Clinical Trial Protocol

Clinical Trial Protocol Number	EMR100070-003
Title	A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma
Short Trial Name	JAVELIN Merkel 200
Trial Phase	Phase II
IND Number	CCI [redacted]
EudraCT Number	2014-000445-79
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]
Clinical Trial Protocol Version	25 May 2018 / Version 12.0
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Current Clinical Trial Protocol Amendment	Amendment No. 11 / 25 May 2018

[redacted]

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Antineutrophil cytoplasmic antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{tau}	Area under the concentration-time curve
β-HCG	β-human chorionic gonadotropin
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval(s)
CK20	Cytokeratin 20
C_{max}	Maximum plasma concentration observed postdose
C_{min}	Minimum postdose (trough) concentration
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
DLT	Dose-limiting toxicity
DRR	Durable response rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EMA	European Medicines Agency
EQ-5D	EuroQol-EQ-5D
EU	European Union
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FDA	Food and Drug Administration
FFPE	Formalin fixed, paraffin embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee

IERC	Independent Endpoint Review Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
CCI	[redacted]
IV	Intravenous
IVRS	Interactive voice response system
LBCI	Lower boundary of the confidence interval
LDH	Lactate dehydrogenase
MCC	Merkel cell carcinoma
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Merkel cell polyoma virus
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Operations
MRI	Magnetic resonance imaging

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
NSAID	Nonsteroidal anti-inflammatory drug
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
PR	Partial response
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SMC	Safety Monitoring Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
T4	Free thyroxine

TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor beta
TLS	Tumor lysis syndrome
t_{max}	Time to reach maximum concentration
TO	Target occupancy
TSH	Thyroid-stimulating hormone
TTP	Time to progression
UBCI	Upper boundary of the confidence interval
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1 Synopsis

Trial title	A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma
Trial number	EMR100070-003
EudraCT number	2014-000445-79
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	II
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial centers/countries	The trial will be conducted globally in approximately 60 sites, including in North America (approximately 15 sites in the United States [US]), European Union (EU), Australia, Japan, and Switzerland.
Planned trial period (first enrollment-last subject out)	First subject in: Q3, 2014 Last subject out: Q2, 2023
Trial objectives	**Primary objective** Part A: The primary objective is to assess the clinical activity of avelumab as determined by the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by an Independent Endpoint Review Committee (IERC) in subjects with metastatic Merkel cells carcinoma (MCC) after failing first-line chemotherapy. Part B: The primary objective is to evaluate the clinical activity of avelumab as first-line treatment for metastatic or distally recurrent MCC as determined by the durable response rate (DRR) according to RECIST 1.1 by an IERC. **Secondary objectives** Part A: Secondary objectives are as follows: • To assess the duration of response according to RECIST 1.1

	• To assess the progression-free survival time (PFS) according to RECIST 1.1 • To assess the safety profile of avelumab in subjects with MCC • To assess the overall survival (OS) time • To assess response status according to RECIST 1.1 at 6 and 12 months after start of study treatment • To characterize the population pharmacokinetics (PK) of avelumab in subjects with MCC by sparse sampling • To evaluate the immunogenicity of avelumab and to correlate it to exposure Part B: Secondary objectives are as follows: • To assess the OS time • To assess ORR according to RECIST 1.1 • To assess the duration of response according to RECIST 1.1 • To assess the PFS according to RECIST 1.1 • To assess the safety profile of avelumab in subjects with MCC • To assess response status according to RECIST 1.1 at 6 and 12 months after start of study treatment • To characterize the population PK of avelumab in subjects with MCC by sparse sampling • To evaluate the immunogenicity of avelumab and to correlate it to exposure CCI [redacted]

	[redacted]
Trial design and plan	This is a multicenter, international, single-arm, open-label, Phase II trial in two parts that will evaluate the efficacy and safety of avelumab in subjects with metastatic MCC. In Part A, subjects must have received at least 1 line of chemotherapy for the treatment of metastatic MCC. In Part B, subjects must be treatment naïve to systemic therapy in the metastatic setting. In Part A, up to 84 eligible subjects will receive avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) once every 2 weeks. In Part B, up to 112 eligible subjects are planned to be enrolled and will receive avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion (-10 minutes / +20 minutes,

	that is, over 50 to 80 minutes) once every 2 weeks. Tumor measurements (including the assessment of skin lesions by physical examination) to determine response will be performed every 6 weeks until 12 months after the first study drug administration, then every 12 weeks and response to the treatment will be evaluated by RECIST 1.1. Treatment will continue until • therapeutic failure (subjects may stay on treatment beyond observation of progressive disease [PD] provided there is no significant clinical deterioration); • unacceptable toxicity; or • any criterion for withdrawal from the trial or the study drug is fulfilled. Significant clinical deterioration is defined as • new symptoms or worsening of symptoms that cannot be managed by optimal supportive care or disease localization that require immediate medical or surgical intervention (for example, lesion close to the spine), and/or • change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to ≥ 3 that lasts more than 14 days. Decisions regarding medical management of subjects will be made by the Investigator; however, the primary and secondary endpoint determinations will be according to tumor assessments performed by the IERC. The date of the first observation of PD by RECIST 1.1 by the IERC will be used to determine the date of the PD as well as the duration of response in all subjects, including the subjects for which treatment was maintained beyond first determination of disease progression. Adverse events will be assessed throughout the trial period and evaluated using the National Cancer Institute (NCI) Common Technology Criteria version 4.0 (CTCAE v 4.0). Health-related quality of life will be assessed using a generic instrument (EuroQol EQ-5D [EQ-5D]), a cancer-specific instrument including a melanoma-specific module (Functional Assessment of Cancer Therapy – Melanoma [FACT-M]), and subject interviews (optional). In Part A there will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least

	3 months and 1 interim analysis for efficacy 6 months after 56 subjects have been enrolled. The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. In Part B there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. For both Parts A and B, subject follow-up for progression and survival will continue until 5 years after the last subject receives the last dose of avelumab or the last subject dies, whichever occurs first. Under some circumstances, subjects may not be followed for 5 years for survival in this study, for example, subjects may be offered to enroll into a rollover study, or the Sponsor may terminate the study early.
Planned number of subjects	Eighty-four subjects are planned to be enrolled in Part A and 112 subjects in Part B of this study.
Schedule of visits and assessments	**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, mapping of skin lesions, 12-lead electrocardiogram (ECG) and a determination of the ECOG PS; AE and concomitant medication assessments; safety laboratory assessments; the tumor evaluation (including brain) by computed tomography (CT) scan or magnetic resonance imaging (MRI; for trial sites in Germany, only MRI is to be used) as well as tumor markers; collection of tumor tissue prior to the first study drug administration is required for all subjects (fresh biopsy or recent biopsy [within 4 weeks prior to enrollment provided as block or slides, blocks preferable], for subjects unable to provide a fresh or recent biopsy, archival material is acceptable [blocks preferable]); bone scan (as clinically indicated); serum β-human chorionic gonadotropin (β-HCG) pregnancy test for females of childbearing potential; blood hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) testing, adrenocorticotropic hormone, antinuclear antibody,

	antineutrophil cytoplasmic antibody, rheumatoid factor, free thyroxine, and thyroid-stimulating hormone. Blood samples for baseline PK and immunogenicity (antidrug antibody [ADA] tests, previously referred to as human antihuman antibody [HAHA]) sampling as well as for CCI (Part A) and exploratory CCI CCI (Part B) will be collected before or on Day 1 before trial treatment starts. The EQ-5D and FACT-M questionnaires will be administered at baseline to collect subjects' baseline health-related quality of life data. In addition, optional subject interviews will be conducted to collect subjects' experience with MCC and their experience with prior treatment for MCC. CCI **Treatment phase** Visits will take place every 2 weeks (1 treatment cycle). Note: subjects with liver metastases at Baseline will have visits every week up to Week 7. Safety (including AEs and concomitant medications, laboratory values, ECOG PS, weight, physical examinations, vital signs, ECG, β-HCG for females of childbearing potential), PK, immunogenicity, and tumor response assessments will be conducted at designated times throughout the trial. The main assessments are as follows: • The EQ-5D and FACT-M will be completed by subjects prior to any study related procedures at Week 7, and then once every 6 weeks thereafter while on treatment. • Subject interviews (optional in both Part A and Part B) will be conducted at Week 13 and at 6 months of treatment to collect subjects' current experience with their disease, the study drug, and their experience within the trial. • Tumor responses (including the assessment of skin lesions by physical examination) will be assessed every 6 weeks, per RECIST 1.1 until 12 months after the first study drug administration, then every 12 weeks.

	• For Part A, PK samples will be collected from all subjects prior to each study drug infusion through Week 15, then Week 25, and then at 12-week intervals while on treatment. Post infusion samples will be collected at Weeks 1, 7, 13, and 25, and then at 12-week intervals while on treatment. For Part B the PK schedule is prior to each study drug infusion through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment. Post study drug administration samples will be collected at the end of infusion at Weeks 1, 7, and 25. • Samples for immunogenicity (ADA analysis) will be collected at Day 1 (Screening / Baseline sample) and within 2 hours before infusion on Days 15, 29, 43 (every 2 weeks) and then every 6 weeks thereafter while on treatment. For Part B the ADA schedule is Day 1 (Screening / Baseline sample) and within 2 hours before infusion through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment. CCI [redacted] CCI [redacted] **Discontinuation visit, End-of-Treatment visit, Safety Follow-up visit, and Post-treatment follow-up** For Part A, all subjects who discontinue trial treatment prematurely for an AE should have a full safety evaluation and immune monitoring and assessment of CCI [redacted] at the time of discontinuation (Discontinuation visit). For Part B, all subjects who discontinue treatment regardless of the reason will have a Discontinuation visit within 7 days of the decision to discontinue treatment. The Discontinuation visit will include a full safety evaluation, PK sampling, and sampling for exploratory CCI [redacted].

	For all subjects who have completed treatment, an End-of-Treatment visit should be scheduled 4 weeks (Part A) / 30 days (Part B) after the last administration of avelumab. The End-of-Treatment visit is scheduled 4 weeks (Part A) / 30 days (Part B) 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, the EQ-5D and FACT-M assessments, immunogenicity (Part B only), PK sampling (Part B only), and immune monitoring and CCI [redacted] and tumor response assessment as appropriate. **Safety and Post-treatment Follow-up** For Part A, 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, immune monitoring and CCI [redacted]. For Part B, all subjects will have a subsequent visit scheduled 90 days (± 1 Week) after the last administration of the study drug. The visit will include a full assessment of safety parameters, immune monitoring and CCI [redacted]. Subjects with an adverse drug reaction (ADR) ongoing at the End-of-Treatment visit must be followed up until the ADR resolves, becomes stable, or is considered not clinically significant by the Investigator. For subjects who discontinue treatment prior to Week 13, off-treatment interviews (optional, both Part A and Part B) will be scheduled for 13 weeks and 6 months from the start of treatment to collect subjects' current experience with their disease, the study drug, and their experience within the trial. In case of discontinuation later than Week 13 but prior to 6 months of treatment, an off-treatment interview (optional, both Part A and Part B) will be scheduled for 6 months from the start of treatment. For both Parts A and B, subjects without PD at the End-of-Treatment visit will be followed until disease progression (CT / MRI scans every 6 weeks until 12 months after the first study drug administration, then every 12 weeks).

	For both parts, 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. For both Parts A and B, 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 for up to 5 years after the last subject receives the last dose of avelumab or last subject dies, whichever occurs earlier.
Diagnosis and main inclusion and exclusion criteria	**Inclusion criteria** 1. Signed written informed consent 2. Male or female subjects aged ≥ 18 years 3. Histologically proven MCC a) Confirmation of the diagnosis by immuno-histochemistry detection of CK20 (or other appropriate cytokeratin expression such as pancytokeratin, AE1/AE3, or Cam5.2; local laboratory testing) in the tumor cell is mandatory b) Subjects must have metastatic disease; subjects with non-metastatic MCC that is only recurrent or unresectable are NOT eligible; for Part B, M1 status must be confirmed at entry c) For Part A: Subjects must have received at least 1 line of chemotherapy for the treatment of metastatic MCC and must have progressed after the most recent line of chemotherapy that was administered. Subjects must have received at least one of the following chemotherapy regimens for treatment of metastatic MCC: Cyclophosphamide, topotecan, doxorubicine, epirubicin, vincristine, carboplatin, cisplatin, etoposide in combination with carboplatin or cisplatin d) For Part B: Subjects must not have received any prior systemic treatment for metastatic MCC. Prior chemotherapy treatment in the adjuvant setting (no clinically detectable disease; no metastatic disease) is allowable if the end of treatment occurred at least 6 months prior to study start.

	4. For Part A: Collection of biopsy material is required (fresh biopsy or recent biopsy [within 4 weeks prior to enrollment], for subjects unable to provide a fresh or recent biopsy, archival material is acceptable). For Part B: 1) Priority: A recently obtained formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue (preferably within 6 months). If no tumor tissue is available, a fresh biopsy will be required. 2) Priority: If the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut (within 1 week). Preferably, 25 slides should be provided; if not possible, a minimum of 10 slides in consultation with the Medical Monitor is required 5. ECOG PS of 0 to 1 at trial entry 6. Estimated life expectancy of more than 12 weeks 7. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1 (including skin lesions) 8. Adequate hematological function defined by white blood cell (WBC) count $\geq 3 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused) 9. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 2.5 \times$ ULN for all subjects 10. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula or by 24 hour urine collection for creatinine clearance or according to local institutional standard method 11. **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.) **Exclusion criteria** 1. Participation in another interventional clinical trial within the past 30 days (participation in observational studies is permitted) 2. Concurrent treatment with a nonpermitted drug 3. Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints) such as antiprogrammed death 1 (PD-1), anti-PD-L1, or anticytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody; for Part B, the Investigator must consult with the Medical Monitor and consider other co-regulatory targets such as 4-1BB 4. Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy, or radiotherapy administered on non-target superficial lesions], immune therapy, or cytokine therapy except for erythropoietin). Radiotherapy administered to superficial lesions is not allowed if such lesions are considered target lesions in the efficacy evaluation or may influence the efficacy evaluation of the investigational agent 5. Major surgery for any reason, except diagnostic biopsy, within 4 weeks and/or if the subject has not fully recovered from the surgery within 4 weeks 6. Concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of trial treatment. Short-term administration of systemic steroids (that is, for allergic reactions or the management of immune-related adverse events [irAE]) while on study is allowed. Also, subjects requiring hormone replacement with corticosteroids for adrenal insufficiency are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent

	prednisone per day. Note: Subjects receiving bisphosphonate or denosumab are eligible 7. Subjects with active central nervous system (CNS) metastases are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy 8. For Part A: Previous malignant disease (other than MCC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ. For Part B: Previous malignant disease (other than MCC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (skin, bladder, cervical, colorectal, breast, or low grade prostatic intraepithelial neoplasia or Grade 1 prostate cancer) 9. Prior organ transplantation, including allogeneic stem-cell transplantation 10. For Part A, known history of testing positive for HIV or known acquired immunodeficiency syndrome (AIDS), or any positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection. For Part B, known history of testing positive for HIV or known AIDS or HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive) 11. Active or history of any autoimmune disease (except for subjects with vitiligo) or immunodeficiencies that required treatment with systemic immunosuppressive drugs 12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade $\geq$ 3 NCI-CTCAE v 4.0), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma) 13. Persisting toxicity related to prior therapy Grade > 1 NCI-CTCAE v 4.0; however, sensory neuropathy Grade $\leq$ 2 is acceptable 14. Pregnancy or lactation

	15. Known alcohol or drug abuse 16. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication 17. All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment 18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent 19. Legal incapacity or limited legal capacity 20. Nononcology vaccine therapies for prevention of infectious disease (for example, seasonal flu vaccine, human papilloma virus vaccine) within 4 weeks of study drug administration. Vaccination while on trial is also prohibited except for administration of inactivated vaccines (for example, inactivated seasonal influenza vaccine)
Investigational Medicinal Product: dose / mode of administration / dosing schedule	Avelumab will be administered as a 1-hour IV infusion (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) at 10 mg/kg once every 2-week treatment cycle. In order to mitigate infusion-related reactions, subjects will receive pretreatment with antihistamine and paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. Steroids as premedication are not acceptable. This regimen may be modified based on local treatment standards and guidelines as appropriate. The dose of avelumab will be calculated based on the weight of the subject determined on the day of (for Part A), or within 3 days of each drug administration (Part B). Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including IV epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be in place for use in the treatment of potential infusion-related reactions. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or hypersensitivity reactions

	(according to NCI-CTCAE v 4.0). Following avelumab infusions, subjects should be observed based upon clinical judgment and presence / severity of prior infusion reactions. In the case of Grade 1 or 2 infusion reactions, the infusion rate should be decreased by 50%.
Reference therapy: dose / mode of administration/dosing schedule	Not applicable.
Planned treatment duration per subject	Subjects will receive avelumab treatment until significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or study drug is fulfilled. For Part A: Subjects who have experienced a confirmed complete response (CR) should be treated for a maximum of 12 months and a minimum of 6 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. Part B: Subjects who have experienced a confirmed CR should be treated for a minimum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. For both Part A and Part B, in case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the 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 endpoint	Part A: The primary endpoint for the trial is the confirmed BOR, per RECIST 1.1, as determined by an IERC. Both CR and partial response (PR) must be confirmed by a second tumor assessment that will be performed preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR.

	Part B: The primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months.
Secondary endpoints CCI [redacted]	Part A: Secondary endpoints include • duration of response according to RECIST 1.1 as determined by an IERC, • PFS time according to RECIST 1.1 as determined by an IERC, • occurrence and severity of treatment-related AEs according to NCI-CTCAE v 4.0, • OS time, • response status according to RECIST 1.1 at 6 and 12 months after start of study treatment, • serum titers of anti-avelumab antibodies, and • population PK profile of avelumab (sparse sampling). CCI [redacted] Part B: Secondary endpoints include • OS time,

	• confirmed BOR per RECIST 1.1 as determined by an IERC, • duration of response according to RECIST 1.1 as determined by an IERC, • PFS time according to RECIST 1.1 as determined by an IERC, • occurrence and severity of treatment-related AEs according to NCI-CTCAE v 4.0, • response status according to RECIST 1.1 at 6 and 12 months after start of study treatment, • serum titers of anti-avelumab antibodies, and • population PK profile of avelumab (sparse sampling). CCI [redacted]
Pharmacokinetics	For Part A, blood samples for determination of avelumab will be collected prior to each study drug infusion through Week 15, then Week 25, and then at 12-week intervals while on treatment. Post infusion samples will be collected at Weeks 1, 7, 13, and 25, and then at 12-week intervals while on treatment. For Part B, blood samples for determination of avelumab will be collected prior to each study drug infusion through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment. Post study drug administration samples will be collected at the end of infusion at Weeks 1, 7, and 25. Samples will also be

	collected at the Discontinuation and End-of-Treatment visits.
Biomarkers/ Pharmacogenetics (PGx)	CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]
Statistical methods (includes sample size calculation)	**Part A** The primary endpoint of the trial is the confirmed BOR according to RECIST 1.1, based on independent review of tumor assessments. The trial aims at demonstrating an ORR greater than 20% by the exact binomial test. The primary analysis population for all analyses of efficacy and safety is the Safety population, consisting of all subjects that received at least 1 dose of trial treatment. Analyses of efficacy variables may also be performed on subgroups of interest as needed. The planned total sample size is 84 subjects. The primary analysis will be performed 6 months after the accrual of the last subject and a further exploratory analysis will be conducted at 12 months after the accrual of the last subject. There will also be an interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months and an interim analysis for efficacy 6 months after 56 subjects have been enrolled. The following assumptions are made for the sample size calculation: • ORR of 35% • overall alpha = 0.025 (1-sided) for the test of the null hypothesis of an ORR ≤ 20%

	The following analyses are planned for the study: • Futility: Enrollment will be stopped for futility if no response (confirmed or unconfirmed) is observed in the first 20 subjects after 3 months of follow-up. • Efficacy: A group sequential testing approach will be applied. The null hypothesis can be rejected if 20 subjects in the interim analysis after 56 subjects, or 25 subjects in the primary analysis after 84 subjects, show a confirmed PR or CR according to RECIST 1.1. The corresponding nominal p-values of the exact binomial test are 0.0045 and 0.0214, respectively. The resulting overall probability of reaching a positive result in the interim or primary analysis under the null hypothesis assumption of an ORR $\leq$ 20% is $\leq$ 0.0225. Under the given assumptions, the power to reject the null hypothesis at the interim or the primary analysis is approximately 87%. **Part B** The primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months. The primary analysis population for all analyses of efficacy and safety is the Safety population, consisting of all subjects that received at least 1 dose of trial treatment. The planned total sample size is 112 subjects for addressing the primary objective, relevant subgroup analyses, consistency, and further safety assessments. Assuming a true DRR of 45%, the probability to observe lower bound of the exact 95% confidence interval (CI) above 20% would be > 99% and above 30% would be 90%. The primary analysis will be performed 15 months after the accrual of the last subject. Part B of the study aims to estimate the DRR with a sufficient level of precision. For example, an observed DRR of 28.6% would lead to an exact (Clopper-Pearson) 95% CI of (20.4%; 37.9%), an observed DRR of 40.2% would lead to a 95% CI of (31.0%; 49.9%), and an observed DRR of 44.6% would lead to an exact 95% CI of (35.2%; 54.3%). An interim exploratory analysis will be conducted at 3 months after the accrual of the 25th subject, with additional interim analyses possible.

	Endpoint analysis The confirmed BOR according to RECIST 1.1 is defined as the best response obtained among all tumor assessment visits after start of trial treatment until documented disease progression, excluding assessments after start of subsequent anticancer therapy, taking into account the following requirement for confirmation: PR or CR needs to be confirmed, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. The duration of response will be calculated for each subject with a confirmed response (CR or PR) as the time from first observation of response until first observation of documented disease progression or death within 12 weeks of the last tumor assessment, whichever occurs first. The duration of response will be analyzed using the Kaplan-Meier method. The PFS time, according to RECIST 1.1, will be defined from first administration of trial treatment until first observation of PD or death within 12 weeks of the last tumor assessment or first administration of trial treatment (whichever is later). The PFS time will be analyzed using the Kaplan-Meier method. In particular, the progression-free rate at 6 months will be estimated with corresponding 2-sided 95% CI. The OS time will be defined as the time from first administration of trial treatment until death. The OS time will be analyzed using the Kaplan-Meier method. In particular, the survival rate at 6 and 12 months will be estimated with corresponding 2-sided 95% CI. Safety endpoints, including AEs, clinical laboratory assessments, vital signs, and ECG parameters, will be analyzed descriptively. The EQ-5D and FACT-M scores will be analyzed descriptively at all scheduled administrations, including a description of missing assessments. Subject interviews will be analyzed by a qualitative thematic analysis on the de-identified transcripts of the interviews using ATLAS.ti software and based on the grounded theory to enable the focus of the analysis on the perspective of the subjects.

	Additional endpoint analysis in Part B: The DRR will be determined as the proportion of subjects with a durable response, that is, with a minimum duration of 6 months.

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 globally in approximately 60 sites, including in North America (approximately 15 sites in the United States [US]), European Union (EU), Australia, Japan, and Switzerland.

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.

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

Safety laboratory assessments will be performed locally by investigational sites and also by a central laboratory. Pharmacokinetic (PK), exploratory CCI assessments will be performed under the responsibility and / or supervision of the Sponsor.

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

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

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

2.3 Review Committees

2.3.1 Safety Monitoring Committee

To ensure subjects' safety during the trial, a safety monitoring committee (SMC) will periodically review safety data. The SMC will be composed of a minimum of 3 members, including a trial Investigator, a statistician, and an independent physician. The SMC consists of permanent members from the Sponsor and/or CRO (Global Drug Safety Representative, Program Lead, Medical Lead, Biostatistician, Medical Monitor), and the Coordinating Investigator. The full membership, mandate, and processes of the SMC is detailed in the SMC charter. As of Protocol Amendment 10, the planned periodic review of safety data by the SMC was no longer scheduled given the safety data have been analysed as per the statistical plan and submitted to health authorities for review.

2.3.2 Independent Endpoint Review Committee

The Independent Endpoint Review Committee (IERC) will be composed of a minimum of 3 members for Part A, and a minimum of 4 members for Part B. The role of the IERC will be to review radiographic image findings and physical findings (skin lesion mapping / physical assessments) for the determination of the BOR and date of disease progression for each subject. The full membership, mandate, and processes of the IERC will be detailed in the IERC charter for Part A, which is a single radiology review and two-oncologist review committee, and for Part B, which is a double radiology review with adjudication and single oncologist review.

3 Background Information

3.1 Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other malignancies by its expression of cytokeratin 20 (CK20, Becker 2010). Although relatively rare, with an estimated 1500 new cases in 2008 in the United States (last date with available data), the incidence of MCC is increasing. The incidence of MCC increases with age, predominantly affects the white population, and is roughly twice as prevalent in white males as white females (Agelli 2003, Albores-Saavedra 2010). More recent data from the Surveillance, Epidemiology, and End Results (SEER) Program database confirm the higher incidence in males compared with females in the US (2). Similar trends are seen in northern European countries (Mills 2006, Kaae 2010, Kukko 2012, Reichgelt 2011). The 5-year survival rate for patients with MCC is 75%, 59%, and 25% for primary tumors, lymph node metastases (and/or local recurrences), and distant metastases, respectively (Becker 2010).

The risk of developing MCC is increased from 5- to 50-fold in immune-suppressed individuals (transplant recipients, individuals with lymphoproliferative malignancies such as chronic lymphocytic leukemia, or individuals with human immunodeficiency virus [HIV] infections [Becker 2010, Bhatia 2011]). Furthermore, MCC tumor regression has been reported following improvement in immune system function in immune compromised individuals (Burak 2003,

Muirhead 2007, Bhatia 2011). These findings suggest a strong link between the immune suppression and development and progression of MCC.

Recently, a polyoma virus, Merkel cell polyoma virus (MCV) has been identified (Feng 2008) and has been detected in 40% to 100% of patient samples (Rollison 2010). While the role of MCV in the pathogenesis of MCC is still unclear, there is evidence that the virus is causal of disease (Spurgeon 2013). Additionally, as with other immunogenic tumors, patients with MCV-positive tumors have a better overall survival compared with patients with MCV-negative tumors (Sihto 2009).

3.2 Treatment Options for Merkel Cell Carcinoma

For local and regional disease, surgery (local excision with wide margins) followed by radiation therapy are the primary treatment options; however, despite local excision, MCC locoregional recurrences are frequent, and usually occur within the first 2 years of primary diagnoses. Approximately one-third of patients will experience recurrence, a significant proportion with metastatic disease (Medina-Franco 2001, Soult 2012).

At the initiation of this study, there was no Food and Drug Administration (FDA) approved treatment for nonresectable, recurrent, advanced, or metastatic MCC. The National Comprehensive Cancer Network (NCCN) guidelines recommend multidisciplinary tumor board consultation for patients with metastatic disease to consider any or a combination of radiation, surgery, and chemotherapy (NCCN 2016). The specific treatment regimen for patients with distant metastasis must be individually tailored.

Most NCCN institutions only use chemotherapy with or without surgery and / or radiation therapy for Stage IV, distant metastatic disease (M1).

The most common regimen used for regional disease is cisplatin or carboplatin with or without etoposide. The NCCN panel recommends cisplatin or carboplatin with or without etoposide as the choice of treatment (Pectasides 2006). Topotecan has also been used in some instances (for example, older patients). Cyclophosphamide in combination with doxorubicin and vincristine used to be a commonly administered regimen, but it is associated with significant toxicity. Despite these recommendations, data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free survival or overall survival in MCC patients with distant metastatic disease (Voog 1999, Tai 2000, Poulsen 2003). In fact, though MCC is often initially chemosensitive, tumor responses are rarely durable, with the 2-year survival rate for patients with stage IV disease at approximately 26% (Lemos 2010).

There are no prospective clinical trial data available for patients who received chemotherapy for second-line treatment of mMCC (Nghiem 2016). The only published report summarizing observations of clinical outcomes in a purely distant mMCC population of subjects who had received first-line chemotherapy and second-line chemotherapy in the metastatic setting is a report by Iyer et al. The DRR observed with 1L chemotherapy was 17.7% (95% CI 9.2, 29.5) and median DOR was 2.8 months for 1L chemotherapy (Iyer 2016 and personal communication).

At the initiation of this study, there was one prospective single-arm trial of subjects with locally advanced and distant metastatic MCC treated with a PD-1 blockade that demonstrates response to this treatment modality (Nghiem 2016).

3.3 Programmed Death Receptor and Ligands

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T-cell death and localized immune suppression (Dong 1999, Freeman 2000, Dong 2002, Topalian 2012a), potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate antitumor activity in nonclinical animal models (Dong 2002, Iwai 2002).

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

Of importance to the current trial, previous studies have demonstrated PD-L1 tumor cell expression in 49% of MCC patient samples (49 patients sampled) and expression in tumor infiltrating lymphocytes in 55% of patient samples. Of note, of the PD-L1 positive samples, 28 of 29 samples showed colocalization with immune infiltrates (Lipson 2013). These findings, coupled with the sited response rates and long response durations in other solid tumors make PD-L1 an attractive target in patients with MCC.

3.4 Avelumab

The Investigational Medicinal Product (IMP) for the present trial is avelumab, a human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono Inc., Rockland, MA, USA. Avelumab has received regulatory approval for treatment of metastatic MCC by health authorities in all countries conducting this protocol.

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2 / PD-1 pathway intact to promote peripheral self-tolerance (Latchman 2001). For complete details of the in vitro and nonclinical studies, please refer to the Investigator's Brochure (IB).

At the time of the initiation of this study, avelumab was in early clinical development with 2 ongoing Phase I studies in subjects with solid tumors (refer to the latest IB for latest information on clinical development and approvals):

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[redacted]

CCI

[redacted]

3.4.1.1 Safety Results

Expansion: All adverse events

CCI

[redacted]

CCI

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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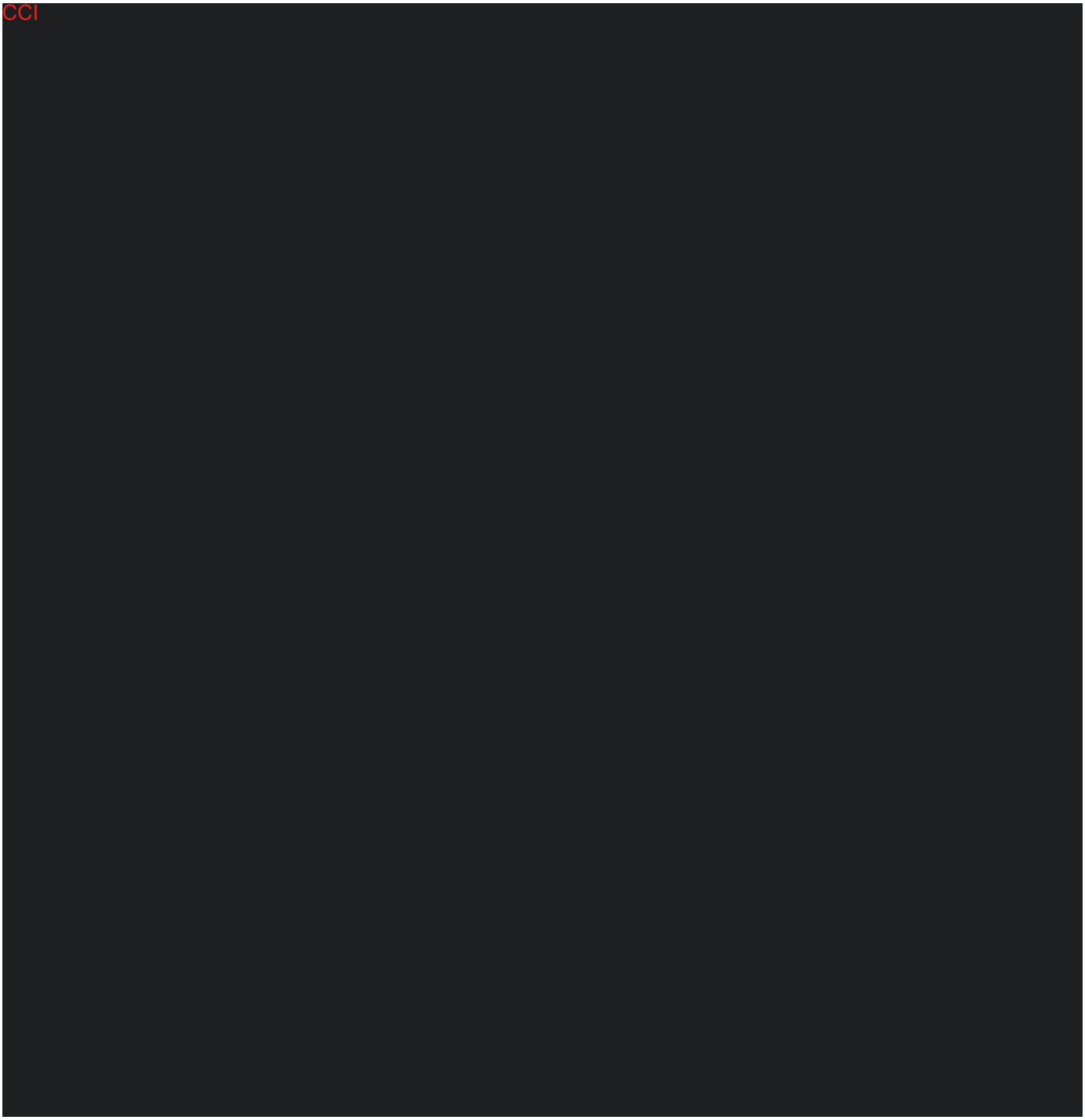

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Blood chemistry

A considerable proportion of subjects (up to over 60% for some measure expansion cohort experienced blood chemistry laboratory abnormalities; how abnormalities were relatively mild (Grade 1 or 2). Grade 3 or 4 blood chem occurred less frequently. The following Grade 3 or 4 abnormalities were ob 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%).

3.4.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

CCI [redacted]

Vital sign and body weight abnormalities were summarized. For this analysis, the abnormalities were defined as:

- Systolic blood pressure ≤ 95 mmHg as well as a decrease from baseline ≥ 20 mmHg or ≥ 160 mmHg as well as an increase from baseline ≥ 20 mmHg
- Diastolic blood pressure ≤ 45 mmHg as well as a decrease from baseline ≥ 10 mmHg or DBP ≥ 110 mmHg as well as an increase from baseline ≥ 10 mmHg
- Pulse rate ≤ 50 beats per minute (bpm) as well as a decrease from baseline ≥ 20 bpm or pulse rate ≥ 120 bpm as well as an increase from baseline ≥ 20 bpm
- Increase or decrease in body weight from baseline ≥ 10%

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

3.4.6 Pharmacokinetic Results

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CCI

[redacted]

CCI

[redacted]

3.4.7 Clinical Pharmacodynamics

CCI

[redacted]

CCI

[redacted]

3.5 Rationale for the Current Clinical Trial

The evaluation of an anti-PD-L1 antibody for the treatment of metastatic MCC is supported by

- the particular biology of this viral-induced tumor and its link to immunosuppression,
- the expression of PD-L1 by MCC tumor cells and by adjacent immune infiltrates, and
- the clinical activity reported by other anti-PD-L1 investigational drugs in the context of the expression of PD-L1 at the surface of the tumor or in the tumor micro-environment.

3.6 Summary of the Overall Benefit and Risk

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

The primary risks of exposure to avelumab include:

- infusion-related reactions and
- irAEs (other than infusion-related reactions).

At the time of preparation of this Amendment, safety data from 50 subjects treated with avelumab at doses ranging from 1 to 20 mg/kg during dose escalation and 480 subjects at a dose of 10 mg/kg in dose expansion were available. Key safety findings, including irAEs and infusion-related reactions, are described in Section 3.4.1.

Overall, the safety data of avelumab suggest an acceptable safety profile of the compound.

Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

Already implemented risk mitigation measures for infusion-related reactions/hypersensitivity have been extended by a mandatory premedication with antihistamine and paracetamol (acetaminophen) for all subjects prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. A premedication regimen of diphenhydramine and paracetamol (acetaminophen, IV or oral equivalent) is recommended. This regimen may be modified based on local treatment standards and guidelines as appropriate.

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

As noted above (Section 3.3), trials with antibodies that block the PD-1 – anti-PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors (Brahmer 2012, Topalian 2012b, Hamid 2013), with response durations of 1 year or more for the majority of patients.

Given the poor prognosis of subjects with metastatic MCC, the lack of treatment options for second-line patients, and the safety profile of avelumab as currently demonstrated by ongoing Phase I trials, the risk-benefit ratio of treatment with avelumab in the targeted trial population is considered positive for Part A of this study.

With regard to Part B, in first-line treatment, patients face poor prognosis and lack of treatment options. The NCCN MCC guidelines highlight clinical trials where possible due to lack of survival evidence for chemotherapy in first line treatment (NCCN 2016). European guidelines similarly note the lack of survival benefit of chemotherapy and mention palliative care due to the poor prognosis, especially in elderly patients (Becker 2010, Boccara 2012). When chemotherapy is used, regimens similar to small cell lung cancer such as carboplatin with etoposide are common, although NCCN notes "the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable". Overall, there is poor prognosis, with 2-year survival rate of 26% in Stage IV disease (Lemos 2010). The benefit of avelumab in metastatic MCC as initial therapy is unknown; however, preliminary results from an ongoing Phase II study in second-line or greater metastatic disease has documented an ORR greater than a predefined futility rate (data not shown). Also, a similar mechanism of action (pembrolizumab, an anti-PD-1 antibody) has demonstrated a substantial ORR (71% in evaluable patients) in treatment naïve metastatic or unresectable MCC (Nghiem 2016). Given the known clinical activity of avelumab in a variety of tumor types (refer to avelumab IB) and given the expression of PD-L1 with CD8 T cell presence in Merkel cell tumors (Afanasiev 2013) it is plausible that avelumab offers benefit. Overall, given the poor prognosis, lack of treatment options based on evidence and its known safety profile, avelumab is considered to have a positive risk-benefit ratio for Part B of this study.

In Part B, subjects with prior adjuvant chemotherapy experience (but not in the metastatic setting) are allowed. This inclusion is justified given the lack of evidence of survival benefit for chemotherapy in the adjuvant setting (NCCN 2016) and, therefore, poor prognosis for first line patients regardless of prior adjuvant treatment history. Such subjects must meet entry criteria that include adequate absolute lymphocyte and neutrophil counts and resolution of prior events must have completed adjuvant chemotherapy more than 6 months prior to the current trial, therefore, they are expected to have largely recovered from immune suppressive effects of chemotherapy.

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

4 Trial Objectives

Primary

Part A: The primary objective of the trial is to assess the clinical activity of avelumab as determined by the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; Eisenhauer 2009) in subjects with metastatic MCC after failing first-line chemotherapy.

Part B: The primary objective is to evaluate the clinical activity of avelumab as first-line treatment for metastatic or distally recurrent MCC as determined by the durable response rate (DRR) according to RECIST 1.1 by an IERC.

Secondary

Part A: Secondary objectives are as follows:

- To assess the duration of response according to RECIST 1.1
- To assess the progression-free survival time (PFS) according to RECIST 1.1
- To assess the safety profile of avelumab in subjects with MCC
- To assess overall survival (OS) time
- To assess response status according to RECIST 1.1 at 6 and 12 months after start of study treatment
- To characterize the population PK of avelumab in subjects with MCC by sparse sampling
- To evaluate the immunogenicity of avelumab and to correlate it to exposure

Part B: Secondary objectives are as follows:

- To assess the OS time
- To assess ORR according to RECIST 1.1
- To assess the duration of response according to RECIST 1.1
- To assess the PFS according to RECIST 1.1
- To assess the safety profile of avelumab in subjects with MCC
- To assess response status according to RECIST 1.1 at 6 and 12 months after start of study treatment
- To characterize the population PK of avelumab in subjects with MCC by sparse sampling
- To evaluate the immunogenicity of avelumab and to correlate it to exposure

Exploratory objectives

Part A: Exploratory objectives are as follows:

CCI [redacted]

Part B: Exploratory objectives are as follows:

CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, international, single-arm, open-label, Phase II, trial in 2 parts that will evaluate the efficacy and safety of avelumab in subjects with metastatic MCC. In Part A, subjects must have received at least one line of chemotherapy for the treatment of metastatic MCC. In Part B, subjects must be treatment naïve to systemic therapy in the metastatic setting. Part B will serve as the confirmatory study required to meet conditions for some health authority approvals of avelumab for treatment of metastatic MCC.

5.1.1 Overall Design

In Part A, up to 84 subjects are planned to be enrolled and in Part B, up to 112 eligible subjects are planned to be enrolled. In both Part A and Part B, subjects will receive avelumab at a dose of 10 mg/kg once every 2 weeks. Tumor measurements (including the assessment of skin lesions by physical examination) to determine response will be performed every 6 weeks until 12 months

after the first study drug administration, then every 12 weeks thereafter and response to the treatment will be evaluated by RECIST 1.1. Treatment will continue until:

- therapeutic failure (subjects may stay on treatment beyond radiological disease progression provided there is no significant clinical deterioration, see Section 5.5.1),
- unacceptable toxicity, or
- any criterion for withdrawal from the trial or study drug is fulfilled (see Section 5.5).

For Part A: Subjects who have experienced a confirmed complete response (CR) should be treated for a minimum of 6 months and a maximum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. Part B: Subjects who have experienced a confirmed CR should be treated for a minimum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. For both Part A and Part B, in case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the 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).

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

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

For Part A, the primary endpoint for the trial will be the confirmed BOR, as per RECIST 1.1, as determined by the IERC. Both CR and partial response (PR) must be confirmed by a second tumor assessment, preferably performed at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR.

For Part B, the primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months.

Safety endpoints include AEs, assessed throughout the trial and evaluated using the NCI Common Technology Criteria version 4.0 (CTCAE v 4.0), clinical laboratory assessments, vital signs, and ECG parameters.

Health-related quality of life questionnaires, EuroQol-EQ-5D (EQ-5D) and Functional Assessment of Cancer Therapy – Melanoma (FACT-M), will be administered to subjects at

baseline, every 6 weeks while on study treatment, and at the End-of Treatment visit. In addition, subject interviews will be conducted in order to collect subjects' previous experience with the disease and its treatment and their current experience within the trial. For Part A and Part B of the study, subject interviews will be optional (box on the Informed Consent Form [ICF] indicating consent for interviews must be checked and a Contact Order Form including subject contact details should be completed and sent to the independent unit in charge of managing the interviews).

For Part A, there will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months and 1 interim analysis for efficacy 6 months after 56 subjects have been enrolled. If no unconfirmed response according to RECIST 1.1 is seen in the first interim analysis, then enrollment will be stopped until the SMC makes a recommendation as to whether the trial should continue. If efficacy goals 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. The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. The trial will continue as specified in Section 5.7.

In Part B, there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. The trial will continue as specified in Section 5.7.

5.1.2 Trial Endpoints

5.1.2.1 Primary Endpoints

For Part A, the primary endpoint is the confirmed BOR for each subject, per RECIST 1.1, as determined by the IERC (see Section 7.3).

For Part B, the primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months.

5.1.2.2 Secondary Endpoints and Exploratory Endpoints

Part A: Secondary endpoints include:

- duration of response according to RECIST 1.1 as determined by an IERC,
- PFS time according to RECIST 1.1 as determined by an IERC,
- occurrence, number, and severity of treatment-related AEs according to NCI-CTCAE v 4.0, clinical laboratory assessments, vital signs, and ECG parameters,
- OS time,
- response status according to RECIST 1.1 at 6 and 12 months after start of study treatment,
- serum titers of anti-avelumab antibodies, and
- population PK profile of avelumab (sparse sampling).

Part A: Exploratory endpoints include:

CCI [redacted]

Part B: Secondary endpoints include:

- OS time,
- confirmed BOR per RECIST 1.1 as determined by an IERC,
- duration of response according to RECIST 1.1 as determined by an IERC,
- PFS time according to RECIST 1.1 as determined by an IERC,
- occurrence and severity of treatment-related AEs according to NCI-CTCAE v 4.0,
- response status according to RECIST 1.1 at 6 and 12 months after start of study treatment,
- serum titers of anti-avelumab antibodies, and
- population PK profile of avelumab (sparse sampling).

Part B: Exploratory endpoints include:

CCI [redacted]

5.1.3 Trial Medication Administration and Schedule

Subjects will receive IV infusion of avelumab (10 mg/kg over 1 hour [-10 minutes / +20 minutes, that is, over 50 to 80 minutes]) once every 2 weeks (one treatment cycle). The trial treatment schedule is illustrated in Appendix I. In order to mitigate infusion-related reactions, a premedication regimen of antihistamine (diphenhydramine or equivalent) and paracetamol (acetaminophen, IV or oral equivalent) is required prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. Steroids as premedication are not acceptable.

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

5.1.4 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

5.1.4.1 Dose Modification

The dose of avelumab will be calculated based on the weight of the subject determined on the day of (for Part A), or within 3 days of each drug administration (Part B).

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

5.1.4.2 Adverse Drug Reactions Requiring Treatment Discontinuation or Modifications

The following ADRs require permanent treatment discontinuation of avelumab:

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

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

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, 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
- Change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)
- Asymptomatic Grade ≥ 3 lipase or amylase elevation not associated with clinical manifestations of pancreatitis. Medical Monitor must be consulted for such lipase and amylase abnormalities.

Any Grade 2 ADR should be managed as follows:

- Infusion should not be given in case of ongoing Grade 2 ADR on the day of study treatment administration.
- Treatment can be resumed according to the original schedule once the ADR has resolved to Grade ≤ 1. Up to 2 subsequent study drug may be omitted. If more than 2 doses are skipped, treatment may be resumed after consultation with the Medical Monitor.

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

5.2 Discussion of Trial Design

This is a Phase II single-arm trial to determine the efficacy and safety of avelumab in subjects with metastatic MCC. There is currently no approved treatment for advanced or metastatic MCC; thus a single-arm trial is appropriate. Furthermore, as there is no solid evidence of therapeutic efficacy in any second-line chemotherapy regimen, no concomitant therapy is justified. Planned interim analyses during the trial ensure a minimum number of subjects are exposed to the study drug in the case of insufficient clinical activity. The dosing regimen is based upon the current ongoing Phase I trials. The primary endpoint will be the confirmed BOR according to RECIST 1.1. Responses provide a direct measure of antitumor activity in subjects treated with the study drug. The confirmed BOR will be used to determine the ORR, which is suitable for a single-arm Phase II trial. The response status at 6 and 12 months after start of treatment, duration of response, and PFS and OS times will also be determined and will serve to assess whether the ORR is associated with lasting clinical benefit. A within-subject comparison of PFS time on study versus TTP on prior treatment will also serve as a comparative evaluation of subjects' outcome under treatment with avelumab.

With regard to Part B, the benefit of avelumab in metastatic MCC as initial therapy is unknown; however, preliminary results from an ongoing Phase II study (Part A of this study) in second-line or greater metastatic disease has documented an ORR greater than a predefined futility rate (data not shown). Also, a similar mechanism of action (pembrolizumab, an anti-PD-1 antibody) has demonstrated a substantial ORR (71% in evaluable patients) in treatment naïve metastatic or

unresectable MCC (Nghiem 2016). Given the known clinical activity of avelumab in a variety of tumor types (refer to avelumab IB) and given the expression of PD-L1 with CD8 T cell presence in Merkel cell tumors (Afanasiev 2013) it is plausible that avelumab offers benefit. Further risk / benefit considerations are discussed in Section 3.6.

With regard to Part B, DRR is reasonable as a primary endpoint based on several factors. In a disease setting that is highly chemoresponsive but with short duration (NCCN 2016), DRR may describe response in a more clinically meaningful way compared with ORR. Adopting DRR of 6 months as a time-sensitive endpoint for the analysis of the Part B appears logical, especially since 6 months is viewed as a clinically relevant timepoint when considering response duration in metastatic MCC patients, given the fact that median survival in metastatic MCC is 9 months (Voog 1999) and that chemo-responses are noted as "not durable" by NCCN with median duration of response in Stage IV cited as 3 to 9 months (Iyer 2016, Satpute 2014, Tai 2000, Voog 1999, Sharma 1991). Also, the recent precedent of Imlygic regular approval by FDA based on a DRR endpoint suggests that DRR of 6 months is clinically meaningful (Imlygic SBA). In order to provide an estimation of the DRR, a total of 112 subjects will be enrolled (see Section 8.1).

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:

1. Signed written informed consent

2. Male or female subjects aged ≥ 18 years

3. Histologically proven MCC

    a. Confirmation of the diagnosis by immunohistochemistry detection of CK20 (or other appropriate cytokeratin expression such as pancytokeratin, AE1/AE3, or Cam5.2; local laboratory testing) in the tumor cell is mandatory

    b. Subjects must have metastatic disease; subjects with non-metastatic MCC that is only recurrent or unresectable are NOT eligible; for Part B, M1 status must be confirmed at entry

    c. For Part A: Subjects must have received at least 1 line of chemotherapy for the treatment of metastatic MCC and must have progressed after the most recent line of chemotherapy that was administered. Subjects must have received at least one of the following chemotherapy regimens for treatment of metastatic MCC: Cyclophosphamide, topotecan, doxorubicine, epirubicin, vincristine, carboplatin, cisplatin, etoposide in combination with carboplatin or cisplatin

d. For Part B: Subjects must not have received any prior systemic treatment for metastatic MCC. Prior chemotherapy treatment in the adjuvant setting (no clinically detectable disease; no metastatic disease) is allowable if the end of treatment occurred at least 6 months prior to study start

4. For Part A: Collection of biopsy material is required (fresh biopsy or recent biopsy [within 4 weeks prior to enrollment], for subjects unable to provide a fresh or recent biopsy, archival material is acceptable).

   For Part B:

   1) Priority: A recently obtained formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue (preferably within 6 months). If no tumor tissue is available, fresh biopsy will be required

   2) Priority: If the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut (within 1 week). Preferably, 25 slides should be provided; if not possible, a minimum of 10 slides in consultation with the Medical Monitor is required

5. ECOG PS of 0 to 1 at trial entry

6. Estimated life expectancy of more than 12 weeks

7. Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1 (including skin lesions)

8. Adequate hematological function defined by WBC count $\geq 3 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

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

10. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula or by 24 hour urine collection for creatinine clearance or according to local institutional standard method

11. **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

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

1. Participation in another interventional clinical trial within the past 30 days (participation in observational studies are permitted)

2. Concurrent treatment with a nonpermitted drug

3. Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anticytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody; for Part B, the Investigator must consult with the Medical Monitor and consider other co-regulatory targets such as 4-1BB

4. Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy, or radiotherapy administered on non-target superficial lesions], immune therapy, or cytokine therapy except for erythropoietin). Radiotherapy administered to superficial lesions is not allowed if such lesions are considered target lesions in the efficacy evaluation or may influence the efficacy evaluation of the investigational agent

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

6. Concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of trial treatment. Short-term administration of systemic steroids (that is, for allergic reactions or the management of irAEs) is allowed while on study. Also, subjects requiring hormone replacement with corticosteroids for adrenal insufficiency are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses $\leq$ 10 mg or equivalent prednisone per day. Note: Subjects receiving bisphosphonate or denosumab are eligible

7. Subjects with active central nervous system (CNS) metastases are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy

8. For Part A: Previous malignant disease (other than MCC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ

   For Part B: Previous malignant disease (other than MCC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (skin, bladder, cervical, colorectal, breast, or low grade prostatic intraepithelial neoplasia or Grade 1 prostate cancer)

9. Prior organ transplantation, including allogeneic stem-cell transplantation

10. For Part A, known history of testing positive for HIV or known acquired immunodeficiency syndrome (AIDS) or any positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection. For Part B, known history of testing positive for HIV or known AIDS or HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)

11. Active or history of any autoimmune disease (except for subjects with vitiligo) or immunodeficiencies that required treatment with systemic immunosuppressive drugs

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.0), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partly controlled asthma)

13. Persisting toxicity related to prior therapy Grade > 1 NCI-CTCAE v 4.0; however, sensory neuropathy Grade ≤ 2 is acceptable

14. Pregnancy or lactation

15. Known alcohol or drug abuse

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

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

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

19. Legal incapacity or limited legal capacity

20. Nononcology vaccine therapies for prevention of infectious disease (for example, seasonal flu vaccine, human papilloma virus vaccine) within 4 weeks of study drug administration. Vaccination while on trial is also prohibited except for administration of inactivated vaccines (for example, inactivated seasonal influenza vaccine)

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

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be 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 Criteria for Withdrawal from Study Drug due to Therapeutic Failure

Subjects may continue avelumab treatment beyond radiological disease progression in the absence of significant clinical deterioration and, if in the opinion of the Investigator, the subject will benefit from continued treatment.

Before stopping the treatment with avelumab, progressive disease (PD) should be confirmed by imaging, preferably 6 weeks (but no later) after progression has been diagnosed according to RECIST 1.1.

If progression is based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan 6 weeks later should be performed. Treatment during the confirmation period should continue as scheduled, despite a first observation of progression (according to RECIST 1.1), until confirmation has been made, and further if there is no significant clinical deterioration defined as:

- there are no new symptoms or worsening of existing symptoms,
- there is no change in ECOG PS to ≥ 3 that lasts more than 14 days, or
- the Investigator does not consider it necessary to administer a salvage therapy.

If disease progression is due to brain metastasis, subjects may continue avelumab treatment after the local treatment of the brain lesions provided the above criteria are met in addition to the following and in consultation with the Medical Monitor:

- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
- Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) that in the opinion of the Investigator may be surgically removed or treated with palliative radiation therapy, subjects may continue avelumab treatment after the local treatment of such a lesion provided that:

- It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the subject has fully recovered from the surgery
- It has been at least 2 weeks since the subject's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to Grade < 2

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

Subjects who experience significant clinical deterioration, as defined above, in the absence of confirmed PD should be discontinued from further treatment with avelumab.

The treatment with avelumab should be stopped immediately, if the subject does not tolerate avelumab anymore or if therapeutic failures occur, which requires urgent additional drug or results in clinical progression/deterioration.

5.5.2 Withdrawal from the Trial

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

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

- Withdrawal of the subject's consent
- Participation in any other therapeutic trial during the treatment duration of this trial

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

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

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

5.5.3 Withdrawal from the Investigational Medicinal Product

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

- Therapeutic failure as outlined in Section 5.5.1
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Therapeutic failure requiring urgent additional drug (if applicable)
- Occurrence of any Grade ≥ 3 ADRs as defined in Section 5.1.4.2
- Occurrence of AEs, resulting in the discontinuation of the study drug being desired or considered necessary by the Investigator and/or the subject
- Occurrence of pregnancy
- Use of a nonpermitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the study drug

- Noncompliance (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 study drug, for example, due to
  - evidence of inefficacy of the study drug,
  - occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - other unfavorable safety findings.

  (Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, for example, toxicology.)
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's study drug

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

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

5.7 Definition of End of Trial

If the trial is not terminated for a reason given in Section 5.6, the survival will continue until 5 years after the last subject receives the last dose of avelumab or the last subject dies, whichever occurs first. Under some circumstances, subjects may not be followed for 5 years for survival in this study, for example, subjects may be offered to enroll into a rollover study, or the Sponsor may terminate the study early.

The Sponsor may terminate the study at any time, but will not do so unless appropriate access to avelumab is in place for subjects receiving it such as an expanded access program, roll-over study, market authorization, or other mechanism.

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

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 10 mg/mL (Part A only) and 20 mg/mL (Part A and Part B) in single-use glass vials closed with a rubber stopper and sealed with an aluminum yellow polypropylene flip off seal and supplied as 1 vial per box (it is allowable subjects in Part A receiving 10 mg/mL study drug to be transitioned to 20 mg/mL drug as needed).

6.2 Dosage and Administration

Subjects will receive an IV infusion of avelumab at a dose of 10 mg/kg (over the duration of 1 hour [-10 minutes / +20 minutes, that is, over 50 to 80 minutes]) once every 2 weeks (refer to Appendix I). A premedication regimen with an antihistamine and paracetamol (acetaminophen) is required prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4.1. The dose of avelumab will be calculated based on the weight of the subject determined on the day of (for Part A), or within 3 days of each drug administration (Part B). Subjects will receive avelumab once every 2 weeks until the criteria in sections 5.5 through 5.7 are met.

6.3 Assignment to Treatment Groups

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. Subject enrollment will be managed by an IVRS.

The Sponsor's / CRO's Responsible Medical must confirm enrollment 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

Subjects must be pretreated with an antihistamine and paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate.

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

subjects should be observed based upon clinical judgment and presence / severity of prior infusion reactions.

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

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

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the study drug may be given at the Investigator's discretion.

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

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

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

Palliative bone-directed radiotherapy may be administered during the trial. Once a skin target lesion is irradiated, all subsequent tumor assessments will be censored from the efficacy analysis. The assessment of PD will be made according to RECIST 1.1 (Eisenhauer 2009) and not based on the necessity for palliative bone directed-radiotherapy.

6.5.2 Nonpermitted Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody or concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy,

or radiotherapy administered on non-target superficial lesions], immune therapy, or cytokine therapy except for erythropoietin), major surgery (excluding prior diagnostic biopsy), concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of trial treatment. Steroids as premedication are not acceptable.

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

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions, management of patients with allergy to radiographic contrast media, or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. Also, hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.
- Any vaccine therapies for the prevention of infectious disease (for example, seasonal flu vaccine, human papilloma virus vaccine) except administration of the inactive 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

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

Medications other than those specifically excluded in this trial (see above) may be administered for the management of symptoms associated with the administration of avelumab as required. These might include analgesics, antinausea medications, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

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

6.5.3 Other Trial Considerations

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

- Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment. For any other surgical interventions planned during the study, study treatment should be delayed to allow subject's recovery, for up to a maximum of 4 weeks (also see Section 5.5.1 for details of treatment management beyond initial assessment of PD)
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)

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

Any diagnostic biopsies collected for clinical reasons during the trial should be documented as a concomitant procedure including the outcome of available pathological reports.

6.5.4 Special Precautions

As a routine precaution, subjects enrolled in this trial should be observed based upon clinical judgment and presence / severity of prior infusion reactions, 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 hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

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

Investigators should also monitor subjects closely for potential irAEs, which may become manifest 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 anti-nuclear antibodies (ANAs) or antineutrophil cytoplasmic antibodies (ANCAs).

6.5.4.1 Infusion-Related Reactions

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

B. Management (and according to Table 4)

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

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

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab.

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

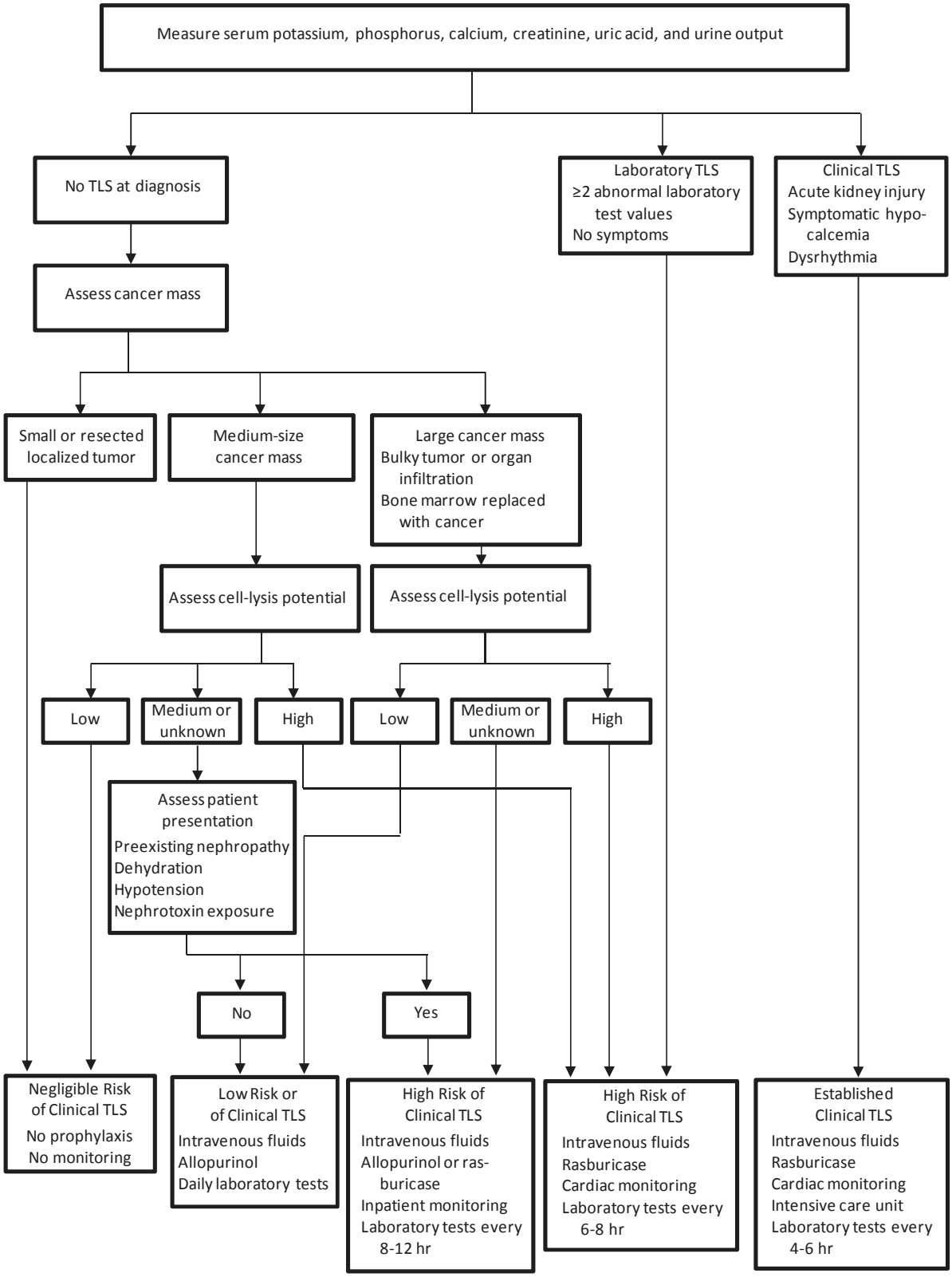
3. Alert ICU for possible transfer if required

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

6.5.4.3 Tumor Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm (Figure 1) published by Howard et al (Howard 2011).

Figure 1 Assessment and Initial Management of Tumor Lysis Syndrome



TLS=tumor lysis syndrome.

6.5.4.4 Immune-Related Adverse Events

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

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

Treatment of irAEs should follow guidelines set forth in Table 5.

Table 5 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.0)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5 to 7 days or recurs: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab therapy for Grade 4 or recurrent Grade 3 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3) If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

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

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

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Creatinine increased > ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 × ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤ 1: Taper steroids over at least 1 month.
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH / IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement / suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. **Continue hormone replacement/suppression therapy as appropriate.**

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-related myocarditis. Guideline based supportive treatment as per cardiology consult.[a] Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related
Immune-related myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.[a] 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
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		
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.

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

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

6.6 Packaging and Labeling

Avelumab is formulated as a 10.0 mg/mL (Part A only) and 20 mg/mL (Part A and Part B) solution and is supplied by the Sponsor in single-use glass vials, stopper with a rubber septum.

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 (1 vial per box). The information on the study drug will be in accordance with approved submission documents.

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

6.7 Storage, Handling, and Preparation

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

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

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

For application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) 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 must not be used for any purpose other than the trial. The administration of study drug to subjects who have not been enrolled into the trial is not covered by the trial insurance.

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

6.8 Investigational Medicinal Product Accountability

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

- Upon receipt of study drug, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator File.
- The dispensing of the study drug will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor's Monitor at each monitoring visit.
- study drug accountability records will include:
  - confirmation of study drug delivery to the trial site;
  - the inventory at the site of study drug provided by the Sponsor and prepared at the site;
  - the use of each dose by each subject;
  - the return to the Sponsor or alternative disposition of unused study drug; and
  - dates, quantities, batch numbers, expiry dates and (for study drug prepared at the site) formulation, as well as the subjects' trial numbers.

- The Investigator should maintain records that adequately document:
  - that the subjects were provided the doses specified by the clinical trial protocol/amendment(s); and
  - that all study drug provided by the Sponsor was fully reconciled.

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

The Sponsor's Monitor will periodically collect the study drug accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.

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

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

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

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

This is to be closely monitored by the trial monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

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

Noncompliance is defined as a subject missing > 1 cycle of trial treatment for nonmedical reasons (see Section 5.5.2). 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 nonmedical 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% than the calculated dose for that particular administration. Any overdose must be recorded in the study drug section of the eCRF.

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

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

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 ICF. 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 MCC, 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 and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS (Appendix II). The EQ-5D and FACT-M questionnaires will be administered to subjects and completed by the subjects at baseline to collect baseline data about their health-related quality of life. Additionally, subjects will be interviewed (optional for both Part A and Part B, see Section 7.7.1) by a trained experienced interviewer in order to collect subjects' experience with MCC and their experience with prior treatment for MCC.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation). Adrenocorticotropic hormone (ACTH), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), free thyroxine (T4), and thyroid-stimulating hormone (TSH) will also be assessed at Screening. CCI [redacted]

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of childbearing potential and blood hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV testing will be performed for all screening subjects as these conditions are trial entry exclusion criteria (see Section 5.3.2). Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.

The tumor evaluation (type and staging, etc.), including mapping of skin lesions, will be performed using computed tomography (CT) scan or magnetic resonance imaging (MRI; if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) as well as tumor markers or any other established methods (see Section 7.2.5 for details). A brain CT / MRI scan is required at Screening if not performed within the previous 6 weeks. A bone scan should be done at Screening as clinically indicated. If any skin lesions are assessed by physical examination and selected as target or nontarget lesions, standardized photographic image collection is required.

Collection of tumor biopsies will also be done during this period, unless tissue (blocks or slides, blocks preferable) from a recent biopsy (within 4 weeks of enrollment) is available. For subjects unable to provide a fresh or recent biopsy, archival material is acceptable [blocks preferable], for Part B, preferably less than 6 months old). Subjects are required to provide tumor tissue samples, see Section 7.6 for details. Criteria for determining the adequacy of tumor tissue are described in the Study Manual. Subjects who undergo a biopsy specifically as part of the Screening

assessments for this protocol will be permitted to participate in the protocol provided they meet all other inclusion criteria and no exclusion criteria.

The blood samples for baseline PK and immunogenicity (antidrug antibody [ADA] tests, previously referred to as human antihuman antibody [HAHA]) as well as for CCI [redacted].

CCI [redacted]

For Part A and Part B, subject eligibility will need to be confirmed by the CRO before the first administration of the study drug.

7.1.2 Treatment Period

In this trial, the treatment will be given until therapeutic failure (see Section 5.5.1), unacceptable toxicity, or any criterion for withdrawal from the trial or study drug is fulfilled (see Section 5.5.3).

For Part A: Subjects who have experienced a confirmed CR should be treated for a minimum of 6 months and a maximum of 12 months and after confirmation, at the discretion of the Investigator. In Part B, subjects should complete a minimum of 12 months after confirmed CR. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. Part B: Subjects who have experienced a confirmed CR should be treated for a minimum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the sponsor. For both Part A and Part B, in case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the 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).

Subjects will be asked to visit the investigational site every 2 weeks while on 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 trial procedures. In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

Subjects will receive avelumab by IV infusion following pretreatment with antihistamine and paracetamol (acetaminophen) once every 2 weeks (see Section 6.2). A premedication regimen of diphenhydramine and paracetamol (acetaminophen, IV or oral equivalent) is recommended prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate.

7.1.2.1 Part A

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

- The EQ-5D and FACT-M will be completed by subjects prior to any study related procedures at Week 7, and then once every 6 weeks thereafter while on treatment.
- Subject interviews (optional) by a trained experienced interviewer to collect subjects' current experience with their disease and its treatment (at Week 13 and at 6 months of treatment, see Section 7.7.1).
- AEs and concomitant medications will be documented at each trial visit.
- ECOG PS will be assessed at Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and at each study visit thereafter.
- Physical examinations will be performed at each treatment visit until Week 13 and every 6 weeks thereafter. Such examinations will include a comprehensive skin examination for tumor.
- Vital signs and body weight will be assessed in each treatment visit.
- A 12-lead ECG (assessed prior to infusion and 2 hours ± 20 minutes after the end of infusion) will be assessed at each treatment visit up to and including Week 13, and every 6 weeks thereafter until 18 months, after which subjects no longer require on treatment ECGs.
- The laboratory hematology, hemostaseology will be assessed at each visit. Core serum chemistry tests will be assessed at Weeks 1, 7, 9, and 11 and after Week 13, every 2 weeks thereafter and full serum chemistry (including core chemistry) will be assessed at Weeks 3, 5, and 13 and then every 6 weeks thereafter. 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. A basic urinalysis (dipstick) will be performed at each on treatment visit. If the basic urinalysis is abnormal, a full urinalysis should be performed.
- A urine β-HCG pregnancy test will be performed at each treatment visit (before each administration of the study drug) for females of childbearing potential.
- Tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks thereafter, with a tumor assessment visiting time window of 5 days prior to dosing. After Week 55 (12 months) from the first treatment, tumor assessments will be every 12 weeks.
- PK samples will be collected from all subjects receiving avelumab within 2 hours prior to each study drug administration through Week 15, then Week 25, and then at 12-week intervals thereafter while on treatment. 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 Weeks 1, 7, 13, and 25, and then at 12-week intervals thereafter while on treatment (see Section 7.5 for details).
- ACTH, ANA, ANCA, RF, free T4, and TSH will be measured at Week 13, Week 25, and if clinically indicated.

- ADA samples will be drawn at Week 1 prior to the first administration of study drug (Screening / Baseline sample) and within 2 hours prior to study drug administration at Weeks 3, 5, 7, and 13 and then every 6 weeks thereafter while on treatment (see Section 7.6.3).
- CCI [redacted]
- CCI [redacted]

7.1.2.2 Part B

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

- The EQ-5D and FACT-M will be completed by subjects prior to any study related procedures at Week 7, and then once every 6 weeks thereafter while on treatment.
- Subject interviews (optional) by a trained experienced interviewer to collect subjects' current experience with their disease and its treatment (at Week 13 and at 6 months of treatment, see Section 7.7.1).
- AEs and concomitant medications will be documented at each treatment visit.
- ECOG PS will be assessed at Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and at each treatment visit thereafter.
- Physical examinations (directed to signs and symptoms) will be performed at each visit through Week 13 and then every 6 weeks thereafter. Such examinations may include a comprehensive skin examination for tumor.
- Vital signs and body weight will be assessed in each treatment visit (body weight may be collected within 3 days prior to infusion).
- The laboratory hematology, hemostaseology will be assessed at each treatment visit. Core serum chemistry tests will be assessed at each visit. A basic urinalysis (dipstick) will be performed on the Day 1 visit prior to administration of study drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed. Urinalysis after Day 1 should be performed as clinically indicated.
- A urine or serum β-HCG pregnancy test according to local practice will be performed at Weeks 1, 5, 9, and 13 and then every 4 weeks thereafter for females of childbearing potential. Results of the most recent pregnancy test should be available prior to the next treatment.
- Tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks thereafter, with a tumor assessment visiting time window of 5 days prior to dosing. After Week 55 (12 months) from the first treatment, tumor assessments will be every 12 weeks.
- PK samples will be collected from all subjects receiving avelumab within 2 hours prior to each study drug infusion through Week 7, every 6 weeks through Week 25, and then at 12-week

intervals thereafter while on treatment. Post study drug administration samples will be collected at the end of infusion at Weeks 1, 7, and 25.

- Free T4, and TSH will be measured at Week 1, Week 7, Week 13, and every 6 weeks during the treatment period.
- ACTH, ANA, ANCA, and RF will be measured at Week 13, Week 25, and if clinically indicated.
- ADA samples will be drawn at Week 1 prior to the first administration of study drug (Screening / Baseline sample) and within 2 hours prior infusion through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment (see Section 7.6.3).
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

7.1.3 End of Treatment

Discontinuation visit

For Part A, a discontinuation visit for safety evaluation should take place as soon as possible after the last administration of avelumab (at least within 7 days) in case treatment was discontinued because of the occurrence of an AE. For Part B, all subjects will have a Discontinuation visit regardless of the reason for discontinuation. The discontinuation visit consists of:

- documentation of AEs and concomitant medication;
- physical examination, including vital signs, and body weight;
- the 12-lead ECGs;
- the laboratory hematology, hemostaseology, and full serum chemistry, and basic urinalysis;
- CCI [redacted] CCI [redacted];
- ECOG PS; and
- PK sampling (subjects in Part B only).

End-of-Treatment visit

The End-of-Treatment visit is scheduled either 28 days (Part A) or 30 Days (±5 days, Part B) 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, and will include the following (refer to Appendix I):

- The EQ-5D and FACT-M questionnaires
- AEs, and concomitant medications, ECOG PS
- Physical examination including vital signs, body weight, and skin tumor extent
- The 12-lead ECGs
- The laboratory hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation)
- The urine β-HCG pregnancy test (in females of childbearing potential)
- The tumor evaluation per 6 or 12 weekly schedule (only to be performed if no disease progression was documented previously)
- ACTH, ANA, ANCA, RF, T4, and TSH levels
- ADA sampling
- PK sampling (Part B only)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

7.1.4 Safety Follow-up

For Part A, all subjects will have a subsequent visit scheduled 10 weeks after the last administration of avelumab. For Part B, the visit will be 90 days (± 1 week). The visit will include the following full assessment of safety parameters (refer to Appendix I):

- AEs and concomitant medications will be documented, including further anticancer therapy.
- Vital signs and body weight will be measured.
- Physical examination will be performed.
- ECOG PS will be assessed.
- 12-lead ECG will be assessed.
- Laboratory testing consisting of the following will be assessed:
  - Hematology, hemostaseology, core serum chemistry, and basic urinalysis (dipstick only)
  - ACTH, ANA, ANCA, RF, T4, and TSH levels
  - PK sample
  - ADA sample (part B only)
- CCI [redacted] CCI [redacted].
- A urine β-HCG pregnancy test (in females of childbearing potential) will be conducted.

7.1.5 Post Treatment Follow-up

Subjects with an ADR ongoing at the End-of Treatment visit must be followed up until the ADR resolves, becomes stable, or is considered not clinically significant by the Investigator. 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.

For subjects who discontinue treatment prior to Week 13, off-treatment interviews (optional for both Part A and Part B) will be scheduled for 13 weeks and 6 months from the start of treatment to collect subjects' current experience with their disease, the study drug, and their experience within the trial. In case of discontinuation later than Week 13 but prior to 6 months of treatment, an off-treatment interview (optional for both Part A and Part B) will be scheduled for 6 months from the start of treatment.

For Part A, subjects without PD at the End-of-Treatment visit will be followed up for disease progression until PD (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks using the same procedures and review as while on treatment; for trial sites in Germany, only MRI is to be used). CCI [redacted]

For Part B, subjects without PD at the End-of-Treatment visit will be followed for disease progression until PD (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks).

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 for up to 5 years after the last subject receives the last dose of avelumab or last subject dies, whichever occurs earlier (see Section 5.7 for details of the end of study).

7.1.6 Blood Draws for Clinical Assessments

The overall amount of blood to be drawn from a single subject must not exceed 120 mL/day and 550 mL in an 8-week period for safety laboratory testing, pregnancy testing, PK analyses, exploratory CCI [redacted] 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 Merkel Cell Carcinoma

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

- detailed history of the tumor, including histopathological diagnosis (including documentation of CK20 or other appropriate cytokeratin expression such as pancytokeratin, AE1/AE3, or Cam5.2), grading, and staging in accordance with the International Union Against Cancer Tumor Node Metastasis Classification of Malignant Tumors at diagnosis;
- all therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy);
- any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy;
- current cancer signs and symptoms and side effects from current and previous anticancer treatments;
- current cancer disease status; and
- for Part B M1 status must be confirmed at entry

7.2.3 Medical History

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

- Past and concomitant nonmalignant diseases and treatments
- All medications 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 trial entry.

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

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

Body weight and height will be recorded.

7.2.5 CT or MRI Scans and Photography for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) 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, including mapping of skin lesions) 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 nontarget lesions (the Screening CT / MRI does not need to be repeated if having been done within 4 weeks prior to first treatment). Baseline tumor burden should be determined as outlined in Section 7.3. A brain CT / MRI scan is required at Screening if not performed within the previous 6 weeks.

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

Any skin lesions assessed by physical examination and selected as a target or nontarget lesion at Baseline will have photographic image collection performed within 18 days prior to trial treatment start in order to document the Baseline status of the tumor disease (see Appendix IV).

7.2.6 Cardiac Assessments

A 12-lead ECG 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

All radiographic images and physical findings including photographs (skin lesion mapping) and physical assessments used for the determination of disease progression must be submitted to the IERC vendor and will be reviewed by an IERC (see Section 5.1.2.2). The IERC will make the determination as to whether the criteria for tumor response or progression according to RECIST 1.1 have been met.

For each subject, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) imaging of the chest/abdomen/pelvis at a minimum plus other anatomical sites as specifically required) and other established assessments of tumor burden if CT / MRI imaging is insufficient for the individual subject. All the scans performed at baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. If lesions are no longer detectable, the same anatomical sites evaluated at baseline must be followed at every tumor assessment visit using the same imaging and photography methods as used at baseline.

An examination for clinical lesions, including mapping of skin lesions, should also be conducted at each tumor assessment. For skin lesions to be identified as target lesions, a minimum longest diameter of 10 mm is required. In the case of skin lesions, documentation by color photography using standardized procedures, including an accurate measurement scale within the image, is required. Refer to Appendix IV for standardized photography procedures with detailed requirements for lesion selection and photographic image acquisition. Clinical lesions will be considered measurable only when they are superficial and visible (for example, skin nodules, palpable lymph nodes). Skin lesions can be used as target lesions using measurements by caliper if they fulfill RECIST 1.1 for target lesions. The presence of new cutaneous lesions will be considered diagnostic of progression for RECIST 1.1, and any lesions detected by physical examination only should be documented by photography.

A brain CT / MRI scan is required at Screening if not performed within the previous 6 weeks. Brain CT / MRI scans should be performed, if clinically indicated by development of new specific symptoms (for trial sites in Germany, only MRI is to be used).

A bone scan should be done at Screening and beyond as clinically indicated.

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).

Tumor responses to treatment will be assigned by the IERC based on the evaluation of the response of target, nontarget, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation, see Eisenhauer 2009).

- To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and nontarget lesions as described in Eisenhauer 2009.

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

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

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

CCI

[redacted]

CCI

[redacted]

7.4 Assessment of Safety

The safety profile of the study drug 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 mechanism of action of the study drug, 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 performed, when clinically indicated, for signs or symptoms of uveitis.

The reporting period for AEs is described in Section 7.4.1.3.

The safety assessments will be performed according to the Schedule of Assessments (refer to Appendix I).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

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 v 4.0 (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 NCI-CTCAE 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 a serious adverse event (SAE; see definition below) 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 one 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 (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the study drug 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 reasonably suspected to be related to the study drug. The AE could not medically (pharmacologically/clinically) be attributed to the study drug under trial in this clinical trial protocol. A reasonable alternative explanation must be available.

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

Abnormal laboratory findings and other abnormal investigational findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) of Grade < 3 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 of Grade < 3 fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Adverse Drug Reaction (ADR)

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

Serious adverse event (SAE)

A 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, or
- 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 one 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 a study drug is also considered a SAE 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 (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs; however, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events not to be considered as AEs / SAEs

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

AE / SAEs observed in association with disease progression

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

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

Predefined AEs of special interest for safety monitoring

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

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit and during subjects interviews (optional for both Part A and Part B), the subject will be queried on changes in his or her condition. During the reporting period of the trial any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

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

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

Specific guidance can be found in the eCRF Completion Guidelines.

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 post-treatment safety follow-up period, defined as 10 weeks (Part A) / 90 days (Part B) after the last study drug administration.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events

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

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

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial

reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made 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.

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

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

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

In accordance with ICH GCP guidelines, the Sponsor 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 (that is, 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 lead IEC / IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC / IRB of any Safety reports provided by the Sponsor or designee and of filing copies of all related correspondence in the Investigator Site File.

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

7.4.1.6 Monitoring of Subjects with Adverse Events

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

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered 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 eCRF. 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 subject is withdrawn from the trial.

The Investigator must notify the Sponsor or designee of these outcomes using the Pregnancy Report Form, and in case of an 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 study drug 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 study drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be taken from nonfasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site and relevant results must be available and checked 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 full safety tests listed in Table 7 will be taken from non-fasted subjects during the Screening phase (18 days prior to the first treatment administration), during the treatment phase as specified in the table and in Appendix I, at the End-of-Treatment visit, and at the Safety Follow-up visit. The ACTH, ANA, ANCA, RF, T4, TSH, and urinalysis will only be assessed at the time points defined in Table 7 and Appendix I. If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 7.1.1.

Table 7 Required Full Laboratory Safety Tests

Full Chemistry	Hematology
Albumin	Absolute lymphocyte count
Alkaline phosphatase*	ANC
ALT*	Hematocrit
Amylase**	Hemoglobin
AST*	Platelet count
GGT	RBC count
BUN/total urea*	WBC count and differential count
Calcium*	RBC morphology
Chloride*	Reticulocytes
Cholesterol	MCH
Creatine kinase	Mean corpuscular volume
Creatinine*	MCHC
CRP	
Glucose*	**Hemostaseology**
LDH	aPTT
Lipase**	Prothrombin time/INR
Phosphorus/Phosphates*	
Magnesium*	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End-of-Treatment visits and a basic urinalysis prior to each administration of the study drug.
Potassium*	
Sodium*	
Total bilirubin*	
Total protein	
Uric acid	Totality of binding ADAs
Triglycerides	
	ACTH, ANA, ANCA, RF, TSH, and T4 For Part A, to be assessed at the Screening visit, Week 13, Week 25, and at the End-of Treatment visit. For Part B, only ACTH, ANA, ANCA, RF, T4, and TSH will be collected at Screening visit, Week 13, Week 25, End-of-Treatment, and Safety Follow-up visits. T4 and TSH to be assessed in Week 1, Week 7, Week 13, and then every 6 weeks while on treatment and at the 30-day End-of-Treatment visit.
Hormone	
FSH (if applicable)	

ADA = antidrug antibody, ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, ANA=antinuclear antibody, ANC=absolute neutrophil count, ANCA=antineutrophil cytoplasmic antibody, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, FSH=follicle-stimulating hormone, GGT=gamma-glutamyultransferase, INR=international normalized ratio, LDH=lactate dehydrogenase, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, RBC=red blood cell, RF=rheumatoid factor; TSH=thyroid-stimulating hormone, T4=free thyroxine, WBC=white blood cell.

* Core serum chemistries in Part A and Part B

** Included in core serum chemistries only for Part B

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

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

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

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

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF (detailed description in Section 7.1). Results of the physical examination, including any abnormalities, will be documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

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

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

For female subjects of childbearing potential, serum β-HCG pregnancy test will be carried out during the Screening phase. A urine β-HCG test will be performed as indicated in the Schedule of Assessments (Appendix I). Subjects that are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and FSH > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

7.5 Pharmacokinetics

For Part A: Blood samples for population PK determinations will be collected from all subjects within 2 hours prior to each study drug administration through Week 15, then at Week 25, and then at 12-week intervals thereafter while on treatment. 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 Weeks 1, 7, 13, and 25, and then at 12-week intervals thereafter while on treatment. Exact sampling times will be recorded. Samples will also be collected at the 10-week Safety Follow-up visit.

For Part B: Blood samples for population PK determinations will be collected from all subjects within 2 hours prior to each study drug administration through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment. Post study drug administration samples will be collected at the end of infusion at Weeks 1, 7, and 25. Samples will also be collected at the 7-day Discontinuation visit, the 30-day End-of-Treatment visit, and the 90-day Safety Follow-up visit.

7.5.1 Body Fluid(s)

Whole blood sufficient to provide 2 mL of plasma / serum will be collected for PK assessments. Further details will be summarized in the Laboratory Manual.

7.5.2 Pharmacokinetic Calculations

The methodology and software to be used and PK calculations and parameters will be specified in the Statistical Analysis Plan (SAP).

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7.6.3 ADA Analysis

For Part A: The blood sample for baseline ADA analysis will be collected before trial treatment start. Further serum samples for ADA analysis will be collected within 2 hours before infusion on Days 15, 29, 43 (every 2 weeks) and then every 6 weeks thereafter while on treatment and at the End-of-Treatment visit. Samples positive for ADAs will be re-analyzed to determine the titer.

For Part B: The blood sample for baseline ADA analysis will be collected before trial treatment start. Further serum samples for ADA analysis will be collected within 2 hours before infusion through Week 7, every 6 weeks through Week 25, then at 12-week intervals thereafter while on treatment, and at the End-of-Treatment visit. Samples positive for ADAs will be re-analyzed to determine the titer.

7.7 Other Assessments

7.7.1 Health-related Quality of Life

Health-related quality of life will be assessed using a generic instrument (EQ-5D), a cancer-specific instrument including a melanoma-specific module (FACT-M), and subject interviews (optional for both Part A and Part B).

EQ-5D. The EuroQol EQ-5D was developed in 1990 to assess health outcome from a wide variety of interventions on a common scale, for purposes of evaluation, allocation and monitoring (EuroQol 1990, Herdman 2011). It includes 5 items assessing mobility, self-care, usual activities, pain / discomfort, anxiety / depression on a 5-level response scale (EQ-5D-5L). It also includes a visual analogue scale ranging from 0 to 100 for self-rated health status. A higher score indicates better health status. Utilities can be derived from the EQ-5D, ranging from 0.0 (worst health state) to 1.0 (best health state).

FACT-M. The FACT-M includes in addition to the generic core (FACT-G) a 24-item module that addresses specific aspects of melanoma (Cormier 2005). The objective of the FACT-G is to measure health-related quality of life of people with chronic illnesses through 27 items across 4 domains: physical well-being, social / family well-being, emotional well-being, and functional well-being. The global score ranges from 0 to 108, with a higher score indicating better quality of life. The FACT-M adds 20 items related to physical well-being, 3 to emotional well-being, and 1 to social well-being. Merkel cell carcinoma and melanoma are both aggressive skin malignancies; despite some differences between MCC and melanoma, including worse prognosis for MCC, the content of the FACT-M seems appropriate to assess quality of life in subjects with MCC.

Subject interviews (optional for both Part A and Part B). Subjects will be invited to participate in semi-structured interviews at the Screening / Baseline visit prior to initiation of trial treatment and at Week 13 and 6 months (for both subjects on treatment and off treatment) in order to collect information about their previous experience with MCC and its treatment and their current experience within the trial, including their experience with the trial treatment. Consent to participate in the interviews will be indicated by a check in the appropriate box on the ICF.

A Contact Order Form including subject contact details will be completed and sent to a dedicated independent unit in charge of scheduling and setting up the interviews.

The interviews will be conducted by a trained experienced interviewer, preferably by telephone, (face to face interviews will be conducted where telephone interviews are not feasible), in the local language and will last approximately 30 minutes. For baseline and on-treatment interviews, the interviews should be scheduled on the day of the visit or within 5 days prior to the visit and will be conducted prior to study drug administration or any other study-related assessments. Wherever possible, if the subject can have access to a quiet room and a phone is available, the interview can be scheduled while the subject is attending the visit at the hospital. In any other case, the subject will be contacted at home. For subjects who discontinue treatment prior to Week 13 or 6 months, subjects will be contacted at home for the scheduled interview.

The main themes to be explored at baseline include subjects' experience of the disease, in order to document the symptoms and manifestations, and the subsequent impact on subjects' lives.

The main theme to be explored during post-baseline interviews (Week 13 and 6 months for both subjects on treatment and off treatment) will be the experience of the treatment received since inclusion into the study.

The interviews will be audio recorded in a de-identified way. The audio files will serve as source documents and will be archived in Trial Master File. Any additional copy of audio recordings temporarily retained by interviewers and / or transcription unit will be destroyed after transcription process completion. The audio recordings will be transcribed word by word for the analysis (see Section 8.5.3.2).

8 Statistics

8.1 Sample Size

Sample Size in Part A:

The primary endpoint of the trial is the confirmed BOR according to RECIST 1.1, based on independent review of tumor assessments. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. The trial aims at demonstrating an ORR greater than 20% by means of an exact binomial test.

The planned total sample size is 84 subjects. There will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months and 1 interim analysis for efficacy 6 months after 56 subjects have been enrolled. The primary analysis will be conducted 6 months after the accrual of the last subject. An exploratory analysis of secondary and exploratory endpoints will be conducted 12 months after the accrual of the last subject.

The following assumptions are made for the sample size calculation:

- ORR of 35%
- overall alpha = 0.025 (1-sided) for the test of the null hypothesis of an ORR $\leq$ 20%

The following analyses are planned:

- Futility: Enrollment will be stopped for futility if no response (confirmed or unconfirmed) is observed in the first 20 subjects after 3 months of follow-up.
- Efficacy: A two-stage group sequential testing approach will be applied for efficacy. The null hypothesis can be rejected if 20 subjects in the interim analysis after 56 subjects, or 25 subjects in the primary analysis after 84 subjects, show a confirmed PR or CR according to RECIST 1.1. The corresponding nominal p-values of the exact binomial test are 0.0045 and 0.0214, respectively. The resulting overall probability of reaching a positive result in the interim or primary analysis under the null hypothesis assumption of an ORR $\leq$ 20% is $\leq$ 0.0225, as derived from the binomial distribution according to Jennison and Turnbull (Jennison 2000); therefore the overall type I error rate is controlled at a level of 2.5% (one-sided).

Under the given assumptions, the power to reject the null hypothesis at the interim or the primary analysis is approximately 87%.

Justification of the assumption of a response rate of 35% to define the trial sample size

Data presented at the International Association for Study of Lung Cancer annual meeting in 2013 suggest the blocking of PD-L1 through the administration of anti-PD-L1 monoclonal antibody has antitumor activity in tumors whose micro-environment express PD-L1. Indeed, a response rate of 83% was reported (5/6) in patients where more than 10% of the immune-infiltrating cells were PD-L1 positive. In addition, the expression of PD-L1 at the surface of the tumor has also been correlated with clinical activity of anti-PD-L1. Robust expression of PD-L1 in the immune-infiltrating cells of MCC has been reported in the literature (Lipson 2013) and confirmed by the Sponsor.

On these grounds, the expression of PD-L1 by the immune infiltrating cells as well as the expression of PD-L1 at the surface of MCC constitute a very strong rationale for the evaluation of avelumab in that disease. Extrapolation of the response rate observed with the Genentech PD-L1 (up to 80% in PD-L1+ tumor cells and up to 80% in patients with more than 10% of the tumor infiltrating cells expressing PD-L1) suggest that a clinically significant overall response rate can be expected from anti PD-L1. Since a response rate of approximately 20% has been reported in several tumor types where only a fraction of the tumors express PD-L1 at the surface of the tumors or at the surface of immune infiltrating cells, it is considered that an expected response rate of 35% is a reasonable hypothesis.

Sample Size in Part B:

The planned total sample size for Part B is 112 subjects for addressing the primary objective, relevant subgroup analyses, consistency, and further safety assessments. Assuming a true DRR of 45%, the probability to observe lower bound of the exact 95% confidence interval (CI) above 20% would be > 99% and above 30% would be 90%.

A historical reference for the DRR under first-line chemotherapy is based on P. Nghiem (personal communication), and Iyer 2016, which showed 11 of 62 patients meeting the definition of 6 months durable response, i.e. a DRR of 17.7% (95% CI: 9.2, 29.5). Part B of the study aims to estimate the DRR with a sufficient level of precision. For example, with 112 subjects, an observed DRR of 28.6% would lead to an exact (Clopper-Pearson) 95% CI of (20.4%; 37.9%), which would exclude the observed DRR in Iyer et al, an observed DRR of 40.2% would lead to a 95% CI of (31.0%; 49.9%), which would exclude the upper bound of the 95% CI of Iyer et al, and an observed DRR of 44.6% would lead to an exact 95% CI of (35.2%; 54.3%).

The two-sided 95% Clopper-Pearson confidence intervals for different observed values for the DRR are provided in Table 8.

Table 8 Confidence Intervals for Different Durable Response Rates

N	DRR (%)	n	LBCI (%)	UBCI (%)
112	28.6	32	20.4	37.9
112	40.2	45	31.0	49.9
112	44.6	50	35.2	54.3

CI = confidence interval; LBCI = lower boundary of the confidence interval; N, n = number of subjects; ORR = objective response rate; UBCI = upper boundary of the confidence interval.

The primary analysis will be conducted 15 months after the accrual of the last subject.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint for Part A of the trial is the confirmed BOR, per RECIST 1.1, as determined by an IERC and defined as the best response obtained among all tumor assessment visits after start of trial treatment until documented disease progression, excluding assessments after start of subsequent anticancer therapy, taking into account the following requirement for confirmation: PR or CR needs to be confirmed at a subsequent tumor assessment, preferably 6 weeks after the initial observation of response and according to the normal 6-week assessment schedule (or a subsequent assessment for PR), but no sooner than 5 weeks after the initial documentation of CR or PR.

For Part B, the primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months. Duration of response will be calculated as specified in Section 8.3.2. Subjects for whom the duration of response is censored will be treated as failures (successes) in the analysis of durable response if the censored duration of response is below (at least) 6 months, respectively.

The date of a tumor assessment is defined as the earliest lesion measurement date corresponding to the respective visit that is documented in the eCRF. Details of determination of tumor response date at each time point will be provided in IERC charter document.

8.3.2 Secondary Endpoints

The duration of response will be calculated for each subject with a confirmed response as the time from first observation of response until first observation of documented disease progression or death within 12 weeks of the last tumor assessment, whichever occurs first.

For subjects with a confirmed response but neither documented disease progression nor death within 12 weeks after the last tumor assessment, as of the cut-off date for the analysis, the duration of response will be censored at the date of the last tumor assessment. Detailed censoring rules for duration of response can be found in Table 9 for Part A and in Table 11 for Part B.

The response status at 6 and 12 months after start of trial treatment according to RECIST 1.1 (as determined by the IERC) will be determined. A subject will be considered to be in response at the given timepoint (6 or 12 months after the start of the subject's treatment) if the subject had a documented response (PR or CR) prior to that timepoint, and neither died nor experienced disease progression according to the RECIST 1.1 nor was lost to follow-up up to the given timepoint.

The PFS time, according to the RECIST 1.1, will be defined from first administration of trial treatment until first observation of PD or death within 12 weeks of the last tumor assessment or first administration of trial treatment (whichever is later). Details on determination of the first disease progression date will be specified in the IERC charter.

If a subject has neither a progression date nor a death date within 12 weeks after the last tumor assessment as of the data inclusion cut-off date for the analysis, the PFS time will be regarded as censored on the date of last known tumor assessment, or date of the first administration of trial treatment if the subject does not have any postbaseline tumor assessment. In Part B, PFS time will be regarded as censored on the date of last adequate tumor assessment (ie, having a result that is not non-evaluable or not available) if the subject begins a new anticancer therapy.

For Part A, subjects with both of the following conditions fulfilled, the general censoring rules apply as presented in Table 9.

- Baseline tumor assessment
- At least one tumor assessment after start of treatment

Table 9 Part A: General Censoring Rules for Progression-free Survival and Duration of Response

		Date of event / censoring	Censoring
PD according to RECIST as assessed by the IERC		Date of PD	No
No PD	If death within 12 weeks after last tumor assessment or first administration of trial treatment	Date of death	No
	If death not within 12 weeks after last tumor assessment or first administration of trial treatment	Date of last known tumor assessment	Yes

IERC=Independent Endpoint Review Committee, PD=progressive disease.

For Part A, subjects with no tumor assessment at baseline or no tumor response assessment postbaseline, the special censoring rules as presented in Table 10, which overrule the general censoring rules, apply.

Table 10 Part A: Special Case Censoring Rules for Progression-free Survival

		Date of event / censoring	Censoring
No tumor assessment at baseline	If death within 12 weeks after first administration of trial treatment	Date of death	No
	If death not within 12 weeks after first administration of trial treatment	Date of first administration of trial treatment	Yes
No tumor response assessment post baseline	If death within 12 weeks after first administration of trial treatment	Date of death	No
	If death not within 12 weeks after first administration of trial treatment	Date of first administration of trial treatment	Yes

For Part B subjects, the censoring rules for PFS and duration of response are presented in Table 11.

Table 11 Part B: Outcome and Event Dates for Progression-free Survival and Duration of Response Analyses

Scenario	Date of event / censoring	Outcome
No baseline assessment	Date of first study treatment	Censored[a]
Progression or death ≤ xx weeks after last tumor assessment or ≤ xx weeks after treatment start date, where xx is 12 weeks through 12 months from start of treatment, and 24 weeks thereafter.	Date of progression or death	Event
Progression or death > xx weeks after the last tumor assessment, where xx is 12 weeks through 12 months from start of treatment, and 24 weeks thereafter.	Date of last adequate tumor assessment	Censored
No progression	Date of last adequate tumor assessment	Censored
Treatment discontinuation due to "Disease progression" without documented progression	Not applicable	Information collected on treatment discontinuation page is ignored since outcome should be derived based on documented progression only. General censoring rule is applied.
New anticancer therapy given	Date of last adequate tumor assessment before anticancer therapy is given	Censored

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

The OS time will be defined as the time from first administration of trial treatment until the date of death. The OS time is considered a key secondary endpoint.

For subjects who are still alive at the time of data analysis or who are lost to follow up, OS time will be censored at the last recorded date that the subject is known to be alive (date of last contact,

last visit date, date of last trial treatment administration or date of last scan, whichever is the latest) as of the data cut-off date for the analysis.

In Part B, BOR as determined by IERC will be defined in the same was as in Part A (see Section 8.3.1).

Other secondary endpoints include serum titers of anti-avelumab antibodies (ADA) and PK profile (sparse sampling).

8.3.3 Safety Endpoints

Safety endpoints include AEs, clinical laboratory assessments, vital signs, and ECG parameters.

8.3.4 Exploratory Endpoints

Exploratory endpoints for Part A include

CCI [redacted]

Exploratory endpoints for Part B include

CCI [redacted]

CCI [redacted]

8.4 Analysis Sets

The primary analysis population for all analyses of efficacy, safety, and health-related quality of life is the Safety population.

The Safety population will include all subjects who received at least 1 dose of trial treatment.

The Per-Protocol (PP) population will be the subset of the Safety population that is compliant with the protocol and excludes subjects with protocol violations. The protocol violation criteria will be outlined in the SAP. The per-protocol population will be used for additional sensitivity analyses for the primary and secondary efficacy endpoints.

Analysis of efficacy variables may also be performed on subgroups of interest and will be outlined in the Statistical Analysis Plan.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

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

All data recorded during the trial 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 in the SAP.

Descriptive statistics will be used to summarize the trial results, that is, 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 estimation of PK parameters will be performed using WinNonlin® version 5.0 or higher. All other statistical analyses will be performed using SAS® version 9.2 or higher, or R (www.r-project.org), version 2.15.2 or higher.

8.5.2 Analysis of Primary Endpoint

Part A

The primary endpoint for Part A is the BOR according to RECIST 1.1, as determined by an IERC. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) will be required, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed

at an assessment later than the next assessment after the initial documentation of PR. A BOR of SD requires that a timepoint overall response of SD has been determined at a timepoint at least 6 weeks after start of study treatment. 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. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR.

The test statistic of the exact binomial test will be calculated and compared with the thresholds given in Section 8.1 to determine whether the null hypothesis of an ORR $\leq$ 20% can be rejected at the interim analysis, or, if not rejected at the interim, at the primary analysis. The 2-sided 99.1% CI and the 95.9% CI will be constructed using the Clopper-Pearson method for ORR to form repeated CIs according to Jennison and Turnbull (Jennison 2000) at the interim analysis and primary analysis, respectively. The nominal p-value from the exact binomial test will also be reported.

Part B:

For Part B, the primary endpoint is durable response, defined as objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months. Duration of response will be calculated as specified in Section 8.3.2. Subjects for whom the duration of response is censored will be treated as failures (successes) in the analysis of durable response if the censored duration of response is below (at least) 6 months, respectively. The number and proportion of subjects with a durable response will be tabulated. The DRR will be determined as the proportion of subjects with a durable response. The 95% CI for the DRR will be calculated using the Clopper-Pearson method. There will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. All interim analyses in Part B will be exploratory.

8.5.3 Analysis of Secondary and Exploratory Endpoints

8.5.3.1 Analysis of Secondary Endpoints

Duration of response will be calculated for each subject with a confirmed response according to RECIST 1.1. The Kaplan-Meier method will be used to estimate parameters for duration of response, PFS time, and OS time (including the median with corresponding 2-sided 95% CIs). In particular, the PFS rate at 6 months will be estimated with corresponding two-sided 95% CIs, and the survival rate at 6 and 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980). The estimate of the standard error will be computed using Greenwood's formula. The PFS time and OS time will also be presented in subject listings.

The proportion of subjects with response at 6 and 12 months after start of study treatment will be determined as the proportion of subjects in response among all subjects that have started study

treatment at least 6 (12) months prior to the time of the analysis, respectively. Clopper-Pearson 95% CIs will be reported as well.

In Part B, the BOR as determined by IERC will be analyzed descriptively, using the same methods outlined in Section 8.5.2 for Part A.

Safety endpoints, including AEs, clinical laboratory assessments, vital signs, and ECG parameters, will be analyzed descriptively.

8.5.3.2 Analysis of Exploratory Endpoints

CCI

[redacted]

8.5.3.3 Pharmacokinetic Profile

Trough serum / plasma concentrations of avelumab will be determined by a validated method at the times listed in the Schedule of Assessments (Appendix I). The primary PK analysis will be a population PK analysis based on sparse sampling. If appropriate, the data may be added to data from other studies.

8.5.3.4 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)
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)
- FDA Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins (FDA; December 2009, draft)

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

CCI [redacted]

8.5.4 Safety Analyses

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

Adverse events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE v 4.0 toxicity grading scale.

The incidence of TEAEs, regardless of attribution and TEAEs 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. Treatment-emergent AEs (TEAEs) are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

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 postbaseline laboratory values will be included in these analyses.

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

Physical examination including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and 12-lead ECG as indicated in 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.

8.5.5 Subgroup Analyses

Analysis of efficacy variables may be performed on subgroups of interest as needed. The detailed subgroups will be outlined in the SAP.

8.6 Interim Analysis

Part A:

There will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months, and 1 interim analysis for efficacy 6 months after 56 subjects have been enrolled. If no unconfirmed response according to RECIST 1.1 is seen in the first interim analysis, then enrollment will be stopped unless the SMC makes a recommendation that the trial should continue. The second interim analysis will be conducted 6 months after enrollment of the 56th subject. It will comprise a full evaluation of all efficacy and safety endpoints. The analysis of efficacy in this interim analysis will be restricted to the first 56 subjects that were enrolled, as determined by the date and time of first administration of study treatment. If efficacy goals 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. The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis of secondary and exploratory endpoints will be conducted 12 months after the accrual of the last subject. The survival follow-up will continue for up to 5 years after the last subject receives the last dose of avelumab or last subject dies, whichever occurs earlier. Before the partial database lock for the primary analysis, there will be no dissemination of the interim analyses results to Investigators beyond the SMC. Other than the two planned interim analyses and the ongoing safety monitoring during the trial, no further interim analyses will be conducted.

Part B:

In Part B there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. The date of accrual is determined as the date of the first dose of study treatment.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He / she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included in the trial.

In 1998, the US 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 study drug (named "covered trials" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest that they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. A separate specific PGx 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 gene(s) may affect the efficacy of avelumab.

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

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

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

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

Subjects will be invited to participate in an optional health-related quality of life interview process. For both Part A and Part B, subjects will be free to accept or refuse to participate. Acceptance to participate in the interviews will be documented by a check mark in the appropriate box on the ICF. Upon acceptance, the subject will be asked to complete a contact order form to enable the scheduling of interviews.

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

For subjects participating in the optional health-related quality of life interviews, interviewers will follow a semi-structured interview guide specifically developed for the current trial. Interviewers will start by mentioning the date of the interview and subject ID. Audio files of the interviews will be transcribed and de-identified (any identifying information such as dates, names, locations will be removed). The de-identified transcripts will be delivered for analysis and a single audiofile will be kept as a source document in the Trial Master File. Any copies of the audiofile will be destroyed immediately upon confirmation of receipt of the transcript.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject contact details and data. Subjects will be informed accordingly and will be requested to give their consent on contact details data handling procedures in accordance with national regulations. In order to secure data privacy protection, patient contact details will be sent to a dedicated unit in charge of scheduling and setting up the interviews independently from study sponsor, monitor, data management and data analysis structures and other study stakeholders. The specific information about patient contact details management will be provided on a Contact Order

Form to be completed by Investigator and patient, signed by the patient and sent to the unit in charge of scheduling and setting up the interviews. This form will not include health data.

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

In cases where the Investigator is not available, Merck Serono / EMD Serono R&D provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

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

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC / IRB. The IEC / IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and

of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

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

The data will be entered into a validated database. The CRO will follow the standards of the sponsor in the database design and data structure. The CRO will be responsible for data review and processing, in accordance with the CRO's data management procedures. Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed. Copies of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

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

- Subject's full name
- Date of birth
- Sex
- Race
- Height
- Weight

- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Tumor disease information
- Trial identification (EMR100070-003)
- Date of subject's inclusion into the trial (that is, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from study drug, if applicable

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

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

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be 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 GCP (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 eCRFs, the study drug, and the subjects' original medical records/files.

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

10.5 Changes to the Clinical Trial Protocol

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

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

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

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

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites, for Part A (Kaufman 2016; Kaufman 2018) and separately for Part B.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor.

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

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Appendices

Appendix I Schedule of Assessments

Part A

Measure	Screening/ Baseline Assessments	Treatment Phase[a]											Discontinuation (x)/ End-of-Treatment Visit (X)	Safety Follow-up Visit	Post-Treatment Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10				
	Day -18 to First Treatment	W1	W2	W3	W4	W5	W6	W7	W9	W11	W13	Until Progression	Up to 7 / 28 Days after Last Treatment[c,d]	10 Weeks after Last Treatment	Every 3 months[b]
		D1	D8	D15	D22	D29	D36	D43	D57	D71	D85				
Written informed consent	X														
Inclusion / exclusion criteria	X														
Medical history	X														
Demographic data	X														
EQ-5D and FACT-M[e]	X							X			X	6 weekly	- /X		
Optional subject interviews[f]	X										X[f]	6 months[f]			
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 PS	X[g]	X		X		X		X	X	X	X	2 weekly	x/X	X	
Enrollment (if eligible)[h]	X														
ECG[i]	X	X		X		X		X	X	X	X	6 weekly[i]	x/X	X	
Hematology and hemostaseology	X	X		X		X		X	X	X	X	2 weekly	x/X	X	
Core serum chemistry[j]		X	X[j]		X[j]		X[j]	X	X	X		2 weekly		X	
Full serum chemistry[k]	X			X		X					X	6 weekly	x/X		
Urinalysis[l]	X	X		X		X		X	X	X	X	2 weekly	x/X	X	
β-HCG pregnancy test[m]	X	X		X		X		X	X	X	X	2 weekly	- /X	X	

Part A

Measure	Screening/ Baseline Assessments	Treatment Phase[a]											Discontinuation (x)/ End-of-Treatment Visit (X)	Safety Follow-up Visit	Post-Treatment Follow-up[b]
	Day -18 to First Treatment	V1 W1 D1	V2 W2 D8	V3 W3 D15	V4 W4 D22	V5 W5 D29	V6 W6 D36	V7 W7 D43	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7 / 28 Days after Last Treatment[c,d]	10 Weeks after Last Treatment	Every 3 months[b]
Tumor evaluation / staging (CT Scan / MRI / mapping skin lesions / tumor markers / other established methods)[n,o]	X							X			X	6 weekly up to 12 months then 12 weekly	- /X		X
Documentation of AEs and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	2 weekly	x/X	X	X
ACTH, ANA, ANCA, RF, free T4, and TSH	X										X	Week 25 and as indicated	- /X	X	
PK sampling[p]		X[p]		X[p]		X[p]		X[p]	X[p]	X[p]	X[p]	Weeks 15 and 25[p] then every 12 weeks		X[p]	
ADA sampling[q]		X		X		X		X			X	6 weekly	- /X		
Pretreatment and study drug administration[r]		X		X		X		X	X	X	X	2 weekly			
CCI [redacted]															
Tumor tissue (biopsy)[t]	X														
CCI [redacted]															

ACTH=adrenocorticotropic hormone, ADA=antidrug antibody, AE=adverse events, ALT=alanine aminotransferase, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, AST=aspartate aminotransferase, β-HCG=β-human chorionic gonadotropin, BUN=blood urea nitrogen, CR=complete response, CT=computer tomography, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EQ-5D=EuroQol-EQ-5D, FACT-M=functional assessment of cancer therapy-melanoma, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, MCV=Merkel cell polyoma virus, MRI=magnetic resonance imaging, PK=pharmacokinetics, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, RF=rheumatoid factor, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures.

b Subjects with an adverse drug reaction ongoing at the End-of-Treatment visit and for any SAE suspected to be related to trial treatment occurring up to 3 months after the last dose of avelumab and thereafter will continue to be followed. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression until PD (CT / MRI scans every 6 weeks; for trial sites in Germany, only MRI is to be used). In addition, subjects will be followed quarterly for survival (including assessment of any further tumor therapy). The survival follow-up will continue for up to 5 years after the last subject receives the last dose of avelumab, or last subject dies, whichever occurs earlier (see Section 7.1.5 for details).

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

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

e The EQ-5D and FACT-M questionnaires should be completed by subjects at Screening, and prior to any study related procedures at Week 7, then once every 6 weeks thereafter while on treatment and at the End-of Treatment visit.

f Subject interviews (optional; box on the Informed Consent Form indicating consent for interviews must be checked) will be conducted at Screening, Week 13, and 6 months (for both subjects on treatment and off treatment; see Section 7.7.1 for details). For subjects consenting to the interviews, a Contact Order Form including subject contact details will be completed and sent to the independent unit in charge of managing the interviews).

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

h 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).

i 12-lead ECG should be assessed during screening, prior to infusion and 2 hours ± 20 minutes after the end of infusion at each visit on Days 1, 15, 29, 43, 57, 71, and 85 and every 6 weeks thereafter (until 18 months, after which on-treatment ECGs will not be required), at the Discontinuation / End-of-Treatment visit and Safety-Follow-up visit.

j Core serum chemistry includes liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN / total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). For subjects with liver metastases at Baseline, additional blood samples for ALT, AST, total bilirubin, and alkaline phosphatase determination will be drawn at Weeks 2, 4, and 6.

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

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

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

n 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 trial, confirmation of the response should be performed according to RECIST 1.1, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) should always be used in addition to mapping of skin lesions. The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

o A brain CT / MRI scan is required at Screening if not performed within the previous 6 weeks, and beyond as clinically indicated. 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.

p Blood samples for PK determinations will be collected from all subjects within 2 hours prior to each study drug administration through Week 15, then at Week 25, and then at 12-week intervals while on treatment. 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 Weeks 1, 7, 13, and 25, and then at 12-week intervals while on treatment. Exact sampling times will be recorded. Samples will be collected at the 10-week Safety Follow-up visit. Remaining sample from the 10-week safety follow-up visit may be used to test ADA. PK and ADA samples collected at the same predose time point may be used interchangeably if the dedicated sample has insufficient quantity, as the subject and his / her parent / legal representative will have consented to all collections and tests.

q The blood sample for Screening / Baseline ADA analysis will be collected prior to study drug administration and on Day 1. On trial samples will be collected within 2 hours prior to study drug infusion on Days 15, 29, 43 (every 2 weeks), then every 6 weeks thereafter while on treatment, and at the End-of-Treatment visit.

r Subjects must receive pretreatment with antihistamine (diphenhydramine, or equivalent) and paracetamol (acetaminophen, oral or IV) prior to the first 4 infusions of avelumab (10 mg/kg IV over 1 hour **[-10 minutes / +20 minutes, that is, over 50 to 80 minutes]**). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate.

CCI [redacted]

t A biopsy should be collected at Screening, unless tissue (blocks or slides) from a recent biopsy (within 4 weeks) is available. Samples can be provided as block or slides (blocks are preferable; see Section 7.6 for details). For subjects unable to provide a fresh or recent biopsy, archival material is acceptable [blocks preferable).

CCI [redacted]

Part B

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								Follow-up[b]			
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -18 to First Treatment	D1	D15	D29	D43	D57	D71	D85	Until Progression	Discontinuation Visit Within 7 days of decision to discontinue[b]	End-of-Treatment Visit 30 (±5) Days after Last Treatment[c,d]	Safety Follow-up Visit 90 Days (±1 week) after Last Treatment	Long-term Follow-up Every 3 months[b]
Written informed consent	X												
Inclusion / exclusion criteria	X												
Medical history	X												
Demographic data	X												
EQ-5D and FACT-M[e]	X				X			X	6 weekly		X		
Subject interviews[f]	X							X[f]	6 months[f]				
HBV, HCV, and HIV testing	X												
Physical examination, including height at Screening[g]	X	X	X	X	X	X	X	X	6 weekly	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	2 weekly	X	X	X	
Weight	X	X	X	X	X	X	X	X	2 weekly	X	X	X	
ECOG PS[h]	X[h]	X	X	X	X	X	X	X	2 weekly	X	X	X	
Enrollment (if eligible)[i]	X												
ECG[j]	X									X	X	X	
Hematology and hemostaseology	X	X	X	X	X	X	X	X	2 weekly	X	X	X	
Core serum chemistry[k]		X	X	X	X	X	X	X	2 weekly			X	
Full serum chemistry[l]	X									X	X		
Urinalysis[m]	X	X								X	X	X	
β-HCG pregnancy test[n]	X	X		X		X		X	4 weekly		X	X	

Part B

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								Follow-up[b]			
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -18 to First Treatment	D1	D15	D29	D43	D57	D71	D85	Until Progression	Discontinuation Visit Within 7 days of decision to discontinue[b]	End-of-Treatment Visit 30 (±5) Days after Last Treatment[c,d]	Safety Follow-up Visit 90 Days (±1 week) after Last Treatment	Long-term Follow-up Every 3 months[b]
Tumor evaluation / staging (CT Scan / MRI / mapping skin lesions / tumor markers / other established methods)[b,o,p]	X				X			X	6 weekly up to 12 months then 12 weekly		X		X[b]
Documentation of AEs and concomitant medication	X	X	X	X	X	X	X	X	2 weekly	X	X	X	
ACTH, ANA, ANCA, and RF	X							X	Week 25 and as indicated		X	X	
Free T4 and TSH	X	X			X			X	6 weekly		X	X	
PK sampling[q]		X[q]	X[q]	X[q]	X[q]			X[q]	6 weekly to Week 25[q] then every 12 weeks	X	X	X	
ADA sampling[r]		X	X	X	X			X	6 weekly to Week 25 then every 12 weeks		X	X	
Pretreatment and study drug administration[s]		X	X	X	X	X	X	X	2 weekly				
CCI [redacted]													
Tumor tissue (biopsy)[u]	X												
CCI [redacted]													

Part B

Measure	Screening/ Baseline Assessments	Treatment Phase[a]								Follow-up[b]			
		V1	V2	V3	V4	V5	V6	V7					
		W1	W3	W5	W7	W9	W11	W13					
	Day -18 to First Treatment	D1	D15	D29	D43	D57	D71	D85	Until Progression	Discontinuation Visit Within 7 days of decision to discontinue[b]	End-of-Treatment Visit 30 (±5) Days after Last Treatment[c,d]	Safety Follow-up Visit 90 Days (±1 week) after Last Treatment	Long-term Follow-up Every 3 months[b]
CCI													
CCI													
CCI													

ACTH=adrenocorticotropic hormone, ADA=antidrug antibody, AE=adverse events, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, β-HCG=β-human chorionic gonadotropin, CR=complete response, CT=computer tomography, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EQ-5D=EuroQol-EQ-5D, FACT-M=functional assessment of cancer therapy-melanoma, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, MCV= Merkel cell polyoma virus, MRI=magnetic resonance imaging, PD=progressive disease, PK=pharmacokinetics, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors version 1.1, RF=rheumatoid factor, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures.

b All subjects in Part B will have a Discontinuation visit within 7 days of the decision to discontinue treatment. Subjects with an adverse drug reaction ongoing at the End-of-Treatment visit and for any SAE suspected to be related to trial treatment occurring up to 3 months after the last dose of avelumab and thereafter will continue to be followed. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression until PD (CT / MRI scans every 6 weeks through 1 year from start of treatment then every 12 weeks thereafter; for trial sites in Germany, only MRI is to be used). In addition, subjects will be followed quarterly for survival (including assessment of any further tumor therapy). The survival follow-up will continue for up to 5 years after the last subject receives the last dose of avelumab, or last subject dies, whichever occurs earlier (see Section 7.1.5 for details).

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

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

e The EQ-5D and FACT-M questionnaires should be completed by subjects at Screening, and prior to any study related procedures (including CT or MRI scans) at Week 7, then once every 6 weeks thereafter while on treatment and at the End-of Treatment visit.

f Subject interviews (optional; box on the Informed Consent Form indicating consent for interviews must be checked) will be conducted at Screening, Week 13, and 6 months (for both subjects on treatment and off treatment; see Section 7.7.1 for details). For subjects consenting to the interviews, a Contact Order Form including subject contact details will be completed and sent to the independent unit in charge of managing the interviews).

g A full physical examination should be performed at Screening and the Discontinuation visit (as required). Physical examinations at all other visits should be directed to signs and symptoms. Only subjects with liver metastases at Baseline are required to have a physical examination at Weeks 4 and 6.

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

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

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

k Core serum chemistry is detailed in Table 7.

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

m Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at Day 1 visit prior to administration of study drug and at the Discontinuation and Safety Follow-up visits. If the basic urinalysis is abnormal, then a full urinalysis should be performed. Urinalysis after Day 1 should be performed as clinically indicated.

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

o 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 trial, confirmation of the response should be performed according to RECIST 1.1, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used) should always be used in addition to mapping of skin lesions. The tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days).

p A brain CT / MRI scan is required at Screening if not performed within the previous 6 weeks, and beyond as clinically indicated. 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.

q Blood samples for PK determinations will be collected from all subjects within 2 hours prior to each study drug administration through Week 7, every 6 weeks through Week 25, and then at 12-week intervals thereafter while on treatment. Post study drug administration samples will be collected at the end of infusion at Weeks 1, 7, and 25. Exact sampling times will be recorded. Samples will also be collected at the 7-day Discontinuation, 30-day End-of-Treatment, and 90-day Safety Follow-up Visits. PK and ADA samples collected at the same predose time point may be used interchangeably if the dedicated sample has insufficient quantity, as the subject and his/her parent/legal representative will have consented to all collections and test.

r The blood sample for Screening / Baseline ADA analysis will be collected prior to study drug administration on Day 1. On trial samples will be collected within 2 hours prior to study drug infusion through Week 7, every 6 weeks through Week 25, and then at 12 week intervals thereafter while on treatment. Samples will also be collected at the 30-day End-of-Treatment visit and the 90-day Safety Follow-up visit. PK and ADA samples collected at the same predose time point may be used interchangeably if the dedicated sample has insufficient quantity, as the subject and his/her parent/legal representative will have consented to all collections and test.

s Subjects must receive pretreatment with antihistamine (diphenhydramine or equivalent) and paracetamol (acetaminophen, oral or IV), prior to the first 4 infusions of avelumab (10 mg/kg IV over 1 hour **[-10 minutes / +20 minutes, that is, over 50 to 80 minutes]**). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate.

CCI [redacted]

u A biopsy should be collected at Screening (see Section 5.3.1, inclusion criterion #4 for details).

CCI [redacted]

CCI [redacted]

CCI [redacted]

Appendix II Eastern Cooperative Oncology Group Performance Status

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

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

a. Oken 1982.

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 Skin Lesion Selection and Photographic Image Acquisition Procedures

Introduction

EMR100070-003 is a Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma.

Tumor measurements (including the assessment of skin lesions by physical examination) to determine response will be performed every 6 weeks until 12 months after the first study drug administration, then every 12 weeks and response to the treatment will be evaluated by RECIST 1.1.

An examination for clinical lesions, including mapping of skin lesions, should also be conducted at each tumor assessment. All radiographic images and physical findings including photographs (skin lesion mapping) and physical assessments will be used for the determination of disease progression.

Disease must be measurable with at least 1 unidimensional measurable lesion by RECIST 1.1 (including skin lesions). Any lesions detected by physical examination only should be documented by photography.

Reference to RECIST 1.1 for Target Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested (Eiesenhauer 2009).

When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Radiographic target lesions must be measured in at least 1 dimension (longest diameter in the plane of measurement will be recorded) with a minimum longest axis of ≥ 10 mm imaged with scale in color photography of a superficial clinical lesion (eg, skin nodule) (Eiesenhauer 2009).

Sites will follow the procedures outlined by Biomedical Systems to set-up the provided camera and equipment, subject preparation, measuring lesions with the measurement scale and acquiring photographs.

Appendix V Protocol Amendments and List of Changes

Previous Protocol Amendments

Amendment Number	Substantial (yes/no)	Date	Region or Country	Included in the current document (Y/N)
Amendment 1	Yes	10 April 2014	Global	Yes
Amendment 2	Yes	06 June 2014	Global	Yes
	No	17 July 2014	Japan	No
	Yes	17 November 2014	France	Yes
Amendment 3	Yes	05 September 2014	Global	Yes
	Yes	05 September 2014	United States	Yes
	No	05 September 2014	European Union	
	Notification only	05 September 2014	Australia	
	No	05 September 2014	Japan	
	Notification only	05 September 2014	Switzerland	
Amendment 4	Yes	17 November	Global	Yes
Amendment 5	Yes	22 December 2014	Global	Yes
Amendment 6	Yes	26 February 2015	Global	Yes
Amendment 7	Yes	08 January 2016	Global	Yes
Amendment 8	Yes	31 March 2016	Global	Yes
Amendment 9	Yes	20 October 2016	Global	Yes
Amendment 10	Yes	23 May 2017	Global	Yes

Amendment Number: Amendment 11.0, 25 May 2018

Rationale: Updated the survival follow-up language for Part A to align with Part B and to ensure complete data collection for both parts of the study.

Major Scientific Changes:

- Clarified that survival follow-up for 5 years is for both Parts A and B
- Added new language regarding continued treatment past initial determination of PD
- Modified mandatory 2-hour post infusion observation to be based on based upon clinical judgment and presence / severity of prior infusion reactions

Administrative Changes

- Change of Coordinating Investigator
- Updated Medical Responsible address and contact information
- Change of Sponsor Biostatistician

List of Changes

Main changes to the clinical study protocol text are presented in the table below. Minor typographical, grammatical, formatting, or other changes not affecting the study conduct are not included.

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

Based on the CT-1 guideline, this amendment is considered substantial due to the change in the Co-ordinating Investigator and a change in post infusion medical monitoring procedures.

Comparison with Clinical Trial Protocol Version 11.0 / Amendment 10, 23 May 2017

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
Updated name of the Coordinating Investigator	Cover page	1	PPD PPD PPD PPD	PPD PPD	Change in Coordinating Investigator
Updated address for Medical Responsible	Cover page	1	PPD PPD ~~Merck Serono SIA~~ ~~23A Duntes str. Riga, LV1005, Latvia~~ ~~Tel:~~ PPD ~~Fax:~~ PPD **45A Middlesex Turnpike** **Billerica, MA 01821, USA** **Tel:** PPD **Fax:** PPD	PPD 45A Middlesex Turnpike Billerica, MA 01821, USA Tel: PPD Fax: PPD	To update most recent contact information
Changed last subject out	Synopsis – Planned trial period (first enrollment-last subject out)	13	Last subject out: ~~Q1, 2029~~ **Q2, 2023**	Last subject out: Q2, 2023	To allow for 5-year survival follow-up
Clarified that survival follow-up for 5 years is for both Parts A and B	Synopsis – Trial design and plan	17	In Part A there will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months and 1 interim analysis for efficacy 6 months after 56 subjects	In Part A there will be 1 interim analysis for futility after 20 subjects have been enrolled and observed for at least 3 months and 1 interim analysis for efficacy 6 months after 56 subjects	For consistency between Part A and Part B and to ensure complete data collection to evaluate

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			have been enrolled. The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. ~~Subject follow-up for progression and survival will continue until 1 year after the last subject receives the last dose of avelumab.~~ In Part B there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. ~~Subject~~ **For both Parts A and B, subject** follow-up for progression and survival will continue until 5 years after the last subject receives the last dose of avelumab or the last subject dies, whichever occurs first. Under some circumstances, subjects may not be followed for 5 years for survival in this study, for example, subjects may be offered to enroll into a rollover study, or the Sponsor may terminate the study early.	have been enrolled. The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. In Part B there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. For both Parts A and B, subject follow-up for progression and survival will continue until 5 years after the last subject receives the last dose of avelumab or the last subject dies, whichever occurs first. Under some circumstances, subjects may not be followed for 5 years for survival in this study, for example, subjects may be offered to enroll into a rollover study, or the Sponsor may terminate the study early.	the duration of response in subjects with response regardless of whether they discontinued study drug or not.
Clarified that survival follow-up for 5 years is for both Parts A and B	Synopsis – Schedule of visits and assessments	21	~~After~~ **For both Parts A and B, 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 for up to 5 years after the last subject receives the last dose of	For both Parts A and B, 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 for up to 5 years after the last subject receives the last dose of	For clarity to ensure complete data collection for both parts of the study

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			avelumab or last subject dies, whichever occurs earlier.	avelumab or last subject dies, whichever occurs earlier.	
Deleted the mandatory 2-hour post-infusion observation	Synopsis - Investigational Medicinal Product: dose / mode of administration / dosing schedule 6.4 Other Drugs to be Used in the Trial	26 64	Following avelumab infusions, subjects ~~must~~ **should** be observed ~~for 2 hours post infusion for potential infusion-related reactions for the first 4 infusions. Starting with the fifth infusion, observation should be~~ based upon clinical judgment and presence / severity of prior infusion reactions.	Following avelumab infusions, subjects should be observed based upon clinical judgment and presence / severity of prior infusion reactions.	Deleted the mandatory observation based on the latest avelumab safety information
Updated language regarding the review of safety data by the SMC	2.3.1 Safety Monitoring Committee	34	To ensure subjects' safety during the trial, a safety monitoring committee (SMC) will periodically review safety data. The SMC will be composed of a minimum of 3 members, including a trial Investigator, a statistician, and an independent physician. The SMC consists of permanent members from the Sponsor and/or CRO (Global Drug Safety Representative, Program Lead, Medical Lead, Biostatistician, Medical Monitor), and the Coordinating Investigator. The full membership, mandate, and processes of the SMC is detailed in the SMC charter. ~~As of the writing of this amendment (Amendment 10), the avelumab safety profile has been well characterized in more than 1500 subjects and is considered generally manageable and tolerable. As such, as of this amendment (Amendment 10), the planned periodic review of safety data by the SMC is no longer intended and~~	To ensure subjects' safety during the trial, a safety monitoring committee (SMC) will periodically review safety data. The SMC will be composed of a minimum of 3 members, including a trial Investigator, a statistician, and an independent physician. The SMC consists of permanent members from the Sponsor and/or CRO (Global Drug Safety Representative, Program Lead, Medical Lead, Biostatistician, Medical Monitor), and the Coordinating Investigator. The full membership, mandate, and processes of the SMC is detailed in the SMC charter. As of Protocol Amendment 10, the planned periodic review of safety data by the SMC was no longer scheduled given the safety data have been analysed as per the statistical plan and submitted to health authorities for review.	Regular review of safety data by the SMC no longer deemed necessary due to the now well characterized avelumab safety profile

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			~~no regular meetings of the SMC will be scheduled.~~ **As of Protocol Amendment 10, the planned periodic review of safety data by the SMC was no longer scheduled given the safety data have been analysed as per the statistical plan and submitted to health authorities for review.**		
Added language regarding regulatory approval and modified text to refer to the latest IB for information on avelumab clinical development	3.4 Avelumab	35	The Investigational Medicinal Product (IMP) for the present trial is avelumab, a ~~fully~~ human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono Inc., Rockland, MA, USA. **Avelumab has received regulatory approval for treatment of metastatic MCC by health authorities in all countries conducting this protocol.** … ~~Avelumab is currently~~ **At the time of the initiation of this study, avelumab was** in **early** clinical development with 2 ongoing Phase I studies in subjects with solid tumors **(refer to the latest IB for latest information on clinical development and approvals)**:	The Investigational Medicinal Product (IMP) for the present trial is avelumab, a human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono Inc., Rockland, MA, USA. Avelumab has received regulatory approval for treatment of metastatic MCC by health authorities in all countries conducting this protocol. … At the time of the initiation of this study, avelumab was in early clinical development with 2 ongoing Phase I studies in subjects with solid tumors (refer to the latest IB for latest information on clinical development and approvals):	Updated to indicate to IRB/IECs the current status of that avelumab is approved for treatment of metastatic MCC by the health authorities in all countries conducting this trial and to reflect ongoing development
Added language specifying importance of Part B	5.1 Overall Trial Design and Plan	51	This is a multicenter, international, single-arm, open-label, Phase II, trial in 2 parts that will evaluate the efficacy and safety of avelumab in subjects with metastatic MCC. In Part A,	This is a multicenter, international, single-arm, open-label, Phase II, trial in 2 parts that will evaluate the efficacy and safety of avelumab in subjects with metastatic MCC. In Part A,	To ensure clarity for Investigators, country reviewers and IRB/IEC reviewers of importance of

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			subjects must have received at least one line of chemotherapy for the treatment of metastatic MCC. In Part B, subjects must be treatment naïve to systemic therapy in the metastatic setting. **Part B will serve as the confirmatory study required to meet conditions for some health authority approvals of avelumab for treatment of metastatic MCC.**	subjects must have received at least one line of chemotherapy for the treatment of metastatic MCC. In Part B, subjects must be treatment naïve to systemic therapy in the metastatic setting. Part B will serve as the confirmatory study required to meet conditions for some health authority approvals of avelumab for treatment of metastatic MCC.	completion of the trial, even with health authority approvals.
Modified end of trial language to correct possible discrepancy	5.1.1 Overall Design	52	… The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. The trial will ~~be continued until 1 year after the last subject receives the last dose of avelumab~~ **continue as specified in Section 5.7**. In Part B, there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. **The trial will continue as specified in Section 5.7.**	… The primary analysis will be conducted 6 months after the accrual of the last subject and a further exploratory analysis will be conducted 12 months after the accrual of the last subject. The trial will continue as specified in Section 5.7. In Part B, there will be 1 interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis will be conducted 15 months after the accrual of the last subject. The trial will continue as specified in Section 5.7.	To correct possible discrepancy and for consistency between Part A and Part B and to ensure complete data collection to evaluate the duration of response in subjects with response regardless of whether they discontinued study drug or not.
Added new language regarding continued treatment past initial determination of PD	5.5.1 Criteria for Withdrawal from Study Drug due to Therapeutic Failure	60	… If progression is based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan 6 weeks later should be performed. Treatment during the confirmation period should continue as scheduled, despite a first observation of progression (according to RECIST	… If progression is based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan 6 weeks later should be performed. Treatment during the confirmation period should continue as scheduled, despite a first observation of progression (according to RECIST	Added for consistency with other protocols in the avelumab program

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			1.1), until confirmation has been made, and further if there is no significant clinical deterioration defined as: • there are no new symptoms or worsening of existing symptoms, • there is no change in ECOG PS to ≥ 3 that lasts more than 14 days, or • the Investigator does not consider it necessary to administer a salvage therapy. **If disease progression is due to brain metastasis, subjects may continue avelumab treatment after the local treatment of the brain lesions provided the above criteria are met in addition to the following and in consultation with the Medical Monitor:** **• Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab** **• There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)** **• Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).** **In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) that in the**	1.1), until confirmation has been made, and further if there is no significant clinical deterioration defined as: • there are no new symptoms or worsening of existing symptoms, • there is no change in ECOG PS to ≥ 3 that lasts more than 14 days, or • the Investigator does not consider it necessary to administer a salvage therapy. If disease progression is due to brain metastasis, subjects may continue avelumab treatment after the local treatment of the brain lesions provided the above criteria are met in addition to the following and in consultation with the Medical Monitor: • Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab • There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable) • Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) that in the opinion of the Investigator may be surgically removed or treated with palliative radiation therapy, subjects may	

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			opinion of the Investigator may be surgically removed or treated with palliative radiation therapy, subjects may continue avelumab treatment after the local treatment of such a lesion provided that: **• It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the subject has fully recovered from the surgery.** **• It has been at least 2 weeks since the subject's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to Grade < 2.** **The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.** Subjects who experience significant clinical deterioration, as defined above, in the absence of confirmed PD should be discontinued from further treatment with avelumab.	continue avelumab treatment after the local treatment of such a lesion provided that: • It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the subject has fully recovered from the surgery. • It has been at least 2 weeks since the subject's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to Grade < 2. The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records. Subjects who experience significant clinical deterioration, as defined above, in the absence of confirmed PD should be discontinued from further treatment with avelumab.	
Modified text to include allowing steroid use for management of patients with allergy to radiographic contrast media	6.5.2 Nonpermitted Medicines	65	• Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions, **management of patients with allergy to radiographic contrast media,** or the management of irAEs) is allowed.	• Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions, management of patients with allergy to radiographic contrast media, or the management of irAEs) is allowed. Steroids with no or	For additional guidance to Investigators and to align with ongoing avelumab development program

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
			Steroids with no or minimal systemic effect (topical, inhalation) are allowed. Also, hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.	minimal systemic effect (topical, inhalation) are allowed. Also, hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.	
Updated language regarding surgery during study treatment	6.5.3 Other Trial Considerations	65	The following nondrug therapies must not be administered during the trial (and within 28 days before the start of trial treatment): • ~~Major surgery (excluding prior diagnostic biopsy)~~ **Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment. For any other surgical interventions planned during the study, study treatment should be delayed to allow subject's recovery, for up to a maximum of 4 weeks (also see Section 5.5.1 for details of treatment management beyond initial assessment of PD)**	The following nondrug therapies must not be administered during the trial (and within 28 days before the start of trial treatment): • Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment. For any other surgical interventions planned during the study, study treatment should be delayed to allow subject's recovery, for up to a maximum of 4 weeks (also see Section 5.5.1 for details of treatment management beyond initial assessment of PD)	For additional guidance to Investigators and to align with ongoing avelumab development program
Deleted the mandatory 2-hour post-infusion observation	6.5.4 Special Precautions	66	As a routine precaution, subjects enrolled in this trial ~~must be observed for 2 hours post infusion for the first 4 infusions~~ **should be observed based upon clinical judgment and presence / severity of prior infusion reactions**, in an area with resuscitation equipment and emergency agents.	As a routine precaution, subjects enrolled in this trial should be observed based upon clinical judgment and presence / severity of prior infusion reactions, in an area with resuscitation equipment and emergency agents.	Changed the mandatory observation based on the latest avelumab safety information
Clarified that persistent Grade 2	6.5.4.4 Immune-Related Adverse	71	If **Grade 2** persists > 1 to 2 weeks or	If Grade 2 persists > 1 to 2 weeks or	For alignment with latest IB resulting

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
dermatologic irAEs should result in treatment delay	Events		recurs: Consider skin biopsy Delay avelumab therapy	recurs: Consider skin biopsy Delay avelumab therapy	from latest safety information
For Part A – deleted "1 year" for limit of follow-up time for disease progression For Part B, modified language to clarify to allow for survival follow-up after PD	7.1.5 Post Treatment Follow-up	86	For Part A, subjects without PD at the End-of-Treatment visit will be followed up for disease progression **until PD** (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks using the same procedures and review as while on treatment; for trial sites in Germany, only MRI is to be used) ~~for up to 1 year~~. CCI [redacted] For Part B, subjects without PD at the End of Treatment visit will be followed ~~until~~ **for** disease progression **until PD** (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks). 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 for up to 5 years after the last subject receives the last dose of avelumab or last subject dies, whichever occurs earlier **(see Section 5.7 for details of the end of study)**.	For Part A, subjects without PD at the End-of-Treatment visit will be followed up for disease progression until PD (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks using the same procedures and review as while on treatment; for trial sites in Germany, only MRI is to be used). CCI [redacted] For Part B, subjects without PD at the End of Treatment visit will be followed for disease progression until PD (CT / MRI scans every 6 weeks until Week 55 [12 months] after the first study drug administration, then every 12 weeks). 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 for up to 5 years after the last subject receives the last dose of avelumab or last subject dies, whichever occurs earlier (see Section 5.7 for details of the end of study).	For consistency between Part A and Part B and to ensure complete data collection to evaluate the duration of response in subjects with response regardless of whether they discontinued study drug or not.

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
Updated address for Medical Responsible	Signature page	172	PPD ~~Riga, LV1005, Latvia~~ PPD PPD **45A Middlesex Turnpike** **Billerica, MA 01821, USA** PPD	PPD 45A Middlesex Turnpike Billerica, MA 01821, USA PPD	To update most recent contact information
Updated name of the Coordinating Investigator	Signature page	173	PPD	PPD	Change in Coordinating Investigator
deleted "1 year" for limit of follow-up time for disease progression	Appendix I Schedule of Assessments – Part A – footnote	129	b Subjects with an adverse drug reaction ongoing at the End-of-Treatment visit and for any SAE suspected to be related to trial	b Subjects with an adverse drug reaction ongoing at the End-of-Treatment visit and for any SAE suspected to be related to trial	For consistency between Part A and Part B and to ensure complete data

Change	Section	Pages	Previous Wording Plus New Wording	New Wording	Rationale
	"b"		treatment occurring up to 3 months after the last dose of avelumab and thereafter will continue to be followed. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression **until PD** (CT / MRI scans every 6 weeks; for trial sites in Germany, only MRI is to be used) ~~for up to 1 year~~. In addition, subjects will be followed quarterly for survival (including assessment of any further tumor therapy). The survival follow-up will continue for up to 5 years after the last subject receives the last dose of avelumab, or last subject dies, whichever occurs earlier (see Section 7.1.5 for details).	treatment occurring up to 3 months after the last dose of avelumab and thereafter will continue to be followed. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression until PD (CT / MRI scans every 6 weeks; for trial sites in Germany, only MRI is to be used). In addition, subjects will be followed quarterly for survival (including assessment of any further tumor therapy). The survival follow-up will continue for up to 5 years after the last subject receives the last dose of avelumab, or last subject dies, whichever occurs earlier (see Section 7.1.5 for details).	collection to evaluate the duration of response in subjects with response regardless of whether they discontinued study drug or not.

Appendix VI Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Title	A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma
IND Number	CCI [redacted]
EudraCT Number	2014-000445-79
Clinical Trial Protocol Date / Version	25 May 2018 / Version 12.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

_____ _____

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 II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma
IND Number	CCI [redacted]
EudraCT Number	2014-000445-79
Clinical Trial Protocol Date / Version	25 May 2018 / Version 12.0

Coordinating Investigator

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.

_____ _____

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

Title	A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma
IND Number	CCI [redacted]
EudraCT Number	2014-000445-79
Clinical Trial Protocol Date / Version	25 May 2018 / Version 12.0

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation (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 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 Strasse 250, Postcode: F135/301, 64293 Darmstadt, Germany
Telephone number	PPD
E-mail address	PPD

Name	PPD
Function	PPD
Institution	EMD Serono Global Clinical Operations
Address	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number	PPD
Fax number	PPD
E-mail address	PPD