after start of treatment of the last subject in the given cohort. Interim analyses will be conducted after 60% of the subjects in the given cohort have been followed up for 13 weeks. The sample size of 150 (or 100) in these efficacy expansion cohorts will provide approximately 91% (or 80%) power under an assumed response rate of 20% to reject the null hypothesis of a response rate ≤10% at a 1-sided significance level of 0.025. For the urothelial carcinoma efficacy expansion cohort, the primary analysis of confirmed BOR will be performed in subjects with PD-L1 positive tumors followed by all treated subjects. Interim analyses will be conducted for the 109 subjects enrolled in the urothelial carcinoma efficacy

	expansion cohort prior to Protocol Amendment 13. Subjects will be considered PD-L1 positive (negative) if at least (less than) 5% of the tumor cells show PD-L1 membrane staining, respectively. If during assay development (based on generic samples) a different cut-off is determined to be more appropriate, this cut-off may be adapted in the SAP prior to analysis of subject samples from this trial. Descriptive statistics and graphical representations will be the main analysis tools. For all analyses, results and graphical representation of data will be presented by dose level (cohort) / expansion cohorts. An interim analysis of response will be conducted in each of the primary expansion cohorts after the first 75 subjects have reached the time point of their second post-baseline tumor assessment scheduled in Week 13, i.e., 13 weeks after start of treatment of the 75th subject. In the NSCLC (post platinum doublet) cohort only, 2 additional interim analyses of efficacy will be conducted, 13 weeks after the start of treatment of the 60th and the last subject, respectively. In the first-line NSCLC primary expansion cohort, an interim analysis of response will be conducted 13 weeks after start of treatment of the 30th subject. For each primary or secondary expansion cohort, an additional interim analysis may be conducted 13 weeks after the start of treatment of the last subject in that cohort. In the secondary cohorts that plan to enroll more than 20 subjects, i.e., the ACC, melanoma, mesothelioma, ovarian cancer, and urothelial carcinoma cohorts, an interim analysis of response will be performed 13 weeks after the start of treatment of the 20th subject. Accrual in each cohort may be paused during the interim analysis. If no unconfirmed response according to RECIST 1.1 is observed in a given cohort in the interim analysis, accrual in that cohort will be stopped. In addition, for the ovarian cancer secondary expansion cohort, an interim analysis of response will be performed for internal planning purposes 13 weeks after the start of treatment of the 75th subject. In the efficacy expansion cohorts, interim analyses for efficacy are planned 13 weeks after the start of treatment of the 30th subject in all cohorts, 13 weeks after start of treatment of the 60th subject in the ovarian cohort, and 13 weeks after start of treatment of the 90th subject in the gastric / GEJ and HNSCC cohorts. No futility rule is

	foreseen because the clinical activity of anti-PD-1 / anti-PD-L1 agents in these tumor types is established, and the patient populations are characterized by a high unmet medical need. If efficacy criteria are met at the second interim analysis, enrollment will continue to the planned full number of subjects in order to collect further data on the primary and secondary endpoints, especially on the association between PD-L1 expression and efficacy endpoints. Statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. The results of the safety evaluations will be tabulated and displayed by dose level/expansion cohorts. With the exception of the hypothesis test for the ORR in the efficacy expansion cohorts, only exploratory statistical analysis will be performed. Descriptive statistics will be examined for indications of dose-related toxicity. Listings will be produced upon completion of each dose escalation cohort of subjects and the decision as to whether to proceed with dose-escalation, dose-reduction or to enroll another cohort at the same dose level will be determined by reviewing these data. Full details of the planned analyses will be described in the trial statistical analysis plan, separately for the dose escalation and the expansion part.

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with avelumab is EMD Serono Inc, Rockland, MA, in the 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 in up to 8 enrolling centers in the USA for the dose escalation part of the trial and up to approximately 160 enrolling centers for the treatment expansion part of the trial (approximately 100 of which are anticipated to be in the USA). The trial will be performed in the USA, Asia, 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 Clinical Trial Supplies department of the Sponsor will supply the trial medication of avelumab, which will be distributed to the sites by the CRO.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetic (PK), pharmacodynamic (PD), CCI and CCI assessments will be performed under the responsibility 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 (DQA) Department, Merck KGaA, Darmstadt, Germany.

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

2.2.1 Safety Monitoring Committee

To ensure subjects' safety during the escalation part as well as the expansion part, a safety monitoring committee (SMC) will review the safety data on a regular basis. The SMC consists of permanent members from the Sponsor and/or CRO (Early clinical development lead, medical lead, biostatistician [in the expansion part], global drug safety representative), the coordinating investigator, and external experts with expertise in the management of cancer patients. During the

escalation part, the SMC will evaluate the safety data and will decide on dose-limiting toxicities (DLTs) relevant for the treatment and will advise on dose escalation or suspension of enrollment, with the final adjudication being a Sponsor prerogative. In 10 mg/kg once weekly cohort the SMC will evaluate overall safety data when all 6 subjects have completed minimum 4 week-treatment period, and after 12 weeks of observation have been completed for all subjects enrolled in this cohort. During the enrollment phase of the expansion part, the SMC will monitor on an ongoing basis (i.e., when 40, 120, 200, 290, 380, 480, 600, 740, 900, 1080, and 1300 subjects have been enrolled and treated for at least 4 weeks and on a quarterly basis thereafter until end of enrolment), all safety information of the participating subjects and will decide by consensus on continuation, modification, or suspension of the trial or of a particular expansion cohort. The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the trial. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

2.2.2 Central Reader and Independent Endpoint Review Committee

A central facility will read and interpret all radiographic scans for subjects enrolled in the efficacy expansion cohorts and the secondary urothelial carcinoma cohort. The data for all images will be transferred from trial sites to the central reading center for evaluation. Scans will be evaluated at the central facility in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The imaging data will be transferred to the Sponsor or designee at regular intervals. A manual from the vendor will be provided to each trial site.

For subjects enrolled in the efficacy expansion cohorts and the secondary urothelial carcinoma cohort, 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 IERC will be composed of a minimum of 3 members, including 1 oncologist. The role of the IERC will be to review radiographic image findings and physical findings for the determination of the time point overall response and date of disease progression according to RECIST 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 Investigational Medicinal Product

The investigational medicinal product (IMP) for the present trial is avelumab (MSB0010718C), a fully human monoclonal antibody of the IgG1 isotype. This anti-PD-L1 therapeutic antibody concept is intended to be developed in oncological settings by Merck KGaA, Darmstadt, Germany and by its affiliate EMD Serono Inc, Rockland MA, USA.

Avelumab drug product is a sterile liquid formulation intended for intravenous injection (i.v.). It is presented at a concentration of 10 mg/mL (process A formulation) and 20 mg/mL (process B formulation) in vials of nominal volume of 8 and 10 mL, respectively (see Section 6.1 and the latest Investigator's Brochure for additional details).

The drug product is presented in type 1 glass vials closed with a rubber stopper and sealed with an aluminum / yellow polypropylene flip off seal. Both of the primary packaging materials are of European Pharmacopeia and United States Pharmacopeia quality.

3.2 Non-Clinical Findings for Avelumab

3.2.1 In vitro and in vivo Pharmacology Findings

Programmed death ligand 1 (PD-L1) is a transmembrane protein that was first identified for its role in the maintenance of self-tolerance and prevention of autoimmunity (1). Engagement of PD-L1 on dendritic cells with the programmed death 1 (PD-1) receptor on T cells delivers an inhibitory signal that promotes T cell anergy or apoptosis (2). This immunoinhibitory checkpoint is often subverted by tumor cells that over-express PD-L1 in order to escape immunosurveillance in the tumor microenvironment. Indeed, there is a strong correlation between PD-L1 expression and prognosis in cancer. Blockade of the interaction between PD-L1 on tumor cells and PD-1 on T cells is expected to reverse T cell suppression within tumors, thereby promoting effective anti-tumor immune responses.

Several antibodies directed against the PD-L1 / PD-1 pathway are in clinical development for cancer treatment (3). Compared with anti-PD-1 antibodies that target T-cells, anti-PD-L1 antibodies that target tumor cells are expected to have less 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 (4). To this end, a fully human IgG1 anti-PD-L1 antibody (avelumab; drug code MSB0010718C) has been produced. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Furthermore, this antibody is cross-reactive with murine PD-L1, thus allowing in vivo pharmacology studies to be conducted in normal laboratory mice. However, due to immunogenicity directed against the fully human avelumab molecule, the dosing regimen was limited to 3 doses given within a week. The key preclinical pharmacology findings for avelumab are summarized below.

- Functional enhancement of primary T cell activation in vitro in response to antigen-specific and antigen non-specific stimuli.
- Significant inhibition of in vivo tumor growth (PD-L1 expressing MC38 colon carcinoma) as a monotherapy.
- In vivo efficacy is driven by $CD8^+$ T cells, as evidenced by complete abrogation of anti-tumor activity when this cell type was systemically depleted.
- Combination with localized, fractionated radiotherapy resulted in complete regression of established tumors with generation of anti-tumor immune memory.
- Chemotherapy combinations also showed promising activity:
  - Additive combination effect when partnered with oxaliplatin and 5-fluorouracil (5-FU) (core components of FOLFOX [oxaliplatin, 5-FU, and folinic acid]) against MC38 colon tumors.
  - Significant increase in survival when partnered with gemcitabine against PANC02 pancreatic tumors.

- Antibody-dependent cell-mediated cytotoxicity (ADCC) was demonstrated against human tumor cells in vitro; furthermore, studies in ADCC deficient settings in vivo support a contribution of ADCC to anti-tumor efficacy.
- No complement-dependent cytotoxicity was observed in vitro.
- Immunomonitoring assays with translational relevance for the clinic further support an immunological mechanism of action:
  - Consistent increases in $CD8^+PD\text{-}1^+$ T cells and $CD8^+$ effector memory T cells as measured by fluorescence-activated cell sorter (FACS).
  - Enhanced tumor-antigen specific $CD8^+$ T cell responses as measured by pentamer staining and enzyme-linked immunosorbent spot (ELISPOT) assays.

3.2.2 Toxicology

The toxicological profile of avelumab was investigated in vivo in mice, rats, and cynomolgus monkeys. In addition, in vitro cytokine release assays in human and cynomolgus whole blood and peripheral blood mononuclear cells (PBMCs) as well as a tissue cross reactivity study in normal human and cynomolgus monkey tissues (experimental part ongoing) were initiated. Repeat-dose toxicity studies with 4-week duration were performed in mice, rats, and cynomolgus monkeys, receiving a once weekly i.v. bolus injection / infusion. An additional pivotal and good laboratory practice (GLP)-compliant repeat-dose toxicity study with intermittent once weekly i.v. infusion (1.5 hours) over 13 weeks followed by an 8-week recovery period was performed in cynomolgus monkeys and included the investigation of safety pharmacologically relevant parameters (electrocardiogram [ECG], arterial blood pressure measurement, central nervous system [CNS] evaluation, respiratory frequency), TK, and immunogenicity (study RF4990, preliminary data).

The available results are summarized as follows:

In a pilot 4-week repeat-dose i.v. toxicity study in Wistar rats, avelumab was tested at dose levels of 20, 40, and 140 mg/kg. Avelumab was systemically and locally tolerated up to 140 mg/kg in rats. However, based on the binding affinity data (see Investigator's Brochure for avelumab, Version 2, February 2014), the rat is not considered to be an appropriate rodent species for non-clinical safety testing.

In the pilot 4-week repeat-dose i.v. toxicity study in CD-1 mice, mortalities occurred at all dose levels, i.e., 20, 40, and 140 mg/kg, within 30 minutes after treatment, mainly after the third administration. Overall, the maximum tolerated dose (MTD) could not be established in this study since mortality was observed at all dose levels. The observed clinical symptoms as well as the histopathological findings (vascular immune complex deposition) are considered to be indicative of hypersensitivity reactions in mice.

A second 4-week repeat-dose i.v. toxicity study in CD-1 mice at a dose level of 20 mg/kg confirmed the hypersensitivity reactions including the clinical findings and the mortality observed in the initial study. Results from an additional study in CD-1 mice suggest that the observed mortality after few repeated treatments with avelumab was due to an immune-mediated

hypersensitivity reaction in this species, the mechanism of which is highly likely to be anaphylaxis (immunoglobulin E [IgE] / immunoglobulin G [IgG] mediated reaction).

In primates (cynomolgus monkeys), neither in the pilot 4-week i.v. repeat-dose toxicity study nor in the pivotal 13-week i.v. infusion repeat-dose toxicity study followed by an 8-week recovery period, clinical signs of hypersensitivity have been seen at the tested dose levels of 20, 60, and 140 mg/kg, respectively. In both studies, avelumab induced, locally at the injection sites, an increased severity in subcutaneous fibroplasia and mononuclear cell infiltrates without dose dependency. In the pivotal 13-week i.v. infusion repeat-dose toxicity study an increase in the hyalinization of the germinal centers of the spleen was observed in a few animals of the 60 and 140 mg/kg dose groups compared to the control group, with this finding being of unclear toxicological significance. All histological changes were completely reversible after an 8-week treatment-free period. In the pilot 4-week as well as in the pivotal 13-week i.v. repeat-dose toxicity study a no observed adverse effect level (NOAEL) of 140 mg/kg was established for systemic toxicity.

The cytokine release assays in male and female whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines.

As only limited information on potential effects of avelumab on the reproductive and developmental system is available, it is mandatory that women of child-bearing potential apply effective contraception during therapy with avelumab and 8 weeks thereafter. Pregnant women must not be included into the trial. No data on the transfer of avelumab into milk is available; thus lactating women should be excluded.

3.3 Pharmacokinetics / Immunogenicity Findings

Preliminary PK assessments have been collected and analyzed in the current ongoing EMR100070-001 trial. The preliminary results based on the data available as of 19 December 2014 are presented under the individual trial headings.

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 57 Caucasian subjects treated in the dose escalation and expansion cohort of the Phase I Trial 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 post-dose (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 2 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 3.7 µg/mL after the first dose, 3.9 µg/mL after the second dose and 8.3 µg/mL after the third dose (n=7 to 12), though some trough values below 1 µg/mL were observed, as well as antidrug antibodies in at least 1 subject in this dose group on Day 85 of the treatment period, accompanied by loss of quantifiable exposure. Median trough concentrations after the 20 mg/kg dose were 44, 70, and 77 µg/mL after the first, second, and third dose, respectively (n=14 to 19).

For the 10 mg/kg dose, the 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).

3.4 Safety

The available safety data for current EMR100070-001 trial are summarized below based on the safety data cut-off date, 05 November 2014. In addition to subjects treated during dose escalation, a total of 480 subjects were enrolled during the dose expansion (NSCLC: 184; metastatic breast cancer: 169; gastric cancer: 47; colorectal cancer: 22; castrate-resistant prostate cancer: 11; ovarian cancer: 37, melanoma: 5; mesothelioma: 1; adrenocortical carcinoma: 1; and urothelial carcinoma: 3), treated with the recommended dose of 10 mg/kg avelumab once every 2 weeks and followed up for at least 4 weeks up to the cut-off date. Further information about the events described below is available in the latest version of the Investigator's Brochure.

All Treatment-emergent Adverse Events

For all subjects treated during the dose expansion, the most frequently affected System Organ Classes (with an incidence > 30%) were general disorders and administration site conditions (59.6%), gastrointestinal disorders (57.3%), respiratory, thoracic and mediastinal disorders (39.8%), musculoskeletal and connective tissue disorders (38.8%), and metabolic and nutrition disorders (32.3%).

Table 3.1, shows the most frequently reported treatment-emergent adverse events (TEAEs) observed in ≥ 10% of subjects during the dose expansion portion of the trial.

Table 3.1 Most Frequently Reported TEAEs During Dose Expansion (≥ 10% of Subjects)

Treatment-emergent Adverse Events[a] Preferred Term (MedDRA)	Subjects (Safety Population, N = 480) N (%)
Fatigue	148 (30.8)
Nausea	127 (26.5)
Vomiting	78 (16.3)
Diarrhoea	70 (14.6)
Constipation	69 (14.4)
Decreased appetite	68 (14.2)
Cough	65 (13.5)
Anaemia	61 (12.7)
Dyspnoea	57 (11.9)
Back pain	52 (10.8)
Dyspnoea exertional	52 (10.8)
Pyrexia	50 (10.4)
Arthralgia	49 (10.2)

MedDRA = Medical Dictionary for Regulatory Activities.
a Only treatment-emergent adverse events started during the on-treatment period are summarized.

TEAEs Grade ≥ 3

Of the 480 subjects treated during dose expansion, 218 (45.4%) experienced at least 1 TEAE that was National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3. Of these, 148 (30.8%), 30 (6.3%), and 40 (8.3%) were Grade 3, Grade 4, and Grade 5 TEAEs, respectively. Of the Grade ≥ 3 TEAEs, the most frequent was dyspnea, reported in 28 subjects (5.8%), followed by anemia reported in 25 subjects (5.2%), disease progression reported in 17 subjects (3.5%), pneumonia reported in 12 subjects (2.5%), hyponatremia and pleural effusion each reported in 10 subjects (2.1%), aspartate aminotransferase increased and back pain each reported in 9 subjects (1.9%), respiratory failure reported in 8 subjects (1.7%); and abdominal pain, arthralgia, gamma-glutamyltransferase (GGT) increased, hyperglycemia, non-cardiac chest pain, and vomiting were each reported in 7 subjects (1.5%; Table 3.2). All of the other Grade ≥ 3 TEAEs were observed in less than 1.5% of subjects.

Table 3.2 Most Frequently Reported TEAEs ≥ Grade 3 During Dose Expansion (> 1.5% of Subjects)

Treatment-emergent Adverse Events[a] Preferred Term (MedDRA)	Subjects (Safety Population, N = 480) N (%)
Dyspnea	28 (5.8)
Anaemia	25 (5.2)
Disease progression	17 (3.5)
Pneumonia	12 (2.5)
Hyponatraemia	10 (2.1)
Pleural effusion	10 (2.1)
Aspartate aminotransferase increased	9 (1.9)
Back pain	9 (1.9)
Respiratory failure	8 (1.7)
Abdominal pain	7 (1.5)
Arthralgia	7 (1.5)
Gamma glutamyltransferase increased	7 (1.5)
Hyperglycaemia	7 (1.5)
Non-cardiac chest pain	7 (1.5)
Vomiting	7 (1.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE – treatment-emergent adverse event.
a Only treatment-emergent adverse events started during the on-treatment period are summarized.

Treatment-related TEAEs

Treatment-related TEAEs occurred in 330 of 480 subjects (68.8%) during the dose expansion, of which 59 (12.3%) were reported as Grade ≥ 3 treatment-related TEAEs. As shown in Table 3.3, the most frequently observed treatment-related TEAE (incidence ≥ 5%) was fatigue (20.2%), followed by nausea (12.9%), infusion-related reaction (9.8%), chills (6.9%), diarrhea (6.9%), decreased appetite (6.3%), pyrexia (5.6%), influenza like illness (5.2%), and arthralgia (5.0%).

Table 3.3 Most Frequently Reported Treatment-related TEAEs During Dose Expansion (≥ 5% of Subjects)

Treatment-emergent Adverse Events[a] Preferred Term (MedDRA)	Subjects (Safety Population, N = 480) N (%)
Fatigue	97 (20.2%)
Nausea	62 (12.9%)
Infusion-related reaction	47 (9.8%)
Chills	33 (6.9%)
Diarrhoea	33 (6.9%)
Decreased appetite	30 (6.3%)
Pyrexia	27 (5.6%)
Influenza like illness	25 (5.2%)
Arthralgia	24 (5.0%)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE – treatment-emergent adverse event.
a Only treatment-emergent adverse events started during the on-treatment period are summarized.

Treatment-related TEAEs Grade ≥ 3

Of the Grade ≥ 3 treatment-related TEAEs (59 subjects; 12.3%), the following occurred in more than 2 subjects: fatigue (5 subjects, 1.0%), anemia (5 subjects, 1.0%), infusion-related reaction, lipase increased, and GGT increased (each in 4 subjects, 0.8%).

Of the 59 subjects who had Grade ≥ 3 treatment-related TEAEs, 44 (9.2%) had Grade 3 treatment-related TEAEs, 11 (2.3%) had Grade 4 treatment-related TEAEs, and 4 (0.8%) had Grade 5 treatment-related TEAEs. One Grade 3 event of encephalopathy (Subject 101-0032), which was initially considered as posterior reversible encephalopathy syndrome, was assessed as related to trial medication with an alternative explanation of hypertension.

Serious Adverse Events

Overall, 176 of the 480 subjects (36.7%) treated during the dose expansion had serious TEAEs. Of these, 22 (4.6%) subjects reported dyspnea, which was the most frequent serious TEAE in this group, followed by 19 subjects (4.0%) reporting disease progression, 12 subjects (2.5%) reporting pleural effusion, 11 subjects (2.3%) reporting pneumonia, and 7 subjects (1.5%) reporting anemia. All other serious TEAEs were each reported in less than 1.5% of subjects.

Of the serious TEAEs considered treatment-related by the investigator (31 subjects; 6.5%), the following were reported for 2 or more subjects: infusion-related reaction (4 subjects, 0.8%), pneumonitis (3 subjects, 0.6%), and disease progression, dyspnea, and hypercalcemia (each in 2 subjects, 0.4%).

Deaths

In total, 134 subjects (27.9%) treated during the dose expansion died up to the cut-off date (05 November 2014). Of these, the majority of deaths (101 deaths; 21.0%) were due to disease progression. An additional 8 deaths (1.7%) were due to TEAEs unrelated to trial treatment, 4 deaths (0.8%) were due to TEAEs related to trial treatment, and the reason for 8 deaths (1.7%) was labeled as other. The reason for 13 deaths (2.7%) was unknown at the time of the data cut-off. Of the 134 subjects who died, 53 subjects (11.0%) died within 30 days of the last administration of trial treatment. Among these deaths, 39 (8.1%) were due to disease progression, 7 (1.5%) were due to TEAEs unrelated to trial treatment, 4 (0.8%) were due to TEAEs related to trial treatment, and 3 (0.6%) were due to other reasons. No death of unknown reason was reported in the 30-day period.

Treatment-emergent AEs Leading to Permanent Discontinuation of Avelumab

A total of 80 subjects (16.7%) treated during the dose expansion withdrew permanently from trial treatment due to 1 or more TEAE. In 25 (6.6%) of these subjects, the TEAEs leading to treatment discontinuation were considered related to trial treatment by the investigator. These TEAEs were infusion-related reaction (6 withdrawals; 1.6%), GGT increased (3 withdrawals, 0.8%), dyspnea (3 withdrawals; 0.8%), and radiation pneumonitis, aspartate aminotransferase (AST) increased, hepatocellular injury, blood creatine phosphokinase increased, blood pressure increased, pneumonitis, anaphylactic reaction, food allergy, adrenal insufficiency, anemia, hypercalcemia, hyperglycemia, arthralgia, arthritis, myositis, pain, abdominal pain lower, chest discomfort, cramps and ache on back and all over body (not yet coded), encephalopathy, syncope, and flushing (1 withdrawal each; 0.3%).

Most of the events of infusion-related reaction and anaphylactic reaction that led to permanent discontinuation of trial treatment (as described above) occurred before implementation of mandatory premedication on 28 January 2014.

Immune-related Adverse Events

As of 05 November 2014, a cumulative review revealed 56 cases of potential immune-related AEs out of 480 subjects (11.7%) treated in the dose expansion part of trial EMR 100070-001 and 4 cases out of 50 subjects (8.0%) treated in the dose escalation part of trial EMR 100070-001. A customized Medical Dictionary for Regulatory Activities (MedDRA) query was used for data retrieval from the clinical database with predefined Preferred Terms of potential immune-related AEs (irAEs).

Of 69 potential irAEs reported, 13 were SAEs (18.8%) and 56 were non-serious AEs (81.1%). In the majority of the cases, there was a plausible temporal association between the event onset and the drug administration. Of these 69 events, 46 events (66.7%) were assessed as treatment-related by the investigator and 23 events (33.3%) were assessed as not treatment-related by the investigator.

Twenty-six events were assessed as Grade 1, 29 events as Grade 2, 11 events as Grade 3, 2 events as Grade 4, and 1 event (pneumonitis) as Grade 5 (Please note: 2 more events of autoimmune

hepatitis had a fatal outcome; however, they were assessed as Grade 3 with a consequent fatal liver failure).

Based on the irAE cases that have been observed, all trial investigators have been trained to be made aware of the frequency and severity of the observed events and to proactively administer steroid treatment for any suspicion of irAEs. Of note, irAEs are considered as an identified risk by the Sponsor.

Infusion-related Reactions

Two suspected unexpected serious adverse reactions (SUSARs; anaphylactic reaction and infusion-related reaction) involving 2 subjects were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions / hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions / hypersensitivity have been classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of histamine H1 receptor (H1) blockers plus acetaminophen was implemented for all trial subjects as of 28 January 2014.

As of 05 November 2014, 49 (10.2%) of the 480 subjects in the expansion cohort experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 subjects, 1.7%) or Grade 2 (36 subjects, 7.5%) in intensity, and Grade 3 (3 subjects, 0.6%) or Grade 4 events (2 subjects, 0.4%) were less frequent. No Grade 5 events were reported. Most of the infusion-related reaction events had an onset after the first (30 subjects, 6.3%) or second (16 subjects, 3.3%) avelumab infusion. In 8 subjects (1.7%), avelumab treatment was discontinued because of infusion-related reaction events.

In addition, 1 subject (2.0%) in the dose escalation cohort reported an infusion-related reaction event (Grade 2).

In addition to the aforementioned 49 subjects, 1 case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The subject died due to an anoxic brain injury 7 days later; no autopsy was performed.

Starting from 29 January 2014, the Sponsor has implemented a mandatory premedication with H1 blockers plus acetaminophen for all subjects who are to receive avelumab. This premedication procedure was applied to 28 and 440 subjects in the dose escalation and the pooled treatment expansion cohort, respectively. Under this premedication procedure, 33 of 440 subjects (7.5%) in the expansion cohort experienced infusion-related reaction events, with 6 subjects (1.4%) having Grade 1, 26 subjects (5.9%) having Grade 2, and 1 subject (0.2%) having Grade 3 events. No infusion-related reaction events were reported in the 28 subjects in the dose escalation cohort.

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) and can be found at https://www.resus.org.uk/pages/reaction.pdf.

Laboratory Abnormalities

Preliminary data relating to laboratory abnormalities observed during dose expansion (cut-off 05 November 2014) are summarized below. Interpretation of these data should reflect the fact that for approximately 40% of subjects laboratory data were unavailable at the time of the safety data cut-off.

Hematology

Various hematology abnormalities were reported in up to approximately 60% of subjects, however, Grade 3 or 4 abnormalities were usually much less frequent. In all subjects treated during dose expansion, the most frequent Grade 3 or 4 abnormality was lymphocyte count decreased, which occurred in 55 subjects (11.5%), all of which were Grade 3. Other less frequent Grade 3 or 4 abnormalities included anemia (all Grade 3) in 25 subjects (5.2%), platelet count decreased in 14 subjects (2.9%), neutrophil count decreased and white blood cell count decreased each in 5 subjects (1.0%).

Blood Chemistry

A considerable proportion of subjects (up to over 60% for some measurements) in the dose expansion cohort experienced abnormalities of blood chemistry; however, most of these abnormalities were mild (Grade 1 or 2). Grade 3 or 4 blood chemistry abnormalities occurred less frequently. The following Grade 3 or 4 abnormalities were observed in > 5% of subjects: GGT increased, which was reported in 87 subjects (18.1%) treated in the dose expansion phase, hyponatremia (32 subjects, 6.7%), and AST increased (30 subjects, 6.3%).

Vital Signs and Body Weight

Data relating to vital signs and body weight observed during dose expansion (cut-off 05 November 2014) are summarized below. Abnormalities of vital signs were defined as:

- Systolic blood pressure (SBP): SBP $\leq$ 95 mmHg as well as a decrease from baseline $\geq$ 20 mmHg, or SBP $\geq$ 160 mmHg as well as an increase from baseline $\geq$ 20 mmHg
- Diastolic blood pressure (DBP): DBP $\leq$ 45 mmHg as well as a decrease from baseline $\geq$ 10 mmHg or DBP $\geq$ 110 mmHg as well as an increase from baseline $\geq$ 10 mmHg
- Pulse rate: $\leq$ 50 beats per minute (bpm) as well as a decrease from baseline $\geq$ 20 bpm or pulse rate $\geq$ 120 bpm as well as an increase from baseline $\geq$ 20 bpm
- Body weight: increase or decrease in body weight from baseline $\geq$ 10%.

A small fraction of all subjects experienced vital sign abnormalities as defined above during trial treatment, with pulse rate $\geq$ 120 bpm and increase from baseline $\geq$ 20 bpm (41 subjects, 8.5%) representing the most notable change.

3.4.1 Clinical Pharmacodynamics

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

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

Based on the observed avelumab serum concentrations in the EMR100070-001 Phase I clinical trial and the in vitro receptor occupancy data, trough concentrations were sufficient to achieve full target occupancy throughout the entire dosing interval in all of the subjects receiving the 10 mg/kg dose. 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 2 weeks was selected as the dose for further investigation in the Phase Ib expansion cohorts and for the subsequent clinical studies.

3.5 Rationale for the Clinical Trial

The administration of avelumab to subjects with advanced malignancies for which no approved / established treatment option exist is justified by the following:

- Avelumab is capable of inhibiting tumor growth in vivo when applied as a monotherapy and its efficacy can be further enhanced via combination with standard-of-care therapies, though the treatment was limited for only 3 doses in the first weeks due to immunogenicity of the humanized antibody in mice.
- The relevance of PD-L1 blockade has been demonstrated in Phase I studies performed with antibodies targeting either PD-L1 or PD-1. One Phase I trial has been reported for BMS-936559 targeting PD-L1 (5). At the time of data cut-off, a total of 160 subjects could be evaluated for clinical efficacy, which was demonstrated in the range of 1-10 mg/kg. Objective clinical responses up to > 1 year were observed in 9 out of 52 subjects with melanoma, 5 out of 49 subjects with non-small cell lung cancer (NSCLC), 2 out of 17 subjects with renal cell carcinoma, and 1 out of 17 subjects with ovarian cancer. No response could be observed in 7 subjects with pancreatic cancer and 18 subjects with colorectal cancer (CRC). Overall, these results are suggestive of relevant clinical efficacy through inhibition of PD-L1, which is further

supported by reported clinical efficacy of the anti-PD-1 monoclonal antibodies, BMS-936558 and CT-011 (6,7).

The starting dose of 1.0 mg/kg has been selected based on the results of 2 complementary approaches reflected in the respective guidelines:

- Data from the pivotal 13-week i.v. infusion repeat-dose toxicity study in cynomolgus monkeys revealed a NOAEL of 140 mg/kg for systemic toxicity. Applying the algorithm given in the Food and Drug Administration (FDA) guideline on "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" this would imply a “Maximum Recommended Starting Dose” of approximately 4.5 mg/kg.
- The International Conference for Harmonization (ICH) guideline S9 (8) states that the primary goal of selecting the clinical start dose is to administer a pharmacologically active dose (PAD) that is reasonably safe to use. This PAD approach is also recommended by the FDA guideline on "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (9). The lowest PAD level can be estimated from xenograft tumor models and from posology of clinical surrogates. The PAD approach for the proposed avelumab first-in-man study is based on the finding that PD-L1 antagonism resulted in tumor growth inhibition for example in a MC38 colorectal syngeneic mouse model, and on the assumption that anti-neoplastic activity is a function of target occupancy. In the MC38 xenograft tumor model, avelumab demonstrated biological activity at doses of 400 µg per mouse i.v., observed 7 to 10 days after the third dose. The regimen was restricted to 3 administrations due to lethal anaphylaxis resulting from the administration of a humanized antibody to mice. Based on these data and our PK model, a human dose of 10 mg/kg would allow a serum concentration above the assumed minimum required trough concentration of 50 µg/mL for a period of approximately 2 weeks. An initial dose of 1 mg/kg is 10-fold lower than this dose, conservatively acknowledging the model´s limitations. In order to supplement and improve the PAD approach for initial dose estimation and dose escalation, PD-L1 target occupancy was assumed as appropriate surrogate: In principle, 100% saturation is expected to generate maximum efficacy. For BMS-936559, it was demonstrated that early indications of anti-neoplastic activity already occur at trough occupancy levels of 65% as measured on CD3 T cells positive cells within a 2-week cycle (5). Using PK and PD data from mice and monkeys, a 2-compartment model with mixed linear and Michaelis-Menten elimination pathways was employed to predict the human PK and corresponding target occupancy for avelumab. Allometric scaled human simulation aiming for at least 95% target occupancy supports the dosing of once every 2 weeks at a human dose level of approximately 7 mg/kg, while the proposed initial dose of 1.0 mg/kg is expected to result in at least 50% target occupancy, which may be sufficient to induce beneficial clinical effects.

The dose escalation scheme was designed based on the following:

- Three dose levels, i.e., 1, 3, and 10 mg/kg, are expected to be sufficient for evaluation of the safety, PK profile, and early indications of efficacy. The PK and extent of target binding will be closely monitored during the dose escalation phase of the clinical study (PD-L1 saturation on T cells as function of exposure).

The dose rationale for the avelumab first-in-man study is supported by the excellent clinical safety profile of BMS-936559 (5). Although it is acknowledged that avelumab and BMS-936559 are different with respect to some features like isotype, terminal half-life, and capability to induce effector functions, they are similar regarding specificity and mode of action. Non-clinical safety evaluation of BMS-936559 (5) resulted in the first-in-man study NCT00729664, the design of which is highly comparable to the concept presented here. Our strategy is further supported by positive safety results from a number of Phase I clinical studies with anti-PD-1 monoclonal antibody BMS-936558, which shares some crucial aspects of the mechanism of action (MoA) with avelumab and MDX-1105 (6,10).

3.5.1 Rationale for 10 mg/kg Once Weekly Dose-Escalation Cohort

With the completion of the dose expansion phase of the study, completion of the safety and PK analysis for the dose-escalation phase, and preliminary safety and PK from the expansion phase (EMR100070-001 interim CSR 2016), a decision has been made to add a cohort of 6 evaluable patients who will be treated with avelumab 10 mg/kg once weekly to this trial. This cohort (N=6) is being added to the dose-escalation phase of the study to provide preliminary PK and safety data with this regimen. This regimen is planned to be further explored in a first-line NSCLC Phase III study; therefore, the preliminary analyses described below are more detailed for this cohort. Subjects in this cohort will receive avelumab at 10 mg/kg once weekly for the first 12 weeks followed by 10 mg/kg once every 2 weeks starting at Week 13. This decision is based on the following:

- An exposure-efficacy response relationship was observed in NSCLC subjects treated with 10 mg/kg once every 2 weeks, based on preliminary analysis. For the first-line NSCLC cohort (n=156), a relationship between steady state trough concentrations and best overall response (BOR) was observed and supported by logistic regression (univariate analysis; p=0.0001): the response rate was higher in subjects with higher PK exposure (approximately 5, 10, 23, and 36% objective response rate in 1st, 2nd, 3rd, and 4th exposure quartile, respectively) regardless of PD-L1 expression. Similarly, for progression-free survival (PFS) and overall survival (OS) endpoints in NSCLC subjects, an exposure-efficacy relationship was suggested by Cox models, though high uncertainty exists in these analyses.
- Population PK analysis and simulation showed that a 10 mg/kg once every week regimen may increase the exposure, such that more than 90% of the subjects dosed with 10 mg/kg once every week will have predicted steady state trough concentrations higher than the observed lower bound of the 4th exposure quartile for the 10 mg/kg once every 2 weeks. Specifically, the median steady state trough concentration is predicted to increase from 22.9 µg/mL (range: 4.2-74.5 µg/mL) in the once every 2 weeks regimen to 83.3 µg/mL (range: 28.6-204 µg/mL) in the once weekly regimen (data on file), potentially enhancing efficacy as suggested by the preliminary exposure-efficacy analyses.
- A significant exposure-efficacy relationship was also observed for the second-line NSCLC cohort of subjects (p=0.005 for BOR correlation with steady state trough concentrations), based on preliminary analysis.

- Similar trends for higher response rates in subjects with higher exposure were observed in urothelial cancer and gastric cancer cohorts, though not significant due to the low number of responders in these data sets.
- Kaplan-Meier plots for preliminary PFS and OS data separated by exposure quartiles showed trends of prolonged PFS and OS for subjects in the higher exposure quartiles based on steady state trough concentration, compared with subjects with lower exposure, for the following cohorts: post-platinum doublet NSCLC, first-line NSCLC, urothelial cancer - secondary and efficacy cohorts, gastric cancer - second-line and switch-maintenance cohorts, metastatic breast cancer, ovarian cancer, mesothelioma, malignant melanoma.
- In both first-line and post-platinum doublet NSCLC cohorts, a trend of higher ORR was observed with increasing PD-L1 expression cut-offs (1, 5, 50, and 80% of cells stained) in subjects in the upper half of the exposure range, but not in subjects in the lower half of the exposure range, suggesting that predictivity of PD-L1 status improves at higher exposure.

The 12-week duration for avelumab once a week administration, followed by once every 2 weeks starting at Week 13 was selected based on preliminary observations from the first-line NSCLC cohort of this study dosed with 10 mg/kg once every 2 weeks, that suggest:

- Majority of responses occurred within 12 weeks of treatment initiation, and
- Majority of responses appeared to be durable.

It is not expected that the exposure at 10 mg/kg once every week for the first 12 weeks would substantially impact the manageable safety profile currently observed with 10 mg/kg once every 2 weeks dosing:

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

In summary, the dosing regimen of 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks starting at Week 13 is supported by the exposure-efficacy relationship, time-to-response analyses, and an acceptable benefit-risk profile, as described above. This regimen may also allow the evaluation of clinical outcomes in subjects with higher exposure and high expression of PD-L1 in subsequent studies with avelumab.

3.5.2 Rationale for Expansion Cohorts

The indications for the initial expansion cohorts have been selected based on several factors:

- PD-L1 over-expression in tumors.
- Clinical activity demonstrated for PD-1 / PD-L1 blocking monoclonal antibodies in solid tumors in the case of NSCLC.
- Unmet medical need.
- Evidence for susceptibility to cancer immunotherapy.

Over-expression of PD-L1 has been described for NSCLC, metastatic breast cancer (MBC), CRC, castrate-resistant prostate cancer (CRPC), melanoma, renal cell carcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma (HNSCC), ovarian, breast, pancreatic, gastro-esophageal and bladder urothelial carcinomas as well as glioblastoma multiforme and certain type of hematopoietic malignancies (11-25).

Recently, the expression of PD-L1 in immune infiltrating cells of gastric cancer micro-environment has been demonstrated (internal data produced by the Sponsor's Biomarker group).

Blockade of PD-L1 led to objective clinical responses in NSCLC, melanoma, and ovarian cancer (5), while blockade of its counterpart PD-1 led to objective clinical responses in NSCLC and melanoma (6). A limited number of subjects with CRC or CRPC, which do not allow to drawing final conclusions on the potential clinical activity of PD-1 / PD-L1 checkpoint inhibitors in these indications, have been treated up to date. However, it should be noted that avelumab is an IgG1 isotype based antibody that potentially exerts ADCC, which differentiates it from the other therapeutic antibodies already being explored for their use in solid tumors (5,6) but lacking such effector functions.

In general, the anti-tumor immunotherapy via blockade of the PD-1 / PD-L1 axis seems not to be limited to any specific tumor types, but there is recent evidence that PD-L1 tumor expression is a pre-requisite to achieve an objective response upon blockade of the PD-1 / PD-L1 axis (6). Seven tumor types, i.e., NSCLC, gastric and gastroesophageal junction (GEJ) cancer, MBC, CRC, CRPC, melanoma, and ovarian cancer, for which a high medical need and evidence for susceptibility to cancer immunotherapy is given, were selected to be explored in the expansion phase of this trial.

3.5.3 Rationale for New Expansion Cohorts / Expanding Initial Expansion Secondary Cohorts

The expansion phase of the trial provides for further exploration of signals in 4 new secondary cohorts and in the expanded melanoma and ovarian cancer secondary cohorts. The rationale is provided below.

Melanoma: The clinical activity of PD-1/PD-L1 blockade in metastatic melanoma has been clearly established (26,27). It is therefore considered appropriate to expand the sample size of the

metastatic melanoma cohort from 20 to 50 subjects in order to obtain more precise estimates of response rate for avelumab and to evaluate its association with PD-L1 expression in this indication.

Ovarian cancer: Initial data from the ovarian cancer expansion cohort include unconfirmed partial responses (PRs). By expanding the cohort from 20 to 75 subjects, these preliminary signals can be further evaluated, and a precise evaluation of the response rate and the association of response and PD-L1 expression can be conducted. A further expansion to 120 subjects is necessary for the development of a potential companion diagnostic for PD-L1 expression in ovarian cancer.

Adrenocortical carcinoma (ACC): Although ACC is a rare malignancy, metastases are common, prognosis is poor and available systemic therapies are toxic with limited benefits (28,29). The First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) established that first line standard of care with the combination of mitotane, etoposide, doxorubicin and cisplatin demonstrates a response rate of 23.3%, with a progression-free survival of 5.0 months and an OS of 14.8 months (30). However, it is of note that 58% of these patients experienced SAEs. In spite of this trial, mitotane remains the only approved treatment for ACC. Defining effective therapies directed at defined molecular targets has not yet yielded results (28). Although immunotherapy has not been extensively explored there is evidence that inactivation of TLR4 and decreased expression of CD14 may be mediated by immune mechanisms that are not yet fully characterized in this disease (31). There is agreement within the oncology community that the dire nature of advanced ACC warrants more aggressive clinical trial involvement (29).

Mesothelioma: Malignant mesothelioma is an uncommon malignancy, with 2,500 cases per year diagnosed in the USA. For patients with unresectable disease, OS is only around 12 months. First-line chemotherapy with cisplatin and pemetrexed is standard with response rates of 41.3% and median survival 12 months (32). Second-line therapies remain inadequate with OS collectively around 9 months with most of that benefit in patients who could be rechallenged with the standard first line agents (33).

PD-L1 is expressed at the surface of mesothelioma tumor cells. In a series of 224 cases of malignant pleural mesothelioma, PD-L1 expression (defined as more than 5% of tumor cells positive by immunohistochemistry [IHC]) was detected in 89 subjects (40%) (34). When compared with other parameters, there were no significant differences in gender, age, decade of diagnosis, or lymphocytic infiltration between PD-L1 positive and negative subjects. Survival was significantly worse for subjects with PD-L1 expression (6 months median, range 4-9 months) compared to those without PD-L1 expression (14 months median, range 11-16 months; $p<0.0001$). Furthermore, PD-L1 expression remained significantly associated with worse survival after adjusting for age, gender, lymphocytic infiltration, and therapeutic surgical intervention ($p=0.0002$).

In a recently published smaller study, 6 of 8 mesothelioma samples were positive for PD-L1 as well as for tumor infiltrating CD68+ macrophages (35). This pattern of inflammation was remarkable for its similarity to T cell inflamed patterns seen with other tumor types such as melanoma. Checkpoint inhibition with the anti-CTLA4 monoclonal antibody trametinib preliminarily has shown a disease control rate of 31% and a 1-year survival of 48.3% in 21 subjects

who had failed first-line therapy with platinum and pemetrexed (36). An updated analysis continues to show clinical benefit with a median OS of 11.3 months (37).

When considered together, the above data suggest that checkpoint inhibition is an important and underexplored therapeutic strategy in mesothelioma. Thus, there is a strong rationale to evaluate an anti-PD-L1 in subjects with mesothelioma who have progressed after a platinum/pemetrexed containing regimen, particularly as there is no established treatment for the management of mesothelioma patients who have progressed after 1 platinum/pemetrexed containing regimen (38).

Urothelial carcinoma: Metastatic urothelial carcinoma (bladder, ureter, renal pelvis, urethra) is considered a chemosensitive tumor with first-line cisplatin-based regimens achieving response rates of approximately 50% and median survival of around 14 months (39,40). However, complete response (CR) is rare and most patients develop resistant disease. Success with second-line agents has been modest, with response rates ranging from 9-33% and progression-free survival around 3 months (41,42). After failure of platinum therapies effective options are limited.

A growing body of evidence suggests that the acquired cell-mediated immune dysfunction observed in urothelial carcinoma may be related to expression of PD-L1 and PD-1 (43). In one study (43) 12.4% of urothelial tumors expressed PD-L1, which was associated with more advanced stage at cystectomy. PD-1 expression was observed on 95.5% of tumor-infiltrating lymphocytes, which was also correlated with more aggressive pathology and PD-L1 expression. Moreover, for the subset of subjects with organ-confined disease (n=167), B7-H1 expression independently predicted all-cause mortality after cystectomy ($p<0.001$). In their sample of 65 subjects with urothelial cancer, Nakanishi et al (44) showed an association between PD-L1 expression and post-operative recurrence and survival. PD-L1 expression has also been observed to be associated with increasingly aggressive pathology and may contribute to failure of local therapies to prevent local progression and muscle invasion (45). Conversely, in subjects who develop metastatic disease, PD-L1 expression in infiltrating mononuclear cells was significantly associated with longer survival (46).

The first demonstration of activity of anti-PD-L1 antibodies was described by Powles et al (47). In a Phase I study, subjects with urothelial bladder cancer received MPDL3280A (an anti-PD-L1 monoclonal antibody) at a dose 15 mg/kg i.v. q3w for up to 1 year. Overall response rate (ORR) (including unconfirmed responses) was assessed by RECIST v1.1 (48). In parallel, tumor and circulating biomarkers were evaluated to study MPDL3280A immune correlates. Efficacy data on 20 PD-L1+ subjects were reported. Subjects were 84% male, median age was 66 years (42-86 years), 57% were Eastern Cooperative Oncology Group (ECOG) performance status 1 and 68% had visceral metastases. Most of the subjects had received prior platinum-based chemotherapy. Subjects evaluable for efficacy at the time of analysis had a median follow up of 2.8 months (1.4 to 5 months). The ORR was 50% (1 CR and 9 PR) with a median time to response of 43 days (39 to 82 days), corresponding to the first radiographic assessment. Subjects who had visceral metastases at baseline also responded, and all responders were still responding at the time of clinical cut-off.

The treatment of patients with advanced urothelial carcinoma appears to have reached a plateau using cytotoxic chemotherapy regimens. An approach that holds promise is immune modulation by targeting the patient's immune system to generate a response that can control the tumor given

that CD8+ T cell activation and infiltration may be associated with better outcomes (49). The absence of satisfactory therapeutic options after failure of first line platinum-based combinations, the association of PD-L1 expression data with outcomes and now evidence of clinical activity of anti-PD-L1 directed therapy, all support further evaluation of these agents for metastatic urothelial carcinoma.

Further details on the trial design and its rationale are provided in Sections 5.1 and 5.2.

The data obtained from this study will form the basis for the dose and regimen selection for further clinical studies involving avelumab and will also be supportive to provide a basis for combination with standard-of-care therapies to be explored in the future.

Renal Cell Carcinoma: The rationale to add a new cohort of subjects with advanced renal cell carcinoma (RCC; n=20 second-line subjects, with expansion of 60 first-line subjects) is supported by the recent clinical data demonstrating single-agent efficacy with an antibody blocking the PD-1/ PD-L1 pathway in RCC patients whose disease has progressed following vascular endothelial growth factor (VEGF) pathway inhibitor therapy. In particular, nivolumab, a fully human anti-PD-1 monoclonal antibody, has shown durable tumor responses with an ORR of approximately 20% and median PFS of approximately 16 weeks in heavily pretreated advanced RCC patients (50). In addition, MPDL3280A, another human monoclonal antibody that targets PD-L1, has shown an ORR of 13% and stable disease $\geq$ 24 weeks in 32% of patients with pretreated RCC (51). Although preliminary, these data demonstrate the potential clinical activity of an anti-PD-1 or PD-L1 antibody in advanced RCC patients. Data from this cohort will provide essential data on the potential clinical activity of avelumab in advanced RCC, and will help inform future development and clinical trials in RCC.

Enrollment of first-line RCC subjects was opened after 2 documented objective responses among the 20 subjects enrolled in the second-line RCC cohort were observed by RECIST 1.1 (2 PRs), and justified further evaluation in this patient population.

3.5.4 Rationale for Adding First-Line NSCLC Cohort

The rationale to enroll NSCLC subjects who have not received a systemic treatment for their metastatic disease and to administer them avelumab is supported by 2 different sets of data:

- The results coming from a study that used an anti-PD-1 to block the interaction between PD-L1 and PD-1 (52).
- The interim analysis of the first 75 subjects with NSCLC (post platinum doublet) that have been enrolled in the current Phase I study and have being followed up for at least 13 weeks.

Gettinger et al (52) have presented the results of an ad hoc analysis of the safety data from a cohort of chemotherapy-naïve patients with Stage IIIB or IV NSCLC and ECOG performance status 0 or 1 who received nivolumab 3 mg/kg i.v. every 2 weeks until progressive disease or unacceptable toxicity. Efficacy was evaluated using RECIST 1.1 at Week 11, Week 17, Week 23, and every 3 months thereafter until disease progression.

The overall median follow-up time was 66.1 weeks (range 13.3 to 89.1 weeks).

An ORR of 30% was reported; 5 of 6 responders (83%) achieved response by first scan (Week 11). Two patients had > 80% target lesion reduction at 18 weeks. Of 15 evaluable tumor samples, 9 were PD-L1+. The ORR was 67% in PD-L1+ patients; no responses were observed in the 6 PD-L1- patients. The ORR was 36% for patients with NSCLC (4 of 11 patients) and 22% in patients with squamous cell lung cancer (2 of 9 patients). Responses were durable (median duration of response not reached, with 5 ongoing responses).

In terms of safety, a total of 17 patients (85%) experienced any-grade treatment-related AEs. Most patients only reported Grade 1 or 2 AEs (13/17 patients, 76%). Five treatment-related Grade 3/4 AEs were reported in 4 patients (20%): 1 case each of increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hyperglycemia, rash, and cardiac failure. All resolved with treatment discontinuation and/or management per guidelines. Treatment-related AEs leading to discontinuation of study medication occurred in 2 patients: Grade 3/4 increased ALT and increased AST (n = 1 each; occurred in the same patient) and cardiac failure (n = 1).

Overall, these preliminary data obtained on a small number of patients suggest that the blockade of the PD-1/PD-L1 axis results in a response rate that compares favorably with the existing standard of care, i.e., platinum based doublets; indeed, it is generally considered that the administration of platinum doublets as a treatment of first-line NSCLC results in a response rate ranging between 15 and 25% that is accompanied with an incidence of Grade 3/4 drug-related adverse events in the range of 20 to 30%.

As specified in the Phase I Study EMR100070-001 protocol, an interim analysis of response was conducted for the NSCLC post platinum doublet expansion cohort 13 weeks after start of treatment of the 75th subject.

Entry to Study EMR100070-001 for subjects with NSCLC was restricted to subjects with measurable disease, defined as at least 1 unidimensional measurable lesion by RECIST 1.1. Tumor burden at baseline was evaluated using a computed tomography (CT) scan or magnetic resonance imaging (MRI; if MRI was used, then CT of chest was mandatory) of the chest, abdomen, and pelvis within 18 days of the start of treatment using RECIST 1.1 for target and non-target lesions. During the study, tumor assessments are performed every 6 weeks for the first 12 months then every 12 weeks until end of treatment, and subjects without progressive disease at the end-of-treatment visit are followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year.

The protocol-specified interim analysis for tumor response was conducted using RECIST 1.1. The BOR according to RECIST 1.1 was determined for each subject as the best response reported by the investigator from the start of treatment until disease progression. No confirmation of response (CR or PR) in a subsequent tumor assessment was required for the interim analysis.

The interim analysis population consisted of all treated subjects (n=75) who started treatment at least 13 weeks prior to the cut-off date of June 24, 2014. The ORR evaluated during the interim analysis was 13.3% (10 of 75 subjects; 95% confidence interval [CI]: 6.6%, 23.2%), including 1 subject with CR, 9 subjects with PR. There were also 25 subjects with stable disease (SD),

29 subjects with progressive disease, 11 subjects who were not evaluable. Subsequently, a further interim analysis of the first 90 treated NSCLC subjects was conducted (cut-off date July 17, 2014; 13 weeks after start of study treatment of the 90th subject, with a median follow-up of 6 months; range: 3 to 10 months). The ORR evaluated during this analysis was 13.3% (12 of 90 subjects; 95% CI: 7.1%, 22.1%), including 1 CR, 11 PR, 30 SD, 35 progressive disease, and 13 not evaluable. Ten out of the 12 responses were still on-going at the cut-off date for this analysis. The onset of response was rapid, with most subjects (7 of 12 [58%]) having their first documented response at Week 7.

Overall, these data support proceeding with an expansion cohort of subjects with Stage IV or recurrent NSCLC who have not received systemic treatment for their metastatic or recurrent disease.

3.5.5 Rationale for Additional Efficacy Expansion Cohorts

The expansion phase of the trial provides for further exploration of signals in 4 new efficacy expansion cohorts. The rationale is provided below.

3.5.5.1 Ovarian Cancer, Platinum Refractory and Prior Liposomal Doxorubicin

An additional expansion cohort of subjects with ovarian cancer (N=100) has been added to enroll specifically subjects with advanced ovarian cancer who are considered refractory to platinum-based chemotherapy and have received prior treatment with liposomal doxorubicin (for example, may be in combination with a platinum regimen, or as monotherapy, or in combination with other therapies) for advanced ovarian cancer. Subjects who have received treatment with platinum-based chemotherapy AND who have progressed during treatment within 6 months from the last dose of chemotherapy are considered refractory to platinum-based therapy. Refractory ovarian cancer is associated with a poor prognosis with few effective therapeutic options. Platinum-based chemotherapy and liposomal doxorubicin have established clinical benefit in advanced ovarian cancer. This expansion cohort seeks to enroll a specific patient population with advanced ovarian cancer that has exhausted all established therapeutic options (for example, platinum-based chemotherapy and liposomal doxorubicin) and thus represent a patient population with a high unmet need for new effective therapies. Data from this cohort may provide important efficacy data that may allow for further development with Phase III clinical trials.

3.5.5.2 Urothelial Carcinoma, Platinum Ineligible or Progressed after at Least 1 Line of Platinum-based Therapy:

An additional expansion cohort of subjects with urothelial carcinoma (N=200) has been added so that a more precise evaluation of response rate and the potential association of response to PD-L1 expression can be conducted. The target population for this cohort is subjects with advanced bladder cancer who have progressed after at least 1 line of platinum-based therapy or who are considered ineligible to receive platinum-based therapy. Ineligibility to treatment with a platinum salt is defined by the presence of any 1 of the following criteria:

- Impaired renal function
- Hearing loss of 25 decibels at 2 contiguous frequencies
- Grade ≥ 2 peripheral neuropathy

Subjects may have received any number of prior systemic therapies for metastatic disease. Subjects must have received at least 1 line of platinum-based chemotherapy. Platinum refractory bladder cancer is associated with a poor prognosis with few effective therapeutic options. Data from this cohort may provide important efficacy data that may allow for further development with Phase III clinical trials.

3.5.5.3 Rationale for Further Expansion of the Urothelial Carcinoma Cohort

The urothelial carcinoma secondary expansion cohort in study EMR100070-001 included 44 subjects with metastatic or locally advanced urothelial carcinoma who progressed after treatment with at least 1 platinum-containing regimen or were platinum ineligible. Subjects included in this cohort were treated with avelumab and followed up for at least 3 months. At a data cut-off date of 19 March 2015, among the 44 subjects in this cohort, there were 7 responders (15.9%), including 1 CR and 6 PR. Six of the 7 responders had responses that were still ongoing at the time of this analysis. The disease control rate was 59.1%, based on 7 responses and 19 subjects with stable disease.

Preliminary results of the role of PD-L1 expression to predict response to avelumab therapy in this initial cohort of subjects with urothelial cancer suggest a potential correlation with PD-L1 tumor expression and response (unpublished data). These early data appear to be consistent with Phase I data from other antibodies that block the anti-PD-1 or PD-L1 pathway (47). As a result, the Sponsor has decided to further expand enrollment in the urothelial carcinoma efficacy expansion cohort (N=200, see Section 8.1), in order to obtain a sufficient number of subjects to better understand the clinical activity of avelumab in this disease and to validate the potential correlation between PD-L1 expression and clinical outcomes. Specifications for a confirmatory analysis based on PD-L1 expression status will be made in the Statistical Analysis Plan (SAP) for study EMR100070-001 prior to any statistical analysis of PD-L1 expression data from the urothelial carcinoma efficacy expansion cohort.

3.5.5.4 Gastric / GEJ Cancer, Third Line:

The rationale to add a new cohort of subjects with metastatic gastric and GEJ cancer (N=150) who have failed both a first-line chemotherapy regimen and subsequent ramucirumab therapy, is supported by the recent data and subsequent regulatory approval of ramucirumab in patients with metastatic gastric cancer. Of note, ramucirumab is a recombinant monoclonal antibody of the IgG1 class that binds to vascular endothelial growth factor receptor-2 (VEGFR-2) and blocks the activation of the receptor.

On 21 April 2014, the U. S. Food and Drug Administration approved ramucirumab for use as a single agent for the treatment of patients with advanced or metastatic gastric or GEJ

adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy. This approval was based on the demonstration of improved OS in a multinational, randomized (2:1), double-blind, multicenter study enrolling 355 patients with previously treated advanced or metastatic, gastric or GEJ adenocarcinoma. Patients were randomized to receive either ramucirumab plus best supportive care (BSC) or placebo plus BSC. The median OS was 5.2 months in the ramucirumab plus BSC arm and 3.8 months in the placebo plus BSC arm (hazard ratio [HR]=0.78; 95% CI: 0.60, 0.998; p =0.047). Median PFS was longer in the ramucirumab arm compared to the placebo arm (HR=0.48; 95% CI: 0.38, 0.62; p <0.001).

The safety of ramucirumab as a single agent was evaluated in 570 patients, including 236 patients with locally advanced or metastatic gastric or GEJ adenocarcinoma, with an ECOG performance status of less than or equal to 1, who received ramucirumab. The most common adverse reactions (all grades) observed in ramucirumab-treated patients at a rate of greater than or equal to 10% and greater than or equal to 2% higher than placebo were hypertension and diarrhea. The Grade 3 to 4 adverse reactions reported at a higher incidence in the ramucirumab arm (greater than or equal to 2% difference between arms) included hypertension and hyponatremia. The most common SAEs with ramucirumab were intestinal obstruction (2.1%) and anemia (3.8%). Other important risks described in labeling include hemorrhage, arterial thrombotic events, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration in patients with cirrhosis, and reversible posterior leukoencephalopathy.

The availability and use of ramucirumab in second-line metastatic gastric cancer has subsequently led to the emergence of a subpopulation of patients who have progressed on both chemotherapy and ramucirumab and now have few, if any, effective therapeutic options. Data from this cohort may provide important insight on the potential role of anti-PD-L1 therapy in these patients.

3.5.5.5 Head and Neck Cancer, Platinum Ineligible or Progressed After at Least 1 Line of Platinum-based Therapy:

The rationale to add a new cohort of subjects with HNSCC (N=150) is the observation that immune escape may play a prominent role in HNSCC, as both human papillomavirus (HPV) positive and HPV-negative HNSCC display a T-cell-inflamed phenotype characterized by the presence of tumor-infiltrating lymphocytes and PD-L1 expression (53).

Recently, promising clinical data has emerged suggesting that antibodies that block the PD-1 / PD-L1 pathway may be an effective therapy for metastatic HNSCC (54). These data demonstrated a 19.6% best overall response rate (11 of 56 responses), with 7 of 11 responders still on treatment. Furthermore, 51% of patients experienced no change or a decrease from baseline in the size of their target lesions. PD-L1 expression appeared to be correlated with response with a 50% ORR in the 12 patients with PD-L1 expression above the cutpoint and 11.4% ORR in the 44 patients with PD-L1 expression below the cutpoint. These data demonstrate promising antitumor activity with an acceptable safety profile in patients with recurrent or metastatic HNSCC and who were treated with an anti-PD-1 agent.

In addition, these data support proceeding with an expansion cohort of subjects with HNSCC who have progressed after at least 1 line of platinum-based therapy or who are considered ineligible to

receive platinum-based therapy. Ineligibility to platinum treatment is defined by the presence of any 1 of the following criteria:

- Impaired renal function
- Hearing loss of 25 decibels at 2 contiguous frequencies
- Grade ≥ 2 peripheral neuropathy

Subjects may have received any number of prior systemic therapies for metastatic disease. Subjects must have received at least 1 line of platinum-based chemotherapy. Platinum refractory HNSCC is associated with a poor prognosis with few effective therapeutic options. Data from this cohort may provide important efficacy data which may allow for further development with Phase III clinical trials.

3.6 Rationale for Expanding Inclusion Criteria for Gastric / GEJ Cohort

Recent data provide evidence of clinical activity of anti-PD-L1 therapy in metastatic gastric cancer patients, which supports the expanded inclusion in this trial of subjects who have progressed on first-line chemotherapy for metastatic disease. The evidence includes:

- Data presented at the American Society for Clinical Oncology Annual Meeting 2014 from a Phase I expansion cohort of 16 subjects with gastroesophageal cancer treated with MEDI4736 (anti-PD-L1), which reported 4 out of 16 responders (55).
- Preliminary data from the gastric and GEJ cancer expansion cohort in the current trial (EMR100070-001), which includes 2 unconfirmed PRs out of 6 subjects who have completed 7 weeks of follow-up (as of 17 July 2014).

Based on the above data, eligibility for this cohort will be expanded to allow subjects who have progressed on first-line chemotherapy for metastatic disease to be enrolled, in addition to subjects who have not progressed.

3.7 Summary of the Overall Benefit and Risk

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the avelumab as specified in this clinical trial protocol. A SMC is planned for the ongoing assessment of the risk-benefit ratio. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable. The risks of exposure to avelumab include:

- Infusion-related reactions
- irAEs.
- Infusion-related reactions are a risk inherent to the administration of any recombinant protein to humans.

Incidence of immunogenicity and character or severity of immunogenicity-induced side effects cannot be predicted by animal models because humanized or fully human proteins usually provoke a much stronger immune-response in rodents or non-human primates than in humans. Avelumab caused lethal immune-mediated anaphylactic hypersensitivity reactions in mice after repeated application, while a control antibody lacking pharmacological activity only triggered a moderate immune reaction. However, in primates (cynomolgus monkeys), as a species closer to human, neither in the pilot 4-week i.v. repeat-dose toxicity study nor in the pivotal 13-week i.v. infusion repeat-dose toxicity study, clinical signs of hypersensitivity have been seen at dose levels of 20, 60, and 140 mg/kg, respectively.

Immune-related AEs are events that are drug-related and can be explained by an immune-phenomenon after other etiologies have been ruled out. Relevant clinical safety experience has been generated with several PD-1/PD-L1 pathway blocking monoclonal antibodies. For the anti-PD-L1 monoclonal antibody MDX-1105, an MTD could not be reached and the most common drug-related AEs were fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritus, and headache. Most events were low grade, with treatment-related Grade 3 or 4 events noted in 19 of 207 subjects (9%) (5). Drug-related AEs of special interest, with potential immune-related causes, were observed in 81 of 207 subjects (39%) and included rash, hypothyroidism, hepatitis, and 1 case each of sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis. These AEs were predominantly Grade 1 or 2 and were managed with treatment interruption or discontinuation. Nine subjects were treated with glucocorticoids for the management of AEs, with improvement or resolution of events in all subjects. Overall, the safety profile for this compound, blocking the PD-1 / PD-L1 axis at the same level as avelumab, is acceptable in the context of the treatment of subjects with advanced malignancies. Nevertheless, especially the occurrence of irAE will be carefully monitored.

In addition, since the drug 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 published by Howard et al (56). See Figure 6.1, Section 6.5.4.3.

At the time of preparation of this Amendment, safety data from 53 subjects treated with avelumab at doses ranging from 1 to 20 mg/kg during dose escalation and > 1400 subjects at a dose of 10 mg/kg in dose expansion were available (refer to current IB).

As one can deduce from the clinical experience with ipilimumab, which blocks cytotoxic T lymphocyte antigen-4 (CTLA-4), a negative regulator of T-cell activation like PD-L1, potential side effects of PD-L1 antagonism include immune-related adverse reactions, which can be severe and may involve the gastrointestinal, liver, skin, endocrine, or other organ systems (57-61). Skin-related AEs can be expected after 2 to 3 weeks, gastrointestinal and hepatic AEs after 6 to 7 weeks, and endocrinologic AEs only after an average of 9 weeks (62) and constitute the clinically most relevant safety concern apart from acute severe infusion reactions. The kinetics of the occurrence of such irAEs have not been reported for either BMS-936559 targeting PD-L1 (5) nor for the anti-PD-1 monoclonal antibody BMS-936558 (6). However, their toxic effects seem to be less common and of lower grade compared with ipilimumab. Nevertheless, careful monitoring of such AEs of special interest (AESI) is implemented in this protocol throughout the complete treatment period and up to 3 months post-treatment for follow-up (see Sections 7.1.4 and 7.4.1.1).

A direct benefit is considered unlikely for participants in this Phase I trial, at least in the low doses of the dose escalation part. However, durable partial responses have been reported with another anti-PD-L1 monoclonal antibody (6). Therefore, only subjects with malignancies for which no standard therapy exists or subjects having experienced a failure of standard therapy are eligible for this part of the study (i.e., 1 and 3 mg/kg). However, allometric scaled human simulations suggests that the proposed initial dose of 1.0 mg/kg is expected to result in at least 50% target occupancy, which may be sufficient to induce beneficial clinical effects. Moreover, expansion on a dose level displaying pharmacological and/or clinical activity, to enrich for subjects in selected indications will be done.

The sample size of 150 for expansion in the primary cohorts (NSCLC [both post platinum doublet and first-line], gastric and GEJ cancer, and MBC) and 2 efficacy expansion cohorts (gastric and GEJ cancer and HNSCC) has been chosen based on knowledge that PD-L1 is clinically active in NSCLC and that PD-L1 is also expressed in MBC, gastric cancer, and HNSCC microenvironment. Data published by Topalian et al, have linked the expression of PD-L1 by tumor cells and clinical activity of agents blocking the PD-1/ PD-L1 pathway (6), but additional results presented at ASCO in 2013 suggest that the response to agents that block the PD-1/PD-L1 pathway does not require the expression of PD-L1 by tumor cells. It might be speculated that PD-L1 has to be involved in the phenomenons that drive the escape from the immune response for an anti-PD-L1 agent to have clinical activity (63,64). Enrollment of 150 subjects will allow for a robust assessment of safety and efficacy endpoints in these indications, including a precise determination of response rates. In addition, data from these cohorts will be used to investigate the association between the pattern of expression of membrane PD-L1 and clinical response to PD-L1 blockade, and to determine whether accrual in future studies should be restricted based on PD-L1 expression status.

The sample size of 20 for each of the 4 original secondary disease specific expansion cohorts was chosen primarily to further explore the safety and efficacy of avelumab in specific indications and to provide preliminary data to aid in future study design. However, following completion of dose escalation in this trial and in the broader context of ongoing research with PD-L1 inhibition, it is considered appropriate to add 4 new secondary cohorts (ACC, mesothelioma, urothelial carcinoma, and RCC) to the expansion phase of this trial and to increase subject enrollment in 2 of the 4 initial secondary cohorts (melanoma and ovarian cancer).

An interim analysis will take place after 75 subjects treated in the primary expansion cohorts have been followed for 3 months or until discontinuation if earlier. This interim analysis will enable a first assessment of the association between PD-L1 expression and tumor response, to support the planning of subsequent studies and the possible development of a companion diagnostic assay. A futility rule will be applied that will imply a stop of enrollment in the given cohort in case of insufficient clinical activity.

In the first-line NSCLC primary expansion cohort, an interim analysis of response will be conducted 13 weeks after start of treatment of the 30th subject.

For the efficacy expansion cohorts, interim analyses for efficacy are planned 13 weeks after the start of treatment of the 30th subject in all cohorts, 13 weeks after start of treatment of the 60th subject in the ovarian cohort, and 13 weeks after start of treatment of the 90th subject in the gastric / GEJ and HNSCC cohorts. No futility rule is foreseen because the clinical activity of Anti-PPD-1

/ Anti-PD-L1 agents in these tumor types is established, and the patient populations are characterized by a high unmet medical need. If efficacy criteria are met at the second interim analysis, enrollment will continue to the planned full number of subjects in order to collect further data on the primary and secondary endpoints, especially on the association between PD-L1 expression and efficacy endpoints.

In addition, in the NSCLC post platinum doublet cohort only, 2 additional interim analyses of efficacy will be conducted, 13 weeks after the start of treatment of the 60th and the last subject, respectively.

For each expansion cohort, an additional interim analysis may be conducted 13 weeks after the start of treatment of the last subject in that cohort.

Also, in the secondary cohorts that plan to enroll more than 20 subjects, i.e., the ACC, melanoma, mesothelioma, ovarian cancer, and urothelial carcinoma cohorts, an interim analysis of response will be performed 13 weeks after the start of treatment of the 20th subject. Accrual in each cohort may be paused during the interim analysis. If no unconfirmed response according to RECIST 1.1 is observed in a given cohort in the interim analysis, accrual in that cohort will be stopped. In addition, for the ovarian cancer secondary expansion cohort, an interim analysis of response will be performed for internal planning purposes 13 weeks after the start of treatment of the 75th subject.

Enrollment of first-line RCC subjects was opened after 2 documented objective responses among the 20 subjects enrolled in the second-line RCC cohort were observed by RECIST 1.1 (2 PRs), and justified further evaluation in this patient population.

In conclusion, the risk-benefit ratio of treatment with avelumab in the targeted trial population is considered positive given the poor prognosis of subjects with advanced malignancies.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, Good Clinical Practice [GCP]) and the applicable national regulatory requirements.

4 Trial Objectives

Primary objective

- To assess the safety and tolerability of avelumab and to determine the MTD of avelumab in subjects with metastatic or locally advanced solid tumors.
- To assess the BOR according to RECIST 1.1 in the efficacy expansion cohorts (ovarian cancer, platinum refractory, prior liposomal doxorubicin; urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy; gastric and GEJ cancer, third line; HNSCC, platinum ineligible or progressed after at least 1 line of platinum-based therapy).

Secondary objectives

- To characterize the PK profile of avelumab and to correlate exposure with target occupancy.

- To evaluate the immunogenicity of avelumab and to correlate it to exposure and biological activity.
- To assess the BOR and PFS according to RECIST 1.1.
- To assess the immune-related BOR (irBOR) and immune-related PFS (irPFS) using the modified Immune-Related Response Criteria (irRC), derived from RECIST 1.1.
- To assess OS.
- To evaluate biological responses to avelumab in blood/serum.
- To evaluate the association between tumor PD-L1 expression and BOR.
- To characterize changes in soluble factors (e.g., cytokine profiles, soluble PD-1 and soluble PD-L1) and immune cell profiling (e.g., natural killer [NK] cells, neutrophils, lymphocytes).

Exploratory objectives (efficacy expansion cohort only)

CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, open-label, dose-escalation trial with consecutive parallel-group expansion in selected solid tumor indications.

5.1.1 Overall Design

The current trial is a standard dose escalation "3 + 3" cohort design, for which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of DLTs (see Section 5.1.4.2.2). This dose escalation phase of the trial is currently being conducted in the USA only.

Cohorts of 3 subjects with metastatic or locally advanced solid tumors, for which no standard therapy exists or a standard therapy has failed, will receive avelumab at escalating dose levels with 3 to 3.3 times of increase in dose (see Section 5.1.4.2). The starting avelumab dose is 1.0 mg/kg; the maximally envisaged dose is 10 mg/kg. At each dose level, subjects will receive avelumab once every 2 weeks until confirmed progression, unacceptable toxicity, or any reason for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a confirmed 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.

Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the

subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

The dose range and schedule for this trial was developed based on safety considerations as well as on preclinical PK / PD modeling. Because peripheral blood T cells express PD-L1, it is possible to assess in vivo receptor occupancy by anti-PD-L1 antibody as a PD measure and potential surrogate for clinical activity. From mouse tumor models, it was concluded that a stable avelumab blood concentration of at least 50 µg/mL has to be realized in order to induce clinically relevant effects. Such an exposure level was corresponding to approximately 95% target occupancy and could be kept over time in the clinical setting by an avelumab dose of 7 mg/kg administered every 2 weeks. Close monitoring of exposure as well as of target saturation on lymphocytes during the clinical trial will enable to modify the protocol, in case the finally aimed target occupancy would not be achieved. The clinical design is nearly identical to study NCT00729664 investigating BMS-936559, hence supported by the excellent safety and very positive efficacy data gained from this trial.

Besides determination of the MTD / maximum feasible dose, it is the intention to establish PK / PD correlations based on PD-L1 receptor occupancy to provide guidance for the dose and regimen to be used in expansion cohorts covering selected tumor indications. The MoA of avelumab in humans will be investigated through monitoring the activation status of the immune system (i.e., leukocyte subsets phenotypes, PD-1 signaling pathway, ADCC, cytokines profiling). Furthermore, explorations of specific anti-tumor immune responses and evaluations of potential predictive/prognostic biomarker candidates are planned in this trial.

Assessment of safety parameters will focus on potential acute side effects like cytokine release syndrome caused by potential exaggerated pharmacological activity of avelumab i.e., overstimulation of cytokine-releasing hematological cells or damage of cytokine containing cells by ADCC. Potential acute side effects also include allergic reactions / hypersensitivities, in the worst case anaphylaxis (65), which could develop as consequence of an immunogenicity response and might be pronounced due to the immunostimulatory properties of avelumab, promoting an immune response against itself.

Evaluation of middle-term safety will cover incidence and severity of potential irAE, which may become manifest earliest after weeks of treatment (57-61,66). 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 anti-nuclear antibodies (ANAs) or antineutrophil cytoplasmic antibodies (ANCAs).

DLTs will be monitored centrally, and the decision to escalate to the next dose level will be proposed by the SMC as outlined in Section 2.2.1.

Once the dose of 10 mg/kg is established as safe (see Section 5.1.4.2), 10 additional subjects at 3 mg/kg and 10 mg/kg each may be enrolled, for the purpose of generating additional safety, PK and receptor occupancy data, if agreed with the SMC.

Once 6 subjects treated at 10 mg/kg have completed the DLT observation period and the safety of 10 mg/kg is established, a dose level of 15 mg/kg (if 1 DLT was observed) or 20 mg/kg (if no DLT was observed) dosing every 2 weeks will be initiated. In this 20 mg/kg dose level, the safety, PK, receptor occupancy, and PD activity of the IMP will be evaluated using the methodology that was used for the other cohorts. Accrual in these dose levels will be completed using a "3+3" method, the same methodology that was used for the completion of the previous dose levels. Once the safety of the 15 and/or 20 mg dose level has been established (i.e., no more than one DLT out of 6 subjects treated), up to 15 additional subjects will be enrolled at 15 or 20 mg/kg without sequential dosing (i.e., not required to wait until 48 hours between 2 subjects). This additional cohort will have the purpose of generating safety data, PK data and receptor occupancy data at a dose of the respective dose.

With the safety of the 10 mg/kg and 20mg/kg once every 2 weeks established, a new cohort of 10 mg/kg administered once weekly for the first 12 weeks is being initiated to assess safety of higher intensity of already established dose. Six evaluable subjects are planned to be included in this cohort. Subjects in this cohort will receive avelumab at 10 mg/kg once weekly for the first 12 weeks. Starting Week 13, dosing with 10 mg/kg will be once every 2 weeks.

Subjects who do not complete 4 weeks of treatment for reasons other than treatment-related AE will be replaced. Subjects in this cohort will be enrolled in selected sites in the USA only.

In 10 mg/kg once weekly cohort the SMC will evaluate overall safety data when all 6 evaluable subjects have completed a minimum 4-week treatment period, and after 12 weeks of observation have been completed for all subjects enrolled in this cohort (see Section 2.2.1).

Expansion cohorts

After an avelumab dose and regimen for further investigation are established, enrollment in expansion cohorts will be opened in up selected tumor indications to determine the safety and clinical activity of avelumab. Subjects will be divided into:

- 4 primary cohorts (N=150 subjects each) of:
  1. NSCLC, post platinum doublet;
  2. NSCLC, first line, does not carry an epidermal growth factor receptor (EGFR) activating mutation or anaplastic lymphoma kinase (ALK) re-arrangements (non-squamous cell histologies require testing if status is unknown);
  3. Gastric and GEJ junction cancer; and
  4. MBC
- 8 secondary cohorts:
  1. CRC (N=20),
  2. CRPC (N=20),
  3. ACC (N=50),
  4. Melanoma (N=50),

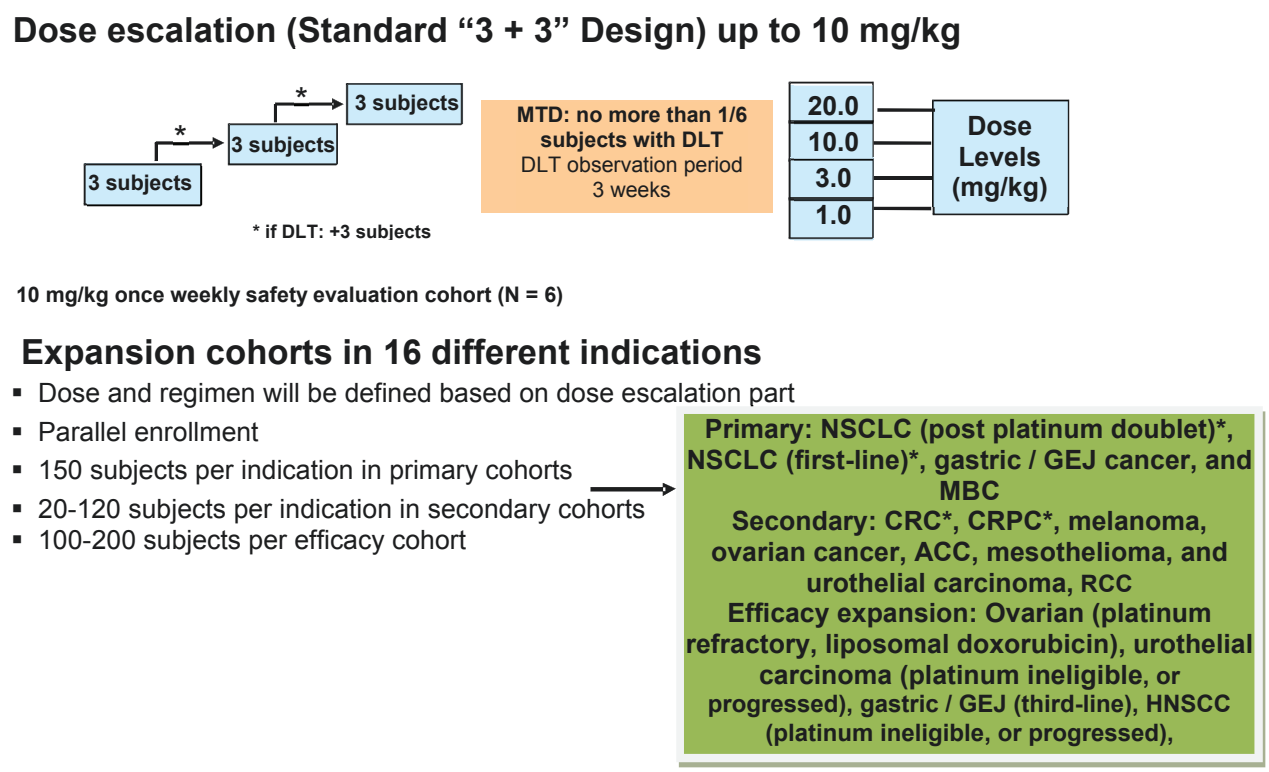
5. Mesothelioma (N=50),
6. Urothelial carcinoma (N=50; note: enrollment is being stopped [N=44] due to the opening of a urothelial efficacy expansion cohort),
7. Ovarian cancer (N=120), and
8. Renal cell carcinoma (RCC), second line, (N=20 with expansion of 60 first-line).

- 4 efficacy expansion cohorts with the primary objective to assess BOR according to RECIST 1.1:
  1. Ovarian cancer, platinum refractory, prior liposomal doxorubicin (N=100);
  2. Urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy (N=200);
  3. Gastric and GEJ cancer, third line (N=150);
  4. HNSCC, platinum ineligible or progressed after at least 1 line of platinum-based therapy (N=150).

Subjects in the NSCLC (post platinum doublet), CRC, and CRPC cohorts will be enrolled in the USA only.

A schematic illustration of the trial design is shown in Figure 5.1.

Figure 5.1 Schematic of Trial Design



* Subjects in the NSCLC (post-platinum doublet), CRC and CRPC cohorts will be enrolled in the USA only.

Abbreviations: ACC: adrenocortical carcinoma; DLT: dose-limiting toxicity; CRC: colorectal cancer, CRPC: castrate-resistant prostate cancer; GEJ: gastroesophageal junction; HNSCC: head and neck squamous cell carcinoma; MBC: metastatic breast cancer; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma.

5.1.2 Trial Endpoints

5.1.2.1 Primary Endpoints

- Occurrence of DLTs during the first 3 weeks of treatment in the dose escalation part (excluding the once weekly 10 mg/kg cohort).
- The confirmed BOR, per RECIST 1.1, as adjudicated by an IERC (see Section 7.3) for subjects enrolled in the efficacy expansion cohorts only.

5.1.2.2 Secondary Endpoints

- Number, severity, and duration of TEAEs for all dose groups / indications according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
- Number, severity, and duration of treatment-related AEs according to NCI-CTCAE v4.0.
- PK profile.

- irBOR and BOR according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
- The confirmed BOR, per RECIST 1.1, as adjudicated by an IERC, for subjects enrolled in the secondary urothelial carcinoma cohort.
- irPFS time and PFS time according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
- OS time.
- Pharmacodynamic profile.
- Serum titers of anti-drug antibodies (ADA).
- Expression of PD-L1 on tumor tissue.
- For the primary expansion cohorts only: Unconfirmed response at Week 13 according to RECIST 1.1, per investigator assessment.
- Duration of response according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
- For the efficacy expansion cohorts only:
    - PFS time, according to RECIST 1.1, per IERC
    - Duration of response according to RECIST 1.1, per IERC.

5.1.3 Trial Medication Administration and Schedule

Subjects will receive i.v. infusion of avelumab (over 1 hour [-10 minutes / +20 minutes, i.e., 50 to 80 minutes]) once every 2 weeks. 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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

For subjects in the 10 mg/kg once weekly cohort, subjects will receive i.v. infusion of avelumab (over 1 hour [-10 minutes / +20 minutes, i.e., 50 to 80 minutes]) once every week for the first 12 weeks, then starting with Week 13, once every 2 weeks thereafter. Premedication will be administered as above.

The trial treatment schedule is illustrated in Appendix I.

The formulation and packaging information of avelumab is provided in Sections 6.1 and 6.6.

5.1.4 Avelumab Dose Escalation

5.1.4.1 Starting Dose

The starting dose of avelumab will be 1.0 mg/kg.

5.1.4.2 Dose Escalation Scheme

The avelumab dose escalation will be performed in cohorts of 3 subjects each according to the following dose levels with a 3 or 3.3 times of dose increase at each escalation:

- 1.0 mg/kg
- 3.0 mg/kg
- 10.0 mg/kg

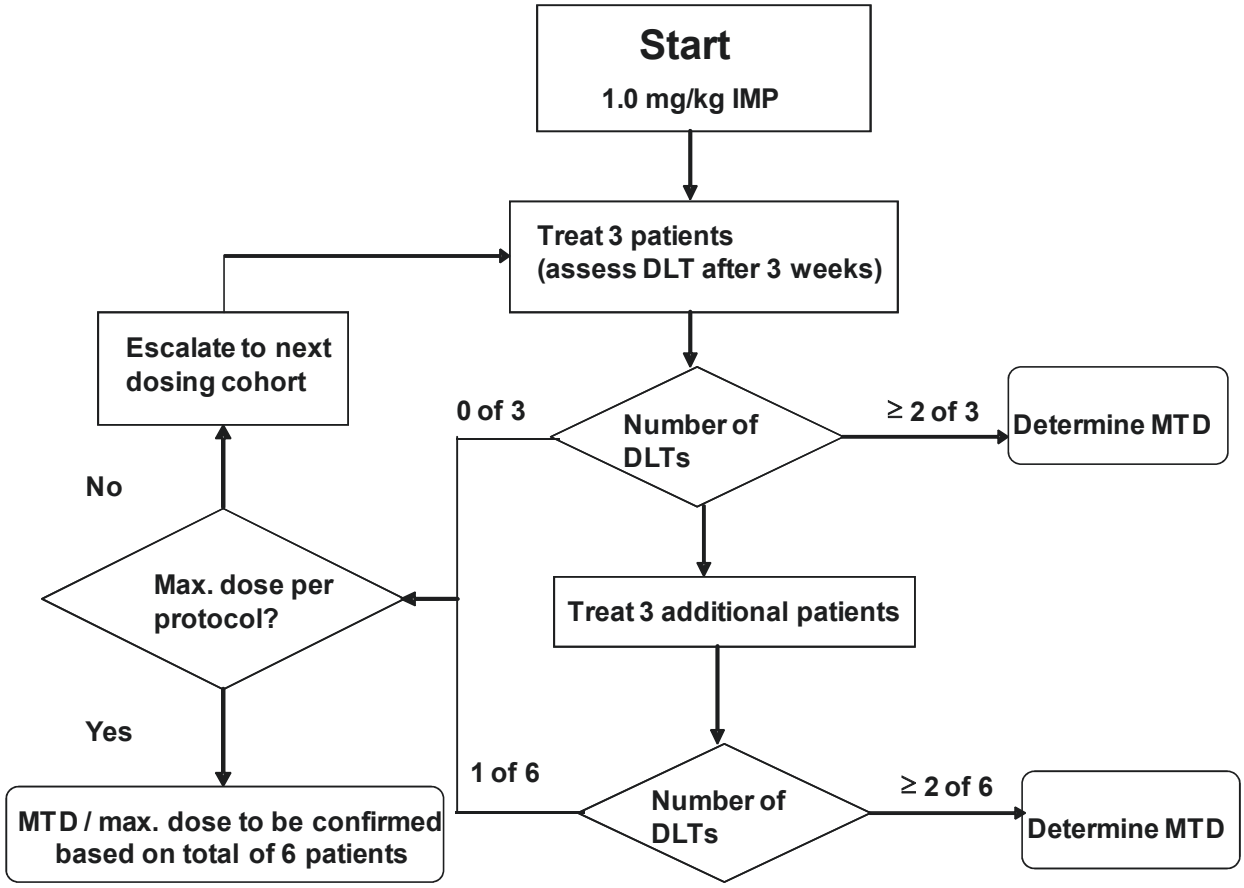
The dose escalation criteria are as follows:

For each dose level, DLTs are assessed during the first 3 weeks. The criteria for moving from one dose level to another do not allow escalation to the next cohort in cases where ≥ 2 of 3 or 6 subjects in a cohort experience a DLT. If 1 of 3 subjects in a cohort experiences a DLT, this cohort will be expanded to 6 subjects. The MTD is defined as the highest dose where fewer than 2 of 6 subjects experience a DLT. Thus, the MTD cohort should accrue at a total of 6 subjects.

Once the MTD or maximum dose to be investigated is reached, the respective dose level cohort will be filled to a total of 6 subjects. Once the dose of 10 mg/kg is established as safe, 10 additional subjects at 3 mg/kg and 10 mg/kg each may be enrolled, for the purpose of generating additional safety, PK and receptor occupancy data, if agreed with the SMC.

A schematic of dose escalation is presented in Figure 5.2.

Figure 5.2 Dose Escalation Algorithm for Doses up to 10 mg/kg



Abbreviations: IMP: investigational medicinal product; DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

Each subject will stay on the dose level assigned at trial entry. The first subject of each cohort should be observed for 16 days (i.e., 48 hours after the second dose) for DLT occurrence before the second subject is to be administered the trial medication. Thereafter, within each cohort of the dose escalation phase, subjects may only be consecutively dosed with an interval of at least 48 hours. However, after 3 subjects have been treated at 10 mg/kg and no DLT has been observed, the other 3 subjects required to complete this cohort can be enrolled without sequential dosing (i.e., not required to wait until 48 hours). If no more than 1 DLT has been observed in these 6 subjects, the safety of 10 mg/kg will have been established.

At the conclusion of the DLT observation period of each cohort, a data review will be conducted. The SMC that includes all principal investigators is responsible for making dose escalation decisions. This committee will make the decision whether or not to escalate the avelumab dose to the next level by reviewing the safety data after all subjects of a cohort have completed Day 21 observation (the DLT evaluation period).

Once 1 subject has experienced DLT at a dose level below 10.0 mg/kg, dose escalation will be reduced as described in Table 5.1:

Table 5.1 Modification of Dose Escalation Based on DLT Observations at Dose Levels Below 10.0 mg/kg

Dose Escalation Schedule Scenarios	Dose of Avelumab (mg/kg)		
Dose Levels	No DLT	DLT at Level 2	DLT at Level 1
Level 1	1.0	1.0	1.0
Level 2	3.0	3.0	1.5
Level 3	10.0	4.5	2.5
Level 4		7.0	3.5
Level 5		10.0	5.0
Level 6			7.5
Level 7			10.0

DLT: dose-limiting toxicity.

If > 1 out of 6 subjects experiences DLT at the first dose level, the SMC will discuss if an avelumab dose lower than the starting dose of 1.0 mg/kg will be tested. Other dose modifications (i.e., de-escalation) may also be considered by the SMC, if deemed necessary.

5.1.4.2.1 Dosing After 6 Subjects Treated at 10 mg/kg

Once the safety of the administration of the IMP at 10 mg/kg has been established in 6 subjects treated at 10 mg/kg and observed during the DLT observation period, subsequent dosing will be determined by the SMC after review of the safety and PK data generated for those 6 subjects.

If 1 DLT was observed in the 6 subjects treated at 10 mg/kg during the DLT observation period, a dose level of 15 mg/kg will be initiated. The safety, PK, receptor occupancy, and PD activity of the drug administered at a dose of 15 mg/kg will be evaluated using the methodology that was used for the other dose levels. If no subjects dosed at 15 mg/kg experience a DLT the next cohort can be dosed at 20 mg/kg. If 1 of 3 subjects dosed at 15 mg/kg experiences a DLT, this cohort will be expanded to 6 subjects.

Once the safety of PD-L1 has been established at 15 mg/kg (defined as no DLT observed in the 3 subjects or up to 1 DLT observed in 6 subjects treated at 15 mg/kg during the DLT observation period), the 20 mg/kg dose level will be initiated.

If there was no DLT observed in the first 6 subjects treated at a dose of 10 mg/kg, the dose escalation will proceed from 10 to 20 mg/kg. In this 20 mg/kg cohort, the safety, PK, receptor occupancy, and PD activity of the drug will also be evaluated using the methodology that was used for the other cohorts. Accrual in the 20 mg/kg cohort will be completed using a "3+3" method that was used for the completion of the previous cohorts.

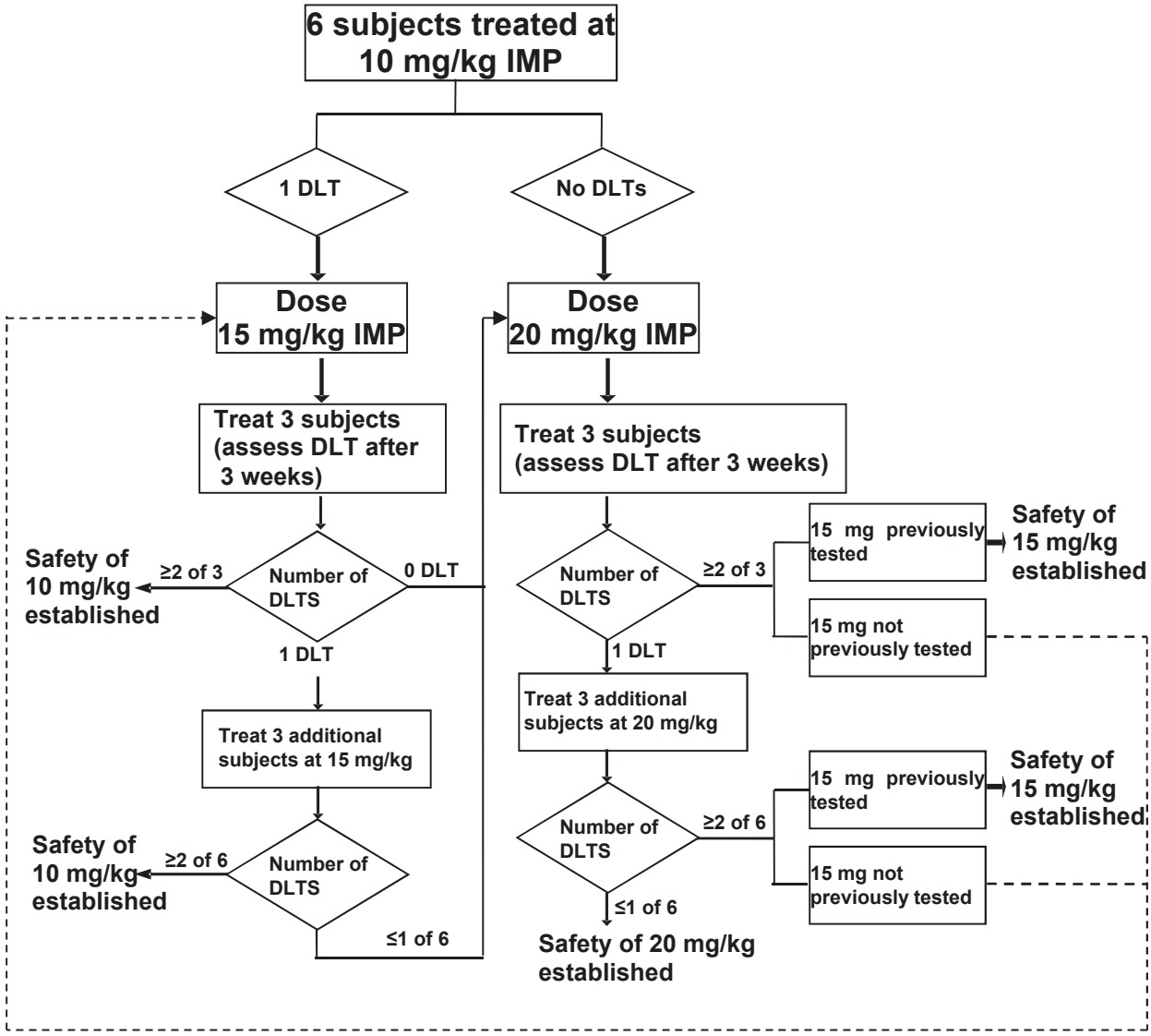
After 3 subjects have been enrolled at a dose of 20 mg/kg and followed up during the DLT period, after the SMC has reviewed the safety data available and has concluded that no DLT occurred, 3 additional subjects will be enrolled at a dose of 20 mg/kg in an unstaggered fashion (i.e., 3 subjects the same day). If ≥ 2 (of 3 or 6) subjects experiences a DLT, the 15 mg/kg dose will have to be explored before the MTD can be determined.

Once the safety of a dose of 15 mg/kg or 20 mg/kg has been established (i.e., no more than 1 DLT out of 6 subjects treated at that dose), the SMC will have the possibility to allow enrollment of up to 15 additional subjects at that dose, without sequential dosing (i.e., not required to wait until 48 hours between 2 subjects). This additional cohort will have the purpose of generating safety, PK, and receptor occupancy data at a dose of 15 or 20 mg/kg.

Based on their review of the safety and PK data, the SMC will have the possibility to enroll an additional 10 subjects at 3 mg/kg and 10 mg/kg each.

A schematic of the dose escalation for 15 and 20 mg/kg is presented in Figure 5.3.

Figure 5.3 Dose Escalation Algorithm for 15 and 20 mg/kg



Abbreviations: IMP: investigational medicinal product; DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

5.1.4.2.2 10 mg/kg Once Weekly Cohort

With the safety of the 10 mg/kg and 20 mg/kg once every 2 weeks established, a new cohort of 10 mg/kg administered once weekly is being initiated in 6 evaluable subjects to assess safety of a more frequent dosing at 10 mg/kg every week for 12 weeks followed by 10 mg/kg every 2 weeks. Subjects in this cohort of 6 evaluable subjects will receive avelumab at 10 mg/kg once weekly for the first 12 weeks. Starting Week 13, dosing with 10 mg/kg will be once every 2 weeks. Overall safety of subjects in this cohort will be monitored by the SMC (see Section 2.2.1).

5.1.4.3 Dose-Limiting Toxicity

A DLT is defined as a ≥ Grade 3 adverse drug reaction (ADR) according to the NCI-CTCAE v4.0, occurring in the DLT evaluation period of the dose escalation cohorts. ADRs are defined in this trial as any AEs suspected to be related to avelumab by the investigator and / or Sponsor.

The observation period for DLTs refers to the first 3 weeks of trial drug treatment in the dose escalation part for all dose cohorts for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD. Additional subjects enrolled in the dose escalation phase will have AEs collected but will not have a specific DLT observation period. A DLT is defined as any ≥ Grade 3 treatment-related toxicity confirmed by the SMC to be relevant for the study drug treatment. The SMC recognizes that in the absence of prior human experience with avelumab, a conservative approach will be adopted in ascribing the relevance of the treatment-related toxicity to drug. Treatment-related SAE will be ascribed as related to drug except where a clear relationship to the underlying disease or recognized co-morbidities is evident. For this trial, the MTD is defined as the highest dose where < 2 of 6 subjects experience a DLT.

A DLT is specifically defined as any one of the following:

Any Grade ≥ 3 toxicity that is possibly, probably, or definitely related to avelumab, occurring during the DLT evaluation period (21 days after administration of avelumab), except for any of the following:

- Grade 3 infusion-related reaction resolving within 6 hours and controlled with medical management.
- 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, emesis that resolves to ≤ Grade 1.
- Grade 3 diarrhea, Grade 3 skin toxicity, or Grade 3 liver function test (ALT, AST, or GGT) increase that resolves to ≤ Grade 1 in less than 7 days after medical management (e.g., immunosuppressant treatment) has been initiated.
- Single laboratory values out of normal range 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.

DLTs requiring treatment discontinuation are described in Section 5.1.7.2.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced.

5.1.5 Planned Number of Subjects

The planned number of the evaluable subjects for this trial is derived from the dose escalation "3+3" design and the expansion cohort sizes:

Dose escalation phase (including the 10 mg/kg once weekly cohort): 18 up to 66 subjects.

Primary and secondary expansion phase: 1040 subjects; 4 cohorts with 150 subjects each, 1 cohort with 120 subjects, 4 cohorts with 50 subjects, and 2 cohorts with 20 subjects each, and 1 cohort with 80 subjects (20 with expansion of an additional 60 subjects).

Efficacy expansion cohorts: 600 subjects; 2 cohorts with 150 subjects each and 1 cohort with 200 subjects and 1 cohort with 100 subjects.

The final sample size, however, may vary depending on the total number of dose levels to be escalated and tested, the subject replacement for DLT evaluations if applicable, and the number of expanded cohorts. At each dose level, 3 or 6 subjects will be treated depending on toxicities observed. A small number of additional subjects might be enrolled to replace the drop-out subjects.

In the event that rapid recruitment in the expansion phase impacts supply of IMP, the screening of new subjects for any cohort may be temporarily paused with 24 hours' notice to investigators.

5.1.6 Planned Treatment Duration

The trial duration for a subject is estimated to be up to 30 weeks. This includes an 18-day screening period (decision will be made in this period for subjects' trial inclusion if all eligibility criteria are met), a treatment duration until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5) and an end-of-treatment visit 4 weeks after the last dose of avelumab administration.

For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

Moreover, any ADRs should be followed until they resolve, return to baseline, or are irreversible (see Section 7.1.4 for details).

Planned first subject in: Q1, 2013.

Planned date last subject out (dose escalation): Q2, 2018.

Planned date last subject out (after expansion and follow-up): Q2, 2019.

In the case of study termination (see Section 5.6), subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).

5.1.7 Dose Modification and ADRs Requiring Treatment Discontinuation

5.1.7.1 Dose Modification

In general, each subject will stay on the avelumab dose level assigned in the trial unless treatment needs to be stopped.

The dose of avelumab will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration.

5.1.7.2 ADRs Requiring Treatment Discontinuation or Modifications

The following ADRs require permanent treatment discontinuation of avelumab:

Any Grade 4 ADRs require treatment discontinuation 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 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, 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.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Study Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Increases in ECOG performance status ≥ 3, which do not resolve to ≤ 2 by cycle Day 14 of the following cycle (infusions should not be given on the following cycle, if the ECOG performance status is ≥ 3 on the day of study drug 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 the guidelines provided in Sections 6.5.4.1, 6.5.4.2 6.5.4.3, 6.5.4.4, respectively.

5.1.8 Analysis Cut-Off Dates

After the end of the dose escalation part of the trial, a full analysis for safety and PK / PD data will be made and a full clinical trial report will be prepared. The cut-off date will be the time point when all subjects complete at least their first three 2-week treatment cycle, i.e., 6 weeks after the last subject of the escalation part has received its first administration of avelumab.

The primary data cut-off for the once weekly 10 mg/kg cohort is 4 weeks after the last evaluable subject in this cohort started treatment.

The primary data cut-off for the expansion cohorts is 6 months after the last subject started treatment.

An interim analysis of response will be conducted for each of the primary expansion cohorts after the first 75 subjects have reached the time point of their second post-baseline tumor assessment scheduled in Week 13, i.e., 13 weeks after start of treatment of the 75th subject. In addition, for the ovarian cancer secondary expansion cohort, an interim analysis of response will be performed for internal planning purposes 13 weeks after the start of treatment of the 75th subject.

In the first-line NSCLC primary expansion cohort, an interim analysis of response will be conducted 13 weeks after start of treatment of the 30th subject.

In the efficacy expansion cohorts, interim analyses for efficacy are planned 13 weeks after the start of treatment of the 30th subject in all cohorts, 13 weeks after start of treatment of the 60th subject in the ovarian cohort, and 13 weeks after start of treatment of the 90th subject in the gastric / GEJ and HNSCC cohorts. No futility rule is foreseen because the clinical activity of anti-PD-1 / anti-PD-L1 agents in these tumor types is established, and the patient populations are characterized by a high unmet medical need. If efficacy criteria are met at the interim analysis, enrollment will continue to the planned full number of subjects in order to collect further data on the primary and secondary endpoints, especially on the association between PD-L1 expression and efficacy endpoints.

An interim analysis will be conducted at 6 months after the last subject's first dose of study treatment for the 109 subjects enrolled in the urothelial carcinoma efficacy expansion cohort prior to Protocol Amendment 13.

In addition, in the NSCLC post platinum doublet cohort only, 2 additional interim analyses of efficacy will be conducted, 13 weeks after the start of treatment of the 60th and the last subject, respectively.

For each primary or secondary expansion cohort, an additional interim analysis may be conducted 13 weeks after the start of treatment of the last subject in that cohort.

Interim analyses for 6 of the 8 secondary cohorts are planned as described in Section 8.6.

Final data cut-off will be 1 year after the last dose of avelumab has been administered.

5.2 Discussion of Trial Design

This is a Phase I, open-label, dose-escalation trial with a planned consecutive expansion part in selected tumor indications. An open-label, unblinded design is appropriate for a dose-escalation trial with consecutive expansion cohorts in cancer subjects.

In this trial, the assessment of the safety and tolerability of the IMP with the determination of the MTD (in the dose escalation part only) is set to be the primary objective. The determination of the MTD is one of the first major steps in the development of a compound entering early clinical development because it is expected to use a dose close to the highest tolerable dose in future clinical development in order to achieve the best efficacy to risk ratio for subjects. The MTD will be determined using a standard "3 + 3 subjects" dose escalation design based on DLT assessments, which is commonly used in first-in-man oncology trials (67). The aim of this design is to maximize the protection to subjects and reduce the chances of more subjects to be exposed to possible drug toxicities. However, at the end of the dose-escalation part, it is intended to fill cohorts as described in Section 5.1.1 to identify a reasonable dose and schedule for the expansion part. All these assessments will be correlated to PK / PD parameters to identify the most meaningful dose for expansion cohorts in selected tumor indications.

The enrichment of dose-escalation cohorts below the MTD is reasonable for immunotherapeutic anticancer compounds (which is in contrast to most chemotherapies, that are typically given at the MTD), as the optimal biological effects are often not exclusively observed at the MTD level but already significantly below (6,68).

A reasonably safe starting dose of 1.0 mg/kg has been identified both via a NOAEL based or a PAD driven approach taking also into account the available information on clinical experience with BMS-936559, an anti-PD-L1 monoclonal antibody, which can be considered as clinical surrogate and gives an estimate of the irAEs to be expected at various dose levels (5). Initial dose setting follows the principle that the start dose should be pharmacologically active but also reasonably safe to use. This initial dose estimation algorithm is proposed in Guideline ICH S9 (8) and applicable for an end-stage cancer population.

In addition to determining the MTD, the study will serve to explore biologic and clinical parameters after exposure to avelumab. Due to a limited understanding of the interaction of the immune system and tumors in cancer subjects, there can be no certainty that the doses to be

examined will be associated with relevant anti-tumor activity. The selection of the dose to be used for further clinical evaluation will be based on the best current scientific knowledge.

The target population for the dose-escalation part comprises subjects with metastatic or locally advanced solid tumors. Based on the literature, tumor indications with an over-expression of PD-L1 are selected. These include NSCLC, gastric / GEJ cancer, MBC, CRC, CRPC, melanoma, ovarian cancer, HNSCC, and RCC. In order to obtain a trend of biological / clinical activity in these and in other relevant indications (ACC, mesothelioma, and urothelial carcinoma) and to collect further safety data, a treatment expansion at a meaningful dose level and regimen to be identified during the dose-escalation part to ensure further development in selected settings is justified. Furthermore, data from the expansion cohorts will allow to explore whether the expression of membrane PD-L1 is associated with clinical response to PD-L1 blockade and whether PD-L1 expression might serve as a marker for patient selection in the future development program of avelumab.

The tests and analyses to examine the biologic effects of the avelumab regimen will be the assessment of general markers of immune activation known to show typical changes after treatment with therapies blocking immune checkpoints. These details are specified in Section 7.6.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

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

Inclusion criteria for dose escalation, including the 10 mg/kg once weekly cohort:

1. Signed written informed consent.
2. Male or female subjects aged ≥ 18 years.
3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no standard therapy exists or standard therapy has failed. Availability of tumor archival material or fresh biopsies is optional for subjects in dose escalation.
4. ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months.
5. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1, except for subjects with metastatic CRPC or MBC who may be enrolled with objective evidence of disease without a measureable lesion.
6. Adequate hematological function defined by white blood cell (WBC) count ≥ 3×10^9/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). For subjects with

gastric cancer only, the acceptable parameters for WBC, ANC, and lymphocytes are as follows: WBC $\geq 2 \times 10^9$/L, ANC $\geq 1.0 \times 10^9$/L, and lymphocyte count $\geq 0.5 \times 10^9$/L.

7. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal range (ULN), an AST level $\leq 2.5 \times$ ULN, and an ALT level $\leq 2.5 \times$ ULN or, for subjects with documented metastatic disease to the liver, AST and ALT levels $\leq 5 \times$ ULN.
8. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula.
9. **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.)

Inclusion criteria for expansion phase:

1. Signed written informed consent.
2. Male or female subjects aged $\geq$ 18 years.
3. Subjects must have relapsed, refractory, or progressive disease following last line of treatment (with the exception of the NSCLC first-line and gastric and GEJ cancer primary cohorts, which do not require progression). Availability of tumor archival material or fresh biopsies (excluding bone biopsies) is mandatory for eligibility in the expansion cohorts. For subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration. Specifically, the following will be required:

   Primary expansion cohorts

   - **NSCLC post platinum doublet:** Histologically or cytologically confirmed stage IIIB or stage IV NSCLC that has progressed after 1 line of platinum-containing doublet chemotherapy. Subjects should have received only 1 line of platinum-containing treatment for metastatic disease (i.e., adjuvant treatment with a platinum-containing regimen is not sufficient for eligibility because not received in the context of a metastatic disease). Subjects in the NSCLC cohort will only be enrolled in the USA.

   - **NSCLC first line:** Stage IV (per 7th International Association for the Study of Lung Cancer [IASLC] classification) or recurrent NSCLC that is histologically proven. Subjects must not have received treatment for their metastatic or recurrent disease. No activating EGFR mutation nor ALK translocation / re-arrangement (non-squamous cell histologies require testing if status is unknown).

   - **Gastric and GEJ cancer, first-line maintenance or second-line:** Histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the gastric

and GEJ, treated with first-line chemotherapy combination in metastatic setting with or without disease progression. Subjects should have received no more than 1 line of treatment for metastatic disease. Subjects should not have been treated with trastuzumab (but can be Human Epidermal growth factor Receptor 2 [HER2] positive). Subjects who received any platinum containing doublet or triplet as a neoadjuvant chemotherapy strategy, but are not ultimately candidates for surgery will also be eligible. In addition, subjects with gastric cancer can enter in the study if their WBC is $\geq 2 \times 10^9$/L with ANC $\geq 1.0 \times 10^9$/L and lymphocyte count $\geq 0.5 \times 10^9$/L.

- **MBC:** Subjects must have histologically confirmed locally advanced or MBC and have tumor that is refractory to or progressive after standard of care therapy. Subjects must have received no more than 3 prior lines of cytotoxic therapy for metastatic disease. Subjects must have received a taxane and an anthracycline, unless contra-indicated.

Secondary expansion cohorts

- **CRC:** Histologically or cytologically confirmed recurrent or refractory metastatic CRC (according to AJCC/UICC TNM Staging System seventh edition) after failure of prior therapy containing oxaliplatin/fluoropyrimidine and/or irinotecan/fluoropyrimidine and, if eligible, cetuximab (Erbitux®) and bevacizumab (Avastin®). These subjects will be enrolled in sites located in the USA only.

- **CRPC:** Histologically or cytologically confirmed asymptomatic metastatic CRPC or minimally symptomatic (according to AJCC/UICC TNM Staging System seventh edition) with objective evidence of disease (non measureable or measurable lesion) with stable, ongoing adequate testosterone suppression proven by castrate levels of testosterone ($\leq$ 50 ng/dL), except for subjects with prior orchiectomy. Minimally symptomatic is defined as patients who do not require consistent treatment with opiates over the last month (less than 7 days of opiates in the last 28 days, and no opiates administered 3 days in a row), for the treatment of their prostate cancer. Additional androgen blockade or treatment with an anti-androgen receptor is acceptable. These subjects will be enrolled in sites located in the USA only.

- **Melanoma:** Histologically or cytologically confirmed stage IIIc or IV unresectable melanoma (according to AJCC/UICC TNM Staging System seventh edition) after failure of at least 1 prior standard therapy for metastatic disease. All subjects with metastatic melanoma will be required to undergo screening with a MRI or CT scan (either, with contrast preferred) to rule out brain metastases, unless imaging has previously been performed within 28 days prior to screening.

- **Ovarian cancer:** Histologically or cytologically confirmed recurrent or refractory (progression within 6 months of platinum-based therapy or progression after subsequent therapy in previously relapsed subjects), stage III-IV epithelial ovarian, fallopian tube or peritoneal cancer subjects (according to AJCC/UICC TNM and International Federation of Gynecology and Obstetrics (FIGO) Staging System seventh edition) who have progressed following adjuvant therapy or therapy for metastatic disease.

- **ACC:** Histologically or cytologically confirmed metastatic ACC. Subjects must have previously received at least 1 line of systemic therapy for metastatic disease, of which at least 1 must be platinum-based. Subjects receiving mitotane may continue to receive mitotane at enrolment and on study.

- **Mesothelioma:** Histologically or cytologically confirmed mesothelioma (pleural or peritoneal) with unresectable disease. Subjects must have received and progressed after either a platinum-pemetrexed containing regimen or a platinum-containing regimen followed by pemetrexed (or vice versa) after disease progression. Subjects must present with at least 1 measurable lesion that has not been irradiated.

- **Urothelial carcinoma:** Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra). A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Subjects can be either: ineligible for cisplatin-based chemotherapy or have progressed after treatment with at least 1 platinum-containing regimen (e.g., platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade $\geq$ 2 peripheral neuropathy. Subjects may have received any number of prior systemic therapies for metastatic disease.

- **Renal cell carcinoma, second-line with first-line expansion:** Histologically or cytologically documented RCC with a component of clear cell subtype, with metastasis. A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Eligible subjects must have measureable disease. Subjects must have failed 1 prior systemic first-line regimen for metastatic RCC (except for subjects enrolled in first-line expansion).

Efficacy expansion cohorts:

- **Gastric and GEJ cancer, third line:** Histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the gastric and GEJ, treated with both a first-line chemotherapy combination and followed by ramucirumab (alone or in combination). Subjects must have progressed during or after ramucirumab therapy. Subjects with gastric cancer can enter into the study if their WBC is $\geq 2 \times 10^9$/L with ANC $\geq 1.0 \times 10^9$/L and lymphocyte count $\geq 0.5 \times 10^9$/L.
- **Ovarian cancer, platinum refractory and prior liposomal doxorubicin:** Histologically or cytologically confirmed, platinum-refractory (progression within 6 months of platinum-based therapy), Stage III-IV epithelial ovarian, fallopian tube, or peritoneal cancer subjects (according to AJCC/UICC TNM and FIGO Staging System, 7th edition). Subjects must have received at least 1 line of prior platinum-based chemotherapy regimen, as well as prior liposomal doxorubicin (monotherapy or combination), in order to be considered eligible for this study. Subjects may have received any additional number of prior systemic therapies for metastatic disease.

- **Urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum-based therapy:** Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra). A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Subjects can be either: ineligible for cisplatin based chemotherapy or have progressed after treatment with at least 1 platinum-containing regimen (e.g., platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade ≥ 2 peripheral neuropathy. Subjects may have received any number of prior systemic therapies for metastatic disease.
- **Head and neck, platinum ineligible or progressed after at least 1 line of platinum-based therapy:** Histologically or cytologically documented recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx. Subjects must have experienced tumor progression or recurrence within 6 months of the last dose of any number of platinum-based chemotherapy regimens given in the adjuvant, primary, recurrent, or metastatic setting. Ineligibility to treatment with a platinum salt is defined by the existing of any (at least 1) of impaired renal function, a hearing loss of 25 decibels at 2 contiguous frequencies, or Grade ≥ 2 peripheral neuropathy. A tumor sample (1 tumor block or at least 7 unstained slides) must be available. Subjects may have received any number of prior systemic therapies for metastatic disease. Except for subjects who are platinum ineligible, subjects must have received at least 1 line of platinum-based chemotherapy.

4. ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months.
5. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1, except for subjects with metastatic CRPC who may be enrolled with objective evidence of disease without a measureable lesion.
6. Adequate hematological function defined by WBC ≥ 3 × 10^9/L with 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). For subjects with gastric cancer only, the acceptable parameters for WBC, ANC, and lymphocytes are as follows: WBC ≥ 2 × 10^9/L, ANC ≥ 1.0 × 10^9/L, and lymphocyte count ≥ 0.5 × 10^9/L.
7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN and an AST level ≤ 2.5 × ULN and an ALT level ≤ 2.5 × ULN for all subjects.
8. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula or measured 24-hour creatinine clearance (or local institutional standard method).
9. **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.)

5.3.2 Exclusion Criteria (applicable to all subjects, including all expansion cohorts)

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

1. Concurrent treatment with a non-permitted drug (see Section 6.5.2).

2. Prior therapy with any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-programmed death 1 (PD-1), anti-PD-L1, or CTLA-4 antibody. For subjects with metastatic melanoma, prior treatment with a CTLA-4 antibody is not an exclusion.

3. Concurrent anticancer treatment within 28 days before the start of trial treatment (e.g., cytoreductive therapy, radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin); major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy); use of hormonal agents within 7 days before the start of trial treatment, except for subjects in the CRPC cohort who may remain on treatment with luteinizing hormone-releasing hormone agonists or antagonists; or use of any investigational drug within 28 days before the start of trial treatment. Subjects in the gastric and GEJ cohort who have not progressed on first-line chemotherapy may be enrolled within the 28-day period following prior treatment provided all toxicity from prior therapy has resolved to Grade ≤ 1.

   Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the study treatment (with the exception of patients with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily). Steroids with no or minimal systemic effect (topical, inhalation) are allowed.

4. Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.

5. Rapidly progressive disease (e.g., tumor lysis syndrome).

6. Active or history of CNS metastases.

7. Receipt of any organ transplantation including allogeneic stem-cell transplantation.

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

- Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive).

9. Active or history of any autoimmune disease (subjects with diabetes Type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible) or immunodeficiencies.

10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.0), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of partly controlled asthma) (71).

11. Persisting toxicity related to prior therapy > Grade 1 NCI-CTCAE v4.0, however sensory neuropathy ≤ Grade 2 is acceptable.

12. Pregnancy or lactation period. Note: a negative pregnancy test is required for women of childbearing potential. Women who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months or follicle-stimulating hormone (FSH) > 40 milli international units per milliliter [mIU/mL]), or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status a FSH level will be included at screening.

13. Known alcohol or drug abuse.

14. Clinically significant (i.e., 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.

15. All other significant diseases (e.g., inflammatory bowel disease), which, in the opinion of the investigator, might impair the subject's tolerance of trial treatment.

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

17. Legal incapacity or limited legal capacity.

18. Vaccination within 4 weeks of the first dose of avelumab and while on study is prohibited except for administration of inactivated vaccines (e.g. inactivated influenza vaccines).

5.4 Criteria for Initiation of Treatment with the Investigational Medicinal Product

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

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal From 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.

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

In case of premature withdrawal from the trial, the investigations scheduled for the last visit should be performed (see Section 7.1.3 for end-of-treatment visit), if possible, with focus on the most relevant assessments. In any case, the appropriate case report form (CRF) section must be completed.

In the dose escalation part of the trial, only subjects who do not complete the DLT observation period (3 weeks) for reasons other than a DLT will be replaced. Subjects who require discontinuation of avelumab due to a DLT will not be replaced. In the expansion part of the trial, if a subject is withdrawn prior to progression for any reason, they will not be replaced except for the rule described above.

5.5.2 Withdrawal From the Investigational Medicinal Product

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

- 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 5.1.7.
- Occurrence of AEs, resulting in the discontinuation of trial drug being desired or considered necessary by the investigator and/or the subject (if applicable).
- Occurrence of pregnancy (if applicable).
- Use of a non-permitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP (the Sponsor may be contacted to discuss whether the trial treatment must be discontinued).
- Non-compliance (see Section 6.9).

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 risk-benefit judgment of the IMP, e.g., due to:
  - Evidence of inefficacy of the IMP.
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions.
  - Other unfavorable safety findings (Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g., toxicology).
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.
- Withdrawal of IMP(s) from the market for safety reasons (applicable to trials with marketed products only).

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.

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

5.7 Definition of End of Trial

The end of the trial will be defined as 1 year after the last subject completes his /her end-of-treatment visit.

If the trial is not terminated for a reason given in Section 5.6, the end of the trial is defined as 1 year after the last subject has received the last dose of avelumab.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term IMP refers to the investigational drug undergoing a clinical trial, as well as to any comparator drug or placebo (as applicable). In this trial, the IMP is avelumab and no comparator drug or placebo is involved.

6.1 Description of Investigational Medicinal Product(s)

Avelumab is a sterile, clear, and colorless solution intended for intravenous administration. It is presented at a concentration of 10 or 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum / yellow polypropylene flip off seal.

Each single-use 10 mg/mL vial contains 80 mg of avelumab as preservative-free acetate buffered solution (pH 5.5) containing mannitol, methionine, and polysorbate 20 (Tween 20), as stabilizers.

Each single-use 20 mg/mL vial contains 200 mg of avelumab as preservative-free acetate buffered solution (pH 5.2) containing mannitol and polysorbate 20 (Tween 20), as stabilizers.

For avelumab drug product, only excipients that conform to the current European Pharmacopeia and / or the current United States Pharmacopeia are used (see the latest Investigator's Brochure for additional details).

6.2 Dosage and Administration

Subjects will receive intravenous infusion of avelumab over 1 hour (-10 minutes / +20 minutes, i.e., 50 to 80 minutes) once every 2 weeks (for subjects in the 10 mg/kg once weekly cohort, once weekly for 12 weeks, then starting with Week 13, once every 2 weeks thereafter) (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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate. Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4.

The starting dose of avelumab in the dose escalation phase is 1.0 mg/kg (dose-escalation according to 3 + 3 design up to 10.0 mg/kg is intended) and the treatment cycle will be 2 weeks (14 days). The dose of avelumab in the expansion phases is 10 mg/kg.

The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation. Subjects will receive avelumab until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a confirmed 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. Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Appendix I).

In the case of study termination (see Section 5.6), subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).

Relevant clinical laboratory results essential for patient management decisions (hematology, biochemistry, liver function tests) must be available and reviewed before administration of avelumab.

6.3 Assignment to Treatment Cohorts

The investigator or delegate will assign a unique subject identifier number to eligible subjects in chronological order at the time of informed consent signature. 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.

The Sponsor's / CRO's medical responsible must confirm enrollment and dose level after receipt of the appropriate information relating to subject entry criteria.

This trial is not randomized. Therefore, no central treatment allocation is planned.

6.4 Other Drugs to be Used in the Trial

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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (i.v. antihistamines), bronchodilators, or equivalents and oxygen should be available for immediate access. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusions, subjects must be observed for 2 hours post infusion for potential infusion-related reactions. Please refer to the guidelines for handling of infusion-related reaction in Section 6.5.4.1.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity reaction according to the National Cancer Institute are found in Section 6.5.4. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and 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.

Further precautions are provided in Section 6.5.4. For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable non-steroidal anti-inflammatory drug (NSAID) dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start

of each dose of avelumab intravenous infusion. Alternative treatments for fever (e.g., paracetamol) may be given to subjects at the discretion of the investigator.

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines and Therapies

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 medication may be given at the investigator's discretion.

Other drugs to be used for prophylaxis, treatment of anaphylactic reactions, infusion-related reactions, severe hypersensitivity reactions / flu-like symptoms and tumor lysis syndrome are described in Sections 5.1.7.2, 6.4 and 6.5.4.

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 CRF.

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 CRF, 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 (48) and not based on the necessity for palliative bone directed radiotherapy.

6.5.2 Non-Permitted Medicines and Therapies

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had chemotherapy, radiotherapy (other than palliative bone directed radiotherapy as described in Section 6.5.1), major surgery, or received another investigational agent within 28 days before the start of study treatment.

The following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs (i.e., 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 (i.e., for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Any vaccine therapies for the prevention of infectious disease, except administration of inactivated vaccines (for example, inactivated influenza vaccine).
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion.

Clarification of Steroid Use:

Data indicate that corticosteroids have an adverse effect on T cell function (68) and that they inhibit and damage lymphocytes (69). Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA4 compounds indicate that short term use of steroids can be employed without compromising clinical outcomes (62). Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: limited to the treatment of infusion-related reactions and short term treatment of ir-AEs. The course of steroid treatment should be completed as soon as clinically feasible.
- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily are acceptable.
- Prophylactic use: prophylactic use, e.g., for the prevention of acute infusion-related reactions, constitutes concomitant use and is prohibited.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Sponsor may be contacted to discuss whether the trial treatment must be discontinued).

Medications others than those specifically excluded in this study (see above) may be administered for the management of symptoms associated with the administration of avelumab as required. These might include analgesics, anti-nausea 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 CRF, noting the name, dose, duration and indication of each drug.

6.5.3 Other Trial Considerations

The following non-drug therapies must not be administered during the study (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (e.g., mistle toe extract) or known to potentially interfere with major organ function (e.g., hypericin)
- Subjects should not abuse alcohol or other drugs during the study.

6.5.4 Special Precautions

As a routine precaution, subjects enrolled in this trial must be observed for 2 hours post infusion, in an area with resuscitation equipment and emergency agents. At all times during avelumab 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 anaphylactic 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 anaphylactic reaction. The treatment recommendations for infusion-related reactions, severe hypersensitivity reactions, and tumor lysis syndrome according to the NCI are outlined in Sections 6.5.4.1, 6.5.4.2 and 6.5.4.3, respectively. All infusion-related reactions, occurring during study drug infusion or after completion of the study drug administration, should be reported as AESIs or SAEs in case any serious criterion is met (see Section 7.4.1.4).

Investigators should also monitor subjects closely for potential irAEs, which may become manifest at the earliest 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 ANAs or ANCAs.

6.5.4.1 Infusion-related Reactions

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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate. Avelumab will be administered by i.v. infusion over a 1-hour period (-10 minutes / +20 minutes, that is, 50 to 80 minutes).

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

B. Management (see 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 recommended total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. 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 (e.g., 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.

i.v.=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

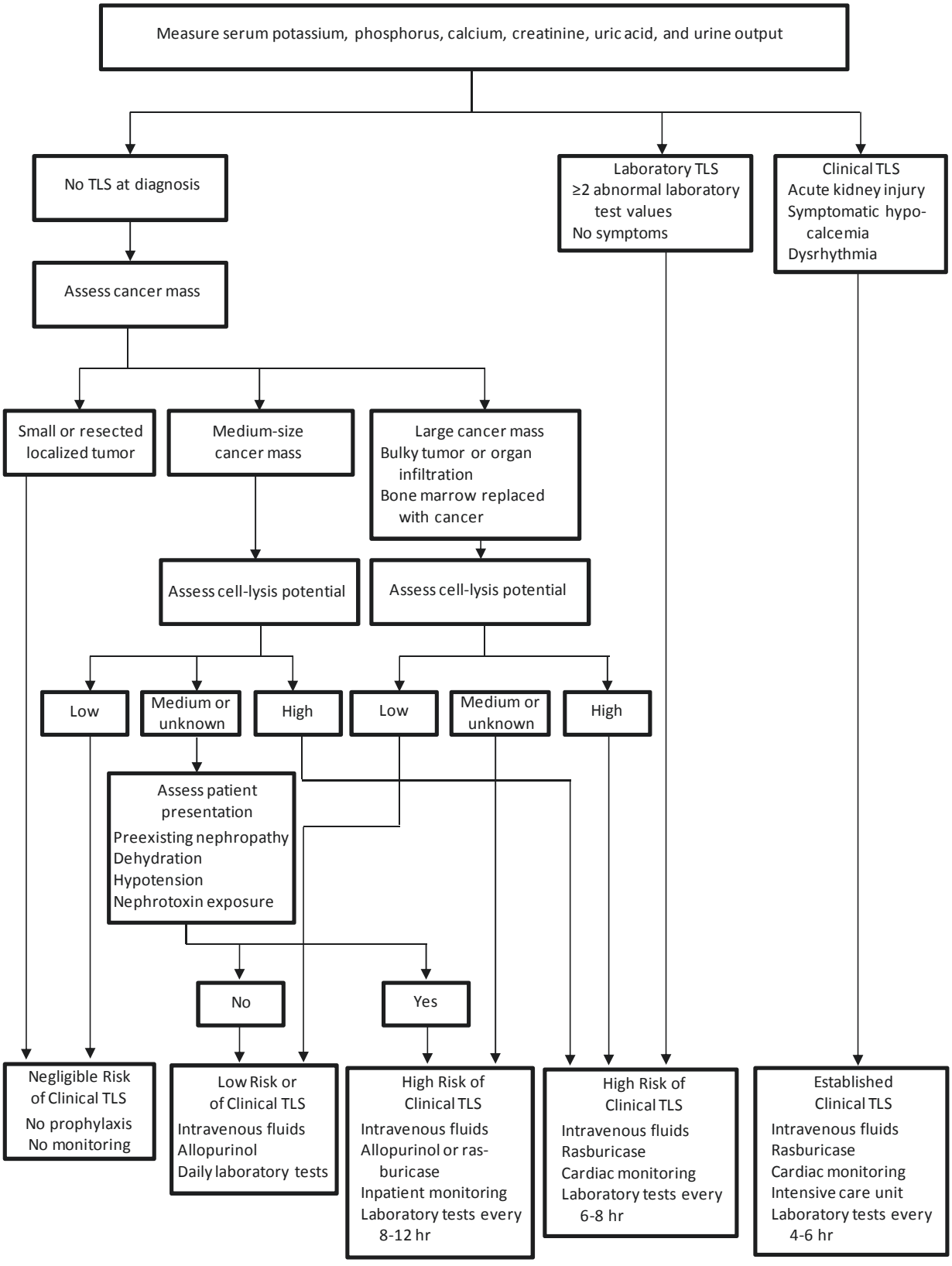
B. Management
   1. Epinephrine injection and dexamethasone infusion
   2. Patient should be placed on monitor immediately
   3. Alert intensive care unit (ICU) for possible transfer if required

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable NSAID dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab i.v. infusion. Alternative treatments for fever (e.g., 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 as per local guidelines and the management algorithm (Figure 6.1) published by Howard et al (56).

Figure 6.1 Assessment and Initial Management of Tumor Lysis Syndrome (TLS)



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, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.[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=computerized 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=non-steroidal 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 10.0 mg/mL or 20 mg/mL solution in single-use glass vials, with a rubber stopper. The Clinical Trial Supplies department of the Sponsor will supply the trial medication of avelumab, which will be distributed to the sites by the CRO.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab will be packed in boxes containing a suitable number of vials. The information on the medication 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 Preparation, Handling and Storage

For application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. 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 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 study center 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.

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

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.

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

6.8 Investigational Medicinal Product Accountability

The investigator is responsible for ensuring accountability for IMP, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of IMP, 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 IMP 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 monitor at each monitoring visit.
- IMP accountability records will include:
  - Confirmation of IMP delivery to the trial site.
  - The inventory at the site of IMP provided by the Sponsor and prepared at the site.
  - The use of each dose by each subject.
  - Destruction of unused treatment product (unused product will not be returned to the Sponsor).
  - Dates, quantities, batch numbers, expiry dates and (for IMP 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).
  - That all IMP provided by the Sponsor was fully reconciled.

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

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

At the conclusion or termination of this study, site study personnel and the clinical study 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 study 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 study).
- All destroyed units at the end of the study.
- Date of destruction(s).
- Name and signature of the investigator/pharmacist.

In addition, it must be ensured at each study site that the study drug is not used:

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

This is to be closely monitored by the study monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive trial treatment (avelumab intravenous infusions) at the investigational site. Well trained medical staffs 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 non-compliance should be documented.

Non-compliance is defined as a subject missing > 1 cycle of study treatment for non-medical reasons. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for non-medical reasons, the criteria of insufficient compliance are met as well.

6.10 Method of Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose 10% greater than the calculated dose for that particular administration. Any overdose must be recorded in the trial medication section of the CRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the Serious Adverse Event Report 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 investigational drug.

6.13 Medical Care of Subjects After End of Trial

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

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

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete schedule of assessments is provided in 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

There is a 28-day washout / recovery period for prior anticancer treatment (e.g., cytoreductive therapy, radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin) and major surgery before the start of trial treatment (Section 5.3.2). The screening procedures and baseline assessments will be completed within 18 days before trial treatment starts.

During the screening period and before any trial related investigations and assessments are started, the subjects will be asked to sign the relevant informed consent form(s) (ICFs). 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 the tumor disease,

previous and 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 complete physical examination including recording body height, vital signs including body weight, 12-lead ECG, and a determination of the ECOG performance status (Appendix II).

The screening laboratory examination includes hematology, hemostaseology, full serum chemistry, serum electrophoresis, and full urinalysis. Free thyroxine (T4), and thyroid-stimulating hormone (TSH) will also be assessed at screening.

During screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for women of child bearing potential and blood hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV testing will be performed for all screening subjects because these conditions are trial entry exclusion criteria (see Section 5.3.2). Women who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months or increased FSH > 40 mIU/ml), or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status an FSH will be drawn at screening.

The tumor evaluation (type / staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory) as well as tumor markers or any other established methods (see Section 7.2.5 for details). For expansion subjects, an MRI or CT scan (either, with contrast preferred) must be performed at screening in order to rule out brain metastases, unless imaging has previously been performed within 6 weeks prior to screening (within 28 days for melanoma cohort subjects). In subjects with gastric/GEJ cancer, HNSCC, ovarian cancer, CRPC, mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated.

Collection of tumor biopsies or archived surgical specimen will also be done during this period, if applicable (optional for the dose escalation phase). Subjects in the expansion phase are required to provide tumor tissue samples (the most recent biopsy or surgical specimen provided as block or slides), see Section 7.6.2.4 for details. In addition:

- For expansion subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration.
- For expansion subjects in the melanoma and mesothelioma cohorts, if an optional fresh biopsy is obtained prior to the first dose of trial treatment, there is no requirement to collect archive tissue for trial entry.

Subject eligibility will need to be confirmed by the CRO / Sponsor before the first administration of the study drug during the expansion phase only.

Following completion of the above screening assessments, baseline samples for ADA, CCI [redacted] and CCI [redacted] assessments should be collected prior to the first administration of avelumab, i.e., either during the screening period or pre-dose on Day 1. The term for ADA on CRF is human-antihuman antibodies (HAHA).

For expansion subjects in the ovarian cancer cohort only, blood sampling for cancer antigen 125 (CA-125) will be performed prior to the first administration of avelumab, i.e., either during the screening period or pre-dose on Day 1.

Subjects in the first-line NSCLC cohort with non-squamous cell histology and unknown EGFR and ALK status will have to be tested and found to be negative for EGFR-activating mutations and ALK rearrangements (see Section 7.6.2.4).

For subjects in the HNSCC cohort only, HPV status will be determined (see Section 7.6.2.4).

7.1.2 Treatment Period

In this trial, the treatment will be given until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a confirmed 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 the case of study termination (see Section 5.6), subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).

Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

Subjects will be asked to visit the investigational site every 2 weeks. 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 study procedures (except optional PK sampling visits on Days 2 and 3; see Section 7.5 for details). In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days). Furthermore, if any screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications. Subjects in the 10 mg/kg once weekly cohort will be asked to visit the investigational site once weekly (± 1 day) for the first 12 weeks then once every 2 weeks (-3/+1 days) starting on Week 13.

Subjects will receive avelumab i.v. infusion once every 2 weeks (subjects in the 10 mg/kg once weekly cohort will receive avelumab i.v. infusion once every week for the first 12 weeks, then once every 2 weeks starting on Week 13). 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] i.v. or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate. Avelumab will be administered by i.v. infusion over a 1-hour period (-10 minutes / +20 minutes, i.e., 50 to 80 minutes).

7.1.2.1 Dose Escalation Phase

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

- Except for the 10 mg/kg once weekly cohort (see Section 2.2.1), DLTs will be assessed during the first 3 weeks of trial treatment for each dose level of the dose escalation part (see Section 5.1.4.2).
- AEs and concomitant medications will be documented in each study visit.
- ECOG performance status will be assessed prior to trial treatment on Day 1 (unless the screening ECOG was performed within 3 days prior to Day 1) and every 2 weeks thereafter and documented in each study visit and at each weekly visit for the 10 mg/kg once weekly cohort.
- Physical examinations will be performed prior to trial treatment in each visit until Week 13 (except Days 2 and 3), and every 6 weeks thereafter.
- Vital signs will be assessed prior to trial treatment in each visit until Week 13 (except Days 2 and 3), and every 2 weeks thereafter.
- Body weight will be assessed prior to trial treatment every 2 weeks and at each weekly visit for the 10 mg/kg once weekly cohort.
- The 12-lead ECGs (assessed prior to infusion and 2 hours ± 20 minutes after infusion) will be assessed every 2 weeks until Visit 13, and every 6 weeks thereafter.
- The laboratory hematology and hemostaseology tests will be assessed prior to trial treatment and every 2 weeks thereafter and at each weekly visit for the 10 mg/kg once weekly cohort.
- Full serum chemistry will be assessed prior to trial treatment at Week 7 and Week 13 and every 6 weeks thereafter. Core serum chemistry will be performed at Week 3, Week 5, Week 9 and Week 11 and then every 2 weeks thereafter (and at each weekly visit for the 10 mg/kg once weekly cohort); if a full and core chemistry are scheduled at the same visit only the full chemistry will be performed. Full urinalysis will be performed at screening and a basic urinalysis will be performed prior to trial treatment every 2 weeks.
- Except for the 10 mg/kg once weekly cohort, a urine β-HCG pregnancy test will be performed prior to each administration of the study drug (if applicable). For the 10 mg/kg once weekly cohort, a pregnancy test should be performed every 4 weeks.
- Except for the 10 mg/kg once weekly cohort, the tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks, with a tumor assessment visiting time window of 5 days prior to dosing. For the 10 mg/kg once weekly cohort, tumor assessments

will be once every 6 weeks for the first 12 months from the first dose (until Week 55), then every 12 weeks thereafter.

- Except for the 10 mg/kg once weekly cohort, PK samples will be drawn on Days 1, 2, 3, 15, 29, 43, 85, 127, and 169 (see Section 7.5 for details). PK sampling on Days 2 and 3 is optional. For the 10 mg/kg once weekly cohort, blood samples for PK determinations will be collected from all subjects within 2 hours prior to each infusion at Weeks 1, 2, 3, 5, and 7 (every 2 weeks), at Weeks 13, 15, 19, and 25, and then at 12-week intervals while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7, 13, and 25.
- ACTH, ANA, ANCA, RF, free T4, and TSH will be measured prior to trial treatment every 6 weeks during the treatment period, from Week 7 onwards. For the 10 mg/kg once weekly cohort, samples for ACTH, ANA, and RF as indicted in the Schedule of Assessments and as clinically indicated. Samples for free T4 and TSH will be 6-weekly.
- ADA samples will be drawn on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 (see Section 7.7.1). For the 10 mg/kg once weekly cohort, samples for ADA determination will be collected Days 1 (baseline), 15, 29, 43, 57, 71, 85, Week 19, and on Week 25 and every 12 weeks thereafter. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1. The term for ADA on CRF is human-antihuman antibodies (HAHA).
- Except for the 10 mg/kg once weekly cohort, receptor occupancy test will be performed on Days 1, 3, 15, 29, 43, and 85 (see Section 7.6.1). Receptor occupancy will not be determined for the 10 mg/kg once weekly cohort.
- The immunomonitoring and soluble factors will be performed as described in Section 7.6.1.2 and Appendix I. Immune monitoring will not be performed for the 10 mg/kg once weekly cohort.

7.1.2.2 Expansion Phase

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

- AEs and concomitant medications will be documented in each study visit.
- ECOG performance status will be assessed prior to trial treatment at Day 1 (unless the screening ECOG was performed within 3 days prior to Day 1) and every 2 weeks thereafter.
- Physical examinations will be performed prior to trial treatment in each visit until Week 13 (except Day 2 and Day 3), and every 6 weeks thereafter.
- Vital signs and body weight will be assessed prior to trial treatment in each visit until Week 13 (except Day 2 and Day 3), and every 2 weeks thereafter.
- The 12-lead ECGs (assessed prior to infusion and 2 hours ± 20 minutes after infusion) will be assessed every 2 weeks until Visit 13, and every 6 weeks thereafter.
- The laboratory hematology and hemostaseology tests will be assessed prior to trial treatment and every 2 weeks thereafter.

- Full serum chemistry will be assessed prior to trial treatment, at Week 7 and Week 13 and then every 6 weeks thereafter. Core serum chemistry will be performed at Week 3, Week 5, Week 9 and Week 11 and every 2 weeks thereafter; if a full and core chemistry are scheduled at the same visit only the full chemistry will be performed. In addition, for subjects with liver metastases at baseline, samples for ALT, AST, total bilirubin, and alkaline phosphatase determination will be collected at Weeks 2, 4, and 6. Full urinalysis will be performed at screening and a basic urinalysis will be performed prior to trial treatment as defined in Appendix I (except for subjects with urothelial cancers, whose urine is usually unfit for analytical purposes).
- The urine β-HCG pregnancy test will be performed every 4 weeks in premenopausal women (before administration of the study drug).
- The tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks for the first 12 months then every 12 weeks thereafter, with a tumor assessment visiting time window of 5 days prior to dosing.

  Melanoma and mesothelioma: For subjects in the melanoma and mesothelioma cohorts only, fresh biopsies may be obtained on Day 43. These biopsies are optional.

  Mesothelioma: For subjects in the mesothelioma cohort only, tumor biopsies (core needle biopsies) may be performed between Cycles 2 and 3, and in the case of disease progression, to differentiate between actual disease progression and a tumor flare resulting from intratumor inflammation. These biopsies are optional. See Section 7.3.

  Efficacy expansion cohorts and first-line NSCLC primary expansion cohort: For subjects in the efficacy expansion cohorts and the first-line NSCLC primary expansion cohort, fresh biopsies may also be collected on Days 43 and at the end-of-treatment visit. These biopsies are optional.
- **Ovarian cancer**: For subjects in the ovarian cancer cohorts only, blood sampling for CA-125 will be performed at Week 7, and then once every 6 weeks.
- PK samples
  - Will be drawn prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 for all subjects in the primary NCSLC (post platinum doublet cohort), gastric / GEJ cancer, and MBC cohorts.
  - Will be drawn prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 for all subjects in the secondary ACC, melanoma, mesothelioma, ovarian cancer, and urothelial carcinoma cohorts.
  - Will be drawn prior to each administration of study drug on Days 1, 2, 3, 15, 29, 43, 85, 127, and 169 (see Section 7.5 for details) for all subjects in the secondary CRC and CRPC cohorts. PK sampling on Days 2 and 3 is optional. Additionally, samples will be drawn on Day 1 at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours post infusion.
  - Will be drawn prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, 99, and 169 for subjects in the first-line NSCLC cohort. Post-study drug administration samples

will also be collected immediately after the end of the infusion and also 2 to 8 hours after the end of infusion (later is better depending on how long the subject will stay in the clinic), on Days 1, 43, 85, and 169 while on treatment. Samples will also be collected at the 10-week safety follow-up visit.

  - Will be drawn prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, and 169 for subjects in the efficacy expansion cohorts and the RCC secondary cohort. Post-study drug administration samples will be collected immediately after the end of infusion and 2 to 8 hours after the end of infusion (later is better, depending on how long the subject will stay in the clinic) at Days 1, 43, 85, and 169. Exact sampling times will be recorded. Samples will be collected at the 10-week Safety Follow-up visit.
  - For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, PK samples will be drawn prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation.

- Free T4 and TSH will be measured prior to trial treatment at Week 13, Week 25, end-of-treatment, and if clinically indicated.
- ADA samples will be drawn on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 (see Section 7.7.1). The term on CRF is human-antihuman antibodies (HAHA).
  - For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, ADA samples will be drawn prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation.
- Receptor occupancy test will be performed for subjects in the CRC and CRPC cohorts only on Days 1, 15, 29, 43, and 85 (see Section 7.6.2.1).
- The immunomonitoring samples will be collected for all subjects enrolled in the secondary expansion cohorts, except for the RCC cohort, as described in Section 7.6.2.2 and Appendix I.
- The soluble factors will be performed on all subjects in the primary and secondary expansion cohorts, except for the RCC cohort, before start of first infusion (Day 1) and on Day 43. In addition, except for the RCC cohort, all subjects enrolled in the secondary expansion cohorts will also have samples drawn 48 hours (±6 hours) after start of first infusion (Day 3, optional). See Section 7.6.2.2 and Appendix I for details. CCI [redacted]
- For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, blood samples for CCI [redacted] will be collected before the start of infusion on Days 1, 15, 29, and 43.

PK sampling on Days 2 and 3 are optional and only applicable for subjects in the secondary CRC and CRPC cohorts (expanded PK sampling). Therefore, the visit at Day 2 is optional; however should a subject attend, blood draws for PK sampling and soluble factors (as applicable) are strongly encouraged.

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 consists of:

- Documentation of AEs and concomitant medication.
- Physical examination including vital signs and body weight.
- The 12-lead ECGs.
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis.
- ECOG performance status will be assessed.

End-of-treatment visit

The end-of-treatment visit is scheduled 4 weeks (28 days) after the last administration of avelumab 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, which will include the following (refer to Appendix I):

- AEs, and concomitant medications, and vital signs and body weight.
- Physical examinations.
- The 12-lead ECGs.
- The laboratory hematology, hemostaseology, full serum chemistry, serum electrophoresis tests and full urinalysis.
- ECOG performance status will be assessed.
- The urine β-HCG pregnancy test (in women of child bearing potential).
- The tumor evaluation (only to be performed, if no disease progression was documented previously).
- ADA sample (any remaining sample may be used for PK determination) (see Section 7.7.1). The term on CRF is human-antihuman antibodies (HAHA). For the 10 mg/kg once weekly cohort, a blood sample for PK determination will be collected.
- The immunomonitoring and soluble factors will be performed as described in Section 7.6.1.2 and Appendix I.

For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, blood samples for CCI [redacted] CCI [redacted]

Melanoma and mesothelioma: For subjects in the melanoma and mesothelioma cohorts only, fresh biopsies may be obtained at the end-of-treatment visit. These biopsies are optional.

Ovarian cancer: For subjects in the ovarian cancer cohort only, blood sampling for CA-125.

- T4 and TSH levels.
- ADA sampling.
- Immunomonitoring for all subjects.
- Soluble factors assessments.

7.1.4 Post-Treatment Safety Follow-Up

All subjects will have a subsequent visit scheduled 10 weeks after the last administration of avelumab. The visit will include the following full assessment of safety parameters (refer to Appendix I):

- Any treatment related AEs and concomitant medications will be documented, including further anti-cancer therapy.
- Vital signs and body weight will be measured.
- Physical examination will be performed.
- ECOG performance status will be assessed.
- 12-lead ECG will be assessed.
- Laboratory testing consisting of the following will be assessed:
  - hematology, hemostaseology, full serum chemistry, and full urinalysis
  - T4 and TSH levels
  - PK sample (any remaining sample may be used for ADA determination)
- A urine β-HCG pregnancy test (in women of child bearing potential) will be conducted.

After the End-of-Treatment visit only treatment-related AEs have to be documented until the Post-treatment Safety Follow-up visit. Subjects with a SAE ongoing at the post-treatment 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."

Subjects without progressive disease according to RECIST 1.1 at the end-of-treatment visit will be followed up for radiographic disease progression (CT / MRI scans) every 12 weeks up to 1 year.

After the end-of-treatment visit, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab.

7.1.5 Blood Consumption 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, PK analyses, exploratory biomarker investigation, and antibody evaluation.

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 recoded:

- Subject identifier
- Date of birth
- Sex
- Race

7.2.2 Diagnosis of Tumor

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

- Detailed history of the tumor including histopathological diagnosis, grading and staging in accordance with the International Union Against Cancer Tumor Node Metastasis Classification at diagnosis (UICC TNM).
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy).
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy.
- Current cancer signs and symptoms and side effects from current and / or previous anticancer treatments.
- Current cancer disease status.
- HER2 status if available (gastric / GEJ cancer only)
- Smoking history.
- EGFR-activating mutation or ALK re-arrangement status (NSCLC non-squamous cell histology only).
- HPV status (HNSCC only).

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 non-malignant diseases and treatments.

- All medications taken and procedures carried out within 30 days prior to screening.

For the trial entry, all 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 study entry.

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

The ECOG performance status will be documented during the screening phase.

Body weight and height will be recorded.

7.2.5 CT or MRI Scans for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis (at a minimum and other established assessments of tumor burden if CT / MRI imaging is not sufficient for the individual subject; other regions as specifically required for specific tumor indications) will be performed within 18 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT / MRI does not need to be performed.

A brain CT / MRI scan (either, contrast preferred) is required at screening if not performed within the previous 6 weeks (within 28 days for subjects in the melanoma cohort). In subjects with gastric/GEJ cancer, HNSCC, ovarian cancer, CRPC, mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.

A bone scan should be done at screening as clinically indicated.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at screening, at regular intervals during treatment, at the end of treatment and at the post-treatment follow-up visit. ECGs will be recorded 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 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

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

A brain CT / MRI scan (either, with contrast preferred) is required at screening if not performed within the previous 6 weeks (within 28 days for subjects in the melanoma cohort). In subjects with gastric/GEJ cancer, HNSCC, ovarian cancer, CRPC, mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated. Thereafter brain CT / MRI scan should be performed, if clinically indicated by development of new specific symptoms. A bone scan should be done at screening and beyond as clinically indicated. Skin metastasis can be used as target lesions according to RECIST 1.1 using measurements by caliper, if they fulfill RECIST 1.1 for target lesions as described below. The presence of new cutaneous lesions will be considered diagnostic of progression for RECIST 1.1, even if not imaged. 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 have to 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).

The foreseen treatment duration is until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). **Before stopping the**

treatment, progressive disease should be confirmed by imaging preferably 6 weeks (but not later) after progression has been diagnosed according to RECIST 1.1. Evidence of progression of prostate cancer within the first 3 months on bone scan only should be interpreted with extreme caution due to risk of tumor flare. If progression is based on the occurrence of a new lesion in an area not scanned at baseline, a further on-study scan 6 weeks later should be considered before performing the end-of-treatment visit. Treatment may be continued despite progression according to RECIST 1.1 at any time if:

- There are no new symptoms or worsening of existing symptoms.
- There is no decrease in ECOG performance status.
- The investigator does not consider it necessary to administer a salvage therapy.

The treatment should be stopped immediately, if the subject does not tolerate avelumab anymore or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression/deterioration.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation, see reference 48).

- 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 non-target lesions as described in reference 48.

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 partial response (PR) should be confirmed as described in reference 48. **In the case of a PR or CR, a confirmatory CT or MRI scan must be done no sooner than 28 days (preferably at the scheduled 6-week interval)**.

The investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the investigator suspects progressive disease.

As outlined in Section 5.1, treatment may continue with the investigational drug(s) and the subject may remain on study according to the investigator's decision and in agreement with the subject in case of progressive disease according to RECIST 1.1. Following PD on RECIST 1.1, modified "immune related response criteria" (irRC; see below and reference 48) should be used as guidance for further clinical care.

Subjects who have experienced a confirmed 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. Subjects who experienced a CR and have already stopped treatment can resume treatment with avelumab at the same dose and schedule. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Appendix I).

Melanoma and mesothelioma: For subjects in the melanoma and mesothelioma cohorts only, fresh biopsies may be obtained on Day 43 and at the end-of-treatment visit. These biopsies are optional.

Mesothelioma: For subjects in the mesothelioma cohort only, tumor biopsies (core needle biopsies) may be performed between Cycles 2 and 3, and in the case of disease progression, to differentiate between actual disease progression and a tumor flare resulting from intratumor inflammation. These biopsies are optional. Should the histology of the biopsy performed be consistent with tumor progression, treatment with avelumab may continue at the discretion of the investigator provided there is no significant clinical deterioration.

Efficacy expansion cohorts and first-line NSCLC primary expansion cohort: For subjects in the efficacy expansion cohorts and the first-line NSCLC primary expansion cohort, fresh biopsies may also be collected on Days 43 and at the end-of-treatment visit. These biopsies are optional.

Modified immune-related response criteria (irRC), derived from RECIST 1.1

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. For this trial, the concepts of the irRC (72) are combined with RECIST 1.1 to come up with the modified irRC, which uses unidimensional measurements.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging (evidence of progression of prostate cancer within the first 3 months on bone scan only should be interpreted with extreme caution due to risk of tumor flare) and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by $\geq$ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm or less.

Overall irPR: Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.

Overall irSD: Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).

Overall irPD: Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Documentation of immune-related PD (based on modified irRC), does not mandate discontinuation of the study treatment even after irPD is confirmed with CT scan 6 weeks after the initial observation of irPD. Please refer to Section 5.5.2 (Withdrawal from the Investigational Medicinal Product) to determine when it is appropriate to discontinue treatment with the study drug.

Overall responses derived from changes in index, non-index, and new lesions as demonstrated in Table 7.1.

Table 7.1 Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)	**Non-Index Lesions**	**New, Non-Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR[1]
Decrease 100%	Stable	Any	irPR[1]
Decrease 100%	Unequivocal progression	Any	irPR[1]
Decrease ≥ 30%	Absent / Stable	Any	irPR[1]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[1]
Decrease < 30% increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

[1] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

7.4 Assessment of Safety

The safety profile of the IMP 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, "Methods of Recording and Assessing Adverse Events"). Given the intended MoA, 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 assessment (refer to Appendix I).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have 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, v4.0 (publication date: 28 May 2009). This is a descriptive terminology that can be used for AE reporting.

A general grading (severity / intensity) scale is provided at the beginning of the referenced document, and specific event Grades are also provided.

If a particular AE's severity/intensity is not specifically graded by the guidance document, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death related to AE

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the investigator must also report the event as an SAE as per Section 7.4.1.4. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets 1 of the serious criteria described below.

In the case of death, the primary cause of death or the 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 separate event. Only if no cause of death can be reported (e.g., 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 IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to avelumab include, but may not be limited to, temporal relationship between the AE and avelumab, known side effects of avelumab, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., 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 an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Adverse Drug Reaction (ADR)

ADRs are defined in this trial as any AEs suspected to be related to avelumab by the investigator and / or Sponsor.

Serious Adverse Event (SAE)

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

- Results in death.
- Is life-threatening.

NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

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 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner 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 (e.g., 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 (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

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

Pre-defined Potential AEs of Special Interest (AESI) for Safety Monitoring

Any infusion reaction, regardless of grade, must be reported in an expeditious manner and will be considered an AE of special interest (AESI).

The reporting of AESI is defined in Section 7.4.1.4.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/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 CRF. Among these AEs, all SAEs and all nonserious AEs of special interest 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 IMP) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the CRF 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 included into the trial (date of first signature of informed consent) and continues through the trial's End-of-Treatment visit, 28 days after last trial drug administration. After the End-of-Treatment visit only treatment-related AEs have to be documented through the post-treatment safety follow-up period, defined as 10 weeks after the last trial drug 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 / Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE (of any Grade) occurring during the reporting period, the investigator must immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the Sponsor or designee by telephone, by fax or by e-mail.

When an event (or follow-up information) is reported by telephone, 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).

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the SAE Report Form.

All written reports should be transmitted using the SAE Report Form, which must be completed by the investigator following specific completion instructions. The AE section of the CRF must be completed. Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs).

In all cases, the information provided in the SAE Report Form must be consistent with the data on the event that is recorded in the corresponding sections of the CRF.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor or designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Monitor, although in exceptional circumstances the Global Drug Safety department of the Sponsor may contact the investigator directly to obtain clarification or to discuss a particularly critical event.

Adverse Events of Special Interest

In the event of a non-serious immune-related reaction, the investigator must complete the AESI Report Form and send it to the Sponsor/designee immediately within 24 hours. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above.

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/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's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor or designee will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or designee will provide appropriate Safety reports directly to the concerned health authority and lead IEC / IRB and will maintain records of these notifications. When direct reporting by the Sponsor or designee 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 Post-treatment Safety Follow-up visit, defined as 10 weeks after the last trial drug administration. All SAEs ongoing at the post-treatment 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 (e.g., resulting from a drug interaction with a contraceptive medication) are considered as 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 CRF. The same rule applies to pregnancies in female subjects and 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 subjects are withdrawn from the trial.

The investigator must notify the Sponsor or designee of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the SAE Report Form when the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form when 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 trial medication immediately. The Sponsor or designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Laboratory Assessments

It is essential that the Sponsor 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 non-fasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site.

Relevant results essential for patient management decisions (hematology, biochemistry, liver function tests) must be available and reviewed before administration of avelumab.

The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the tests listed in Table 7.2 will be taken from non-fasted subjects during the screening phase (within 18 days prior to the first treatment administration), at the end-of-treatment visit, and during the treatment phase as specified in Appendix I. Serum electrophoresis, T4, TSH and urinalysis will be assessed at the time points defined in 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 7.2 Required Laboratory Panel Tests

Full Chemistry	**Hematology**
Albumin	Absolute lymphocyte count
Alkaline phosphatase*	Absolute neutrophil count
ALT (SGPT)*	Hematocrit
Amylase	Hemoglobin
AST (SGOT)*	Platelet count
Gamma glutamyltransferase (GGT)	Red blood cells (RBC)
Blood urea nitrogen (BUN)/Total urea*	WBC and differential count
Calcium*	RBC morphology[#]
Chloride*	Reticulocytes[#]
Cholesterol	Mean corpuscular hemoglobin (MCH)
Creatine kinase	Mean corpuscular volume (MCV)
Creatinine*	Mean corpuscular hemoglobin concentration (MCHC)
C-reactive protein (CRP)	
Glucose*	**Hemostaseology**
Lactate dehydrogenase (LDH)	Activated partial thromboplastin time (aPTT)
Lipase	Prothrombin time (INR)
Phosphorus/Phosphates*	
Magnesium*	**Urinalysis***** **Full:** protein content**, albumin **Basic (dipstick)**: protein content only**
Potassium*	
Serum electrophoresis[#]	
Sodium*	
Total bilirubin*	
Total protein	Totality of binding ADA
Uric acid	
Triglycerides	ACTH (10 mg/kg once weekly cohort), ANA (10 mg/kg once weekly cohort), RF (10 mg/kg once weekly cohort), **TSH, and T4**.
Hormone	
Follicle-stimulating hormone (if applicable)	

ACTH: adrenocorticotropic hormone; ADA: anti-drug antibody; ALT: alanine aminotransferase; ANA: anti-nuclear antibody; AST: aspartate aminotransferase; RF: rheumatoid factor; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; T4: Free thyroxine; TSH: Thyroid-stimulating hormone.

*Core serum chemistries.
**If urinalysis is positive for protein, sediment will also be evaluated.
*** Urinalysis does not have to be performed on subjects with urothelial cancers.
[#] Only if clinically indicated.

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 performance status will be assessed at screening and at subsequent visits as indicated in the schedule of assessments and documented in the CRF.

Body weight will be measured at screening and at subsequent visits as indicated in the schedule of assessments and documented in the CRF. 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 CRF (detailed description in Section 7.1). Results of the physical examination including any abnormalities will be documented in the CRF. Abnormal findings are to be reassessed at subsequent visits.

A 12-lead ECG will be recorded at screening and at study visits as indicated in the schedule of assessment.

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

For female subjects of childbearing potential, serum β-HCG pregnancy test will be carried out during the screening phase. A urine β-HCG test will be performed before administration of IMP during the treatment phase according to schedules of assessments (Appendix I), at the end-of-treatment visit and at the post-treatment follow-up visit. Results of the most recent pregnancy test should be available prior to the next dosing of IMP. Subjects that are postmenopausal (age-related amenorrhea ≥ 12 consecutive months or FSH > 40 mIU/ml), or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

7.5 Pharmacokinetics

7.5.1 Dose Escalation Phase

Pharmacokinetic parameters include $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, λz, C_{max}, t_{max}, and $t^{1}/_{2}$ (for definitions, see Section 8.5.3.2). Blood samples for the analysis of serum concentrations of avelumab will be drawn in all subjects according to the schedule listed below and the Schedule of Assessments (see Appendix I).

- Day 1: prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours after infusion.
- Day 2: 24 and 36 hours after infusion (optional).
- Day 3: 48 hours after infusion (±6 hours) (optional).
- Days 15, 29, 43, 85, 127, and 169: prior to infusion (trough value) and immediately after infusion is completed (peak value).

- For the 10 mg/kg of avelumab once weekly cohort, blood samples for PK determinations will be collected from all subjects within 2 hours prior to each infusion at Weeks 1, 2, 3, 5, and 7 (every 2 weeks), at Weeks 13, 15, 19, and 25, and then at 12-week intervals while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7, 13, and 25. Samples will be collected at the End-of-Treatment visit and the Safety Follow-up visit.

7.5.2 Expansion Phase

- PK samples will be obtained prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 for all subjects in the primary cohorts (NCSLC post platinum doublet, gastric / GEJ cancer, and MBC).
- PK samples will be obtained prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 for all subjects in the ACC, melanoma, mesothelioma, ovarian cancer, and urothelial carcinoma secondary cohorts.
- Expanded PK sampling will be performed for all subjects in the CRC and CRPC secondary cohorts as follows:
    - Day 1: prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours after infusion.
    - Day 2: 24 and 36 hours after infusion (optional).
    - Day 3: 48 hours after infusion (±6 hours) (optional).
    - Days 15, 29, 43, 85, 127, and 169: prior to infusion (trough value) and immediately after infusion is completed (peak value).
- Expanded PK sampling will be performed for all subjects in the first-line NSCLC cohort as follows:
    - Within 2 hours prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, 99, and 169.
    - Post-study drug administration samples will be collected at the end of the infusion and also 2 to 8 hours after the end of infusion (later is better depending on how long the subject will stay in the clinic), on Days 1, 43, 85, and 169.
    - Samples will also be collected at the 10-week safety follow-up visit (any remaining sample may be used for ADA determination).
- For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, samples for PK determination will be collected as follows:
    - Within 2 hours prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, and 169.
    - Post-study drug administration samples will be collected at the end of infusion and 2 to 8 hours after the end of infusion (later is better, depending on how long the subject will stay in the clinic) at Days 1, 43, 85, and 169. Exact sampling times will be recorded.

- Samples will be collected at the 10-week Safety Follow-up visit (any remaining sample may be used for ADA determination).

- For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, PK samples will be drawn as follows:
  - Within 2 hours prior to the second retreatment infusion, then prior to infusion 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation (e.g., pre-dose at Weeks 3, 5, 11, 17, and 23).

7.5.3 Body Fluid

Whole blood sufficient to provide 2 mL of plasma/serum will be collected for PK assessments. Post-infusion samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on the days of infusion. If the infusion is interrupted, the reason for interruption will be documented on the CRF.

Further details will be summarized in the Laboratory Manual.

7.6 Biomarkers and CCI [redacted]

Due to limited understanding of the biological activities induced by avelumab in cancer subjects, there can be no certainty that the doses examined will be associated with relevant anti-tumor immune activities. As the consequence, in addition to determining the MTD, the study will serve to 1) evaluate receptor occupancy at different levels, 2) investigate the mechanism of action of the drug by monitoring the activation status of the immune system (e.g., leukocyte subsets, PD-1 signaling pathway, ADCC-related activities, cytokines profile, soluble PD-1, and soluble PD-L1) in order to establish the optimal biological dose, 3) investigate safety markers (see Section 7.4), 4) explore anti-tumor specific immune responses induced by the exposure to avelumab, and 5) evaluate potential predictive / prognostic biomarker candidates related to the drug and/or the cancer (e.g., level of PD-L1 tumor expression, profile of tumor infiltrating cells).

Details of time points and sampling are provided in Appendix I. Time points and markers proposed in the expansion part may change based on biological activities to be observed in the escalation part and /or indications.

In order to complete all the assessments on tumor materials, blood (plasma and serum samples), the Sponsor or the designated CRO will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. Please refer to the Laboratory Manual for detailed information.

CCI [redacted]

CCI [redacted]

7.6.1 Biomarker Investigation in Dose Escalation Cohorts

7.6.1.1 Receptor Occupancy – Dose Escalation Phase

Eight mL of blood will be collected in heparinized tube (one 8 mL Cell Preparation Tube™ [CPT]) to analyze receptor occupancy on Day 1 before start of the infusion, at 4 and 48 hours (±6 hours; Day 3) after the start of infusion, and before the start of each infusion on Days 15, 29, 43, and 85 for subjects in dose escalation phase. Note: no samples will be obtained for receptor occupancy from the 10 mg/kg once weekly cohort.

7.6.1.2 Immunomonitoring

As biomarker research is constantly evolving, the selection of markers with the highest specificity and relevance to treatment effect may change.

Leukocyte subpopulations and immune activation status will be assessed by flow cytometry (FACS) on PBMC from heparinized blood samples (16 mL, two 8 mL CPTs) drawn before start of each infusion, and 48 hours (±6 hours) after start of each infusion on Days 1, 43, 85, and before start of infusion only on Days 15, 127, and 169. Supplementary 16 mL (two 8 mL CPTs) of blood will be collected at the end-of-treatment visit (within 28 days after the last treatment) for biological follow-up. A complete differential blood count will be provided for each time point for calculations of the absolute count of leukocyte subpopulations. From these samples, plasma (3 to 5 mL) will be collected for retrospective analyses, if technically feasible. Note: no samples will be obtained for immune monitoring from the 10 mg/kg once weekly cohort.

Soluble factors (e.g., cytokines profile, soluble PD-1, and soluble PD-L1) will be assessed on blood (plasma/serum) samples collected before start of each infusion and 48 hours (±6 hours) after start of each infusion on Days 1 (baseline value, if not collected at screening), 43, 85, and before start of infusion only on Days 15, 127, and 169. One additional blood sample for soluble factors will be collected at the end-of-treatment visit (within 28 days after the last treatment) for biological follow-up. In addition, any remaining backup PK and ADA serum samples may be used for assessment of soluble factors if needed. For the 10 mg/kg once weekly cohort, blood samples for soluble factors will be collected before start of each infusion on Days 1 (baseline), 8, 15, 29, 43, and 85.

CCI [redacted]

7.6.2 Biomarkers Investigation in Expansion Cohorts

Of note, time points and markers in this section may change on the basis of the results to be observed in the escalation part and /or indication.

7.6.2.1 Receptor Occupancy – CRPC and CRC Cohorts

Eight mL of blood will be collected in heparinized tube (one 8 mL CPT) to analyze receptor occupancy on Day 1 before start of the infusion, at 4 hours (±6 hours) after the start of infusion, and before the start of each infusion on Days 15, 29, 43, and 85 for subjects in the CRPC and CRC cohorts.

7.6.2.2 Immunomonitoring

Primary Cohorts (NSCLC post platinum doublet and first-line, Gastric / GEJ Cancer, MBC):

Soluble factors (e.g., cytokines profile) will be assessed on blood samples collected before start of infusion (Day 1), Day 43, and at the end-of-treatment visit (within 28 days after the last treatment). In addition, any remaining backup PK and ADA serum samples may be used for assessment of soluble factors if needed.

Secondary Cohorts (except for the RCC Cohort):

Leukocyte subpopulations and immune activation status will be assessed by flow cytometry using heparinized blood. All expansion subjects in the secondary cohorts will have 40 mL of blood (five 8 mL CPTs) collected before start of infusion at Days 1 (if not collected at screening), 15, 43, and 85, and at the end-of-treatment visit. Additionally, 40 mL of blood will be collected 48 hours (±6 hours; Day 3) after the start of the first infusion only of IMP in these subjects (this sample is optional). Until completion of the escalation part, it is planned to consider similar markers (see Section 7.6.1.2).

CCI [redacted]

Soluble factors (e.g. cytokines profile) will be assessed on blood samples at the same times as the primary cohorts (Day 1, Day 43, and at the end-of-treatment visit [within 28 days after the last treatment]). In addition, subjects in the secondary expansion cohorts will have blood drawn 48 hours after start of first infusion only (±6 hours; Day 3; this sample is optional). In addition, any remaining backup PK and ADA serum samples may be used for assessment of soluble factors if needed.

CCI [redacted]

Efficacy Expansion Cohorts and the RCC Secondary Cohort:

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.6.2.4 Predictive/Prognostic Biomarkers

It is important to identify biomarkers that help to predict and/or evaluate the efficacy of the therapy, in order to achieve the optimal benefit from targeted therapies. No thoroughly validated biomarkers are available to date for anti-PD-1 / PD-L1 therapies. Therefore, this trial plans to evaluate biomarkers from archived tumor and/or biopsies (excluding bone biopsies) and blood samples that might be predictive of therapy outcome for all indications. Of note, availability of tumor archival material and/or fresh biopsies will be a prerequisite for all subjects to be enrolled in the expansion part.

The following requirements apply to the archived and fresh tissue samples collected during the trial:

Tissue collection: Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies and surgical specimens are suited. Fine needle aspiration biopsies are not suited. The most recent biopsy or surgical specimen is required. For expansion subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration.

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

Tissue storage: Fresh tumor tissue obtained from subjects in the melanoma and mesothelioma cohorts for the evaluation of efficacy should be stored in defined cryopreservation medium containing 10% dimethyl sulfoxide [CryoStor® CS10]. (This additional tumor biopsy is optional).

Provision of samples: 1. priority: tumor containing formalin fixed, paraffin embedded (FFPE) tissue block; 2. priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided which are freshly cut, 4 µm thick and mounted on positively-charged microscope slides. SuperFrost Plus glass slides are recommended. Preferably, 25 slides should be provided; if not possible a minimum of 7 slides is required.

For subjects in the first-line NSCLC primary expansion cohort with non-squamous cell histology and unknown EGFR and ALK status, additional slides may be necessary for determination if EGFR and ALK status prior enrollment. Please refer to the Laboratory Manual for detailed information.

For subjects in the HNSCC cohort additional slides may be necessary for determination of tumor HPV status. Please refer to the Laboratory Manual for detailed information.

Sample shipment: The tumor blocks and freshly prepared slides should be sent with next shipment to the central lab at room temperature.

Sample storage: At the central laboratory the FFPE tissue blocks shall be stored at room temperature and the tumor slides shall be frozen in sealed containers at -20°C.

A panel of putative markers including molecular, soluble and cellular markers may be analyzed at baseline from archived tumor tissue (or fresh tumor biopsy, if available), whole blood, and serum samples to investigate a possible correlation between clinical efficacy and analyzed markers.

The following assessment will be considered:

Mandatory (for all indications in the expansion cohorts, including efficacy expansion cohorts):

- Level of PD-L1 expression in archived tumor and/or fresh biopsy by immunohistochemistry staining (IHC). Of note, further techniques to evaluate the expression of PD-L1 and/or marker candidates impacting the targeting or contributing to improve its expression may be also investigated if needed.
- Mandatory for ovarian cancer cohorts only:
  - Blood levels of CA-125, at screening, Week 7 and every 6 weeks thereafter.

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.7 Other Assessments

7.7.1 ADA Analysis

The blood sample for baseline ADA analysis will be collected before trial treatment start. Further serum samples for ADA analysis will be collected on Days 15, 29, 43, 57, 71, 85 (every 2 weeks), on Days 127 and 169 (every 6 weeks) prior administration of study drug, and at the End-of-Treatment visit (any remaining sample from this visit may be used for PK determination). For the 10 mg/kg once weekly cohort, samples for ADA determination will be collected Days 1 (baseline), 15, 29, 43, 57, 71, 85, Week 19, and on Week 25 and every 12 weeks thereafter. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1. The term for ADA on CRF is human-antihuman antibodies (HAHA).

For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, ADA samples will be drawn prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation (e.g. pre-dose at Weeks 3, 5, 11, 17, and 23).

Samples positive for ADA will be re-analyzed to determine the titer and characterized for the presence of neutralizing antibodies that block binding to PD-L1.

CCI [redacted]

8 Statistics

8.1 Sample Size

The sample size for the dose-escalation part of the trial is not based on any statistical assumptions. Rather, it follows the "3 + 3 rule", a well-established methodology in the design of dose-finding trials in oncology.

This trial plans for cohorts of 3 subjects to be treated at each escalating dose level. After the appearance of a single DLT, the cohort for that dose level will be expanded to 6 subjects.

Therefore, the number of subjects enrolled in the dose-escalation phase of the trial will depend on the number of dose escalation steps needed to reach the MTD. Once the dose of 10 mg/kg is

established as safe, accrual of 10 additional subjects at 3 mg/kg and 10 mg/kg each may be enrolled, for the purpose of generating additional safety, PK and receptor occupancy data, if agreed with the SMC. Once the safety of a dose of 15 mg/kg or 20 mg/kg has been established, the SMC will have the possibility to allow enrollment of up to 15 additional subjects at that dose.

Together with the 6 subjects in the once weekly 10 mg/kg cohort, the expected total sample size in the dose escalation phase of the trial will be up to 66 subjects.

The primary endpoint of the efficacy expansion cohorts is the confirmed BOR according to RECIST 1.1, as adjudicated by an IERC. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. For each of these cohorts, the trial aims at demonstrating an ORR greater than 10% by means of an exact binomial test with an overall 1-sided alpha level of 0.025.

Based on an assumed ORR of 20% in an unselected population, the sample size of 150 subjects (gastric / GEJ cancer, HNSCC) will provide approximately 91% power, and the sample size of 100 subjects (ovarian cancer) will provide approximately 80% power to reject the null hypothesis of ORR $\leq$ 10% at the primary analysis.

The sample size of 200 subjects in the urothelial carcinoma efficacy expansion cohort is expected to result in 50-60 PD-L1 positive subjects (based on an expected proportion of 85% PD-L1-evaluable subjects and a proportion of 30 to 35% PD-L1 positive subjects among those that are evaluable). Under the assumption of an ORR of 27% in PD-L1 positive subjects, the sample size of 50 to 60 PD-L1 positive subjects will provide at least 90% power to reject the null hypothesis of ORR $\leq$ 10%.

The assumption of an ORR of 27% in PD-L1 positive subjects in the urothelial carcinoma efficacy expansion cohort is supported by preliminary results of the urothelial carcinoma secondary expansion cohort.

In the given populations of refractory metastatic cancer patients, it is considered that superiority compared with an ORR of 10% may indicate clinical benefit if the observed responses are durable. The assumption of an ORR of 20% in an unselected population in gastric / GEJ cancer, HNSCC, and ovarian cancer is supported by results from clinical studies with anti-PD-1 / anti-PD-L1 agents.

The sample size of 150 for each of the 4 primary disease specific expansion cohorts has been chosen primarily to further explore the safety and efficacy of avelumab in specific indications, as well as in subgroups defined by PD-L1 tumor expression status, and to provide data to aid in future study design.

From an efficacy perspective, the sample size of 150 in each of the primary expansion cohorts will provide estimates and 95% Clopper-Pearson CIs for response rate of 10% (5.7%, 16.0%) in the case of 15 responders out of 150 subjects, and of 20% (13.9%, 27.3%) in the case of 30 responders out of 150 subjects.

Furthermore, the following can be said regarding the precision of estimated response rates in subjects that are positive for PD-L1 expression: For given proportions of PD-L1 positive subjects

in an expected range of 30 to 70% and given response rates in the subgroup of PD-L1 positive subjects in an expected range from 20 to 33%, the subgroup analysis 95% Clopper-Pearson CIs based on a total sample size of 150 will be as shown in Table 8.1.

Table 8.1 95% Confidence Intervals of Estimated Response Rates

	Response rate in PD-L1 positive subjects	
	20%	**33.3%**
Proportion and absolute number of PD-L1 positive subjects (N=150)	95% CI	95% CI
30% (45)	(9.6%, 34.6%)	(20.0%, 49.0%)
50% (75)	(11.6%, 30.8%)	(22.9%, 45.2%)
70% (105)	(12.8%, 28.9%)	(24.4%, 43.2%)

CI: confidence interval; PD-L1: Programmed death ligand 1.

The sample size of 120 in the ovarian cancer secondary expansion cohort will provide estimates and 95% Clopper-Pearson CIs for response rate of 10% (5.3%, 16.8%) in the case of 12 responders out of 120 subjects, and of 20% (13.3%, 28.3%) in the case of 24 responders out of 120 subjects.

The sample size of 50 in the secondary expansion cohorts of ACC, melanoma, mesothelioma, and urothelial carcinoma will provide estimates and 95% Clopper-Pearson CIs for response rate of 10% (3.3%, 21.8%) in the case of 5 responders out of 50 subjects, and of 20% (10.0%, 33.7%) in the case of 10 responders out of 50 subjects.

For the secondary expansion RCC cohort, the 20 subjects of second-line RCC and 60 subjects of first-line RCC will be analyzed separately. The sample size of 20 second-line RCC subjects will enable observation of at least 2 responders with a probability of at least 89.8% if the true response rate is at least 18%, which is considered an effect of interest. The sample size of 60 first-line RCC subjects will provide estimates and 95% Clopper-Pearson CIs for response rate of 20% (10.8%, 32.3%) in the case of 12 responders out of 60 subjects, and of 25% (14.7%, 37.9%) in the case of 15 responders out of 60 subjects.

The sample size of 20 subjects for the interim evaluation of clinical activity in each of the ACC, melanoma, mesothelioma, ovarian cancer, and urothelial carcinoma secondary cohorts will enable observation of at least 1 responder with a probability of at least 93% (79%, 98%) if the true response rate in PD-L1 positive subjects is at least 25%, which is considered as an effect of interest, and the prevalence of PD-L1 positivity is 50% (30%, 70%), respectively. Thus, the failure to detect at least 1 response among the first 20 subjects is seen as an indicator of insufficient clinical activity in a given cohort. See also Section 8.6.

The sample size of 109 subjects for the interim evaluation of tumor activity in urothelial carcinoma efficacy cohort will provide estimates and 95% Clopper-Pearson CIs for response rate of 23% (9.9%, 42.3%) in the case of 7 responders of 30 PD-L1 positive subjects, of 27% (12.2%, 45.9%) in the case of 8 responders of 30 PD-L1 positive subjects, and of 33% (17.2%, 52.8%) in the case of 10 responders of 30 PD-L1 positive subjects.

From a safety assessment perspective, the total sample size of 1640 from all 16 cohorts will provide sufficient data to detect safety signals. Specifically, for toxicities with an incidence rate of 0.5%, the probability of observing at least 1 event will be >99%.

The total sample size at the end of the trial (based on the dose escalation part and the expansion cohorts) is expected to be up to approximately 1706 treated subjects.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

- Occurrence of DLTs during the first 3 weeks of treatment in the dose escalation part (excluding the once weekly 10 mg/kg cohort).
- The confirmed BOR, per RECIST 1.1, as adjudicated by an IERC (see Section 7.3) for subjects enrolled in the efficacy expansion cohorts.

8.3.2 Secondary Endpoints

- Number, severity, and duration of TEAEs for all dose groups / indications according to the NCI-CTCAE) v4.0.
- Number, severity, and duration of treatment-related AEs according to NCI-CTCAE v4.0.

  PK profile.
- irBOR and BOR according to modified irRC and to RECIST 1.1, respectively, per investigator assessment.
- The confirmed BOR, per RECIST 1.1, as adjudicated by an IERC (see Section 7.3) for subjects enrolled in the secondary urothelial carcinoma cohort
- irPFS time and PFS time, according to modified irRC and to RECIST 1.1, respectively, per investigator assessment, defined from first administration of trial treatment until first observation of progressive disease or death when death occurs within 12 weeks of the last tumor assessment or first administration of trial treatment (whichever is later). Any subject with neither assessment of tumor progression, nor death date within 12 weeks after last tumor assessment will be censored on the date of last tumor assessment or first administration of trial treatment.
- OS time defined as the time from first administration of trial treatment to death. For subjects who are still alive at the time of data cut-off for the trial analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject is known to be alive, as of the cut-off date for the analysis.
- Pharmacodynamic profile.
- Serum titers of ADA.

- Expression of PD-L1 on tumor tissue.
- For the primary expansion cohorts only: Unconfirmed response at Week 13 according to RECIST 1.1, per investigator assessment.
- Duration of response, according to modified irRC and to RECIST 1.1, per investigator assessment, defined as the time from the first observation of response to the first observation of documented disease progression (or death within 12 weeks of the last tumor assessment). Subjects without an event at the analysis cut-off date will be censored on the date of the last tumor assessment.
- For the efficacy expansion cohorts only:
    - PFS time, according to RECIST 1.1, per IERC
    - Duration of response according to RECIST 1.1, per IERC.

8.3.3 Safety Endpoints

Besides the endpoints specified as primary and secondary variables the following endpoints will be evaluated:

- Laboratory parameters

8.4 Analysis Sets

The following analysis sets will be defined separately for the dose escalation part and the expansion cohorts in this trial, as applicable:

- **DLT population (dose escalation part)**: all subjects with data used for implementing the dose-escalation schedule. These subjects should have received all study treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.
- **Safety population:** all subjects who have received at least 1 dose of trial treatment.
- **Full analysis set (FAS)**: all subjects who have received at least 1 dose of trial treatment.
- **PD-L1 positive FAS (urothelial carcinoma efficacy expansion cohort):** all PD-L1+ subjects who have received at least 1 dose of trial treatment.
- **PK population:** All subjects who have completed at least 1 infusion of study drug, and who have provided sufficient concentration measurements.
- **Efficacy population (efficacy expansion cohorts):** all subjects who have received at least 1 dose of trial treatment and have measurable disease at baseline according to IERC assessment.
- **PD-L1 positive efficacy population (urothelial carcinoma efficacy expansion cohort)**: all PD-L1+ subjects who have received at least 1 dose of trial treatment and have measurable disease at baseline according to IERC assessment.

- **Efficacy population (primary and secondary expansion cohorts):** all subjects who have received at least 1 dose of trial treatment and have measurable disease at baseline according to investigator assessment.

The definition of the Safety Population and the FAS are identical in this non-randomized study; the Safety population will be used for the safety analysis and the FAS will be used for efficacy analysis. The PD-L1 positive FAS will be the primary analysis population for the primary endpoint of BOR by IERC in the urothelial carcinoma efficacy expansion cohort.

PD-L1 status is assessed by immunohistochemistry. Subjects will be considered PD-L1 positive (negative) for the urothelial carcinoma efficacy expansion cohort if at least (less than) 5% of the tumor cells show PD-L1 membrane staining, respectively. If during assay development (based on generic samples) a different cut-off is determined to be more appropriate, this cut-off may be adapted in the SAP prior to analysis of subject samples from this trial.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

All data recorded during the study will be presented in individual data listings performed on the safety population. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified. All data will be presented in a descriptive manner. Confirmatory analyses will be conducted for the primary endpoint of the efficacy expansion cohorts. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be performed. All other analyses are considered as exploratory, even if statistical tests are used.

Descriptive statistics will be used to summarize the trial results, i.e., statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by CIs. 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.

The DLT population is the underlying data set for the MTD determination. Safety analyses will be performed on the safety population and efficacy analyses will be performed on the FAS. Sensitivity analysis of the BOR on the efficacy population will be conducted according to further specifications in the SAP. Analyses of PK variables will be performed on the PK population.

The estimation of PK parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher, or R, Version 2.10.1 or higher.

Full details of the planned analyses will be described in the trial statistical analysis plan (SAP), separately for the dose escalation and the expansion part of the trial.

Unless otherwise specified, the endpoint analyses described in the following will be performed separately for both the dose escalation part and the expansion cohorts of the trial. The primary analysis of the once weekly 10 mg/kg cohort is a safety analysis, which will be done in the framework of the first SMC meeting in this cohort.

8.5.2 Analysis of Primary Endpoints

8.5.2.1 Maximum Tolerated Dose Determination

For determination of the MTD, individual subject data from the dose escalation part will be reported.

In addition, for the final statistical analysis, the following will be analyzed:

- At each dose level, the number and proportion of subjects in the DLT population who experience a DLT during the first DLT evaluation period.
- At each dose level, the number and proportion of TEAEs experienced by subjects in the DLT population during the first DLT evaluation period.

The MTD will be determined according to the dose-escalation plan described in Section 5.1.4.2. The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT.

8.5.2.2 Confirmed Best Overall Response per RECIST 1.1 by IERC

The primary endpoint in the efficacy expansion cohorts is the BOR according to RECIST 1.1 and as adjudicated by an IERC (see Section 2.2.2), defined as the best response obtained among all tumor assessment visits after start of trial treatment until documented disease progression, taking into account the following requirement for confirmation. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (48) will be required, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 4 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A BOR of SD requires that a time point overall response of SD has been determined at a time point at least 37 days after start of study treatment. The response at each scheduled tumor assessment and the BOR will be listed for each subject.

For the gastric / GEJ cancer, HNSCC, and ovarian cancer efficacy expansion cohorts, the primary analysis of the BOR by IERC will be conducted in the FAS, defined as all treated subjects. The number and proportion of BOR (defined as CR + PR) will be tabulated. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. An exact binomial test will be performed at a 1-sided alpha level of 0.025. The primary analysis is planned 6 months after start of treatment of the last subject in the given cohort. Interim analyses will be conducted after 60% of the subjects in the given cohort have been followed up for 13 weeks. Analyses are considered positive if the lower limit of the 95% confidence interval exceed 10%. Confidence intervals will be constructed using the Clopper-Pearson method.

For the urothelial carcinoma efficacy expansion cohort, the analysis of the BOR by IERC will be conducted in the PD-L1 positive FAS (see Section 8.5.3.1) followed by the FAS. The number and proportion of BOR (defined as CR + PR) will be tabulated. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. An exact binomial test will be performed in the PD-L1 positive FAS and in the FAS to determine whether the null hypothesis of an ORR ≤ 10% can be rejected at the 1-sided alpha level of 0.025. Interim analyses will be conducted for the 109 subjects enrolled in the urothelial carcinoma efficacy expansion cohort prior to Protocol Amendment 13. Analyses are considered positive if the lower limit of the 95% CI of the confirmed BOR exceeds 10%. Confidence intervals will be constructed using the Clopper-Pearson method.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Efficacy Parameters

Clinical efficacy parameters will be analyzed descriptively in the FAS, and, in addition, for the urothelial carcinoma efficacy expansion cohort, in the PD-L1 positive FAS. Response rates will in addition be calculated in the efficacy population according to further specifications in the SAP. Pooling of data from secondary and efficacy expansion cohorts may be considered to enhance precision of estimates. Further details will be specified in the SAP.

The primary efficacy parameter in the expansion part is the Best Overall Response according to RECIST 1.1.

The BOR per investigator assessment will be determined according to RECIST 1.1 and modified irRC, respectively. The BOR will be evaluated over the whole trial period. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (48) will be required. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The number and proportion of BOR (defined as CR+PR) will be tabulated by cohort.

Duration of response, according to modified irRC and to RECIST 1.1, will be calculated for each subject with a confirmed response in the expansion cohorts and will be analyzed using the Kaplan-Meier method in the primary expansion cohorts.

PFS time, irPFS time, and OS time will be presented in subject listings and analyzed using the Kaplan-Meier method in the FAS analysis set of the expansion cohorts that enrolled the full planned number of subjects.

In the expansion cohorts, subgroup analyses of efficacy parameters will be performed according to tumor PD-L1 expression status (positive, negative). Subjects will be considered PD-L1 positive (negative) if at least (less than) 5% of the tumor cells show PD-L1 membrane staining, respectively. If during assay development (based on generic samples) a different cut-off is determined to be more appropriate, this cut-off may be adapted in the SAP prior to analysis of subject samples from this trial. The association between PD-L1 expression status (positive, negative) and response (according to RECIST 1.1 as well as according to modified irRC) will be assessed using Fisher's exact test. CCI [redacted]

CCI [redacted]

8.5.3.2 Pharmacokinetic Profile

Plasma concentrations of avelumab will be determined by a validated method at the times listed in Schedule of Assessments (Appendix I).

The following PK parameters will be estimated and reported:

- $AUC_{0\rightarrow t}$: Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).
- $AUC_{0\rightarrow \infty}$: Area under the curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using $C_{last}/\lambda z$).
- λz: Terminal elimination rate constant. The value of λz is determined from the slope of the regression line of log (concentration) vs. time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time, and (iii) the correlation coefficient (r) of regression must be ≥ 0.95.
- C_{max}: Maximum plasma concentration observed post-dose.
- t_{max}: Time at which the C_{max} occurs.
- $t_{½}$: Elimination half-life, determined as $0.693/\lambda z$.

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation.

8.5.3.3 Serum Titers of Anti-Avelumab Antibodies (ADA)

Immunogenicity testing strategy will be implemented and conducted in line with:

- Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006) (73).
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010) (74).
- FDA (2009, draft) Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins (75).

A qualified method that uses an acid dissociation step to detect ADA in the presence of excess drug in human serum will be applied. Removal of drug after acid treatment is not required. ADA

titers of positive samples will be determined and characterized for the presence of neutralizing antibodies that block binding to PD-L1.

In case anaphylactic reactions occur, the ADA samples from these subjects will be investigated for the presence of drug-specific IgE using a novel Phadia® ImmunoCAP® method, developed for this purpose. The analysis will also be performed in 50 randomly selected subjects enrolled in the expansion cohort that have not presented with anaphylactic reactions to serve as a control.

CCI [redacted]

8.5.4 Safety Analyses

The extent of exposure to avelumab will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

Safety analyses will be performed on the safety population. The safety endpoints will be tabulated by dose-level and cohort, using descriptive statistics.

Safety assessments will be based on review of the incidence of AEs including AEs of special interest, 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 dose of study treatment to the last dose of study treatment + 30 days, or the earliest date of new anticancer therapy – 1 day, whichever occurs first.

Adverse events

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE v4.0 toxicity grading scale.

Treatment emergent adverse events (TEAEs) are those adverse events with onset dates during the on-treatment period, or if the worsening of an event is during the on-treatment period. The incidence of TEAEs regardless of attribution and AEs defined as possibly related to avelumab will be summarized by preferred term and system organ class, and described in terms of intensity and relationship to avelumab. All premature terminations will be summarized by primary reason for study withdrawal.

Descriptive statistics will be examined for indications of dose-related ADRs.

Laboratory variables

Laboratory results will be classified by Grade according to NCI-CTCAE. The worst on-trial Grades after the first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest Grade 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.

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 ECG recorded according to the Schedule of Assessments (Appendix I) will be presented.

Further details will be provided in the SAP based on current safety experience applying the latest MedDRA version.

8.6 Interim Analysis

In the dose escalation part, the trial data will be evaluated before decision is made to go to the next dose level or to start with treatment in expansion cohorts.

For the NSCLC (post platinum doublet and first-line), gastric / GEJ cancer, and MBC expansion cohorts, an interim analysis will be performed after the first 75 subjects have reached the time point of the second post-baseline tumor assessment scheduled in Week 13, i.e. 13 weeks after start of treatment of the 75th subject. Efficacy in this 75 subject subset of the cohort will be analyzed in terms of the unconfirmed response at Week 13. If the rate of unconfirmed response at Week 13 (according to RECIST 1.1) in the efficacy population defined as all treated subjects with measurable disease at baseline is less than 5%, enrollment in the given cohort will be stopped. Other efficacy and safety endpoints will be analyzed as well, as detailed in the SAP.

Based on a comprehensive review of the efficacy and safety data it may be considered whether recruitment in a subgroup of the study population of the given indication, defined by PD-L1 expression status, might be resumed by means of a substantial Protocol Amendment.

Statistical considerations related to this futility rule:

Under different assumptions on the true response rate in the overall population, the probabilities of observing a response rate of less than 5% in this analysis (i.e., 3 or less responders out of 75 subjects) are noted in Table 8.2.

Table 8.2 Probability of Observing a Response Rate of Less Than 5% in Interim Analysis

True response rate in overall population	Probability of 3 or less responders in 75 patients
0.03	0.81
0.05	0.48
0.10	0.05
0.15	0.002

In the NSCLC cohort only, 2 additional interim analyses of efficacy parameters are planned for internal planning purposes at the following time points:

- 13 weeks after start of treatment of the 60th subject
- 13 weeks after start of treatment of the last subject.

In the first-line NSCLC primary expansion cohort, an interim analysis of response will be conducted 13 weeks after start of treatment of the 30th subject.

In the efficacy expansion cohorts, interim analyses for efficacy are planned 13 weeks after the start of treatment of the 30th subject in all cohorts, 13 weeks after start of treatment of the 60th subject in the ovarian cohort, and 13 weeks after start of treatment of the 90th subject in the gastric / GEJ and HNSCC cohorts. The interim analyses after 60/90 subjects aim to demonstrate efficacy as specified in Section 8.5.2.2. No futility rule is foreseen because the clinical activity of anti-PD-1 / anti-PD-L1 agents in these tumor types is established, and the patient populations are characterized by a high unmet medical need. If efficacy criteria are met at the interim analysis, enrollment will continue to the planned full number of subjects in order to collect further data on the primary and secondary endpoints, especially on the association between PD-L1 expression and efficacy endpoints.

In the RCC cohort, one interim analysis of response will be performed 13 weeks after the start of treatment of the 20th subject of second line RCC.

In addition, in the other secondary cohorts that plan to enroll more than 20 subjects, i.e., the ACC, melanoma, mesothelioma, ovarian cancer and urothelial carcinoma cohorts, an interim analysis of response will be performed 13 weeks after the start of treatment of the 20th subject. Accrual in each cohort may be paused during the interim analysis. If no unconfirmed response according to RECIST 1.1 is observed in a given cohort in the interim analysis, accrual in that cohort will be stopped. In addition, for the ovarian cancer secondary expansion cohort, an interim analysis of response will be performed for internal planning purposes 13 weeks after the start of treatment of the 75th subject.

For the purpose of internal planning and for reporting to regulatory authorities, the primary analysis results of the secondary urothelial carcinoma cohort will be updated. The efficacy endpoints such as BOR, PFS, OS, and safety endpoints such as the occurrence of TEAE will be included for these additional analyses. Interim analyses will be conducted for the 109 subjects enrolled in the urothelial carcinoma efficacy expansion cohort prior to Protocol Amendment 13.

The results of this analysis may be subject to reporting to regulatory authorities. The interim analysis is considered positive if the lower limit of the 95% CI of the confirmed BOR exceeds 10%. Results will be presented for PD-L1 positive FAS and FAS. Further details will be provided in the SAP.

The sequence of statistical analyses planned for urothelical cancer subjects will consider the objective to evaluate the association between tumor PD-L1 expression and BOR prospectively. In a first step, the secondary urothelial carcinoma cohort served as a "training set" for the identification of a PD-L1 expression cut-off that is most likely to identify a subset of the subject population with enhanced clinical benefit. The PD-L1 expression cut-off was specified prior to any statistical analysis of the PD-L1 expression data from the urothelial carcinoma efficacy expansion cohort. In the next step, the cut-off will be verified by conducting an interim evaluation with data from subjects of the efficacy expansion cohort at 6 months after the last subject's first dose of study treatment for the 109 subjects enrolled in the urothelial carcinoma efficacy expansion cohort prior to Protocol Amendment 13. In case the cut-offs are not mutually supportive in terms of clinical efficacy endpoints the cut-off could be refined and the remainder of approximately 100 subjects of the efficacy expansion cohort will serve as the "validation set" to qualify the tumor PD-L1 expression cut-off. Otherwise, data from subjects of the urothelial carcinoma expansion cohort will be pooled for the final efficacy analyses of the expansion cohort.

For each primary and secondary expansion cohort, an additional interim analysis may be conducted 13 weeks after the start of treatment of the last subject in that cohort. In general, interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

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 Good Clinical Practice (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 into the trial.

In 1998, the FDA introduced a regulation (21 CFR, 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 IMP (named "covered trials" by the FDA), the investigator and all sub-investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his / her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. A separate specific CCI ICF will be provided to subjects who are willing to participate in this optional procedure, which refers to the extraction and analysis of DNA from blood and / or tumor biopsy in order to better understand how CCI) may affect the efficacy of avelumab.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on Good Clinical Practice (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, 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. The subject's original medical data that are reviewed at the site during source data verification by the 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; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

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, s/he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the investigators.

In cases where the investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

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

The trial must not start at a site before the Sponsor 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 (e.g., 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 electronic CRF (eCRF) provided by the CRO and follow the data standards of the Sponsor. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the trial.

10.2 Source Data and Subject Files

The investigator must keep a 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 (EMR 100070-001),
- Date of subject's inclusion into the trial (i.e., 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, and
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable.

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

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must bear 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 thus 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 Good Clinical Practice (ICH Topic E6, 1996). The site 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 CRFs, the IMP(s), and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedures, 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, or completion of a particular cohort or cohorts if applicable, a clinical trial report according to ICH Topic E3 will be written by the Sponsor or the designated CRO in consultation with the principal 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 that participated in the dose escalation phase of the trial.

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 pre-submission 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 Schedule of Assessments

Dose Escalation Phase (excepting 10 mg/kg once weekly cohort)

Measure	Screening/ Baseline Assessments	Treatment Phase											Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (18)
	Day -18 to First Treatment	V1	V2	V3	V4#	V5	V6#	V7	V8	V9	V10	V11	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (18)
		W1	W1	W1		W3		W5	W7	W9	W11	W13				
		d1	d2*	d3*		d15		d29	d43	d57	d71	d85				
Written informed consent	X															
In- and exclusion criteria	X	X (23)														
Medical history	X															
Demographic data	X															
HBV, HCV, and HIV testing	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 performance status	X (19)	X				X		X	X	X	X	X	2·weekly	x/X	X	
Enrollment (if eligible) (3)	X															
IMP administration		X				X		X	X	X	X	X	2·weekly			
DLT Assessment (20)		X				X										
12-lead ECG (4)	X	X				X		X	X	X	X	X	6·weekly	x/X	X	
Hematology and hemostaseology	X					X		X	X	X	X	X	2·weekly	x/X	X	
Core serum chemistry (5)						X		X		X	X		2·weekly			
Full serum chemistry (21)	X								X			X	6·weekly	x/X	X	
Urinalysis (22)	X					X		X	X	X	X	X	2·weekly	x/X	X	
β-HCG pregnancy test (if applicable) (6)	X	X				X		X	X	X	X	X	2·weekly	- /X	X	
Tumor evaluation / staging (CT Scan/ MRI/ Tumor markers / other established methods) (7,8,9,10)	X								X			X	6·weekly	- /X		X

Measure	Screening/ Baseline Assessments	Treatment Phase												Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (18)
	Day -18 to First Treatment	V1	V2	V3	V4#	V5	V6#	V7	V8	V9	V10	V11	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (18)
		W1	W1	W1		W3		W5	W7	W9	W11	W13				
		d1	d2*	d3*		d15		d29	d43	d57	d71	d85				
Documentation of AEs and concomitant medication	X	X	X*	X*		X		X	X	X	X	X	2·weekly	x/X	X (18)	X (18)
ACTH, ANA, ANCA, RF, free T4, and TSH	X								X			X	6·weekly	- /X	X	
PK sampling (11)		X	X*	X*		X		X	X			X	6·weekly up to incl. week 25		X	
ADA sampling (12)	X					X		X	X	X	X	X	6·weekly up to incl. week 25	- /X		
Receptor occupancy (13)		X		X*		X		X	X			X				
Immunomonitoring (14)		X		X*		X			X			X	6·weekly up to incl. week 25	- /X		
Soluble factors (14)		X		X*		X			X			X	6·weekly up to incl. week 25	- /X		
Tumor biopsy or archived surgical	X								X					- /X		

CCI [redacted]

ACTH: adrenocorticotropic hormone; ADA: anti-drug antibody; AE: adverse events; ANA: anti-nuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; β-HCG: β-human chorionic gonadotropin; CT: computer tomography; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PK: pharmacokinetics; RF: rheumatoid factor; SAE: serious adverse event; TSH: Thyroid-stimulating hormone, T4: Free thyroxine.

#Following approval of Protocol Amendment 7, the visits at Weeks 2 and 4 (Visit 4/Day 8 and Visit 6/Day 22) are no longer required and subjects will not be required to attend these visits.

*Sampling on Days 2 and 3 is optional. As a result, the visit at Day 2 is optional. However, the visit at Day 3 is required for all dose escalation subjects in order that relevant biomarker samples can be collected as described in the corresponding footnotes.

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 study procedures (except Days 2 and 3), except for body weight, which should be obtained on the same day as study drug administration. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

1. Tumor evaluation at the end-of-treatment visit should only be performed if no disease progression was documented previously.
2. 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.
3. 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).
4. 12-lead ECG should be assessed before infusion and 2 hours (± 20 minutes) after infusion.
5. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen (BUN)/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
6. In serum at screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next dosing of IMP.
7. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST 1.1 is documented during the course of the study confirmation of the response should be performed according to RECIST 1.1 after 6 weeks. CT scan or MRI (if MRI is used, CT of chest is mandatory) should always be used.
8. A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis will be performed within 18 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT / MRI does not need to be performed.
9. Brain CT/MRI scan (either, with contrast preferred) is required at screening if not performed within the previous 6 weeks. In subjects with ovarian cancer, castrate-resistant prostate cancer (CRPC), mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.
10. A bone scan should be done at screening and beyond as clinically indicated. Bone metastases detected at screening need to be followed at the tumor evaluation visits.
11. PK serum samples will be drawn on Day 1 before and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours post infusion. PK sampling on Days 2 and 3 is optional. Where performed, on Day 2, samples will be collected 24 and 36 hours post infusion and on Day 3, a single sample will be drawn 48 hours post infusion (± 6 hours). On Days 15, 29, 43, 85, 127, and 169, samples will be collected prior to infusion (trough value) and immediately after infusion is completed (peak value).
12. ADA serum samples will be collected prior to trial treatment on Days 1 (baseline), 15, 29, 43, 57, 71, 85 (every 2 weeks) and on Days 127, and 169 (every 6 weeks). The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1.
13. Blood samples for receptor occupancy will be collected on Day 1 before start of the infusion, 4 and 48 hours (Day 3, ± 6 hours) after the start of infusion, and before the start of each infusion on Days 15, 29, 43, and 85.
14. Blood samples for immunomonitoring will be collected before start of each infusion and 48 hours (± 6 hours) after start of each infusion on Days 1 (baseline), 43, 85, and only before start of infusion on Days 15, 127, and 169. One additional blood sample will be collected at the end-of-treatment visit (within 28 days after the last treatment). A complete differential blood count will be provided for each time point for calculations of the absolute count of leukocyte

subpopulations. From these samples, plasma (3 to 5 mL) will be collected for retrospective analyses. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1.

15. Blood samples for soluble factors will be collected before start of each infusion and 48 hours (± 6 hours) after start of each infusion on Days 1 (baseline), 43, 85, and only before start of infusion on Days 15, 127 and 169. One additional sample will be collected at the end-of-treatment visit (within 28 days after the last treatment) for biological follow-up. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1.
16. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies and surgical specimens are suited. Fine needle aspiration biopsies are not suited. Samples can be provided as block or slides (see Section 7.6.2.4 for details). CCI [redacted]

CCI [redacted]

18. Adverse events will be documented at each trial visit until the End-of-Treatment visit. After the End-of-Treatment visit only treatment-related AEs have to be documented until the Post-treatment Safety Follow-up visit. Subjects with a SAE ongoing at the post-treatment 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 the end-of-treatment visit will be followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year. In addition, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab. See Section 7.1.4 for details.
19. If the screening ECOG was performed within 3 days prior to Day 1 it does not have to be repeated at Visit 2.
20. The observation period for DLTs refers to the first 3 weeks of trial drug treatment in the dose escalation part for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD. Additional subjects enrolled in the dose escalation phase will have AEs collected but will not have a specific DLT observation period.
21. Full chemistry panel and other laboratory studies are detailed in Table 7.2. Serum electrophoresis only at screening and end-of-treatment. Follicle-stimulation hormone at screening, if applicable (Section 7.1.1).
22. Full urinalysis at screening and end-of-treatment and basic urinalysis (protein content only) at each visit indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.
23. Prior to the first administration of trial treatment, subject eligibility should be re-confirmed with respect to data collected on Day 1.

Dose Escalation Phase – 10 mg/kg once weekly cohort

Measure	Screening/ Baseline Assessments	Treatment Phase														Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (16)
	Day -18 to First Treatment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (16)
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13				
		d1	d8	d15	d22	d29	d36	d43	d50	d57	d63	d71	d78	d85				
Written informed consent	X																	
In- and exclusion criteria	X																	
Medical history	X																	
Demographic data	X																	
HBV, HCV, and HIV testing	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	X	X	X	X	X	X	2-weekly	x/X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
Enrollment (if eligible) (3)	X																	
IMP administration		X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly			
12-lead ECG (4)	X	X		X		X		X		X		X		X	6-weekly	x/X	X	
Hematology and hemostaseology	X		X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
Core serum chemistry (5)			X	X	X	X	X		X	X	X	X	X		2-weekly			
Full serum chemistry (17)	X							X						X	6-weekly	x/X	X	
Urinalysis (18)	X			X		X		X		X		X		X	2-weekly	x/X	X	
β-HCG pregnancy test (if applicable) (6)	X	X				X				X				X	4-weekly	- /X	X	
Tumor evaluation / staging (CT Scan/ MRI/ Tumor markers / other established methods) (7,8,9,10)	X							X						X	6-weekly for first 12 months, then 12-weekly	- /X		X (16)
Documentation of AEs and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X (16)	X (16)
ACTH, ANA, RF	X	As clinically indicated													6-weekly	- /X	X	

Measure	Screening/ Baseline Assessments	Treatment Phase														Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (16)
	Day -18 to First Treatment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (16)
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13				
		d1	d8	d15	d22	d29	d36	d43	d50	d57	d63	d71	d78	d85				
Free T4 and TSH	X							X						X	6-weekly	- /X	X	
PK sampling (11)		X	X	X		X		X						X	W15, W19, W25 then 12-weekly	-/X	X	
ADA sampling (12)		X		X		X		X		X		X		X	W19, W25 then 12-weekly	- /X	X	
Soluble factors (13)		X	X	X		X		X						X				
Tumor biopsy or archived surgical specimen (optional) (14)	X							X								- /X		

CCI [redacted]

ACTH: adrenocorticotropic hormone; ADA: anti-drug antibody; AE: adverse events; ANA: anti-nuclear antibody; β-HCG: β-human chorionic gonadotropin; CT: computer tomography; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PK: pharmacokinetics; RF: rheumatoid factor; SAE: serious adverse event; TSH: Thyroid-stimulating hormone, T4: Free thyroxine.

A time window of 1 day before or 1 day after the scheduled visit day (±1 day) will be permitted for all study procedures for the first 12 weeks and then up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) starting at Week 13. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

1. Tumor evaluation at the end-of-treatment visit should only be performed if no disease progression was documented previously.
2. 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.
3. 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).
4. 12-lead ECG should be assessed before infusion and 2 hours (± 20 minutes) after infusion.

5. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen (BUN)/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
6. In serum at screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next dosing of IMP.
7. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST 1.1 is documented during the course of the study confirmation of the response should be performed according to RECIST 1.1 after 6 weeks. CT scan or MRI (if MRI is used, CT of chest is mandatory) should always be used.
8. A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis will be performed within 18 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT / MRI does not need to be performed.
9. Brain CT/MRI scan (either, with contrast preferred) is required at screening if not performed within the previous 6 weeks. In subjects with ovarian cancer, castrate-resistant prostate cancer (CRPC), mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.
10. A bone scan should be done at screening and beyond as clinically indicated. Bone metastases detected at screening need to be followed at the tumor evaluation visits.
11. Blood samples for PK determinations will be collected from all subjects within 2 hours prior to each infusion at Weeks 1, 2, 3, 5, and 7 (every 2 weeks), at Weeks 13, 15, 19, and 25, and then at 12-week intervals while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7, 13, and 25. Samples will be collected at the EoT visit and the Safety Follow-up visit.
12. ADA serum samples will be collected prior to trial treatment on Days 1 (baseline), 15, 29, 43, 57, 71, 85, and on Week 19 and Week 25, then every 12 weeks thereafter. Samples will be collected at the EoT visit and the Safety Follow-up visit. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1. The term for ADA on CRF is human-antihuman antibodies (HAHA).
13. Blood samples for soluble factors will be collected before start of each infusion on Days 1 (baseline), 8, 15, 29, 43, and 85.
14. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies and surgical specimens are suited. Fine needle aspiration biopsies are not suited. Samples can be provided as block or slides (see Section 7.6.2.4 for details). Optional tumor biopsies will be collected prior to infusion on Day 1, Day 43, and at the end-of-treatment visit (see Section 7.6.2.4 for details).

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16. Adverse events will be documented at each trial visit until the End-of-Treatment visit. After the End-of-Treatment visit only treatment-related AEs have to be documented until the Post-treatment Safety Follow-up visit. Subjects with a SAE ongoing at the post-treatment 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 the end-of-treatment visit will be followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year or until disease progression, whichever is first. In addition, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab. See Section 7.1.4 for details.

17. Full chemistry panel and other laboratory studies are detailed in Table 7.2. Follicle-stimulation hormone at screening, if applicable (Section 7.1.1).
18. Full urinalysis at screening, the end-of-treatment, and the 10-week safety follow-up and basic urinalysis (protein content only) at each visit indicated prior to administration of study drug and at the discontinuation visit. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.

Expansion Phase

Measure	Washout[$]/ Screening/ Baseline Assessments	Treatment Phase													Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (18)
	Day -28[$]/ -18 to First Treatment	V1 W1 d1	V2 W1 d2*	V3 W1 d3*	V4# W2 d8	V5 W3 d15	V6# W4 d22	V7 W5 d29	V8# W6 d36	V9 W7 d43	V10 W9 d57	V11 W11 d71	V12 W13 d85	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (18)
Written informed consent	X																
In- and exclusion criteria	X																
Medical history	X																
Demographic data	X																
HBV, HCV, and HIV testing	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 performance status	X (19)	X				X		X		X	X	X	X	2·weekly	x/X	X	
Enrollment (if eligible) (3)	X																
IMP administration		X				X		X		X	X	X	X	2·weekly			
12-lead ECG (4)	X	X				X		X		X	X	X	X	6 weekly	x/X	X	
Hematology and hemostaseology	X					X		X		X	X	X	X	2 weekly	x/X	X	
Core serum chemistry (5)					X	X	X	X	X		X	X		2 weekly			
Full serum chemistry (20)	X									X			X	6 weekly	x/X	X	
Urinalysis (6)	X					X		X		X	X	X	X	2·weekly	x/X	X	
β-HCG pregnancy test (if applicable) (7)	X	X						X			X		X	4·weekly	- /X	X	
Tumor evaluation / staging (CT Scan/ MRI/ Tumor markers / other established methods) (8,9,10,11, 24)	X									X			X	6·weekly for first 12 months, then 12-weekly	- /X		X
Optional fresh biopsies (melanoma and mesothelioma cohorts, fist-line NSCLC, and efficacy expansion cohorts) (23)	X									X					- /X		
Documentation of AEs and concomitant medication	X	X	X*	X*		X		X		X	X	X	X	2·weekly	x/X	X (18)	X (18)

Measure	Washout[$]/ Screening/ Baseline Assessments	Treatment Phase													Discontinuation/ End-of-Treatment Visits	Post Treatment Safety Follow-up Visit	Post-Treatment Survival Follow-up (18)
	Day -28[$]/ -18 to First Treatment	V1 W1 d1	V2 W1 d2*	V3 W1 d3*	V4# W2 d8	V5 W3 d15	V6# W4 d22	V7 W5 d29	V8# W6 d36	V9 W7 d43	V10 W9 d57	V11 W11 d71	V12 W13 d85	Until Progression	Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (18)
Free T4, and TSH	X												X	Week 25 and as indicated	- /X	X	
CA-125 sampling (22)		X								X			X	6-weekly	- /X		
PK sampling (12)		X	X*	X*		X		X		X	X	X	X	6-weekly or 12-weekly up to incl. week 25 (see footnote 12 for specifics)	-[13]	X	
ADA sampling (13)	X					X		X		X	X	X	X	6-weekly up to incl. week 25	- /X	-[12]	
Receptor occupancy (21)		X				X		X		X			X				
Immunomonitoring (14)		X		X*		X				X			X		- /X		
Soluble factors (15)		X		X*		X (15)		X (15)		X					- /X		
Tumor tissue (biopsy or archived surgical specimen); HPV determination for subjects in HNSCC cohort only (16)	X																
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AE: adverse events; ADA: anti-drug antibody (ADA); β-HCG: β-human chorionic gonadotropin; CA-125: cancer antigen 125; CT: computer tomography; CRPC: castrate-resistant prostate cancer; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; GEJ: Gastro-esophageal junction; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HNSCC: head and neck squamous cell carcinoma; HPV: human papilloma virus; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PK: pharmacokinetics; SAE: serious adverse event; TSH: thyroid-stimulating hormone, T4: Free thyroxine.

$ There is a 28-day washout / recovery period for prior anticancer treatment (e.g., cytoreductive therapy, radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin) and major surgery before the start of trial treatment (Section 5.3.2). The screening procedures and baseline assessments will be completed within 18 days before trial treatment starts.

 # Following approval of Protocol Amendment 9, the visits at Weeks 2, 4, and 6 (Visit 4/Day 8, Visit 6/Day 22 and Visit 8/Day 36) have been restored for subjects with liver metastases at baseline for the collection of blood samples for ALT, AST, total bilirubin, and alkaline phosphatase determination.

* PK and ADA sampling on Days 2 and 3 are optional and only applicable for subjects in the secondary CRC and CRPC cohorts (expanded PK sampling) and the efficacy expansion cohorts (ADA sampling). Therefore, the visit at Day 2 is optional; however should a subject attend, blood draws for PK sampling and soluble factors (as applicable) are strongly encouraged.

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 study procedures (except Days 2 and 3), except for body weight, which should be obtained on the same day as study drug administration. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

1. Tumor evaluation at the end-of-treatment visit should only be performed if no disease progression was documented previously.
2. 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.
3. 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).
4. 12-lead ECG should be assessed before infusion and 2 hours (± 20 minutes) after infusion.
5. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen (BUN)/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed. Subjects with liver metastases at baseline will have visits every week, up to Week 7 for collection of blood samples for ALT, AST, total bilirubin, and alkaline phosphatase determination.
6. Full urinalysis at screening and end-of-treatment and basic urinalysis (protein content only) at each visit as indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein (dipstick), sediment will be evaluated. Urinalysis does not have to be performed in subjects with urothelial cancers.
7. In serum at screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next dosing of IMP.
8. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST 1.1 is documented during the course of the study confirmation of the response should be performed according to RECIST 1.1 after 6 weeks. CT scan or MRI (if MRI is used, CT of chest is mandatory) should always be used.
9. A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis will be performed within 18 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions. However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the screening CT / MRI does not need to be performed.
10. Brain CT/MRI scan (either, with contrast preferred) is required at screening if not performed within the previous 6 weeks. In subjects with gastric/GEJ cancer, HNSCC, ovarian cancer, CRPC, mesothelioma, or urothelial carcinoma this scan is only necessary if clinically indicated. For expansion subjects in the melanoma cohort, an MRI or CT scan (either, with contrast preferred) must be performed at screening in order to rule out brain metastases, unless imaging has previously been performed within 28 days prior to screening. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.
11. A bone scan should be done at screening and beyond as clinically indicated. Bone metastases detected at screening need to be followed at the tumor evaluation visits.

12. PK samples will be obtained prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, 127, and 169 for all subjects in the primary cohorts (NCSLC post platinum doublet, gastric / GEJ cancer, and MBC) and the ACC, melanoma, mesothelioma, ovarian, and urothelial secondary cohorts. All expansion subjects in the CRC and CRPC secondary cohorts will have PK serum samples collected on Day 1 before and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours post infusion. PK sampling on Days 2 and 3 is optional. Where performed, on Day 2, samples will be collected 24 and 36 hours post infusion and, on Day 3, a single sample will be drawn 48 hours post infusion (± 6 hours). On Days 15, 29, 43, 85, 127, and 169, samples will be collected prior to infusion (trough value) and immediately after infusion is completed (peak value). For subjects in the first-line NSCLC cohort, samples for PK analysis will be collected prior to each study drug administration on Days 1, 15, 29, 43, 57, 71, 85, 99, and 169. Post-study drug administration samples will also be collected immediately after the end of the infusion and also 2 to 8 hours after the end of infusion (later is better depending on how long the subject will stay in the clinic), on Days 1, 43, 85, and 169. Samples will also be collected at the 10-week safety follow-up visit, and remaining sample from this visit may be used to test for ADA. For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, samples for PK determination will be collected prior to each administration of study drug on Days 1, 15, 29, 43, 57, 71, 85, and 169. Post-study drug administration samples will be collected immediately after the end of infusion and 2 to 8 hours after the end of infusion (later is better, depending on how long the subject will stay in the clinic) at Days 1, 43, 85, and 169. Exact sampling times will be recorded. Samples will be collected at the 10-week Safety Follow-up visit, and remaining sample from this visit may be used to test for ADA.

13. ADA serum samples will be collected on Days 1 (baseline), 15, 29, 43, 57, 71, 85 (every 2 weeks) on Days 127, and 169 (every 6 weeks), and at the end-of-treatment visit (within 28 days after the last treatment). Remaining sample from the end-of-treatment visit may be used to test for PK. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1. The term for ADA on CRF is human-antihuman antibodies (HAHA).

14. All subjects in the secondary expansion cohorts, except for the RCC cohort, will have 40 mL of blood (five 8 mL CTPs) collected before start of infusion at Days 1 (baseline), 15, 43, and 85 and at the end-of treatment visit for immunomonitoring. Additionally, 40 mL of blood will be collected 48 hours (Day 3, ± 6 hours) after the start of the first infusion only of IMP in these subjects (this sample is optional). A complete differential blood count will be provided for each time point for calculations of the absolute count of leukocyte subpopulations. From these samples, plasma (3 to 5 mL) will be collected for retrospective analyses. The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1.

15. Soluble factors samples will be collected for all subjects in the primary and secondary expansion cohorts, except for the RCC cohort, before start of infusion on Days 1 (baseline) and 43, and at the end-of-treatment visit (within 28 days after the last treatment). In addition, except for the RCC cohort, a serum sample will be collected from subjects in the secondary expansion cohorts 48 hours after the start of the first infusion only (Day 3, ± 6 hours; this sample is optional). The baseline sample should be collected prior to the first administration of trial treatment, i.e., either during the screening period or pre-dose on Day 1. For subjects enrolled in the efficacy expansion cohorts and the RCC secondary cohort, CCI [redacted]

16. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies and surgical specimens are suited. Fine needle aspiration biopsies are not suited. The most recent biopsy or surgical specimen is required. For subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first IMP administration. Samples can be provided as block or slides (see Section 7.6.2.4 for details). In the melanoma and mesothelioma cohorts, optional tumor biopsies will be collected prior to infusion on Day 1, Day 43, and at the end-of-treatment visit (see Section 7.6.2.2 for details). For subjects in the HNSCC cohort additional slides may be necessary for determination of tumor HPV status. Please refer to the Laboratory Manual for detailed information.

CCI [redacted]

18. Adverse events will be documented at each trial visit until the End-of-Treatment visit. After the End-of-Treatment visit only treatment-related AEs have to be documented until the Post-treatment Safety Follow-up visit. Subjects with a SAE ongoing at the post-treatment 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 the end-of-treatment visit will be followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year or until disease progression, whichever is first. In addition, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab. See Section 7.1.4 for details.
19. If the screening ECOG was performed within 3 days prior to Day 1 it does not have to be repeated at Visit 2.
20. Full chemistry panel and other laboratory studies are detailed in Table 7.2. Serum electrophoresis only at screening and end-of-treatment. Follicle-stimulation hormone at screening, if applicable (Section 7.1.1).
21. The blood sample for receptor occupancy will be collected on Day 1 before start of the infusion, 4 hours after the start of infusion, and before the start of each infusion on Days 15, 29, 43, and 85 for expansion subjects in the CRC and CRPC cohorts.
22. Ovarian cancer cohort only: Blood samples for CA-125 will be collected prior to trial treatment on Days 1, 43, 85, 127, and 169 (every 6 weeks), and at the end-of-treatment visit.
23. Melanoma and mesothelioma cohorts only: If optional fresh biopsy is taken prior to first dose of trial treatment, archive tumor material is not required for trial entry. Fresh biopsies may also be collected on Day 43 and at the end-of-treatment visit. These biopsies are optional. For subjects in the efficacy expansion cohorts and the first-line NSCLC primary expansion cohort, fresh biopsies may also be collected on Days 43 and at the end of treatment visit. These biopsies are optional.
24. Mesothelioma cohort only: Tumor biopsies (core needle biopsies) may be performed between Cycles 2 and 3, and in the case of disease progression, to differentiate between actual disease progression and a tumor flare resulting from intratumor inflammation. These biopsies are optional. See Section 7.3.

CCI [redacted]

Subjects with Complete Response who Subsequently Progress After Stopping Therapy Then Re-initiate Therapy

	Treatment Phase								Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Post-Treatment Follow-up (3)
	V1	V2	V3	V4	V5	V6	V7				
	W1	W3	W5	W7	W9	W11	W13				
Measure	d1	d15	d29	d43	d57	d71	d85	**Until Progression**	**Up to ≤ 7/28 Days after Last Treatment (1,2)**	**10 Weeks after Last Treatment**	**Every 3 months (3)**
Physical examination	X			X			X	6·weekly	x/X	X	
Vital signs	X	X	X	X	X	X	X	2·weekly	x/X	X	
Weight	X	X	X	X	X	X	X	2·weekly	x/X	X	
ECOG performance status	X	X	X	X	X	X	X	2·weekly	x/X	X	
IMP administration	X	X	X	X	X	X	X	2·weekly			
12-lead ECG (4)	X			X			X	6 weekly	x/X	X	
Hematology and hemostaseology	X	X	X	X	X	X	X	2 weekly	x/X	X	
Core serum chemistry (5)		X	X		X	X		2 weekly			
Full serum chemistry (6)	X			X			X	6 weekly	x/X	X	
Urinalysis (7)	X	X	X	X	X	X	X	2·weekly	x/X	X	
β-HCG pregnancy test (if applicable) (8)	X		X		X		X	4·weekly	- /X	X	
Tumor evaluation / staging (CT Scan/ MRI/ Tumor markers / other established methods) (9,10,11,12)	X			X			X	6·weekly for first 12 months, then 12-weekly	- /X		X
Optional fresh biopsies (melanoma and mesothelioma cohorts only) (13)	X								- /X		
Documentation of AEs and concomitant medication	X	X	X	X	X	X	X	2·weekly	x/X	X	X (3)
Free T4, and TSH								Week 25 and as indicated	- /X	X	
CA-125 sampling (14)	X			X			X	6-weekly	- /X		
PK sampling (15)		X	X			X		6·weekly until 6 months		X	
ADA sampling (16)		X	X			X		6·weekly until 6 months	- /X		
CCI [redacted]											
Soluble factors (18)	X								- /X		

	Treatment Phase								Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Post-Treatment Follow-up (3)
	V1	V2	V3	V4	V5	V6	V7				
	W1	W3	W5	W7	W9	W11	W13		Up to ≤ 7/28 Days after Last Treatment (1,2)	10 Weeks after Last Treatment	Every 3 months (3)
Measure	d1	d15	d29	d43	d57	d71	d85	**Until Progression**			

AE: adverse events; ADA: anti-drug antibody; β-HCG: β-human chorionic gonadotropin; CA-125: cancer antigen 125; CT: computer tomography; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PK: pharmacokinetics; TSH: Thyroid-stimulating hormone, T4: Free thyroxine.

For subjects who achieve a CR on avelumab therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment.

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 study procedures (except Days 2 and 3), except for body weight, which should be obtained on the same day as study drug administration. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

1. Tumor evaluation at the end-of-treatment visit should only be performed if no disease progression was documented previously.
2. 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.
3. Subjects with an ADR ongoing at the end of the treatment visit and for any AE suspected to be related to trial treatment occurring up to 3 months after the last dose of avelumab will continue to be followed. Subjects without progressive disease at the end-of-treatment visit will be followed up for disease progression (CT / MRI scans every 12 weeks) up to 1 year or until disease progression, whichever is first. In addition, subjects will be followed quarterly (± 14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of avelumab. See Section 7.1.4 for details.
4. 12-lead ECG should be assessed before infusion and 2 hours (± 20 minutes) after infusion.
5. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen (BUN)/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
6. Full chemistry panel and other laboratory studies are detailed in Table 7.2. Serum electrophoresis only at end-of-treatment.

7. Full urinalysis at Week 1/Day 1 and end-of-treatment and basic urinalysis (protein content only) at each visit as indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein (dipstick), sediment will be evaluated. Urinalysis does not have to be performed in subjects with urothelial cancers.
8. Results of the most recent pregnancy test (urine β-HCG) should be available prior to next dosing of IMP.
9. In general, the tumor visit time window is 5 days prior to dosing. In case a tumor response according to RECIST 1.1 is documented during the course of the study confirmation of the response should be performed according to RECIST 1.1 after 6 weeks. CT scan or MRI (if MRI is used, CT of chest is mandatory) should always be used.
10. Brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.
11. A bone scan should be done as clinically indicated. Bone metastases that had been detected at screening need to be followed at the tumor evaluation visits.
12. Mesothelioma cohort only: Tumor biopsies (core needle biopsies) may be performed between Cycles 2 and 3, and in the case of disease progression, to differentiate between actual disease progression and a tumor flare resulting from intratumor inflammation. These biopsies are optional. See Section 7.3.
13. Melanoma and mesothelioma cohorts only: Optional fresh biopsy is taken prior to first dose of trial treatment. These biopsies are optional.
14. Ovarian cancer cohort only: Blood samples for CA-125 will be collected prior to trial treatment on Days 1, 43, 85, 127, and 169 (every 6 weeks), and at the end-of-treatment visit.
15. PK samples will be obtained within 2 hours prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation (e.g., pre-dose at Weeks 3, 5, 11, 17, and 23).
16. ADA samples will be drawn prior to the second retreatment infusion, then 2 weeks later, and then every 6 weeks until 6 months after treatment re-initiation (e.g., pre-dose at Weeks 3, 5, 11, 17, and 23).

CCI [redacted]

18. Soluble factors samples will be collected before start of the first infusion on Days 1 and at the end-of-treatment visit (within 28 days after the last treatment).

Appendix II ECOG Performance Status

ECOG Performance Status[1]	
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, e.g., 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

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

Appendix III Guidance on Contraception

Birth control methods considered as highly effective

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

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation1 (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation1 (oral, injectable, implantable[2])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

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

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

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

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

Appendix IV Protocol Amendments and List of Changes

Table of 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 1	Yes	13 December 2012	Global	Yes
Amendment 2	Yes	29 May 2013	Global	Yes
Amendment 3	Yes	12 August 2013	Global	Yes
Amendment 4	Yes	20 September 2013	Local: EU	Yes
Amendment 5	Yes	08 October 2013	Local: EU	Yes
Amendment 6	Yes	28 October 2013	Global	Yes
Amendment 7	Yes	30 July 2014	Global	Yes
Amendment 8	Yes	19 November 2014	Global	Yes
Amendment 9	Yes	22 December 2014	Global	Yes
Amendment 10	Yes	04 March 2015	Global	Yes
Amendment 11	Yes	16 April 2015	Global	Yes
Amendment 12	Yes	10 July 2015	Global	Yes
Amendment 13	Yes	20 October 2015	Global	Yes
Amendment 14	Yes	11 March 2016	Global	Yes
Amendment 15	Yes	25 April 2016	Global	Yes
Amendment 16	Notification only	28 October 2016	Global	Yes
Amendment 17	Notification only	02 March 2017	Global	Yes

The purpose of this protocol amendment (Amendment 18, 06 August 2018) is provide language regarding continued access to study treatment for subjects who may continue to benefit from continued treatment if the study is terminated.

This amendment is not considered substantial.

List of Changes

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 with Clinical Trial Protocol Version 18.0 / Amendment 17.0, 02 March 2017

Change	Section	Pages	Previous Wording	New Wording	Rationale
Updated Medical Responsible	Cover page	1	Medical Responsible: PPD ~~Merck KGaA, Frankfurter Str. 250~~ ~~64293 Darmstadt, Germany~~ ~~Tel:~~ PPD ~~Fax:~~ PPD PPD PPD **45A Middlesex Turnpike** **Billerica, MA 01821, USA** **Tel:** PPD **Fax:** PPD	Medical Responsible: PPD PPD 45A Middlesex Turnpike Billerica, MA 01821, USA Tel: PPD Fax: PPD	New Medical Responsible assigned
Updated projected last subject out date	Synopsis – Planned trial period (first enrollment-last subject out) 5.1.6 Planned Treatment Duration	15 81	Last subject out (after expansion and follow-up): Q2, ~~2018~~ **2019**.	Last subject out (after expansion and follow-up): Q2, 2019.	Subjects staying on therapy longer than expected
Added language regarding availability of study drug through rollover study for subjects continuing to benefit from study treatment	Synopsis – Trial design and plan	21	Subjects who re initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments. **In the case of study termination, subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).**	Subjects who re initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments. In the case of study termination, subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).	In order to not deny access to study treatment for subjects who continue to benefit after termination of the study

Change	Section	Pages	Previous Wording	New Wording	Rationale
Added language regarding availability of study drug through rollover study for subjects continuing to benefit from study treatment	5.1.6 Planned Treatment Duration 6.2 Dosage and Administration 7.1.2 Treatment Period	81 93 110	… **In the case of study termination (see Section 5.6), subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).**	… In the case of study termination (see Section 5.6), subjects continuing to benefit from study treatment may still have access to study treatment via enrollment in a rollover study if not available through some other mechanism (eg, expanded access, marketed product).	In order to not deny access to study treatment for subjects who continue to benefit after termination of the study
Added language regarding availability of study drug through rollover study for subjects continuing to benefit from study treatment	5.6 Premature Discontinuation of the Trial	81	The whole trial may be terminated or suspended upon request of health authorities. **The Sponsor may terminate the study at any time once access to study treatment for subjects still benefitting is provisioned via a rollover study, expanded access, marketed product, or another mechanism of access as appropriate.**	The whole trial may be terminated or suspended upon request of health authorities. The Sponsor may terminate the study at any time once access to study treatment for subjects still benefitting is provisioned via a rollover study, expanded access, marketed product, or another mechanism of access as appropriate.	In order to not deny access to study treatment for subjects who continue to benefit after termination of the study
Updated Medical Responsible	Signature page – Protocol lead	186	PPD ~~Merck KGaA, Frankfurter Str. 250~~ ~~64293 Darmstadt, Germany~~ ~~Tel:~~ PPD ~~Fax:~~ PPD PPD PPD **Merck Serono SIA** **45A Middlesex Turnpike** **Billerica, MA 01821, USA**	PPD PPD Merck Serono SIA 45A Middlesex Turnpike Billerica, MA 01821, USA Tel: PPD Fax: PPD PPD	New Medical Responsible assigned

Change	Section	Pages	Previous Wording	New Wording	Rationale
			Tel: PPD **Fax:** PPD PPD		
Updated Clinical Trial Leader information	Further Sponsor Responsible Persons	189	PPD ~~EMD Serono Research & Development, Inc.~~ ~~45 Middlesex Turnpike, Billerica, MA 01821, USA~~ PPD PPD PPD **EMD Serono Research & Development, Inc.** **45 Middlesex Turnpike, Billerica, MA 01821, USA** PPD PPD	PPD PPD EMD Serono Research & Development, Inc. 45 Middlesex Turnpike, Billerica, MA 01821, USA PPD PPD PPD	New Leader assigned

Appendix V Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
IND Number	CCI [redacted]
EudraCT Number	2013-002834-19
Clinical Trial Protocol Date / Version	06 August 2018 / Version 19.0

I approve the design of the clinical trial.

PPD [redacted]

Signature Date of Signature

Name, academic degree	PPD [redacted]
Function	PPD [redacted]
Institution	Merck Serono SIA
Address	45A Middlesex Turnpike Billerica, MA 01821, USA
Telephone number	PPD [redacted]
Fax number	PPD [redacted]
E-mail address	PPD [redacted]

Signature Page – Coordinating Investigator

Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
IND Number	CCI [redacted]
EudraCT Number	2013-002834-19
Clinical Trial Protocol Date / Version	06 August 2018 / Version 19.0

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

PPD [redacted]

Signature Date of Signature

Name, academic degree	PPD [redacted]
Function	
Institution	PPD [redacted]
Address	
Telephone number	PPD [redacted]
Fax number	PPD [redacted]
E-mail address	PPD [redacted]

Signature Page – Principal Investigator

Trial Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
IND Number	CCI [redacted]
EudraCT Number	2013-002834-19
Clinical Trial Protocol Date / Version:	06 August 2018 / Version 19.0
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, the approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some regulatory Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected 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.

Signature	Date of Signature
Name, academic qualifications	_____
Position (job title)	_____
Address of Institution	_____
Phone, fax, e-mail	_____

Further Sponsor Responsible Persons

Name, academic degree	PPD
Function	PPD
Institution	Merck KGaA
Address	Frankfurter Str. 250 64293 Darmstadt, Germany
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Name	PPD
Function	PPD
Institution	EMD Serono Research & Development, Inc.
Address	45 Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number	PPD
Fax number	PPD
E-mail address	PPD