# Clinical Trial Protocol

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| **Clinical Trial Protocol Number** | MS201781-0031 |
| **Title** | A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors |
| **Phase** | Ib |
| CCI [redacted] | [redacted] |
| **EudraCT Number** | 2017-002212-13 |
| **Coordinating Investigator** | PPD<br>PPD |
| **Sponsor** | United States:<br>EMD Serono Research & Development Institute, Inc., Billerica, MA, US<br>Sites outside of United States:<br>Merck KGaA<br>Frankfurter Strasse 250<br>64293 Darmstadt, Germany<br>Medical Responsible:<br>PPD<br>Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany<br>PPD<br>PPD |
| **Clinical Trial Protocol Version** | 22 July 2019 / Version 8.0, Amendment 7.0 (Global) |
| **Replaces Version** | Global: Version 7 0, Amendment 6.0, 26 April 2019 |

## Protocol Amendment Summary of Changes

### Protocol History

| Version Number | Type | Version Date |
|---|---|---|
| 1.0 | Original protocol | 07-Oct-2016 |
| 2.0 | Global Amendment 1.0 | 18-Nov-2016 |
| 3.0 | Global Amendment 2.0 | 06-Dec-2016 |
| 4.0 | Global Amendment 3.0 | 06-Apr-2017 |
| 5.0 | Global Amendment 4.0 | 01-Jun-2017 |
| 5.1 | Local Amendment 4.1 | 12-Dec-2017 |
| 5.2 | Local Amendment 4.2 | 23-Apr-2018 |
| 6.0 | Global Amendment 5.0 | 10-Dec-2018 |
| 6.1 | Local Amendment 5.1 | 20-Feb-2019 |
| 6.2 | Local Amendment 5.2 | 11-Mar-2019 |
| 7.0 | Global Amendment 6.0 | 26-Apr-2019 |
| 8.0 | Global Amendment 7.0 | 22-Jul-2019 |

### Protocol Version [8.0] (22-July-2019)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

### Overall Rationale for the Amendment

The purpose of this amendment is to allow greater flexibility in tissue requirement inclusion criteria for the UC expansion cohort at Stage 1.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: Other assessments Part B: Pharmacogenetics | Removed tumor samples language from Pharmacogenetics assessments text. | To be consistent with Schedule of Assessments. |
| Synopsis; Other assessments Part B: Expansion Cohorts, Tumor Tissue | Added that collection of tumor tissue at baseline is highly recommended for subjects in the urothelial carcinoma (UC) expansion cohort at Stage 1. | To allow greater flexibility in tumor tissue requirement for the UC expansion cohort at Stage 1. |
| Synopsis; Key Inclusion Criteria for Expansion Cohorts; | Clarified that collection of tumor tissue is not mandatory but strongly recommended for the UC expansion cohort at Stage 1. Also, language on tumor tissue requirement at baseline updated for the colorectal carcinoma (CRC), NSCLC expansion cohorts, and the UC cohort at Stage 2. | To allow greater flexibility in tumor tissue requirement inclusion criteria for the UC expansion cohort at Stage 1 and to clarify the tumor tissue requirement for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis; Key Inclusion Criteria for Expansion Cohorts; | Language updated to allow all cohorts (not just RCC), if usable tumor tissue is not obtained after 2 separate biopsies, the enrollment may be considered after the discussion with the Medical Monitor. | To provide clarity and to avoid over burdening subjects in all cohorts, not just the RCC cohort. |
| Table 5 Schedule of Assessments | Updated to include a visit for physical examination at Cycle 1 Day 2 with correction of Footnote c to state that the limited physical evaluation is required on C1D2, not C1D3. | Revised to be consistent with the Schedule of Assessments. |
| Table 5 Schedule of Assessments | Added in footnote h that, for the UC expansion cohort at Stage 1, collection of tumor tissue is not mandatory for the eligibility but is strongly recommended. Also, language on tumor tissue requirement at baseline updated for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. | To allow greater flexibility in tumor tissue requirement inclusion criteria for the UC expansion cohort at Stage 1 and to clarify tumor tissue requirement for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. |
| Table 5 Schedule of Assessments | Language updated to allow all cohorts (not just RCC), if usable tumor tissue is not obtained after 2 separate biopsies, the enrollment may be considered after the discussion with the Medical Monitor. | To provide clarity and to avoid over burdening subjects in all cohorts, not just the RCC cohort. |
| 5.3.1.2 Inclusion Criteria for Expansion Cohorts; #3, d | Deletion of sentence "If a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor" for RCC, to clarify and allow all cohorts (not just RCC). | To provide clarity and to avoid over burdening subjects in all cohorts, not just the RCC cohort. |
| 5.3.1.2 Inclusion Criteria for Expansion Cohorts; #4 | Clarified that collection of tumor tissue is not mandatory but strongly recommended for the UC expansion cohort at Stage 1. Also, language on tumor tissue requirement at baseline updated for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. | To allow greater flexibility in tumor tissue requirement inclusion criteria for the UC expansion cohort at Stage 1 and to clarify the tumor tissue requirement for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. |
| 5.3.1.2 Inclusion Criteria for Expansion Cohorts; #4 | Language updated to allow all cohorts (not just RCC), if usable tumor tissue is not obtained after 2 separate biopsies, the enrollment may be considered after the discussion with the Medical Monitor. | To provide clarity and to avoid over burdening subjects in all cohorts, not just the RCC cohort. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.5.4 Special Precautions | Clarified that subjects must remain close to the medical center for 5 days only after the first dose of study drug administration in Cycle 1. In addition, language was added to state that the requirement to remain at the site for observation for 2 hours post dose will be for at least the first 4 administrations. | To provide clarity on the safety requirements post study drug administration. |
| 7.1.2.2 Treatment Period for Expansion Cohorts | Clarified that baseline tumor biopsy or archival tumor tissue collection for the CRC, NSCLC, and renal cell carcinoma (RCC) expansion cohorts, and UC expansion cohort at Stage 2 is required but is highly recommended for the UC expansion cohort at Stage 1. | To allow greater flexibility in tumor tissue requirement eligibility criteria for the UC expansion cohort at Stage 1. |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments: Pharmacogenetics | Removed tumor samples language from Pharmacogenetics assessments text. | To be consistent with Schedule of Assessments. |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments: Tumor Tissue | Clarified that collection of tumor tissue is not mandatory but strongly recommended for the UC expansion cohort at Stage 1. Also, language on tumor tissue requirement at baseline updated for the CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. | To allow greater flexibility in tumor tissue requirement inclusion criteria for the UC expansion cohort at Stage 1 and to clarify the tumor tissue requirement for CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2. |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments: Tumor Tissue | Language updated to allow all cohorts (not just RCC), if usable tumor tissue is not obtained after 2 separate biopsies, the enrollment may be considered after discussion with the Medical Monitor. | To provide clarity and to avoid over burdening subjects in all cohorts, not just the RCC cohort. |
| Throughout | Minor editorial and document formatting revisions. | Minor, therefore have not been summarized. |

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## Protocol Table of Contents

## Table of In-Text Tables



## Table of In-Text Figures

## List of Abbreviations

| | |
|---|---|
| ADA | anti-drug antibody |
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| ADL | activities of daily living |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| AP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BOR | best overall response |
| BUN | blood urea nitrogen |
| CK-MB | creatine kinase-MB |
| CLIA | Clinical Laboratory Improvement Amendments |
| $C_{max}$ | maximum serum concentration observed post-dose |
| $C_{min}$ | minimum serum concentration observed post-dose |
| CR | complete response |
| CRC | colorectal carcinoma |
| CRO | Contract Research Organization |
| CRPC | castration-resistant prostate cancer |
| CRS | Cytokine release syndrome |
| CT | computerized tomography |

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|---|---|
| CTC | circulating tumor cell(s) |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | anticytotoxic T lymphocyte antigen-4 |
| DC | dendritic cell |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECLA | electrochemiluminescence Immunoassay |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| eCRF | electronic case report form |
| EGFR | epidermal growth factor receptor |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument |
| EORTC QLQ-CR29 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal Cancer Module |
| EORTC QLQ-NMIBC24 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Non-Muscle Invasive Bladder Cancer Module |
| EORTC QLQ-RCC10 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Renal Cell Carcinoma Module |
| EOT | End-of-Treatment |
| EU | European Union |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed paraffin-embedded |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |

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|---|---|
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HCVAb | hepatitis C virus antibody |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IHC | immunohistochemistry |
| IL-12 | interleukin 12 |
| IMP | investigational medicinal product |
| irAE | immune-related adverse event |
| irBOR | immune-related best overall response |
| IRB | Institutional Review Board |
| irRECIST | immune-related RECIST |
| IV | intravenous |
| IWRS | Interactive Web Response System |
| LDH | lactate dehydrogenase |

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|---|---|
| LFT | liver function test |
| LLN | lower limit of normal |
| LLOQ | lower limit of quantification |
| MAD | maximum administered dose |
| MIG | monokine induced by gamma interferon |
| MRI | magnetic resonance imaging |
| MSI | microsatellite instability |
| MSS | microsatellite stable |
| MTD | maximum-tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCI | National Cancer Institute |
| NK | natural killer (cell) |
| NR | not reportable |
| NSAID | nonsteroidal antiinflammatory drug |
| NSCLC | non-small cell lung cancer |
| NSCLC-SAQ | Non-Small Cell Lung Cancer Symptom Assessment Questionnaire |
| ORR | objective response rate |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PD | progressive Disease |
| PD-1 | programmed death 1 |
| PD-L1 | programmed death ligand 1 |
| PFS | progression free survival |

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|---|---|
| PGIS | Patient Global Impression of Severity |
| PGt | pharmacogenetics / pharmacogenomics |
| PK | pharmacokinetics |
| PR | partial response |
| PRO | patient-reported outcomes |
| q4w | every 4 weeks |
| RCC | renal cell carcinoma |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors Version 1.1 |
| RNA | ribonucleic acid |
| RP2D | recommended Phase II dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous(ly) |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SMC | Safety Monitoring Committee |
| TEAE | treatment-emergent adverse event |
| TILS | tumor-infiltrating lymphocytes |
| TRAE | treatment-related adverse event |
| TSH | thyroid-stimulating hormone |
| T4 | free thyroxine |
| TNM | Tumor Node Metastasis Classification of Malignant Tumors (UICC) |
| UC | urothelial carcinoma |

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|---|---|
| UICC | Union Internationale Contre le Cancer |
| ULN | upper limit of normal |
| VHP | Voluntary Harmonization Procedure |
| WBC | white blood cells |

# 1 Synopsis

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|---|---|
| **Clinical Trial Protocol Number** | MS201781-0031 |
| **Title** | A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors |
| **Trial Phase** | Ib |
| CCI [redacted] | [redacted] |
| **FDA covered study** | Yes |
| **EudraCT Number** | 2017-002212-13 |
| **Coordinating Investigator** | PPD |
| **Sponsor** | United States:<br>EMD Serono Research & Development Institute, Inc., Billerica, MA, US<br>Sites outside of United States:<br>Merck KGaA<br>Frankfurter Strasse 250<br>64293 Darmstadt, Germany |
| **Study centers/countries** | Approximately 65 enrolling sites globally. |
| **Planned study period (first subject in-last subject out)** | First subject in: Q4, 2016<br>Last subject out (dose-escalation): Q2, 2019<br>Last subject out (after follow-up): Q1, 2022 |
| **Trial Registry** | Clinicaltrials.gov, EudraCT, and all other required registries |

**Objectives:**

Primary:

Part A: Dose Escalation

The primary objective for the dose-escalation part of the study is to determine the safety, tolerability, and maximum-tolerated dose (MTD) of M9241 and avelumab when given in combination in subjects with metastatic or locally advanced solid tumors.

Part B: Expansion Cohorts

- To evaluate the confirmed best overall response (BOR) as assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) of avelumab in combination with M9241 at the recommended Phase II dose (RP2D) in selected tumor types
- To evaluate the safety and tolerability of combination therapy with avelumab and M9241 at the RP2D.

Secondary:

Part A: Dose Escalation

- To characterize pharmacokinetic (PK) profiles of avelumab and M9241 when given in combination
- To determine the RP2D of M9241 and avelumab when given in combination
- To evaluate the immunogenicity of combination therapy with M9241 and avelumab
- To evaluate preliminary antitumor activity of combination therapy with M9241 and avelumab.

Part B: Expansion Cohorts

- To characterize PK profiles of avelumab and M9241 at the RP2D when given in combination
- To evaluate the immunogenicity of combination therapy with avelumab and M9241
- To evaluate antitumor activity of combination therapy with avelumab and M9241 in selected solid tumor types.

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**Methodology:**

This is a Phase Ib, open-label, dose-escalation study with consecutive parallel-group expansion in selected solid tumor types.

**Part A: Dose Escalation**

Part A of the study will be conducted in the United States (US) only. This is a Phase Ib open-label, dose-finding study with a modified 3 + 3 study design. Once 3 subjects at a given dose level of M9241 have completed the combination treatment with the investigational medicinal products (IMPs) during the first 3 weeks (or at least 1 week after the second dose of avelumab, whichever is later), a safety review will be performed by the Safety Monitoring Committee (SMC) in order to make a decision on the next dose level. Successive cohorts of 3 to 6 subjects will be treated with escalating subcutaneous (SC) doses of M9241 every 4 weeks (q4w) with a fixed avelumab dose.

The observation period for dose-limiting toxicities (DLT) will be the first 3 weeks after IMPs for all dose cohorts and for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD. Subjects will be considered evaluable for dose-escalation decisions if they have completed the minimum safety evaluations (hematology, chemistry, and clinical assessments) after the combination administration during the DLT observation period and have received at least 1 SC injection of M9241 and 2 IV infusions of avelumab. Subjects who are not evaluable for DLT during this time for any reason other than a DLT will be replaced.

The SMC will review the safety data on a regular basis. The SMC will decide on relevant DLTs for protocol criteria and will decide by consensus on dose-escalation, dose de-escalation, or suspension of enrollment and/or declaration of the MTD.

The decision to escalate to the next dose level will be guided by the following rules:

- If none of the 3 evaluable subjects in a cohort experiences a DLT during the first 3 weeks then the dose can be escalated to the next dose level.
- If 1 of 3 evaluable subjects in a cohort experiences a DLT during the first 3 weeks then up to 3 additional subjects will be included at this dose level. If none of the additional

evaluable subjects experiences a DLT (1 of up to 6 evaluable subjects in the cohort total has DLT) then dose-escalation can resume.

- If 2 of 3 to 6 evaluable subjects in a dose cohort experience a DLT then the dose-escalation will be stopped and this dose will be defined as the maximum administered dose (MAD).
- The MTD is defined as the highest dose at which no more than 1 of 6 evaluable subjects' experiences a DLT. The decision on the MTD will be made by the SMC. No intra-subject dose-escalation will be permitted (dose reductions are permitted).

Each cohort up to MAD will be expanded to 6 evaluable subjects. Subject enrollment will be prioritized to fill the dose level undergoing safety assessment (per modified 3 + 3 design). During SMC closures between dose level decisions, an additional 3 subjects (total of 6) will be enrolled per cohort that has already been deemed safe by the SMC, beginning at the lowest dose level still needing to be filled. Subjects 4 through 6 of each cohort will continue to be evaluated for DLTs but will not drive dose-escalation decisions if 0 of the first 3 subjects did not experience any DLTs. In the event that DLTs occur in Subjects 4 through 6 after a higher dose level has been opened, the data will be reviewed by the Sponsor and the SMC to determine the best course of action for currently enrolling subjects at the highest dose level. Additional subjects may be enrolled in dose level 4 for PK / pharmacodynamics assessments.

In addition to the above M9241 escalation cohorts, an avelumab once weekly cohort will be opened. For this cohort, subjects will receive avelumab at 800 mg once weekly for the first 12 weeks in combination with M9241 at the M9241 MTD once every 4 weeks, then avelumab at 800 mg once every 2 weeks plus M9241 at the M9241 MTD once every 4 weeks until a criterion for treatment discontinuation has been met. The Sponsor may also open similar avelumab once weekly cohorts at a lower M9241 dose. The avelumab once weekly cohort will enroll up to 6 subjects using the same 3 + 3 rules as outlined.

Study visits for study treatment and assessments will take place on scheduled days according to the Schedule of Assessments. Assessments will include treatment-emergent adverse events (TEAE) and TRAE as well as concomitant medications, laboratory assessment, Eastern Cooperative Oncology Group performance status (ECOG PS), physical examination, and vital signs. Imaging by computerized tomography (CT) or magnetic resonance imaging (MRI) occurs every 8 weeks for tumor assessments for the first 6 months of treatment, then every 12 weeks thereafter.

Bioanalytical samples, including PK, immunogenicity, and biomarkers, will be drawn at predefined time points following administration of the IMPs.

**Part B: Expansion Cohorts**

After the RP2D for M9241 in combination with avelumab has been selected, enrollment in several expansion cohorts will be opened in selected tumor types to determine the safety and clinical activity of M9241 in combination with avelumab. The randomization between combination therapy and avelumab weekly induction monotherapy in Stage 2 of the urothelial carcinoma (UC) expansion cohort will allow an early assessment of the contribution of each individual investigational agent in the combination. In the European Union countries, the Sponsor commits to provide a dose justification summary prior to the enrollment of subjects in expansion cohorts. The dose justification will be based on the available safety, PK, and

pharmacodynamic data obtained from subjects at all available dose levels upon MTD determination. The indications for expansion were chosen since they offer the potential for transformative treatment with ability to establish an initial proof of concept of antitumor activity of M9241 in combination with avelumab with good feasibility.

Study visits will take place on scheduled days according to the Schedule of Assessments. Assessments will include TEAEs and TRAEs as well as concomitant medications, laboratory assessments, ECOG PS, physical examination, and vital signs. Imaging by CT or MRI occurs every 8 weeks for tumor assessments for the first 6 months of treatment then every 12 weeks thereafter. Bioanalytical samples, including PK, immunogenicity, and biomarkers, will be drawn at predefined time points following administration of the IMPs.

Avelumab and M9241 combination will be administered according to the RP2D. M9241 should be administered immediately prior to avelumab infusion. Based on review of available safety, PK, and pharmacodynamics data, the dose for the expansion cohorts will be avelumab 800 mg once weekly for the first 12 weeks in combination with M9241 at 16.8 µg/kg once every 4 weeks, then continuation with the combination of avelumab at 800 mg once every 2 weeks and M9241 at 16.8 µg/kg once every 4 weeks.

Subjects receiving avelumab weekly induction monotherapy will receive avelumab 800 mg once weekly for the first 12 weeks, then avelumab at 800 mg once every 2 weeks until any criterion for treatment discontinuation is met.

**Planned number of subjects:**

Part A: Dose Escalation

Approximately 45 subjects.

Part B: Expansion Cohorts

Approximately 170 subjects will be enrolled across 4 expansion cohorts.

**Primary endpoints:**

**Part A: Dose Escalation**

- Occurrence, severity, and duration of TEAEs and TRAEs, graded according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (v4.03)
- Occurrence of DLTs during the first 3 weeks of treatment.

**Part B: Expansion Cohorts**

- Confirmed best overall response (BOR) by Investigator assessment according to RECIST v1.1 by selected tumor type
- Occurrence, severity, and duration of TEAEs and TRAEs, graded according to the NCI CTCAE v4.03.

**Secondary endpoints:**

**Part A: Dose Escalation**

- PK profiles of avelumab and M9241
- Immunogenicity of avelumab and immunogenicity of M9241 in combination therapy, as measured by antidrug antibody (ADA) assays
- Confirmed BOR according to RECIST v1.1
- Immune-related BOR (irBOR) using the immune-related RECIST (irRECIST), derived from RECIST v1.1.

**Part B: Expansion Cohorts**

- Progression-free survival (PFS) time
- Overall survival (OS) time
- Duration of response (DOR)
- PK profiles of avelumab and M9241
- Immunogenicity of avelumab and immunogenicity of M9241 in combination therapy, as measured by ADA assays.

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**Pharmacokinetics:**

The following PK parameters will be measured for M9241 and avelumab during the dose-escalation part of the study:

- $AUC_{0-t}$ - area under the concentration-time curve (AUC) from time zero to the time of the last observation
- $AUC_{0-\infty}$ -AUC from time zero extrapolated to infinity
- $AUC_{tau}$ -AUC from the time zero to the length of a dosing interval tau

- $\lambda_z$ -terminal elimination rate constant
- $C_{max}$ - maximum serum concentration observed post-dose
- $C_{min}$ - minimum serum concentration observed post-dose
- $t_{max}$ -time to reach maximum concentration
- $t_{1/2}$ - apparent terminal half-life, calculated by ln2/$\lambda$z.

The following PK parameters will be measured for M9241 (for combination therapy only) and avelumab during the expansion part of the study:

- $C_{max}$ - maximum serum concentration observed post-dose (for M9241)
- $C_{eoi}$ – concentration at end of infusion (for avelumab)
- $C_{trough}$ – trough serum concentration (for both avelumab and M9241).

**Immunogenicity:**

Samples for avelumab ADA will be measured in all subjects that receive combination therapy or avelumab weekly induction monotherapy. Subjects will be characterized by immunogenicity status for each molecule. Drug concentration in serum for ADA ever-positive subjects versus ADA never-positive subjects will be descriptively summarized to evaluate the potential effect of ADA on PK.

**Other assessments:**

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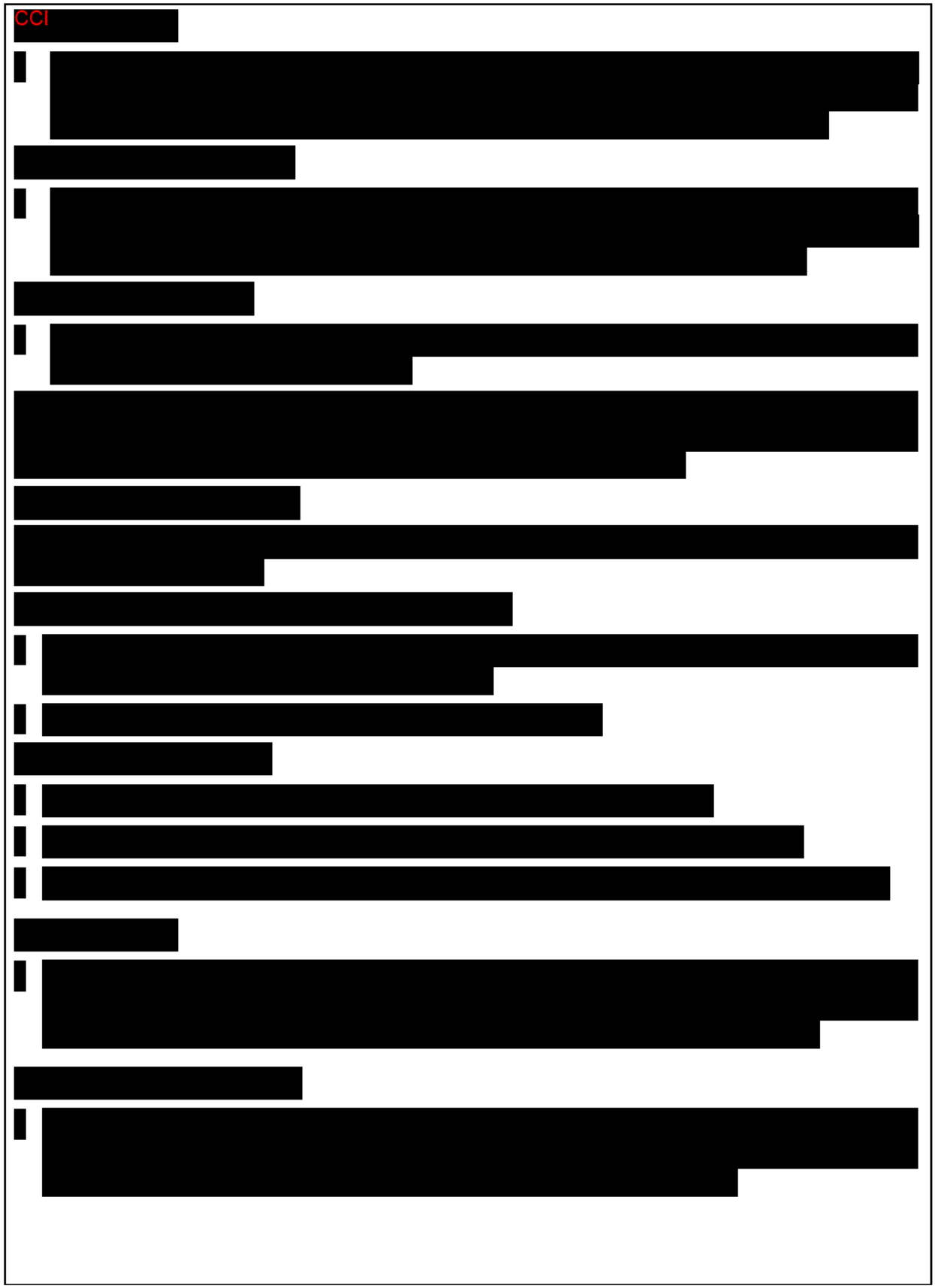
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**Diagnosis and key inclusion and exclusion criteria:**

**Inclusion Criteria (all cohorts except as noted for individual expansion cohorts)**

1. Signed written informed consent
2. Male or female subjects of age ≥ 18 years
3. Except as outlined below for the expansion cohorts, subjects must have histologically or cytologically proven metastatic or locally advanced solid tumors for which no standard therapy exists, standard therapy has failed, subject is intolerant of established therapy known to provide clinical benefit for their condition, or standard therapy is not acceptable to the subject.
4. Subjects who have been treated previously with a checkpoint inhibitor may enroll (except as outlined below for expansion cohorts).
5. At least 1 unidimensional radiographically measurable lesion based on RECIST v1.1, except for subjects with metastatic castration-resistant prostate cancer or metastatic breast cancer who may be enrolled with objective evidence of disease without a measurable lesion.
6. ECOG PS of 0 to 1 at Screening
7. Estimated life expectancy of more than 12 weeks
8. Adequate hematological function as defined below:
   a. White blood cells (WBC) count ≥ $3.0 \times 10^9$/L
   b. Absolute neutrophil count ≥ $1.5 \times 10^9$/L
   c. Lymphocyte count ≥ $0.5 \times 10^9$/L
   d. Platelet count ≥ $100 \times 10^9$/L
   e. Hemoglobin ≥ 9 g/dL (may have been transfused)
9. Adequate hepatic function as defined below:
   a. A total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range

b. Aspartate aminotransferase (AST) levels $\leq 2.5 \times$ ULN ($\leq 3 \times$ ULN for expansion cohorts)

c. Alanine aminotransferase (ALT) levels $\leq 2.5 \times$ ULN ($\leq 3 \times$ ULN for expansion cohorts)

d. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 but less than $3 \times$ ULN.

10. Adequate renal function as defined by an estimated creatinine clearance $\geq 50$ mL/min according to the Cockcroft-Gault formula

11. Negative blood pregnancy test at Screening for women of childbearing potential. For the purposes of this study, women of childbearing potential are defined as all female subjects after puberty unless they are postmenopausal for at least 1 year, are surgically sterile, or are sexually inactive.

12. Highly effective contraception (ie, methods with a failure rate of less than 1% per year) must be used before the start of treatment, for the duration of the study treatment, and for at least 50 days after stopping study treatment for both men and women if the risk of conception exists. The effects of avelumab and M9241 on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, as defined in the study protocol.

**Key Inclusion Criteria for Expansion Cohorts Include:**

- Availability of a fresh tumor biopsy is mandatory for eligibility in the RCC cohort. The biopsy or surgical specimen should be collected within 28 days prior to the first IMP administration. For UC expansion cohort at Stage 1, collection of tumor tissue is not mandatory for eligibility but is strongly recommended. For CRC and NSCLC expansion cohorts, and the UC expansion cohort at Stage 2, availability of either tumor archival material (< 6 months old) or fresh biopsies (obtained within 28 days) is acceptable with one of these being mandatory. For formalin-fixed paraffin-embedded samples, either block or sections (> 15) may be provided. Tumor biopsies and tumor archival material must be suitable for biomarker assessment. On fresh biopsy, if subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor.

- Locally advanced or metastatic UC that has progressed during or after at least one previous platinum-based chemotherapy and not previously treated with anti-PD-1/PD-L1 agents (PD-x naïve): Histologically or cytologically confirmed locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra). Subjects must have progressed during or after treatment with at least 1 platinum-containing regimen for inoperable locally advanced or metastatic UC or disease recurrence. Subjects who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing regimen will be considered as second line. Subjects with mixed histologies are required to have a dominant transitional cell pattern

- Non-small cell lung cancer (NSCLC), first-line metastatic: Stage IV (per seventh International Association for the Study of Lung Cancer classification) histologically confirmed NSCLC. Subjects must not have received treatment for their metastatic disease. Subjects could have received adjuvant chemotherapy or loco-regional treatment that included chemotherapy for locally advanced disease, as long as disease recurrence occurred at least 6 months after the completion of the last administration of chemotherapy. Only epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type are allowed (ie, EGFR mutation and ALK translocation / re-arrangement excluded). Nonsquamous cell histologies and never / former light smoker (< 15 pack years) squamous cell carcinoma subjects (per local standard of care) require testing if status is unknown. Subjects must have low tumor PD-L1 expression defined as < 50% tumor proportion score determined using PD-L1 IHC 22C3 pharmDx test or an equivalent Food and Drug Administration (FDA)-approved PD-L1 test. This cohort will not be opened for enrollment in Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom
- Colorectal cancer (CRC): Histologically or cytologically confirmed recurrent or refractory metastatic CRC (according to American Joint Committee on Cancer / International Union Against Cancer Tumor Node Metastasis [TNM] Staging System seventh edition) after failure of prior therapy containing oxaliplatin / fluoropyrimidine and / or irinotecan / fluoropyrimidine and, if eligible, cetuximab (Erbitux®) and bevacizumab (Avastin®). Only subjects with microsatellite instability (MSI)-low or microsatellite stable (MSS) metastatic CRC are eligible. Subjects without existing MSI test results will have MSI status performed locally by a Clinical Laboratory Improvement Amendments (CLIA)-certified IHC or polymerase chain reaction (PCR)-based test (PCR-based MSI test is preferred). Subjects must be willing to undergo an on-treatment biopsy procedure. For Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom, subjects in the second-line setting should have exhausted or be considered ineligible or intolerant (in the opinion of the Investigator) of available second-line chemotherapy options
- Renal cell carcinoma (RCC), primary immune checkpoint inhibitor failure: Histologically or cytologically documented metastatic RCC with a component of clear cell subtype. Subjects must have had progressive disease (PD) within 6 months or best overall response of stable disease (SD) for ≥ 6 months following start of therapy with any antibody / drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anticytotoxic T lymphocyte antigen-4 (CTLA-4) for advanced or metastatic disease (either as monotherapy or combination therapy, in any line). Fresh tumor biopsy is required for enrollment. If a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor. Subjects must be willing to undergo an on-treatment biopsy procedure. In France, in addition to having received checkpoint inhibitor therapy, subjects should have already received recommended local-standard therapy per the discretion of the Investigator

**Exclusion Criteria**

1. Concurrent treatment with a non-permitted drug/intervention (listed below)

a. Anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug within 4 weeks or 5 half-lives, whichever is shorter, prior to start of study treatment, or not recovered from adverse events (AE) related to such therapies, with the following exceptions:

   i. Palliative radiotherapy delivered in a normal organ-sparing technique is permitted (concurrently or within pretreatment period).

   ii. Erythropoietin, darbepoetin-α, and granulocyte colony-stimulating factor are permitted.

   iii. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.

b. Major surgery (as deemed by Investigator) for any reason (except diagnostic biopsy) within 4 weeks prior to start of study treatment, or not fully recovered from surgery within 4 weeks prior to start of study treatment

c. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before start of study treatment, with the following exceptions:

   i. Subjects with adrenal insufficiency, may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily.

   ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) is permitted.

   iii. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to ≤ 10 mg prednisone daily.

2. Any prior treatment with any form of IL-12
3. For the NSCLC, CRC, and UC expansion cohorts, prior therapy with any antibody / drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anticytotoxic T lymphocyte antigen-4 (CTLA-4) antibody is prohibited
4. Intolerance to checkpoint inhibitor therapy, as defined by the occurrence of an AE requiring drug discontinuation.
5. Active or history of primary or metastatic central nervous system tumors
6. Prior organ transplantation, including allogeneic stem-cell transplantation
7. Previous malignant disease (other than the indication for this study) within the last 5 years (except adequately treated nonmelanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the subject was deemed to have been cured with no additional therapy required or anticipated to be required.
8. Significant acute or chronic infections requiring systemic therapy including, among others:

a. History of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome

b. Hepatitis B or C infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive hepatitis C virus [HCV] antibody with reflex to positive HCV RNA). Subjects with history of infection must have PCR documentation that infection is cleared

c. Active tuberculosis (history of exposure or history of positive tuberculosis test with presence of clinical symptoms, physical, or radiographic findings)

9. Active or history of autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible if they are stable on other medical treatment and do not fulfill exclusion criterion 15
10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade $\geq 3$ NCI-CTCAE v4.03), or uncontrolled asthma (ie, 3 or more features of partially controlled asthma)
11. History of allergic reaction to methotrexate (trace methotrexate may be present in M9241 as a part of the manufacturing process) or history of severe hypersensitivity reaction to any other ingredient of the study drug(s) and / or their excipients. Since M9241 contains sucrose as an excipient, subjects suffering from hereditary fructose intolerance are also excluded
12. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v4.03 with the following exceptions:
    a. Neuropathy Grade $\leq 2$ is acceptable.
    b. All grades of alopecia are acceptable.
    c. Endocrine dysfunction on replacement therapy is acceptable.
13. Pregnancy or lactation
14. Known alcohol or drug abuse as deemed by the Investigator
15. Uncontrolled intercurrent illness including, but not limited to:
    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
    b. Uncontrolled active infection
    c. Uncontrolled diabetes (eg, glycosylated hemoglobin $\geq 8\%$)
16. Clinically significant (or 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 $\geq$ II), or serious cardiac arrhythmia requiring medication
17. All other significant diseases (eg, inflammatory bowel disease, current severe acute or chronic colitis) or chronic medical conditions (including laboratory abnormalities) that in

the opinion of the Investigator might impair the subject's tolerance of study treatment or interpretation of study results.

18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements
19. Legal incapacity or limited legal capacity
20. Administration of a live vaccine within 30 days prior to study entry
21. Any subject with possible area of ongoing necrosis (non-disease related), such as active ulcer, non-healing wound, or intercurrent bone fracture that may be at risk of delayed healing due to protocol therapy
22. Oxygen saturation < 90% at rest, known pulmonary fibrosis, or active interstitial lung disease
23. History of congenital or active immunodeficiency, with the exception of acquired treatment-related hypogammaglobulinemia requiring periodic IV immunoglobulin infusion.

**Investigational Medicinal Product: dose/mode of administration/ dosing schedule:**

Avelumab: With the exception of the avelumab once weekly cohort, subjects in the dose-escalation part of the study will receive avelumab 10 mg/kg IV infusion at time 0 over approximately 1 hour every 2 weeks on Day 1 and Day 15 of each cycle. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

Subjects in the avelumab once weekly cohort will receive avelumab at 800 mg IV infusion at time 0 over approximately 1 hour once weekly for the first 12 weeks, then 800 mg once every 2 weeks thereafter.

Subjects in the expansion cohorts will receive avelumab weekly induction monotherapy: avelumab 800 mg once weekly for the first 12 weeks then avelumab at 800 mg once every 2 weeks thereafter.

In order to mitigate infusion-related reactions, subjects will receive pretreatment with histamine H1 receptor (H1) blockers and acetaminophen prior to avelumab infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is recommended prior to the first 4 infusions of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate. Premedication may be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions.

M9241 – Dose Escalation: Subjects will receive M9241 in escalating doses of 2, 4, 8, 12, 16.8 µg/kg at a starting dose level of 4 µg/kg by SC injection at time (up to -20 minutes) relative to the start of avelumab infusion (time 0), q4w on Day 1 of each cycle. The dose of M9241 will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of M9241 used for the previous administration can be repeated if the

change in the subject's weight is 10% or less than the weight used for the last dose calculation. No intra-subject dose-escalation will be permitted. Dose reductions are permitted.

M9241 – Expansion Cohorts: Subjects will receive M9241 at 16.8 µg/kg by SC injection at time (up to -20 minutes) relative to the start of avelumab infusion (time 0), q4w on Day 1 of each cycle. The dose of M9241 will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of M9241 used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

**Reference therapy: dose/mode of administration/dosing schedule:**

Not applicable.

**Planned study and treatment duration per subject:**

Screening Period: -28 to -1 days

Treatment Period: A single treatment cycle is 28 days long. Avelumab administration will be according to cohort (dose-escalation / avelumab once weekly cohort or expansion cohort); M9241 will be administered only on Day 1 of each cycle, immediately prior to avelumab infusion. Subjects in this study will receive combination therapy with avelumab and M9241 or avelumab weekly induction monotherapy until 1 of the criteria for withdrawal from study treatment as described in the protocol is met.

Subjects from either the dose-escalation or the expansion portions of the study who have experienced a complete response (CR), partial response (PR), or who have stable disease (SD) may be treated for up to 24 months for subjects with CR (although additional treatment is possible) and continuously for PR or SD. If the Investigator believes that a subject with a CR may benefit from treatment beyond 24 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in this protocol. If there is further evidence of PD thereafter, study treatment should be discontinued; however, continued treatment is possible in consultation with the Medical Monitor and the Sponsor Medical Responsible. For subjects who achieve a CR or PR and then subsequently develop disease progression after stopping therapy, but prior to the end of the study, 1 re-initiation course of treatment at the same dose and schedule and treatment duration of up to 24 months is allowed at the discretion of the Investigator and agreement of the study Medical Monitor and Medical Responsible. The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation.

Follow-Up Period: Subjects without PD and who are not receiving subsequent anticancer therapy after the End-of-Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, and for survival for the first year, and then every 6 months thereafter until PD according to RECIST v1.1. The survival follow-up will continue until up to 1 year after the last subject receives the last dose of IP, or the last subject dies, whichever comes first.

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CCI [redacted]

## 1.1 Schedules of Assessments

**Table 1 Clinical Schedule of Assessments – Part A: M9241 Dose Escalation**

| | Screening Days -28 to -1 | Treatment Phase[a] (-3 / +1 days) | | | | | | | | End of Treatment | Safety Follow-Up | | Long-Term Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | Cycle 3 | | | | |
| | | D1 | D2 | D3 | D15 | D1 | D3 | D15 | D1 | Cycle 3 D1 Until Progression | Within 7 Days of decision to discontinue[b] | 30 Days[c] (±5 days) | 90 Days[c] (±1 week) | Every 3 Months[c] (±1 week) |
| Informed consent, Screening[d] | X | | | | | | | | | | | | | |
| Medical history[d] | X | | | | | | | | | | | | | |
| Physical examination[e] | X | X | X | X | X | X | | X | X | Q2 weeks | X | X | | |
| ECOG PS | X | X | | | X | X | | X | X | Q2 weeks | X | X | | |
| Vital signs, height, weight[f] | X | X | X | X | X | X | | X | X | Q2 weeks | X | X | | |
| 12-lead ECG[g] | X | X[g] | | X[g] | | X[g] | X[g] | | X | Q8-12 weeks (with each tumor evaluation)[g] | X | X | | |
| Tumor evaluation[h] | X | | | | | | | | X | Q8-12 weeks[i] | | | | X[i] |
| Documentation of concomitant medications and procedures[j] | X | X | | | X | X | | X | X | Q2 weeks | X | X | | |
| Documentation of AE[k] | X | X | X | X | X[l] | X | X | X | X | Q2 weeks | X | X | X | |
| M9241 administration | | X | | | | X | | | X | Q4 weeks | | | | |
| Avelumab administration | | X | | | X | X | | X | X | Q2 weeks | | | | |
| Overall survival[m] | | | | | | | | | | | | | | X |
| **Laboratory Studies[n]** | | | | | | | | | | | | | | |
| HBV, HCV[o] | X | | | | | | | | | | | | | |
| Hematology/ hemostaseology[p] | X | X | | | X | X | | X | X | Q2 weeks | X | X | | |
| Full serum chemistry[q] | X | X | | | | X | | | X | Q4 weeks | X | X | | |
| Core serum chemistry[q] | | | | | X | | | X | | Q4 weeks | | | | |
| Urinalysis[r] | X | X | | | X | X | | X | X | Q2 weeks | X | X | | |
| β-HCG pregnancy test (if applicable)[s] | X | | | | | X | | | X | Q4 weeks | | | | |
| Free T4, TSH | X | | | | | | | | X | Q8 weeks | X | X | | |

| | Screening Days -28 to -1 | Treatment Phase[a] (-3 / +1 days) | | | | | | | | End of Treatment | Safety Follow-Up | | Long-Term Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | Cycle 3 | Cycle 3 D1 Until Progression | Within 7 Days of decision to discontinue[b] | 30 Days[c] (±5 days) | 90 Days[c] (±1 week) | Every 3 Months[c] (±1 week) |
| | | D1 | D2 | D3 | D15 | D1 | D3 | D15 | D1 | | | | | |
| Correlative research studies | See Table 2 | | | | | | | | | | | | | |

β-HCG = β-human chorionic gonadotropin; AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; D = day; diff = differential count; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End-of-Treatment; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; IMP = investigational medicinal product; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; plt = platelets; Q2weeks = every 2 weeks; Q4weeks = every 4 weeks; Q8-12weeks = every 8 to 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone; T4 = thyroxine; UC = urothelial carcinoma.

a. A time window of up to 3 days before or 1 day after the scheduled visit (-3 / +1 days) will be permitted for all treatment phase procedures, except as otherwise noted. The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous schedule was off.

b. All subjects discontinuing protocol therapy for any reason must undergo an End-of-Treatment Visit within 7 days after decision to discontinue study treatment, but (if possible) before any new anti-neoplastic therapy is started.

c. The 30-Day (±5 days) and 90-Day (±1 week) Safety Follow-up assessments should be conducted, if possible, prior to the start of any new anti-neoplastic therapy. The 3-Month Long-Term Follow-Up visits start after completion of the 90-Day Safety Follow-Up Visit.

d. Screening history should include review of inclusion/exclusion criteria, medical history, cancer history, prior anticancer therapy (surgery, medications, radiation, etc), other prior medications, and demographic data.

e. Screening, Day 1 of each cycle, End-of-Treatment Visits, and Safety Visit should include a full physical examination. C1D2 Visit should include limited physical examination focusing on signs/symptoms of cytokine release. All other visits should have a focused physical examination with attention paid to immune-related AEs. Eye signs and symptoms should be checked at each visit. If there are clinically relevant findings then an appropriate ophthalmology examination should be obtained within 2 days.

f. Height to be measured at Screening only. During C1D2 and C1D3 Visit only vital signs to be measured. Weight measured at each visit for dose calculation (see Section 6.2.1 for details). Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. See Section 7.4.4.1 for additional details on vital signs collection.

g. ECG on Cycle 1, Day 1 does not need to be repeated if screening ECG was within 14 days. ECG assessment should be performed prior to dosing (on dosing days) and prior to blood sample collection, such that the blood sample is collected at the planned time. ECGs on C1D3 and C2D3 and at each tumor restaging are not required for subjects in M9241 dose level 4 and should be performed according to Investigator discretion.

h. Tumor evaluations during Screening must be performed within 28 days prior to Cycle 1, Day 1 in order to document the baseline status of the tumor disease using RECIST v1.1 target and non-target lesions. Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. In subjects with UC, this scan is only necessary if clinically indicated. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.

i. Radiographic tumor evaluations have a time window of up to 5 days prior to Day 1 drug dosing and should be done at the end of Cycles 2, 4, and 6. Timing of imaging is independent from treatment delays. Subjects without progressive disease and who are not receiving subsequent anticancer therapy after the

End-of-Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, until progressive disease according to RECIST v1.1.

j. Concomitant medications and procedures will be documented at each study visit until the 30-day Safety Follow-Up visit.

k. All AEs will be documented until the 30-day Safety Follow-Up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

l. For C1D15 Visit, If AEs are present on Day 15 evaluation, consider optional Day 22 physical examination, laboratory studies, and AE assessment for confirmation, by the end of the 21 day DLT observation period.

m. Long-term follow-up for survival will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

n. Screening laboratory samples can be used if drawn within one week prior to Day 1, Cycle 1.

o. Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM; hepatitis C screening: HCVAb with reflex to HCV RNA.

p. See Table 14 for list. Hematology results must be available and reviewed prior to dose administration by the local Investigator.

q. See Table 14 for list of core and full (includes core) serum chemistry analytes. Serum chemistry results must be available and reviewed prior to dose administration by the local Investigator.

r. If urinalysis is positive for protein, sediment (microscopy) will be evaluated. Urinalysis results must be available and reviewed prior to dose administration by the local Investigator. Urinalysis does not have to be performed for subjects with UC.

s. β-HCG must be determined from serum at Screening and then in urine thereafter. Results of the most recent pregnancy test (done within 28 days) should be reviewed prior to the next dosing of IMP. FSH may be performed at Screening to confirm post-menopausal status. Women who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

**Table 2 Bioanalytical and Biomarkers Schedule of Assessments – Part A: M9241 Dose Escalation**

| Measure | Screening/ Baseline Assessments | Treatment Phase Cycle 1 | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days -28 to 0 | D1 | | | | D2 | D3 | D8 | D11 | D15 | | | | D16 | D17 | D22 | D25 |
| | | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6h | ±6h | ±1d | ±1d | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6h | ± 6h | ± 1d | ± 1d |
| Avelumab PK | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[b] | X[b] | X[b] |
| M9241 PK | | X | X | X | X | X | X | X | X | X | | | | | | | |
| ADA | X | | | | | | | | | X | | | | | | | |
| Soluble factors | | X | | | X | X | X | X | | X | | | | X | | X[b] | X[b] |
| Tumor tissue[c] | X | | | | | | | | | | | | | | | | |
| PGt (optional) | X | | | | | | | | | | | | | | | | |
| Gene expression | | X | | | | X | | | | X | | | | X | | | |
| Target Occupancy[d] | | X | | | | X | X | X | | X | | | | X | | X[b] | X[b] |
| Immunophenotyping and other immune end points[e] | X | | | | | | | | | X | | | | | | | |

ADA = antidrug antibody; d/D = day; EOI (1h) = end of 1-hour infusion (as close to completion of infusion as possible); h = hours; m = minute; PGt = pharmacogenetics; PK = pharmacokinetic.

a. Predose is prior to avelumab and when applicable M9241 administration. Sample should be collected as close to the start of infusion as possible and within 2 hours prior to administration.

b. Samples are optional.

c. Tumor biopsy or archival tissue (optional, see Section 7.6.1).

d. If sampling is missed at baseline for a subject, no further target occupancy timepoints for that subject need to be collected during the study.

e. In the event of an immune-related adverse event requiring steroids, an additional immunophenotyping sample may be collected prior to the start of steroids. Collection of this additional sample is preferred, but not required.

| Measure | Treatment Phase – Cycle 2 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | D1 | | | | D2 | D3 | D8 | D15 | | D16 |
| | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6h | ±6h | ±1d | Predose[a] | EOI (1h) + 30m | 24h ± 6h |
| Avelumab PK | X | X | X | X | X | X | X | X | X | X |
| M9241 PK | X | X | X | X | X | X | X | X | | |
| ADA | X | | | | | | | | | |
| Soluble factors | X | | | X | X | X | X | X | | X |
| Gene expression | X | | | | X | | | X | | |
| Target Occupancy[b] | X | | | | X | | X | X | | |
| Immuophenotyping and other immune end points[c] | X | | | | | | | | | |

| Measure | Treatment Phase – Cycle 3 and Beyond | | | | | | | Off Therapy | |
|---|---|---|---|---|---|---|---|---|---|
| | Cycle 3 D1 | | | Cycle 4 D1 | | | C7 and Beyond | EOT | Safety |
| | D1 | | D3 | D1 | | D3 | D1 | Within 7 Days of decision to discontinue | 30 days (±5 days) |
| | Predose[a] | EOI (1h) + 30m | (±6h) | Predose[a] | EOI (1h) + 30m | (±6h) | | | |
| Avelumab PK | X | X | X[d] | X | X | X[d] | Predose[a] only every 3 cycles after C4 (starting C7) | X | X |
| M9241 PK | X | X | X[d] | X | X | X[d] | Predose[a] only every 3 cycles after C4 (starting C7) | X | X |
| ADA | X | | | X | | | Predose[a] only every 3 cycles after C4 (starting C7) | | X |
| Soluble factors | X | | X[d] | X | | X[d] | | | |
| Gene expression | X | | | | | | | | |
| Immunophenotyping and other immune end points[c] | | | | X | | | Every 3 cycles (Starting C7) | X | |

ADA = antidrug antibody; C = cycle; d/D=day; EOI (1h) = End of 1-hour infusion (as close to completion of infusion as possible); EOT = end of treatment; h = hour; PK = pharmacokinetics.

a. Predose is prior to avelumab and when applicable M9241 administration. Sample should be collected as close to the start of infusion as possible and within 2 hours prior to administration.

b. If sampling is missed at baseline for a subject, no further target occupancy timepoints for that subject need to be collected during the study.

c. In the event of an immune-related adverse event requiring steroids, an additional immunophenotyping sample may be collected prior to the start of steroids. Collection of this additional sample is preferred, but not required.
d. Samples are optional.

**Table 3 Clinical Schedule of Assessments – Part A: Dose Escalation – Avelumab Once Weekly Cohort**

| | Screening | Treatment Phase[a] (± 1 day) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | Cycle 2 | | | | Cycle 3 | | | | Cycle 4 D1 Until Progression and Off-Treatment Visits – Rollover into Once Every 2 Week Avelumab Dosing Schedule of Assessments (Table 1) |
| | D -28 to -1 | D1 | D2 | D3 | D8 | D15 | D22 | D1 | D8 | D15 | D22 | D1 | D8 | D15 | D22 | |
| Informed consent, Screening[b] | X | | | | | | | | | | | | | | | |
| Medical history[b] | X | | | | | | | | | | | | | | | |
| Physical examination[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECOG PS | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Height, weight[d] | X | X | | | | X | | X | | X | | X | | X | | X |
| Vital signs[e] | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[f] | X | X | | | | | | | | | | | | | | |
| Tumor evaluation | X[g] | | | | | | | | | | | X[h] | | | | X[h] |
| Documentation of concomitant medications and procedures[i] | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Documentation of AE[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| M9241 administration | | X | | | | | | X | | | | X | | | | Once every 4 weeks (Day 1 of each cycle) |
| Avelumab administration | | X | | | X | X | X | X | X | X | X | X | X | X | X | Once every 2 weeks (Days 1 and 15 of each cycle) |
| Overall survival[k] | | | | | | | | | | | | | | | | X[k] |
| **Laboratory Studies**[l] | | | | | | | | | | | | | | | | |
| HBV, HCV[m] | X | | | | | | | | | | | | | | | |
| Hematology/ hemostaseology[n] | X | X | | | | X | | X | | X | | X | | X | | X |

| | Screening | Treatment Phase[a] (± 1 day) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | Cycle 2 | | | | Cycle 3 | | | | Cycle 4 D1 Until Progression and Off-Treatment Visits – Rollover into Once Every 2 Week Avelumab Dosing Schedule of Assessments (Table 1) |
| | D -28 to -1 | D1 | D2 | D3 | D8 | D15 | D22 | D1 | D8 | D15 | D22 | D1 | D8 | D15 | D22 | |
| Full serum chemistry[o] | X | X | | | | | | X | | | | X | | | | X (full and core alternating every 2 weeks) |
| Core serum chemistry[o] | | | | | | X | | | | X | | | | X | | |
| Urinalysis[p] | X | X | | | | X | | X | | X | | X | | X | | X (every 2 weeks) |
| β-HCG pregnancy test (if applicable)[q] | X | | | | | | | X | | | | X | | | | X (every 4 weeks) |
| Free T4, TSH | X | | | | | | | | | | | X | | | | X (Q8 weeks) |
| Correlative research studies | See Table 4 | | | | | | | | | | | | | | | |

β-HCG = β-human chorionic gonadotropin; AE = adverse events; C = cycle; CT = computed tomography; D = day; diff = differential count; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End-of-Treatment; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; Q2weeks = every 2 weeks; Q4weeks = every 4 weeks; Q8-12weeks = every 8 to 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone; T4 = thyroxine; UC = urothelial carcinoma.

a. A time window of up to 1 day before or 1 day after the scheduled visit (-1 / +1 days) will be permitted for all treatment phase procedures, except as otherwise noted. The weekly schedule should be strictly adhered to, returning to the target date even if the previous schedule was off.

b. Screening history should include review of inclusion/exclusion criteria, medical history, cancer history, prior anticancer therapy (surgery, medications, radiation, etc), other prior medications, and demographic data.

c. Screening, Day 1 of each cycle, End-of-Treatment Visits, and Safety Visit should include a full physical examination. C1D3 Visit should include limited physical examination focusing on signs/symptoms of cytokine release. All other visits should have a focused physical examination with attention paid to immune-related AEs. Eye signs and symptoms should be checked at each visit. If there are clinically relevant findings then an appropriate ophthalmology examination should be obtained within 2 days.

d. Height to be measured at Screening only.

e. Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. See Section 7.4.4.1 for additional details on vital signs collection.

f. ECG on Cycle 1, Day 1 does not need to be repeated if screening ECG was within 14 days. ECG assessment should be performed prior to dosing (on dosing days) and prior to blood sample collection, such that the blood sample is collected at the planned time.

g. Tumor evaluations during Screening must be performed within 28 days prior to Cycle 1, Day 1 in order to document the baseline status of the tumor disease using RECIST v1.1 target and non-target lesions. Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous

6 weeks. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.

h. Radiographic tumor evaluations have a time window of up to 5 days prior to Day 1 drug dosing and should be done at the end of Cycles 2, 4, and 6. Timing of imaging is independent from treatment delays. Subjects without progressive disease and who are not receiving subsequent anticancer therapy after the End-of-Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, until progressive disease according to RECIST v1.1.

i. Concomitant medications and procedures will be documented at each study visit until the 30-day Safety Follow-Up visit.

j. All AEs will be documented until the 30-day Safety Follow-Up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

k. Long-term follow-up for survival will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

l. Screening laboratory samples can be used if drawn within one week prior to Day 1, Cycle 1.

m. Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM; hepatitis C screening: HCVAb with reflex to HCV RNA.

n. See Table 14 for list. Hematology results must be available and reviewed prior to dose administration by the local Investigator.

o. See Table 14 for list of core and full (includes core) serum chemistry analytes. Serum chemistry results must be available and reviewed prior to dose administration by the local Investigator.

p. If urinalysis is positive for protein, sediment (microscopy) will be evaluated. Urinalysis results must be available and reviewed prior to dose administration by the local Investigator. Urinalysis does not have to be performed for subjects with UC.

q. β-HCG must be determined from serum at Screening and then in urine thereafter. Results of the most recent pregnancy test (done within 28 days) should be reviewed prior to the next dosing of IMP. FSH may be performed at Screening to confirm post-menopausal status. Women who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

**Table 4** **Bioanalytical and Biomarkers Schedule of Assessments – Part A: Dose Escalation – Avelumab Once weekly Cohort**

| Measure | Screening/ Baseline | Treatment Phase Cycle 1 | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D -28 to 0 | D1 | | | | D2 | D3 | D8 | | D15 | | D22 | | | | D23 | D24 |
| | | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6h | 48h ±6h | Predose[a] | EOI (1h) + 30m | Predose[a] | EOI (1h) + 30m | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6h | 48h ±6h |
| Avelumab PK | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| M9241 PK | | X | X | X | X | X | X | X | | X | | X | | | | X | X |
| ADA | | X | | | | | | | | X | | | | | | | |
| Soluble factors | | X | | | X | X | X | X | | X | | X | | | | | |
| Tumor tissue[b] | X | | | | | | | | | | | | | | | | |
| PGt | X | | | | | | | | | | | | | | | | |
| Gene expression | | X | | | | | | | | X | | | | | | | |
| Target Occupancy[c] | | X | | | | X | X | X | | X | | X | | | | | |
| Immunophenotyping and other immune end points[d] | X | | | | | | | | | X | | | | | | | |

ADA = antidrug antibody; d/D = day; EOI (1h) = end of 1-hour infusion (as close to completion of infusion as possible); h = hours; m = minutes; PGt = pharmacogenetics; PK = pharmacokinetic.

a. Predose is prior to avelumab and when applicable M9241 administration. Sample should be collected as close to the start of infusion as possible and within 2 hours prior to administration.

b. Tumor biopsy or archival tissue (optional).

c. If sampling is missed at baseline for a subject, no further target occupancy timepoints for that subject need to be collected during the study.

d. In the event of an immune-related adverse event requiring steroids, an additional immunophenotyping sample may be collected prior to the start of steroids. Collection of this additional sample is preferred, but not required.

| Measure | Treatment Phase – Cycle 2 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D1 | | | | D2 | D3 | D8 | | D15 | | D22 | |
| | Predose[a] | EOI (1h) + 30m | 4h ± 30m | 8h ± 1h | 24h ± 6 h | 48h ± 6 h | Predose[a] | EOI (1h) + 30m | Predose[a] | EOI (1h) + 30m | Predose[a] | EOI (1h) + 30m |
| Avelumab PK | X | X | X | X | X | X | X | x | X | X | X | X |
| M9241 PK | X | X | X | X | X | X | X | | X | | X | |
| ADA | X | | | | | | | | | | | |
| Soluble factors | X | | | X | X | X | X | | X | | X | |
| Gene expression | X | | | | | | | | X | | | |
| Target Occupancy[b] | X | | | | X | | X | | X | | X | |
| Immunophenotyping and other immune end points[c] | X | | | | | | | | | | | |

| Measure | Treatment Phase – Cycle 3 and Beyond | | | | | | | | | | | Off Therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 3 | | | Cycle 4 (Start of Avelumab Once Every 2 Week Dosing) | | | | | Cycle 5 | | Cycle 7 and Beyond | EOT | Safety |
| | D1 | | D2 | D1 | | D2 | D8 | D15 | | D1 | | D1 | | |
| | Predose[a] | EOI (1h) + 30m | (±6h) | Predose[a] | EOI (1h) + 30m | (±6h) | ±1d | Predose[a] | EOI (1h) + 30m | Predose[a] | EOI (1h) + 30m | Predose[a] | Within 7 Days | 30 days (±5 days) |
| Avelumab PK | X | X | X | X | X | X | X | X | X | X | X | Predose only, every 3 cycles starting C7 | X | X |
| M9241 PK | X | X | X | X | X | X | X | X | | X | X | Predose only, every 3 cycles starting C7 | X | X |
| ADA | X | | | X | | | | | | | | Predose every 3 cycles starting C7 | | X |
| Soluble factors | X | | X | X | | X | X | X | | | | | | |
| Gene expression | X | | | | | | | | | X | | | X | |
| Immunophenotyping and other immune end points[c] | | | | X | | | | | | X | | Predose only, every 3 cycles starting C7 | X | |

ADA = antidrug antibody; C = cycle; d/D=day; EOI (1h) = End of 1-hour infusion (as close to completion of infusion as possible); EOT = end of treatment; h = hour; PK = pharmacokinetics.

a. Predose is prior to avelumab and when applicable M9241 administration. Sample should be collected as close to the start of infusion as possible and within 2 hours prior to administration.
b. If sampling is missed at baseline for a subject, no further target occupancy timepoints for that subject need to be collected during the study.
c. In the event of an immune-related adverse event requiring steroids, an additional immunophenotyping sample may be collected prior to the start of steroids. Collection of this additional sample is preferred, but not required.

**Table 5 Clinical Schedule of Assessments – Part B: Expansion Cohorts – Screening Through Cycle 3**

| | Screening | Treatment Phase[a] (± 1 day) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | Cycle 2 | | | | | Cycle 3 | | | | | Cycle 4 D1 Until Progression and Off-Treatment Visits – Roll-over into Once Every 2 Week Avelumab Dosing (Table 6) |
| | D -28 to -1 | D1 | D2 | D8 | D15 | D22 | D1 | D2 | D8 | D15 | D22 | D1 | D4 | D8 | D15 | D22 | |
| Informed consent, Screening[b] | X | | | | | | | | | | | | | | | | |
| Medical history[b] | X | | | | | | | | | | | | | | | | |
| Physical examination[c], ECOG PS | X | X | X | X | X | X | X | | X | X | X | X | | X | X | X | X |
| Height, weight[d] | X | X | | | X | | X | | | X | | X | | | X | | X |
| Vital signs[e] | X | X | | X | X | X | X | | X | X | X | X | | X | X | X | X |
| 12-lead ECG | X | X[f] | X[f] | | | | X[f] | X[f] | | | | | | | | | |
| MSI testing (CRC cohort)[g] | X | | | | | | | | | | | | | | | | |
| Tumor tissue[h] | X[h] | | | | | | | | | | | | X[h] | | | | |
| Tumor evaluation[j] | X[i] | | | | | | | | | | | X[i] | | | | | see Table 6 |
| Documentation of concomitant medications and procedures[k] | X | X | | X | X | X | X | | X | X | X | X | | X | X | X | X |
| Documentation of AE[l] | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X |
| PRO evaluation[m] | X[n] | | | X | X | X | X | | X | X | X | X | | X | X | X | X |
| M9241 administration[o] | | X | | | | | X | | | | | X | | | | | Once every 4 weeks (Day 1 of each cycle) |
| Avelumab administration | | X | | X | X | X | X | | X | X | X | X | | X | X | X | Once every 2 weeks (Days 1 and 15 of each cycle |

| | Screening | Treatment Phase[a] (± 1 day) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | Cycle 2 | | | | | Cycle 3 | | | | | Cycle 4 D1 Until Progression and Off-Treatment Visits – Roll-over into Once Every 2 Week Avelumab Dosing (Table 6) |
| | D -28 to -1 | D1 | D2 | D8 | D15 | D22 | D1 | D2 | D8 | D15 | D22 | D1 | D4 | D8 | D15 | D22 | |
| Overall survival[p] | | | | | | | | | | | | | | | | | X |
| **Laboratory Studies[q]** | | | | | | | | | | | | | | | | | |
| HBV, HCV[r] | X | | | | | | | | | | | | | | | | |
| Hematology/ hemostaseology[s] | X | X | | | X | | X | | | X | | X | | | X | | X |
| Full serum chemistry[t] | X | X | | | | | X | | | | | X | | | | | X |
| Core serum chemistry[t] | | | | | X | | | | | X | | | | | X | | X |
| Urinalysis[u] | X | X | | | X | | X | | | X | | X | | | X | | X (every 2 weeks) |
| β-HCG pregnancy test (if applicable)[v] | X | | | | | | X | | | | | X | | | | | X (every 4 weeks) |
| Free T4, TSH | X | | | | | | | | | | | X | | | | | X (every 8 weeks) |
| Correlative research studies | See Table 7 | | | | | | | | | | | | | | | | |

β-HCG = β-human chorionic gonadotropin; AE = adverse events; C = cycle; CLIA = Clinical Laboratory Improvement Amendments; CRC = colorectal cancer; CT =computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC = European Organisation for Research and Treatment of Cancer; EOT = End-of-Treatment; FFPE = formalin-fixed paraffin-embedded; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; IMP = investigational medicinal product; MRI = magnetic resonance imaging; MSI = microsatellite instability; MSS = microsatellite stable; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; PCR = polymerase chain reaction; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcomes; Q2weeks = every 2 weeks; Q4weeks = every 4 weeks; Q8-12weeks = every 8 to 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core; QLQ-NMIBC24 = Non-Muscle Invasive Bladder Cancer Module; QLQ-CR29 = Colorectal Cancer Module; QLQ-RCC10 = Renal Cell Carcinoma Module; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone; T4 = thyroxine; UC = urothelial carcinoma.

a. A time window of up to 1 day before or 1 day after the scheduled visit (-1 / +1 days) will be permitted for all treatment phase procedures, except as otherwise noted. The weekly schedule should be strictly adhered to, returning to the target date even if the previous schedule was off.

b. Screening history should include review of inclusion/exclusion criteria, medical history, cancer history, prior anticancer therapy (surgery, medications, radiation, etc), other prior medications, and demographic data.

c. Screening, Day 1 of each cycle, End-of-Treatment Visits, and Safety Visit should include a full physical examination. C1D2 Visit should include limited physical examination focusing on signs/symptoms of cytokine release. All other visits should have a focused physical examination with attention paid to immune-related AEs. Eye signs and symptoms should be checked at each visit. If there are clinically relevant findings then an appropriate ophthalmology examination should be obtained within 2 days.

d. Height to be measured at Screening only.

e. Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. See Section 7.4.4.1 for additional details on vital signs collection.

f. On the indicated days in the M9241/avelumab combination cohorts, Day 1 of Cycle 1 and Cycle 2 predose (within 4 hours before avelumab infusion and before M9241 dose) and Day 2 of Cycle 1 and Cycle 2, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart with digital upload for centralized analysis (see Section 7.4.4.2 for additional details). Unless specified above, all other ECGs are single locally read ECGs. For the avelumab weekly induction monotherapy cohort, ECGs are NOT collected on Day 2, Cycle 1 and Cycle 2, and Day 1, Cycle 2, while on Day 1 Cycle 1 single ECG is collected at pre-dose (within 4 hours before avelumab infusion) for local reading.

g. Only subjects with MSI-low or MSS metastatic CRC are eligible. Subjects without existing MSI test results will have MSI status performed locally by a CLIA-certified IHC or PCR-based test (PCR-based MSI test is preferred).

h. Availability of fresh pretreatment tumor biopsy is mandatory for eligibility in the RCC cohort. The biopsy or surgical specimen should be collected within 28 days prior to the first IMP administration. For the UC expansion cohort at Stage 1, collection of tumor tissue is not mandatory for eligibility but is strongly recommended. For CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2, availability of either tumor archival material (< 6 months old) or fresh biopsies within 28 days is acceptable with one of these being mandatory. For FFPE samples, either block or sections (> 15) may be provided. Tumor biopsies and tumor archival material must be suitable for biomarker assessment. On-treatment biopsies are required for subjects in the RCC and CRC cohorts and optional for subjects in the NSCLC and UC cohorts. On fresh biopsy, if a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor. The on-treatment biopsy should occur on Cycle 3 Day 4 (± 1 day; refer to the Central Laboratory Manual/Flowchart for details). Further biopsy material that may be available from unscheduled (eg, standard of care biopsy) or Investigator-driven biopsies during the course of the study may also be collected.

i. Tumor evaluations during Screening must be performed within 28 days prior to Cycle 1, Day 1 in order to document the baseline status of the tumor disease using RECIST v1.1 target and non-target lesions. Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.

j. Radiographic tumor evaluations have a time window of up to 5 days prior to Day 1 drug dosing and should be done at the end of Cycles 2, 4, and 6. Timing of imaging is independent from treatment delays. Subjects without progressive disease and who are not receiving subsequent anticancer therapy after the End-of-Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, until progressive disease according to RECIST v1.1.

k. Concomitant medications and procedures will be documented at each study visit until the 50-day Safety Follow-Up visit.

l. All AEs will be documented until the 50-day Safety Follow-Up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

m. Assessments include PGIS and select items from the EORTC QLQ-C30 for all subjects and select items from the QLQ-NMIBC24 for subjects with UC, NSCLC-SAQ for subjects with NSCLC, QLQ-CR29 for subjects with CRC, and QLQ-RCC10 for subjects with RCC, respectively. Whenever possible the PRO assessment (physical functioning and disease related symptom from the EORTC item bank) should be completed by the subject prior to a health care intervention

of any nature, regardless of whether it is study related or not. A protocol deviation occurs only when study-related interventions occur PRIOR to PRO assessments, other than vital signs, demographics, and clinical history information.

n. Baseline assessments should be completed at Screening; if this does not occur, it can be done at Visit 1 (Day 1) prior to interventional assessments and dosing.

o. Not applicable for the avelumab weekly induction monotherapy cohort.

p. Long-term follow-up for survival will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

q. Screening laboratory samples can be used if drawn within one week prior to Day 1, Cycle 1.

r. Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM; hepatitis C screening: HCVAb with reflex to HCV RNA.

s. See Table 14 for list. Hematology results must be available and reviewed prior to dose administration by the local Investigator.

t. See Table 14 for list of core and full (includes core) serum chemistry analytes. Serum chemistry results must be available and reviewed prior to dose administration by the local Investigator.

u. If urinalysis is positive for protein, sediment (microscopy) will be evaluated. Urinalysis results must be available and reviewed prior to dose administration by the local Investigator. Urinalysis does not have to be performed for subjects with UC.

v. β-HCG must be determined from serum at Screening and then in urine thereafter. Results of the most recent pregnancy test (done within 28 days) should be reviewed prior to the next dosing of IMP. Following treatment discontinuation, monthly pregnancy testing should continue through the 50-Day Safety Follow-up visit. In case the 50-Day Safety Follow-up visit is combined with the End-of-Treatment visit, monthly pregnancy testing should continue until 50 days post last study treatment administration. FSH may be performed at Screening to confirm post-menopausal status. Women who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

**Table 6 Clinical Schedule of Assessments – Part B: Expansion Cohorts – Cycle 4 Through Long-term Follow-up**

| | Treatment Phase[a] (-3 / +1 days) | End of Treatment | Safety Follow-Up | | Long-Term Follow-Up |
|---|---|---|---|---|---|
| | Cycle 4 D1 Until Progression | Within 7 Days of decision to discontinue[b] | 50 Days[c] (±5 days) | 90 Days[c] (±1 week) | Every 3 Months[c] (±1 week) |
| Physical examination[d], ECOG PS | Q2 weeks | X | X | | |
| Vital signs, height, weight[e] | Q2 weeks | X | X | | |
| 12-lead ECG | | X | X | | |
| Tumor evaluation[f] | Q8-12 weeks[g] | | | | X[g] |
| Documentation of concomitant medications and procedures[h] | Q2 weeks | X | X | | |
| Documentation of AE[i] | Q2 weeks | X | X | X | |
| PRO evaluation[j] | Q2 weeks | X | X | | |
| M9241 administration[k] | Q4 weeks | | | | |
| Avelumab administration | Q2 weeks | | | | |
| Overall survival[l] | | | | | X |
| **Laboratory Studies** | | | | | |
| Hematology/ hemostaseology[m] | Q2 weeks | X | X | | |
| Full serum chemistry[n] | Q4 weeks | X | X | | |
| Core serum chemistry[n] | Q4 weeks | | | | |
| Urinalysis[o] | Q2 weeks | X | X | | |
| β-HCG pregnancy test (if applicable)[p] | Q4 weeks | Test monthly through D 50 Safety Follow-up | | | |
| Free T4, TSH | Q8 weeks | X | X | | |
| Correlative research studies | See Table 7 | | | | |

β-HCG = β-human chorionic gonadotropin; AE = adverse events; C = cycle; CLIA = Clinical Laboratory Improvement Amendments; CRC = colorectal cancer; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC = European Organisation for Research and Treatment of Cancer; EOT = End-of-Treatment; FFPE = formalin-fixed paraffin-embedded; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; IMP = investigational medicinal product; MRI = magnetic resonance imaging; MSI = microsatellite instability; MSS = microsatellite stable; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; PCR = polymerase chain reaction; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcomes; Q2weeks = every 2 weeks; Q4weeks = every 4 weeks; Q8-12weeks = every 8 to 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core; QLQ-NMIBC24 = Non-Muscle Invasive Bladder Cancer Module; QLQ-CR29 = Colorectal Cancer Module; QLQ-RCC10 = Renal Cell Carcinoma Module; RCC = renal

cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone; T4 = thyroxine; UC = urothelial carcinoma.

a. A time window of up to 3 days before or 1 day after the scheduled visit (-3 / +1 days) will be permitted for all treatment phase procedures, except as otherwise noted. The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous schedule was off.

b. All subjects discontinuing protocol therapy for any reason must undergo an EOT Visit within 7 days after decision to discontinue study treatment, but (if possible) before any new anti-neoplastic therapy is started.

c. The 50-Day (± 5 days) and 90-Day (± 1 week) Safety Follow-up assessments should be conducted, if possible, prior to the start of any new anti-neoplastic therapy. The 90-Day visit should be conducted as a 90-day Safety Follow-up Phone Call. The 3-Month (±1 week) Long-Term Follow-Up visits start after completion of the 90-Day Safety Follow-Up Visit.

d. Day 1 of each cycle, EOT Visits, and Safety Visit should include a full physical examination. All other visits should have a focused physical examination with attention paid to immune-related AEs. Eye signs and symptoms should be checked at each visit. If there are clinically relevant findings then an appropriate ophthalmology examination should be obtained within 2 days.

e. Weight measured at each visit for dose calculation (see Section 6.2.1 for details). Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. See Section 7.4.4.1 for additional details on vital signs collection.

f. Tumor evaluations during Screening must be performed within 28 days prior to Cycle 1, Day 1 in order to document the baseline status of the tumor disease using RECIST v1.1 target and non-target lesions. Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.

g. Radiographic tumor evaluations have a time window of up to 5 days prior to Day 1 drug dosing and should be performed every 8 weeks while on treatment for the first 6 months (ie, at the end of Cycles 2, 4, 6) and then every 12 weeks thereafter while on treatment. Timing of imaging is independent from treatment delays. Subjects without progressive disease and who are not receiving subsequent anticancer therapy after the EOT Visit will be followed every 8 weeks with radiographic disease evaluation for the first 6 months and then every 12 weeks thereafter, until progressive disease according to RECIST v1.1.

h. Concomitant medications and procedures will be documented at each study visit until the 50-day Safety Follow-Up visit.

i. All AEs will be documented until the 50-day Safety Follow-Up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

j. Assessments include PGIS and select items from the EORTC QLQ-C30 for all subjects and select items from the QLQ-NMIBC24 for subjects with UC, NSCLC-SAQ for subjects with NSCLC, QLQ-CR29 for subjects with CRC, and QLQ-RCC10 for subjects with RCC, respectively. Whenever possible the PRO assessment (physical functioning and disease related symptom from the EORTC item bank) should be completed by the subject prior to a health care intervention of any nature, regardless of whether it is study related or not. A protocol deviation occurs only when study-related interventions occur PRIOR to PRO assessments, other than vital signs, demographics, and clinical history information.

k. Not applicable for the avelumab weekly induction monotherapy cohort.

l. Long-term follow-up for survival will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

m. See Table 14 for list. Hematology results must be available and reviewed prior to dose administration by the local Investigator.

n. See Table 14 for list of core and full (includes core) serum chemistry analytes. Serum chemistry results must be available and reviewed prior to dose administration by the local Investigator.

o. If urinalysis is positive for protein, sediment (microscopy) will be evaluated. Urinalysis results must be available and reviewed prior to dose administration by the local Investigator. Urinalysis does not have to be performed for subjects with UC.

p. β-HCG must be determined from serum at Screening and then in urine thereafter. Results of the most recent pregnancy test (done within 28 days) should be reviewed prior to the next dosing of IMP. Following treatment discontinuation, monthly pregnancy testing should continue through the 50-Day Safety Follow-up visit. In case the 50-Day Safety Follow-up visit is combined with the End-of-Treatment visit, monthly pregnancy testing should continue until 50 days post last study treatment administration. FSH may be performed at Screening to confirm post-menopausal status. Women who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

**Table 7 Bioanalytical and Biomarkers Schedule of Assessments — Part B: Expansion Cohorts**

| Measure | Screening/ Baseline | Treatment Phase Cycle | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 and Cycle 2 | | | | | | | Cycle 3 | Cycle 4 (start of q2w dosing) | | | Cycle 5 | | Cycle 6 and beyond – see below |
| | D -28 to 0 | D1 | | D2 | D8 | D15 | | D22 | D1 | D1 | | D15 | D1 | | |
| | | Predose[a] | EOI (1h) + 30m | 24h ±6h[b] | Predose[a] | Predose[a] | EOI (1h) + 30m | Predose[a] | Predose[a] | Predose[a] | EOI (1h) + 30m | Predose[a] | Predose[a] | EOI (1h) + 30m | |
| Avelumab PK | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| M9241 PK[c] | | X | X | X | X | X | | X | X | X | X | X | X | X | |
| ADA[d] | | X | | | | X | | | X | X | | | X | | |
| Soluble factors | | X | | X | X | X | | X | X | X | | X | X | | |
| PGt (optional)[e] | X | | | | | | | | | | | | | | |
| Gene expression | | X | | X | X | | | | X | X | | | X | | |
| CTC | | X | | | | | | | X | | | | X | | |
| Liquid biopsy | X | X (Cycle 2 only) | | | | | | | X | | | | X | | |
| Immunophenotyping[f] | | X | | | | X | | | X | X | | | X | | |

| Measure | Treatment Phase | Off Therapy | |
|---|---|---|---|
| | Cycle 7 and Beyond | EOT | Safety |
| | D1 Predose[a] | Within 7 Days of decision to discontinue | 50 Days (±5 days) |
| Avelumab PK | C7D1 and Every 3 cycles after C7 | X | X |
| M9241 PK[c] | C7D1 and Every 3 cycles after C7 | X | X |
| ADA[d] | C7D1 and Every 3 cycles after C7 | | X |
| Soluble factors | C7D1 only | | |
| Gene expression | | X | |
| Liquid biopsy | | X | |
| Immunophenotyping[f] | X (C7D1 only) | X | |

ADA = antidrug antibody; C = cycle; CTC = circulating tumor cells; d/D=day; EOI (1h) = End of 1-hour infusion (as close to completion of infusion as possible); EOT = end of treatment; h = hour; PGt = pharmacogenetics; PK = pharmacokinetics.

a. Predose is prior to avelumab and when applicable M9241 administration. Sample should be collected as close to the start of infusion as possible and within 2 hours prior to administration.

b. From start of avelumab infusion.

c. M9241 PK is collected for the combination therapy only.

d. M9241 ADA is collected for the combination therapy only.

e. Blood samples for PGt analysis (optional for subjects who sign the separate PGt ICF) will be collected before or on Day 1 before trial treatment starts. If not collected at Baseline, the blood sample for PGt may be obtained at any other point of time during the study but will be collected only once.

f. In the event of an immune-related adverse event requiring steroids, an additional immunophenotyping sample may be collected prior to the start of steroids. Collection of this additional sample is preferred, but not required.

# 2 Sponsor, Investigators and Study Administrative Structure

The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States (US). The Sponsor outside of the US is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

The study will appear in the following clinical study registry: ClinicalTrials.gov, EudraCT, and all other required registries.

## 2.1 Investigational Sites

This study will be conducted in approximately 65 sites globally.

## 2.2 Coordinating Investigator

The Coordinating Investigator represents all Investigators for decisions and discussions regarding this study, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical study report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are provided in Appendix IV.

## 2.3 Key Parties and Service Providers

A contract research organization (CRO), IQVIA, Durham, NC, US, will undertake the operational aspects of this study. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan maintained by IQVIA. The Integrated Project Management Plan will be prepared by the IQVIA Clinical Project Manager in cooperation with other IQVIA operational team leads.

## 2.4 Study Coordination / Monitoring

The Sponsor will coordinate the study and will subcontract to the CRO, for the management of most of the activities of the study.

The Sponsor will supply the investigational medicinal products (IMP) to the site. Safety laboratory assessments will be performed locally by each investigational site. Pharmacokinetics (PK) and biomarker analyses will be performed under the responsibility of the Sponsor.

The Sponsor's Global Patient Safety Department or its designated representative will supervise all drug safety activities and the timely reporting of adverse events (AEs) and serious adverse events (SAEs). Safety reporting to Health Authorities, according to local regulatory requirements, will be the responsibility of the Sponsor or its designated representatives.

Monitoring and data management will be performed by IQVIA, and the Sponsor will be responsible for regulatory submission. Quality assurance of the study conduct will be performed by the Sponsor's Development Quality Assurance. IQVIA will write the study Statistical Analysis Plan (SAP), perform the statistical analyses, and will provide the outputs from the statistical analyses.

## 2.5 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review the safety data on a regular basis throughout the duration of the study. The SMC consists of permanent members from the Sponsor and/or CRO (early clinical development lead, medical lead, biostatistician, and global patient safety representative), the Coordinating Investigator, and other optional members with expertise in the management of cancer subjects.

The SMC will decide on relevant dose-limiting toxicities (DLT) for protocol criteria and will decide by consensus on dose-escalation, dose de-escalation, or suspension of enrollment and/or declaration of the maximum tolerated dose (MTD).

CCI [redacted]

The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

# 3 Background Information

Interest in immunotherapy as a means of antitumor therapy has rapidly grown in the medical oncology community, largely due to positive studies with a variety of immune checkpoint inhibitors (Topalian 2012, Brahmer 21012, Wolchock 2013, Postow 2015a). Although overall radiographic response rates have been encouraging in many solid tumors, others, such as colorectal cancer rarely respond to immune checkpoint inhibition (Brahmer 21012, Wolchock 2013, Postow 2015a, Royal 2010, Robert 2015, Postow 2015b, Motzer 2015, McDermott 2015, Le 2015, Herbst 2016, Garon 2015, Brahmer 2015, Borghaei 2015). This means that approximately 75% to 80% of patients with any type of solid tumor will not receive significant benefit from these agents. Rationally selected combinations of agents are needed to achieve clinical benefit with immunotherapy in a greater proportion of patients. The purpose of this study is to evaluate the safety and preliminary efficacy of the Programmed death ligand 1 (PD-L1) inhibitor avelumab in combination with M9241 in subjects with metastatic or locally advanced unresectable solid tumors in order to achieve greater clinical benefit with immunotherapy.

Programmed death 1 (PD-1) is a negative regulator of T-cell activity that limits the activity of T-cells at a variety of stages of the immune response when it interacts with its two ligands, PD-L1 and PD-L2 (Ishida 1992, Keir 2006, Freeman 2000). When engaged by a ligand, through phosphatase activity, PD-1 inhibits kinase-signaling pathways that normally lead to T-cell

activation. A number of antibodies that disrupt the PD-1 axis have entered clinical development. PD-L1 is also believed to exert negative signals on T cells by interacting with B7 (Butte 2007), and PD-L1-blocking antibodies prevent this interaction. Immune checkpoint inhibitors also enhance the function of tumor-infiltrating lymphocytes (TILs), which augments antitumor immunity within the tumor microenvironment. The presence of TILs has been correlated with better prognosis in many cancer types, including bladder (Lipponen 1993, Tsujihashi 1988, Sharma 2007), lung (Geng 2015), breast (Adams 2014), renal (Li 1998), colon (Maby 2015), and esophageal (Liu 2015) carcinomas. Thus, PD-L1$^+$ TILs have been shown to be indicators of response to immune checkpoint blockade, and a lack of TILs may be a predictive marker for lack of response to PD-1/L1 blockade (Curran 2010, Huang 2011, Herbst 2014).

Interleukin 12 (IL-12), a proinflammatory cytokine produced by activated phagocytes and dendritic cells (DCs), plays a critical role in regulating the transition from innate to adaptive immunity. IL-12 acts directly upon cytotoxic immune effector cells, namely natural killer (NK) cells, NK T cells, and CD8$^+$ T cells, to stimulate their proliferation and increase their cytotoxic functions. Furthermore, IL-12 drives differentiation of helper T cells down the Th1 pathway, thereby promoting the production of cytokines (most notably interferon [IFN]-γ) that favor cell-mediated immunity (van Herpen 2008). There is also evidence that IL-12 acts directly on DCs to further stimulate IL-12 production and enhance antigen presentation (Grohmann 1998). By amplifying these positive immunostimulatory effects, therapeutic administration of exogenous IL-12 has the potential to promote effective antitumor immune responses. IL-12 has shown some promising clinical activity in Phase I studies, including stabilization of disease in renal cancer patients with partial regression of a metastatic lesion (Gollob 2000). Objective responses with IL-12 have been reported in T-cell lymphoma (56%; Rook 1999), non-Hodgkin's lymphoma (21%; Younes 2004), and AIDS-related Kaposi's sarcoma (50% to 71%; Little 2006); however, IL-12 has yet to be approved for any indication due to its toxic side effects, which has limited its use and ability to induce objective responses (Del Vecchio 2007, Lacy 2009).

The combination of PD-L1 inhibitors with IL-12 may work synergistically to increase anti-tumor activity (Tugues 2015). It is hypothesized, based on the mechanism described above, that IL-12 shifts the tumor microenvironment from suppressed to inflamed by driving NK and T-cell activation, potentially resulting in increased PD-L1 expression within the tumor, while avelumab blocks the inhibitory effect of PD-L1, resulting in a higher rate of response when given in combination. Furthermore, combination therapy with IL-12 and a PD-L1 inhibitor may rescue anti-PD-L1 refractory tumors or may make primary anti-PD-L1 unresponsive tumor types susceptible to checkpoint inhibition by inducing local inflammation and immunogenicity (ie, IL-12 may be used as an immune sensitizer / primer).

The purpose of this study is to evaluate the safety and preliminary efficacy of avelumab in combination with M9241 in subjects with metastatic or locally advanced unresectable solid tumors. This dose escalation study will establish a safe dose of M9241 and avelumab when given in combination. After determination of the recommended Phase II dose (RP2D), enrollment in 4 expansion cohorts will be opened to assess the safety and a preliminary estimate of clinical activity for the combination regimen in selected tumor types and, where data available, allow an early assessment of the contribution of each individual investigational agent in the combination (Section 3.4).

## 3.1 M9241

M9241 immunocytokine is composed of two IL-12 heterodimers, each fused to one of the H chains of the NHS76 antibody. NHS76 is a fully human, phage display-derived IgG1 antibody that has affinity for both single- and double-stranded DNA and targets regions of tumor necrosis where DNA has become exposed. This antibody-cytokine conjugate was evaluated in a Phase I study with the goal of achieving a high concentration of IL-12 within the tumor while giving a relatively low systemic dose of IL-12 and thereby reducing toxicity (Fallon 2014).

The M9241 concept is a strategy to reduce the toxicity associated with systemic administration of recombinant human IL-12 by selectively targeting delivery to tumors. This strategy increases intratumoral IL-12 exposure, thus enhancing antitumor activity and reducing systemic exposure, thereby improving tolerability.

### 3.1.1 Supporting Clinical Data for M9241

One clinical study is currently ongoing with M9241 (NHS-IL2, also referenced as MSB0010360N) monotherapy in subjects with metastatic solid tumors. The study is being conducted at the Center of Cancer Research of the NCI under the protocol number NCT01417546 (IND 112497).

The NCI study NCT01417546 is a first in-human Phase I study of M9241 conducted in subjects with metastatic or locally advanced solid epithelial or mesenchymal tumors to investigate the tolerability, safety, PK, biological and clinical activity of M9241 (Strauss 2019). During the dose escalation phase of the study, DLTs were assessed and the MTD for M9241 administered subcutaneously (SC) every 4 weeks (q4w) was determined.

As of 20 May 2016, 58 subjects have been treated with M9241, receiving doses from 0.1 up to 21.8 µg/kg. Dose escalation was performed with single dosing at dose levels 0.1, 0.5, 1.0, 2.0, 4.0, 8.0, and 12 µg/kg and with multiple dosing (q4w) at dose levels 2.0, 4.0, 8.0, 12.0, 16.8, and 21.8 µg/kg. Overall, 4 subjects (6.9%) were still on treatment and 54 subjects (93.1%) completed or discontinued study treatment. The primary reason for treatment discontinuation was disease progression (20 subjects; 34.5%), followed by adverse event (4 subjects; 6.9%). The study is currently ongoing in the Expansion Phase.

The most up-to-date data can be found in the latest version of the M9241 Investigator's Brochure (IB).

**Safety**

The safety data presented here includes data from the ongoing Phase I study with a data extraction date of 20 May 2016.

Forty-seven subjects (81.0%) reported treatment-related treatment-emergent adverse events (TEAEs) (Table 8), with 12 subjects (20.7%) experiencing at least one Grade ≥ 3 treatment-related TEAE (11 Grade 3 events, 1 Grade 4 event, no Grade 5 events). The most frequently observed treatment-related TEAE are shown in Table 9. Grade ≥ 3 events included lymphocyte count decreased (n=5; 8.6%), neutrophil count decreased (n=4; 6.9%), alanine aminotransferase (ALT)

increased (n=3; 5.2%), white blood cell decreased (n=2; 3.4%), and alkaline phosphatase (AP) increased, AST, lipase increased, hypokalemia, and hyperhidrosis (n=1; 1.7%).

The most up-to-date data can be found in the latest version of the M9241 IB.

**Table 8** **Overview of Treatment-related TEAEs**

| TEAE categories | Overall (N = 54) n (%) |
|---|---|
| Any treatment-related TEAE | 47 (81.0) |
| Any treatment-related Grade ≥ 3 TEAE | 12 (20.7) |
| Any treatment-related serious TEAE | 2 (3.4) |

TEAE = treatment-emergent adverse event.

**Table 9** **Most Frequently Reported Treatment-Related TEAEs (any Grade, Incidence ≥ 10%)**

| CTCAE Term | Overall (N=58) n (%) |
|---|---|
| **Number of subjects with at least 1 treatment-related TEAE** | 47 (81.0) |
| Lymphocyte count decreased | 27 (46.6) |
| White blood cell decreased | 24 (41.4) |
| Fever | 21 (36.2) |
| Aspartate aminotransferase increased | 21 (36.2) |
| Alanine aminotransferase increased | 20 (34.5) |
| Anemia | 18 (31.0) |
| Flu like symptoms | 17 (29.3) |
| Alkaline phosphatase increased | 13 (22.4) |
| Platelet count decreased | 12 (20.7) |
| Fatigue | 10 (17.2) |
| Hyperglycemia | 10 (17.2) |
| Neutrophil count decreased | 10 (17.2) |
| Hypophosphatemia | 6 (10.3) |
| Hypoalbuminemia | 6 (10.3) |

CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

### Other Serious Adverse Events

Serious treatment-related TEAE were observed in 2 subjects (3.4%) and included the events fever, ALT increased and AST increased. One subject experienced mild to moderate fever 1 day after the second dose and 29 days after the first dose of M9241 at the dose level of 16.8 µg/kg. No actions were taken and the subject recovered from the event. The other subject reported an increase

of the liver enzymes ALT and AST, both Grade 3, related to M9241 and regarded as DLT, 4 days after the first and only dose of M9241 at dose level 21.8 µg/kg. The treatment was discontinued and the subject recovered.

The most up-to-date data can be found in the latest version of the M9241 IB.

**Dose-Limiting Toxicities during Dose Escalation**

The primary objective of study NCT01417546 was to determine the MTD by monitoring DLTs.

In study NCT01417546, a DLT was defined as any Grade ≥ 4 hematologic toxicity or Grade ≥ 3 thrombocytopenia (with a platelet count of 25 to 50 × $10^9$/L) with associated bleeding or any Grade ≥ 3 non-hematologic toxicity occurring in the DLT evaluation period, except for transient (≤ 48 hour) Grade 3 fatigue, local reactions, flu like symptoms, fever, headache, nausea, emesis, diarrhea not controlled with adequate medical management, or any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 skin toxicity lasting less than 5 days (in addition to other certain exceptions clearly described in the protocol). The DLT evaluation period refers to the 6 weeks after the first study drug injection, or 2 weeks after the second study drug injection, whichever is longer, following a classical 3 + 3 design. The severity criteria are based on the NCI-CTCAE, Version 4.0 (v4.0). Dose escalation was performed with single dosing at dose levels 0.1, 0.5, 1.0, 2.0, 4.0, 8.0, and 12 µg/kg and with multiple dosing (q4w) at dose levels 2.0, 4.0, 8.0, 12.0, 16.8, and 21.8 µg/kg.

None of the subjects treated with single or multiple doses up to and including 12.0 µg/kg experienced a DLT.

At the dose level of 16.8 µg/kg, 1 out of 6 subjects presented a DLT: a subject with prostate cancer experienced a Grade 3 elevation of ALT associated with elevations of AST (Grade 2), and AP (Grade 1) during the DLT evaluation period. All events were non-serious and all recovered.

At dose level 21.8 µg/kg, 2 out of 6 subjects presented a DLT and the MTD was exceeded: one subject with ovarian cancer experienced Grade 3 elevations of AST and ALT, both assessed as serious and both recovered, and 1 subject with colon cancer had a non-serious clinically insignificant Grade 3 lipase elevation, which also resolved.

According to the study protocol the MTD was exceeded with the last dose level of 21.8 µg/kg and the MTD of 16.8 µg/kg for M9241 monotherapy administered subcutaneously was determined.

The most up-to-date data can be found in the latest version of the M9241 IB.

**Clinical Efficacy**

Study NCT01417546 is a First-In-Human study, which is ongoing at the NCI. A total of 58 subjects were enrolled and treated with either single or multiple doses of M9241.

In single dose escalation cohorts, efficacy was not assessed as subjects stayed on the study for 28 days after the single injection of M9241. No efficacy data are available from the subjects in the single dose escalation cohorts.

In the multiple dose escalation cohorts, 36 subjects were enrolled and treated. As of 20 May 2016, 32 subjects discontinued and 4 subjects were still on treatment. Among the 32 discontinued subjects, 20 subjects discontinued due to disease progression, 4 subjects discontinued due to AEs, 1 subject died due to progressive disease (PD), 3 subjects switched to other treatments; 2 subjects refused further treatment; 1 subject discontinued due to a surgery that was scheduled while on the study, and 1 subject wanted to reconsider whether to continue with the study or not.

No objective responses occurred. Among the 36 subjects enrolled in the multiple dosing schedule which includes both dose escalation and expansion, 30 subjects have complete efficacy assessments. Out of 30 tumor evaluable subjects, 15 subjects had stable disease (SD) and 15 subjects had results of PD.

The most up-to-date data can be found in the latest version of the M9241 IB.

## 3.2 Avelumab

Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody designed to bind to PD-L1 and block it from binding to the T-cell receptor PD-1, thereby inhibiting the negative feedback loop (checkpoint) between tumor cells and T cells.

### 3.2.1 Supporting Clinical Data for Avelumab

Avelumab is currently in clinical development across Phases I, II, and III. At the time of the initial protocol, the following 4 clinical studies were underway (see current IB for updated information):

- EMR100070-001: A Phase I, open-label, multiple ascending dose study to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR100070-002: A Phase I study to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR100070-003: A Phase II, single arm, open-label, multicenter study to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma
- EMR100070-004: A Phase III open-label, multicenter study of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet.

EMR100070-001 is a Phase I, open-label, multiple ascending dose study to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This study consists of 2 parts. In the dose-escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks and 10.0 mg/kg once weekly for 12 weeks) with a 3 + 3 algorithm design for determination of the MTD of avelumab; in the treatment Expansion Phase, subjects in different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until confirmed progression, unacceptable toxicity, or

any reason for withdrawal occurs. More than 1500 subjects have been enrolled in Study EMR100070-001.

The 3 + 3 dose-escalation algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and pharmacodynamic observations. The treatment expansion part of the study consists of 16 tumor treatment cohorts. In addition a cohort of 10 mg/kg administered once weekly for 12 weeks followed by 10 mg/kg every 2 weeks has been initiated. As of 05 November 2015, 53 subjects in the dose-escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for at least 4 weeks.

The most up-to-date data can be found in the latest avelumab IB.

**Safety**

At the time of the initial protocol, data was available from 1300 subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Study EMR100070-001 (as of 05 November 2015, see current IB for updated information). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer (CRC), castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma (RCC), and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Study EMR100070-002 and for 88 subjects in the ongoing Phase II Study EMR100070-003 (as of 17 December 2015). For Study EMR100070-004, an overview of the SAEs is provided in the IB.

Most of the observed AEs were either in line with those expected in subjects with advanced solid tumors or with class effects of monoclonal antibody blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

The most up-to-date data can be found in the latest avelumab IB.

**Clinical Efficacy**

The clinical efficacy information summarized in the IB includes data from the following expansion cohorts of the ongoing Phase I Study EMR100070-001: NSCLC (second-line and first-line cohorts), ovarian cancer, gastric and gastroesophageal junction cancer, urothelial cancer (UC), mesothelioma, and adrenocortical carcinoma. In addition, efficacy results for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Study EMR100070-002 and 88 subjects in Part A of the ongoing Phase I Study EMR100070-003 in metastatic Merkel cell carcinoma are summarized.

Avelumab at a dose of 10 mg/kg once every 2 weeks has demonstrated meaningful clinical activity across the various tumor types and treatment settings. Across different tumor types, responses with avelumab were typically observed early during treatment and appear durable in nature, including

ongoing responses lasting > 1 year in several of the different cohorts. Overall, most responders were still experiencing ongoing response at the time of the data cutoff for the analysis. Detailed summaries of the efficacy results with avelumab are presented by study and cohort in the IB. Data relevant to the expansion cohorts in the current study are included below.

Of relevance to this protocol, Study EMR100070-001 enrolled 2 cohorts of subjects with locally advanced or metastatic UC who were either cisplatin ineligible or had PD after at least 1 line of platinum-based therapy and a cohort of subjects with advanced NSCLC not previously treated systemically for metastatic or recurrent disease, without an activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, and not preselected for PD-L1 expression. Good clinical activity was observed, with early and durable responses observed in both tumor indications (refer to the current IB for the most recent cohort-specific data).

## 3.3 Supporting Data for Avelumab and M9241 Combination

Based on the complementary and potentially synergistic mechanisms of M9241 and avelumab, the combination was explored preclinical models. When IL-12 was combined with avelumab, there was a significant increase in antibody-dependent cell-mediated cytotoxicity (ADCC) lysis in most cell lines, including lung and colorectal carcinoma. It was concluded that the increased lysis in these cases was due to increased NK-cell activity, not to increased avelumab-mediated ADCC.

Preclinical data from an in vivo study showed that the combination of NHS-muIL12 and avelumab elevated the percentage of $TBET^+$ NK cells and $CD8^+$ T cells, synergistically stimulated the differentiation of central memory T cells and effector memory T cells, significantly increased IFN-γ generation (but not IDO activation), and dramatically enhanced the necrotic fraction and $CD8^+$ T-cell infiltration in EMT6 tumors.

CCI [redacted]

In other experiments, NHS-muIL12 (2.0 µg) showed combination activity in the MC38 colon tumor model by decreasing tumor volume over time and significantly improved survival. Avelumab (200 µg) and NHS-muIL12 (2.0 µg) combination treatment generated an additive antitumor effect in MB49 bladder cancer.

These data provide evidence that an IL-12-based therapeutic agent such as M9241 can be combined with avelumab to enhance antitumor responses via T-cell and NK cell-mediated killing, including ADCC.

CCI [redacted]

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### 3.5.1 Rationale for Endpoints

#### 3.5.1.1 Part A: Dose Escalation

The primary endpoints for the dose-escalation part of the study (including the avelumab once weekly cohort), AEs and DLTs according to the NCI CTCAE Version 4.03 (v4.03), are standard objective measures of safety. Secondary endpoints of area under the concentration-time curve (AUC), maximum serum concentration observed post-dose ($C_{max}$), minimum serum concentration observed post-dose ($C_{min}$), and half-life are also standard PK measurements. CCI

[redacted]

#### 3.5.1.2 Part B: Expansion Cohorts

The primary efficacy endpoint for the expansion cohorts will be the confirmed BOR according to RECIST 1.1. Responses provide a direct measure of antitumor activity in subjects treated with the IMP. The confirmed BOR will be used to determine the ORR, which is suitable for a single-arm early-phase study. The DOR, and PFS and OS times will also be determined and will serve to assess whether the ORR is associated with lasting clinical benefit.

## 3.6 Justification of Dose

### 3.6.1 Dose-Escalation

The avelumab dose of 10 mg/kg for dose escalation was selected after review of the PK, pharmacodynamics, receptor occupancy, and preliminary clinical safety and efficacy data observed in the ongoing Phase I to III monotherapy studies of over 1700 subjects that have received this dose. CCI [redacted] Depending on the results of ongoing PK studies of avelumab and M9241, the dose of avelumab may be increased up to 20 mg/kg (the highest tested dose in EMR100070-001 study, which did not reach MTD), and paired with a safe and tolerable dose of M9241 as determined by the study Sponsor and the SMC.

The starting dose of M9241 in this study (4 µg/kg) is 3 dose levels below the monotherapy MTD of 16.8 µg/kg (Study 11-C-0225 conducted at the NCI, IND No. 112497). In human subjects receiving M9241 monotherapy, an increase in IFNγ was first seen in 1 of 3 subjects at dose level 5 of 4 µg/kg. Those experiencing DLTs at the maximum administered dose of 21.8 µg/kg had serum IFNγ peaks of approximately 30,000 to 60,000 pg/mL (but not in other subjects at this dose level).

### 3.6.2 Avelumab Flat Dose

Avelumab was originally dosed on a mg/kg basis; however, emerging data for monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab, reveal that body weight based dosing regimens do not result in less variability in measures of exposure over flat dosing (ie, body weight independent) regimens (Wang 2009, Freshwater 2017, Zhao 2017). Additionally, flat dosing offers the advantages of reducing potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired data across 3 studies in 1827 subjects with 14 different types of cancer. The PK simulations suggest that exposures to avelumab across the target range of body weights are less variable with 800 mg every 2 weeks compared with 10 mg/kg every 2 weeks; exposures were similar near the population median weight. Low weight subjects tended towards mildly lower exposures relative to the rest of the population when weight based dosing was used, and marginally higher exposures when flat dosing was applied; however, the implications of these mildly exposure differences are not expected to be clinically meaningful at any weight across the entire population. Furthermore, the 800 mg once every 2 weeks and 800 mg weekly dosing regimens are expected to result in $C_{trough} > 1$ µg/mL associated with

avelumab serum concentrations at > 95% target occupancy (throughout the entire dosing interval in all weight categories). Therefore, a flat dose of 800 mg avelumab will be studied in the avelumab dose escalation cohort and expansion cohorts.

### 3.6.3 Avelumab Once Weekly Dosing Regimen

An intense avelumab flat dose regimen with avelumab 800 mg once weekly for the first 12 weeks in combination with M9241 at the M9241 MTD once every 4 weeks, followed by avelumab at 800 mg every 2 weeks in combination with M9241 at the M9241 MTD once every 4 weeks, is being added in order to increase the chance of maintaining sufficient avelumab exposure when administered in combination with M9241.

Upregulation of PD-L1 by M9241 was observed in preclinical studies. Due to this pharmacological activity of M9241, a PK and / or PD interaction between M9241 and avelumab via target (PD-L1)-mediated mechanisms cannot be ruled out.

The intense avelumab once weekly regimen when administered in combination with M9241 is justified, because:

1) the minimal effective target exposure for avelumab monotherapy has not been definitely established;

2) there may be reductions in avelumab exposure due to a possible PK interaction with M9241; and

3) the minimal effective avelumab exposure in combination with M9241 may be higher compared to that without M9241 due to potential M9241-mediated induction of PD-L1.

Furthermore, it is not expected that the avelumab exposure at 800 mg (equivalent to 10 mg/kg for an 80 kg subject) once weekly administered as monotherapy would substantially impact the avelumab safety profile compared to that observed at approved dose regimen of 10 mg/kg every 2 weeks due to:

1) the fact that the projected exposures ($C_{max}$ and AUC) at the avelumab 800 mg once weekly regimen are at or below those at 20 mg/kg once every 2 weeks, which was the highest dose tested in Study EMR100070-001 and no MTD reached in that study and

2) the preliminary safety data from avelumab monotherapy Study EMR100070-005 suggesting that the safety profile from the 10 mg/kg once weekly for the first 12 weeks followed by 10 mg/kg once every 2 weeks dosing arm that is similar to that in 10 mg/kg once every 2 weeks arm.

As noted above, when avelumab is co-administered with M9241, avelumab exposures are not expected to exceed those when given a monotherapy at the same dosing regimen; rather a potential PK interaction may result in reduced avelumab exposure.

The 12-week avelumab once weekly induction schedule, followed by an avelumab once every 2 weeks maintenance in combination with M9241 once every 4 weeks at the MTD dose was

selected based on preliminary observations from the avelumab monotherapy Study EMR100070-001 that showed approximately 80% of responses occurred within 12 weeks of treatment initiation, and the majority of responses appeared to be durable.

### 3.6.4 Dose for Expansion Cohorts

Based on review of available safety, PK, and pharmacodynamics data, the dose for the expansion cohorts receiving combination therapy will be avelumab 800 mg once weekly for the first 12 weeks in combination with M9241 16.8 µg/kg once every 4 weeks, then continuation with the combination of avelumab at 800 mg once every 2 weeks and M9241 at 16.8 µg/kg once every 4 weeks. The dose for subjects receiving avelumab weekly induction monotherapy in Stage 2 of the UC expansion cohort will be avelumab 800 mg once weekly for the first 12 weeks, then avelumab at 800 mg once every 2 weeks. This is based on the following data from the dose-escalation part of the study:

**Safety data**

As of 16 August 2018, 32 subjects have been enrolled in the dose-escalation part of the study and received M9241 in combination with avelumab.

All 32 subjects (100.0%) reported ≥ 1 TEAE. The most common Preferred Terms were pyrexia (17 subjects [53.1%]), fatigue and anemia (16 subjects [50.0%], each), and decreased lymphocyte count (14 subjects [43.8%]). No TEAEs evaluated by the Investigator as related to either study drug led to death. No clear dose response pattern has emerged with respect to the TEAEs.

Thirteen subjects (40.6%) had TEAEs evaluated by the Investigator as related to avelumab treatment; the most common were pyrexia (4 subjects [12.5%]) and nausea, chills, cytokine release syndrome (CRS), and infusion-related reaction (3 subjects [9.6%], each). The majority of the events evaluated by the Investigator as related to avelumab treatment (12 of 13 subjects) were mild to moderate (CTCAE Grade ≤ 2), with the exception of 1 Grade 4 TEAE of gamma-glutamyltransferase (GGT) increased that was associated with the reported DLT of autoimmune hepatitis (see below).

A total 25 subjects (78.1%) had TEAEs evaluated by the Investigator as related to M9241 treatment. The most common were pyrexia (12 subjects [37.5%]) and influenza-like illness (11 subjects [34.4%]). The majority of the events evaluated by the Investigator as related to M9241 treatment (in 24 of 25 subjects) were mild to moderate (Grade ≤ 2), with the exception of 1 Grade 4 TEAE of GGT increased (see below).

As of the safety data cutoff date, there were 14 subjects (43.8%) with SAEs in the study. The only SAE reported for more than 1 subject was disease progression (2 subjects [6.3%]). Two subjects [6.3%] were reported SAEs evaluated by the Investigator to be related to both avelumab and M9241 (Grade 3 autoimmune hepatitis in the 12 µg/kg M9241 + 10 mg/kg avelumab cohort [see below], and Grade 2 CRS in the 16 µg/kg M9241 + 10 mg/kg avelumab cohort, respectively); no other IMP-related SAEs were reported.

Across all dose-escalation cohorts, a single DLT of Grade 3 autoimmune hepatitis (onset Study Day 15) was reported for Subject 102-0001 (M9241 at 12 µg/kg in combination with avelumab 10 mg/kg). This event was considered an SAE and assessed by the Investigator as related to both M9241 and avelumab. In addition, a Grade 4 GGT increased was reported for this subject on Study Day 18 and was considered related to both study drugs and clinically consistent with the event of autoimmune hepatitis. The subject discontinued the study therapy and recovered following treatment that included steroids.

Three subjects reported CRS, which is defined by NCI-CTCAE Version 4.03 as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath caused by the release of cytokines from the cells. The 3 reports (in Subjects 103-0001 [Dose Level 4], 103-0002, and 103-0003 [both in Dose Level 5]) were based on clinical symptoms of Grade 1 to 2 pyrexia, chills, and hypotension which was reported in the SAE narrative for 1 subject. It is unclear whether those reports were infusion-related reactions or CRS due to overlapping symptomatology and/or timing. None of the reports were based on the actual cytokine level measurements at the time of the event. No actual uncontrolled release of measured cytokines was observed either in these or any other subjects in the trial (of note, blood samples for exploration of soluble factors, including cytokines, were collected per-protocol on days when the subjects happened to report events of CRS, however, the cytokine levels became available later, when the sample analysis was performed). The subjects recovered with minimal symptomatic treatment (no steroids were required) and continued with study therapy without any changes. No re-occurrence of CRS was reported with further dosing. Overall, the available evidence is insufficient to establish a causal link between the CRS and the combination of avelumab with M9241 at the administered doses.

The combination of 16.8 µg/kg M9241 and 800 mg avelumab appeared well tolerated based on the data collected during the DLT observation period from the first 3 subjects treated with this dose; in this cohort, reported TEAEs were Grade $\leq 2$ and non-serious. No DLTs were reported at this dose level.

The available safety information from the dose-escalation part of this study is limited; it does not alter the known safety profile of either avelumab or M9241. At present, no adverse drug reactions (ADRs) are expected for M9241.

**Pharmacokinetic Data**

**Avelumab PK:** Based on available data from 3 subjects in dose-level 5 (800 mg avelumab once weekly, 16.8 µg/kg M9241), avelumab $C_{trough}$ at Cycle 1 Day 8 was similar to the median population PK model-predicted $C_{trough}$ for avelumab monotherapy at 800 mg once weekly. These data suggest that PD-L1-mediated avelumab clearance is saturated with 800 mg avelumab once weekly in combination with 16.8 µg/kg M9241.

In contrast to dose-level 5, in dose-level 4 (10 mg/kg avelumab once every 2 weeks, 16.8 µg/kg M9241), avelumab $C_{trough}$ at Cycle 1 Day 15 was reduced compared with that in monotherapy at the approved efficacious dose of 10 mg/kg once every 2 weeks (n = 6). This reduction in avelumab $C_{trough}$ appeared to be transient, since observed $C_{trough}$ values tended to approach the corresponding model-predicted monotherapy values after multiple dosing. These clinical PK observations in

dose-level 4 are consistent with the preclinical data and the mechanism of action of M9241 and suggest that PD-L1-mediated avelumab clearance may not be saturated with 10 mg/kg avelumab once every 2 weeks in combination with 16.8 µg/kg M9241.

In summary, avelumab PK data support the selection of avelumab weekly (800 mg once weekly for the first 12 weeks) dosing regimen for the Expansion Phase in combination with M9241 (16.8 µg/kg q4w).

**M9241 PK:** M9241 exposure tended to increase with dose of M9241. At 16.8 µg/kg dose (dose levels 4 and 5), the exposure values were overlapping with those observed in an M9241 monotherapy study (Strauss 2019).

**Pharmacodynamic Data**

The IFNγ induction (PD biomarker for M9241) profile in this combination study was similar to that observed for the M9241 monotherapy at the 4 to 16.8 µg/kg dose range of NHS-IL12 (Strauss 2019). Specifically, a transient and mild increase in cytokine levels including IFNγ were observed on Days 2 to 3 following NHS-IL12 administration. Cytokine levels decreased to baseline by Days 8 to 15. The IFNγ induction kinetics were consistent with NHS-IL12 PK.

No unexpected PK or pharmacodynamic findings, such as high exposure or high IFNγ levels, were observed in Subject 102-0001 who was reported with the DLT of Grade 3 autoimmune hepatitis.

**The Avelumab Monotherapy Arm**

The avelumab monotherapy arm will explore the contribution of M9241 to the clinical activity of the avelumab/M9241 combination at the recommended Phase II dose (RP2D) in Stage 2 of the UC expansion cohort. The dosing regimen of the avelumab monotherapy expansion arm will match that of avelumab in the combination arm: avelumab 800 mg once weekly for the first 12 weeks, then avelumab at 800 mg once every 2 weeks thereafter (avelumab weekly induction monotherapy). The available safety and PK exposure data supporting the avelumab 800 mg QW dosing regimen are summarized in Section 3.6.3.

## 3.7 Known and Potential Risks and Benefits to Human Subjects

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

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Subjects are at risk of developing drug hypersensitivity reactions due to M9241, mainly mild to moderate, but which may also be life-threatening. Guidelines for management of identified and potential risks have been provided in Section 6.5.4.

Cytokine release has previously been observed with M9241, which needs further investigation and evaluation. No uncontrolled release of measured cytokines has been observed in this study, including at the RP2D. Guidelines for management of symptoms of cytokine release have been provided in Section 6.5.4.1.

Adverse effects reported from clinical studies with IL-12-based therapies include: flu-like symptoms, fever, injection site reactions, myalgia and arthralgia, fatigue, stomatitis, anorexia, hepatic toxicity with increased transaminases, neutropenia, lymphocytopenia, thrombocytopenia, anemia, dyspnea, vascular leak syndrome, gastrointestinal hemorrhage, and sepsis-like syndrome.

Combination therapy with M9241 may enhance the effectiveness of avelumab in sensitive tumors, may rescue anti-PD-L1 refractory tumors, or may make primary anti-PD-L1 unresponsive tumor types susceptible to checkpoint inhibition by inducing local inflammation and immunogenicity (ie, M9241 may be used as an immune sensitizer/primer).

This clinical study will be conducted in compliance with the clinical study protocol, ICH GCP, and any additional applicable regulatory requirements.

# 4 Study Objectives

## 4.1 Primary Objectives

### 4.1.1 Part A: Dose Escalation

The primary objective for the dose-escalation part of the study is to determine the safety, tolerability, and MTD of M9241 and avelumab when given in combination in subjects with metastatic or locally advanced solid tumors.

### 4.1.2 Part B: Expansion Cohorts

The primary objectives for the expansion cohorts are:

- To evaluate the confirmed best overall response (BOR) as assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) of avelumab in combination with M9241 at the RP2D in selected tumor types
- To evaluate the safety and tolerability of combination therapy with avelumab and M9241 at the RP2D.

## 4.2 Secondary Objectives

### 4.2.1 Part A: Dose Escalation

The secondary objectives for the dose-escalation part of the study are:

- To characterize PK profiles of avelumab and M9241 when given in combination
- To determine the RP2D of M9241 and avelumab when given in combination
- To evaluate the immunogenicity of combination therapy with M9241 and avelumab

- To evaluate preliminary antitumor activity of combination therapy with M9241 and avelumab.

### 4.2.2 Part B: Expansion Cohorts

The secondary objectives for the expansion-part of the study are:

- To characterize PK profiles of avelumab and M9241 at the RP2D when given in combination
- To evaluate the immunogenicity of combination therapy with avelumab and M9241
- To evaluate antitumor activity of combination therapy with avelumab and M9241 in selected solid tumor types.

CCI [redacted]

## 5 Investigational Plan

### 5.1 Overall Study Design and Plan

This is a Phase Ib open-label, dose-finding study with consecutive parallel-group expansion in selected solid tumor types.

**Dose Escalation**

The dose escalation phase (Part A of the study, conducted in the US only) is a modified 3 + 3 study design to evaluate the safety, tolerability, and PK of avelumab in combination with M9241 in subjects with locally advanced, unresectable, or metastatic solid tumors.

A schematic of the dose enrollment and cohort expansion decision tree is shown in Figure 1. Once 3 subjects at a given dose level of M9241 have completed the combination treatment with the IMPs during the first 3 weeks (or at least 1 week after the second dose of avelumab, whichever is later), a safety review will be performed by the SMC in order to make a decision on the next dose level. Successive cohorts of 3 to 6 subjects will be treated with escalating doses of M9241 with avelumab at 10 mg/kg intravenous (IV). Additional subjects may be added to dose level 4 for PK and pharmacodynamic evaluations.

The first subject of each cohort should be observed for 7 days for DLT occurrence before the second subject is to be administered the first dose of study medication. After the second subject in each dose level has received the initial combination treatment on Cycle 1 Day 1, subjects who enroll during the safety DLT evaluation period of each dose level will be observed for 24 hours prior to initiating treatment of a subsequent subject.

The observation period for DLTs refers to the first 3 weeks after IMPs for all dose cohorts and for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD. Subjects will be considered evaluable for dose-escalation decisions if they have completed the minimum safety evaluations (hematology, chemistry, and clinical assessments) after the combination administration during the DLT observation period and have received at least 1 injection of M9241 and 2 infusions of avelumab or should have stopped treatment because of DLTs in the DLT evaluation period. Subjects who are not evaluable for DLT during this time for any reason other than a DLT will be replaced. Subjects enrolled in dose-levels 2 through 4 who experience a DLT will be allowed to step down 1 dose level of M9241 and continue treatment provided the subject has no concurrent AE requiring discontinuation. If the subject experiences a DLT at the lower dose level, the subject should be discontinued from further treatment with M9241.

The SMC will review the safety data on a regular basis. The SMC will decide on relevant DLTs for protocol criteria and will decide by consensus on dose-escalation, dose de-escalation, or suspension of enrollment and/or declaration of the MTD.

The decision to escalate to the next dose level will be guided by the following rules:

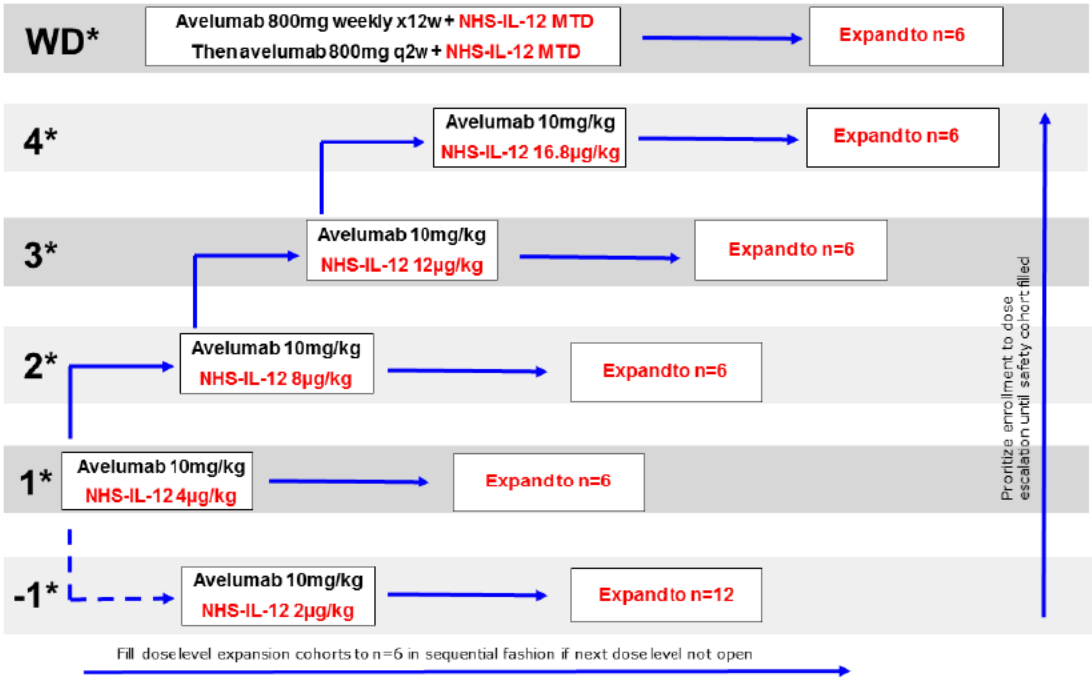
- If none of the 3 evaluable subjects in a cohort experiences a DLT during the first 3 weeks then the dose can be escalated to the next dose level.
- If 1 of 3 evaluable subjects in a cohort experiences a DLT during the first 3 weeks then up to 3 additional subjects will be included at this dose level. If none of the additional evaluable subjects experiences a DLT (1 of up to 6 evaluable subjects in the cohort total has DLT) then dose-escalation can resume.
- If 2 of 3 to 6 evaluable subjects in a dose cohort experience a DLT then the dose-escalation will be stopped and this dose will be defined as the maximum administered dose (MAD).

- The MTD is defined as the highest dose at which no more than 1 of 6 evaluable subjects experiences a DLT. The decision on the MTD will be made by the SMC. No intra-subject dose-escalation will be permitted.

Each cohort up to MAD will be expanded to 6 evaluable subjects. Subject enrollment will be prioritized to fill the dose level undergoing safety assessment (per modified 3 + 3 design). During SMC closures between dose level decisions, an additional 3 subjects (total of 6) will be enrolled per cohort that has already been deemed safe by the SMC, beginning at the lowest dose level still needing to be filled. Subjects 4 through 6 of each cohort will continue to be evaluated for DLTs but will not drive dose-escalation decisions if 0 of the first 3 subjects did not experience any DLTs.

In the event that DLTs occur in Subjects 4 through 6 after a higher dose level has been opened, the data will be reviewed by the Sponsor and the SMC to determine the best course of action for currently enrolling subjects at the highest dose level.

**Figure 1** **Dose Enrollment and M9241 Dose Level Expansion**



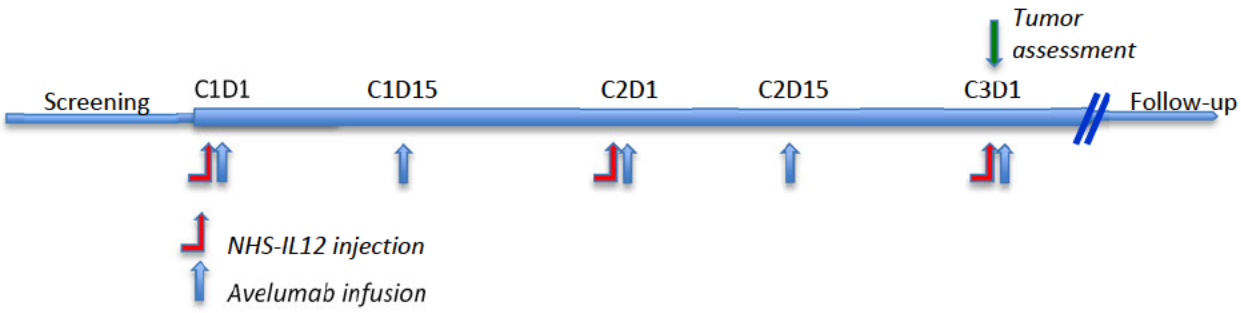

ADA=antidrug antibody; n = number of subjects; PK=pharmacokinetics; WD = weekly avelumab dosing.
* PK, ADA, and biomarker assays will be reviewed. Depending on results, avelumab may be increased or drug administration schedule may change.

Depending on the results of ongoing PK studies of avelumab and M9241, dose level "X" may be opened, with a higher dose of avelumab of up to 20 mg/kg (the highest dose tested in EMR100070-001, which did not reach MTD), paired with a safe and tolerable dose of M9241 as determined by the study Sponsor and the SMC. If DLT is demonstrated at dose level 1, the dose of M9241 will either be reduced by 50% (2 µg/kg, dose level -1), or the drug administration schedule may be changed to stagger the timing of M9241 and avelumab such that there is a 7-day gap between each drug dose. This decision will be made based on available PK / pharmacodynamic data. This decision would be made by the Sponsor in conjunction with the

SMC. If dose level -1 is opened and determined to be the MTD, this cohort may be expanded to 12 subjects. In the event of a dose schedule change, a protocol amendment would be submitted.

A schematic of dosing and tumor assessment is shown in Figure 2. A single treatment cycle is 28 days long. Avelumab will be administered on Day 1 and Day 15 of each cycle; M9241 will be administered on Day 1 only of each cycle, immediately prior to avelumab infusion. Study visits will take place according to the Schedule of Assessments. Assessments will include TEAEs as well as concomitant medications, laboratory assessment, Eastern Cooperative Oncology Group performance status (ECOG PS), electrocardiograms (ECG), physical examination, and vital signs. Imaging by computerized tomography (CT) or magnetic resonance imaging (MRI) occurs every 8 weeks for tumor assessments for the first 6 months on treatment.

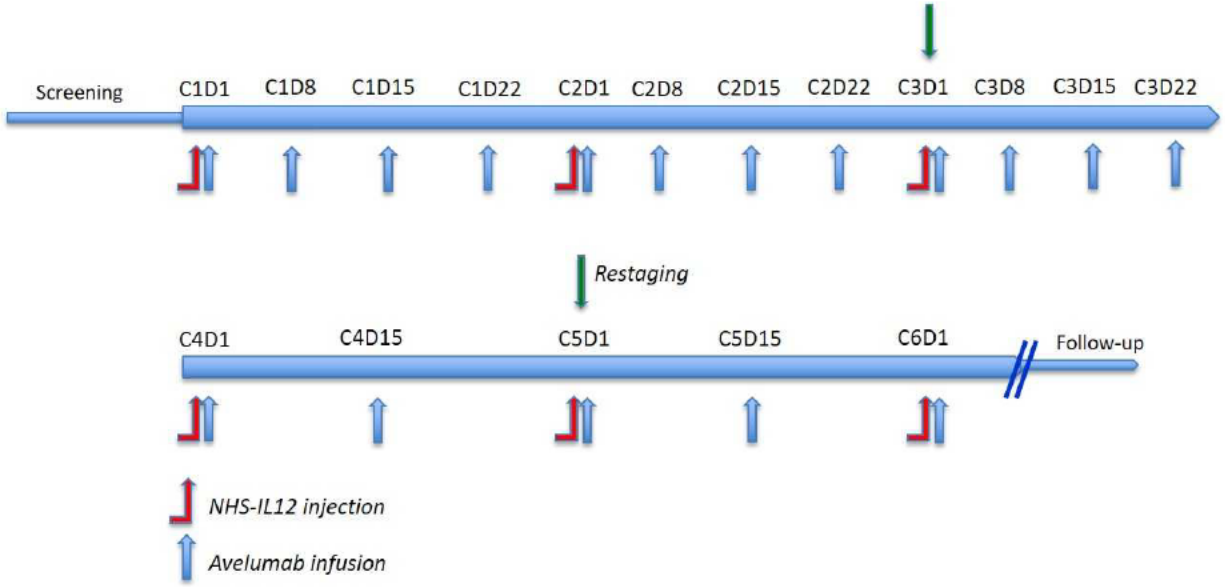
**Figure 2** **Scheme of Biweekly Avelumab Dosing and Tumor Assessment**




C=Cycle; D=Day.

In addition to the above M9241 escalation cohort, an avelumab once weekly cohort will be opened (Figure 3). For this cohort, subjects will receive avelumab at 800 mg once weekly in combination with M9241 at the M9241 MTD once every 4 weeks for the first 12 weeks, then avelumab at 800 mg once every 2 weeks plus M9241 at the M9241 MTD once every 4 weeks until a criteria for treatment discontinuation has been met. The avelumab once weekly cohort will enroll up to 6 subjects using the same 3 + 3 rules as outlined. The Sponsor may also open similar avelumab once weekly cohorts at a lower M9241 dose and expansion once weekly cohorts.

**Figure 3** **Scheme of Dosing and Tumor Assessments for Avelumab Once Weekly Cohort**




C=Cycle; D=Day.

Detailed schedules of study procedures and assessments and bioanalytical research studies, including PK, immunogenicity, and biomarkers, are provided in the Schedules of Assessments.

**Expansion Cohorts**

After determination of the RP2D, enrollment in 4 expansion cohorts will be opened to assess the safety and clinical activity for the combination regimen in selected tumor types, based on the rationale described in Section 3.4. The indications for the 4 expansion cohorts comprise UC, NSCLC, RCC, and CRC. In the EU countries, the Sponsor commits to provide a dose justification summary prior to the enrollment of subjects in expansion cohorts. The dose justification will be based on the available safety, PK, and pharmacodynamic data obtained from subjects at all available dose levels upon MTD determination.

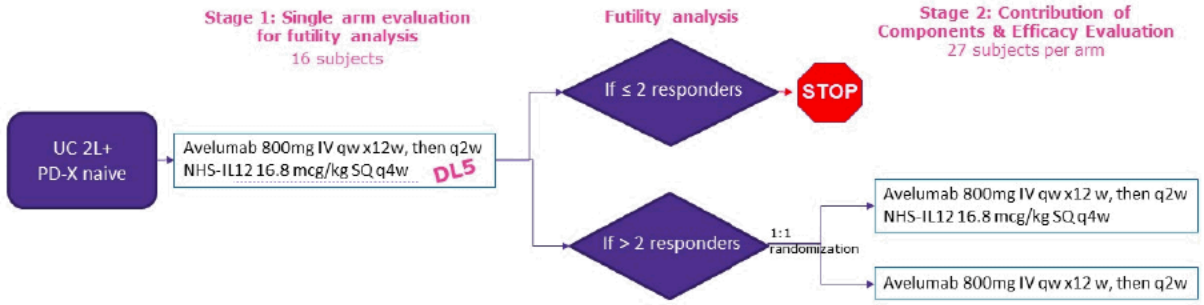
Approximately 170 subjects will be enrolled across the 4 expansion cohorts: 40 subjects in the NSCLC cohort, 70 subjects in the UC cohort using a 2-stage design, and 30 subjects each in the CRC and RCC cohorts. There will be a waiting period of at least 24 hours between the dosing of the first 16 subjects in the expansion phase.

For the UC cohort, a total of 70 subjects is planned as part of a 2-stage design (Figure 4):

- Stage 1 (single arm): 16 subjects are planned to receive combination therapy

  Based on results of the futility analysis, Stage 2 would be initiated.
- Stage 2 (1:1 randomization, controlled, open-label): 27 subjects are planned per arm to receive either combination therapy or avelumab weekly induction monotherapy.

**Figure 4** **Urothelial Carcinoma Expansion Cohort Design Schema**




DL5=Dose Level 5; IV=intravenous; qw=weekly' q2w=every 2 weeks; UC=urothelial carcinoma.

During the Expansion Phase, the SMC will continue to review the safety data on a regular basis. The specific working procedures of the SMC will be described in an SMC charter.

For subjects in all expansion cohorts, PROs will be collected to evaluate the change from Baseline in physical function and symptom severity using the following PRO questionnaires:

- Patient Global Impression of Severity (PGIS)
- Select items from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core instrument (QLQ-C30)

For subjects in the UC cohort, 1 additional PRO questionnaire will be used:

- Select items from the EORTC Non-Muscle Invasive Bladder Cancer Module (QLQ-NMIBC24)

For subjects in the NSCLC cohort, 1 additional PRO questionnaire will be used:

- Select items from the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)

For subjects in the CRC cohort, 1 additional PRO questionnaire will be used:

- Select items from the EORTC Colorectal Cancer Module (QLQ-CR29)

For subjects in the RCC cohort, 1 additional PRO questionnaire will be used:

- Select items from the EORTC Renal Cell Carcinoma Module (QLQ-RCC10)

**Planned Study and Treatment Duration per Subject**

Screening Period: -28 to -1 days

Treatment Period: A single treatment cycle is 28 days long. Avelumab administration will be according to cohort (dose-escalation / avelumab once weekly cohort or expansion cohort); M9241 will be administered only on Day 1 of each cycle, immediately prior to avelumab infusion. Subjects in this study will receive combination therapy with avelumab and M9241 or avelumab weekly induction monotherapy until 1 of the criteria for withdrawal from study treatment as described in the protocol is met (see Section 5.5.1).

Subjects from either the dose-escalation or the expansion portions of the study who have experienced a CR, PR, or have SD may continue treatment for up to 24 months for subjects with CR (although additional treatment is possible) and continuously for PR or SD. If the Investigator believes that a subject with a CR may benefit from treatment beyond 24 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in this protocol. If there is further evidence of PD thereafter, study treatment should be discontinued; however, continued treatment is possible in consultation with the Medical Monitor. For subjects who achieve a CR or PR and then subsequently develop disease progression after stopping therapy, but prior to the end of the study, 1 re-initiation course of treatment at the same dose and schedule and treatment duration of up to 24 months is allowed at the discretion of the Investigator and agreement of the study Medical Responsible. The Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation.

Follow-Up Period: Subjects without PD and who are not receiving subsequent anticancer therapy after the End of Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, and for survival for the first year, and then every 6 months thereafter until PD according to RECIST v1.1. The survival follow-up will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

**Duration of the Whole Study**

The anticipated duration of the whole study including follow-up period is 222 weeks. The actual duration of recruitment period will be based on the study set-up process.

The medical care of subjects after the termination of this study is described in Section 6.13.

## 5.2 Discussion of Study Design

For the dose-escalation part of this study, the assessment of the safety, tolerability, and MTD of M9241 when given in combination with avelumab is set to be the primary objective. The determination of the MTD is one of the first major steps in the development of a compound entering early clinical development. In this study the MTD will be determined using a "3 + 3 subjects" dose-escalation design based on DLT assessments, which is commonly used in

first-in-man oncology studies. This design aims to maximize the protection of study subjects by reducing the number exposed to possible drug toxicities at each new dose.

A modification of standard "3 + 3 subjects" design (expansion of each cohort to 6 during SMC closures) is being employed to provide data to assess the PK / pharmacodynamics of avelumab and M9241 when given in combination and to determine the RP2D.

The expansion part of the study is designed to provide a preliminary assessment of efficacy in selected tumor types that may benefit from the combination of avelumab and M9241. The randomization between combination therapy and avelumab weekly induction monotherapy in Stage 2 of the UC expansion cohort will allow an early assessment of the contribution of each individual investigational agent in the combination.

The inclusion and exclusion criteria were chosen to maximize the potential for subject safety and possible benefit from avelumab and M9241 when given in combination.

### 5.2.1 Inclusion of Special Populations

Not applicable.

## 5.3 Selection of Study Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the study as subjects. Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative (note: legal representative is not applicable for subjects in Germany) has provided written informed consent following the procedure described in Section 9.2.

### 5.3.1 Inclusion Criteria

To be eligible the subject must fulfill all of the following criteria:

#### 5.3.1.1 Inclusion Criteria for Dose Escalation:

1. Signed written informed consent
2. Male or female subjects of age ≥ 18 years
3. Subjects must have histologically or cytologically proven metastatic or locally advanced solid tumors for which no standard therapy exists, standard therapy has failed, subject is intolerant of established therapy known to provide clinical benefit for their condition, or standard therapy is not acceptable to the subject
4. Subjects who have been treated previously with a checkpoint inhibitor may enroll
5. At least 1 unidimensional radiographically measurable lesion based on RECIST v1.1, except for subjects with metastatic castration-resistant prostate cancer (CRPC) or metastatic breast cancer who may be enrolled with objective evidence of disease without a measurable lesion
6. ECOG PS of 0 to 1 at Screening

7. Estimated life expectancy of more than 12 weeks
8. Adequate hematological function as defined below:
   a. White blood cells (WBC) count $\geq 3.0 \times 10^9$/L
   b. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   c. Lymphocyte count $\geq 0.5 \times 10^9$/L
   d. Platelet count $\geq 100 \times 10^9$/L
   e. Hemoglobin $\geq 9$ g/dL (may have been transfused)
9. Adequate hepatic function as defined below:
   a. A total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range
   b. AST levels $\leq 2.5 \times$ ULN
   c. ALT levels $\leq 2.5 \times$ ULN
   d. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 but less than $3 \times$ ULN
10. Adequate renal function as defined by an estimated creatinine clearance $\geq$ 50 mL/min according to the Cockcroft-Gault formula
11. Negative blood pregnancy test at Screening for women of childbearing potential. For the purposes of this study, women of childbearing potential are defined as all female subjects after puberty unless they are postmenopausal for at least 1 year, are surgically sterile, or are sexually inactive (see Appendix I for details)
12. Highly effective contraception (ie, methods with a failure rate of less than 1% per year) must be used before the start of treatment, for the duration of the study treatment, and for at least 50 days after stopping study treatment for both men and women if the risk of conception exists. The effects of avelumab and M9241 on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, as defined in Appendix I

#### 5.3.1.2 Inclusion Criteria for Expansion Cohorts:

1. Signed written informed consent
2. Male or female subjects age $\geq$ 18 years
3. Subjects must have one of the following tumor specific indications:
   a. **Locally advanced or metastatic urothelial carcinoma that has progressed during or after at least one platinum-based chemotherapy and not previously been treated with anti-PD-1/PD-L1 agents (PD-x naïve):** Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra). Subjects must have progressed during or after treatment with at least 1 platinum-containing regimen (eg, platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc) for inoperable locally advanced or metastatic UC or disease recurrence. Subjects who received prior adjuvant/neoadjuvant

chemotherapy and progressed within 12 months of treatment with a platinum-containing regimen will be considered as second line. Subjects with mixed histologies are required to have a dominant transitional cell pattern

b. **Non-small cell lung cancer, first-line metastatic:** Histologically proven Stage IV (per seventh International Association for the Study of Lung Cancer classification) NSCLC. Subjects must not have received treatment for their metastatic disease. Subjects could have received adjuvant chemotherapy or loco-regional treatment that included chemotherapy for locally advanced disease, as long as disease recurrence occurred at least 6 months after the completion of the last administration of chemotherapy. Only epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type are allowed (ie, EGFR mutation and ALK translocation / re-arrangement excluded). Nonsquamous cell histologies and never / former light smoker (< 15 pack years) squamous cell carcinoma subjects (per local standard of care) require testing if status is unknown. Subjects must have low tumor PD-L1 expression defined as < 50% tumor proportion score determined using PD-L1 IHC 22C3 pharmDx test or an equivalent FDA-approved PD-L1 test. This cohort will not be opened for enrollment in Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom

c. **Colorectal cancer, second line or later:** Histologically or cytologically confirmed recurrent or refractory metastatic CRC (according to American Joint Committee on Cancer / International Union Against Cancer Tumor Node Metastasis [TNM] Staging System seventh edition) after failure of prior therapy containing oxaliplatin / fluoropyrimidine and / or irinotecan / fluoropyrimidine and, if eligible, cetuximab (Erbitux®) and bevacizumab (Avastin®). Only subjects with MSI-low or MSS metastatic CRC are eligible. Subjects without existing MSI test results will have MSI status performed locally by a CLIA-certified IHC or PCR-based test (PCR-based MSI test is preferred). Subjects must be willing to undergo an on-treatment biopsy procedure. For Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom, subjects in the second-line setting should have exhausted or be considered ineligible or intolerant (in the opinion of the Investigator) of available second-line chemotherapy options

d. **Renal cell carcinoma, primary immune checkpoint inhibitor failure:** Histologically or cytologically documented metastatic RCC with a component of clear cell subtype. Subjects must have had PD within 6 months or SD for ≥ 6 months following therapy with any antibody / drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or CTLA-4 for advanced or metastatic disease (either as monotherapy or combination therapy, in any line). Fresh tumor biopsy is required for enrollment. Subjects must be willing to undergo an on-treatment biopsy procedure. In France, in addition to having received checkpoint inhibitor therapy, subjects should have already received recommended local standard therapy per the discretion of the Investigator

4. Availability of fresh tumor biopsy is mandatory for eligibility in the RCC cohort. The biopsy or surgical specimen should be collected within 28 days prior to the first IMP administration. For the UC expansion cohort at Stage 1, collection of tumor tissue is not mandatory for the eligibility but is strongly recommended. For CRC, NSCLC expansion cohorts, and the UC expansion cohort at Stage 2, availability of either tumor archival material (< 6 months old) or

fresh biopsies (obtained within 28 days) is acceptable with one of these being mandatory. For formalin-fixed paraffin-embedded (FFPE) samples, either block or sections (> 15) may be provided. Tumor biopsies and tumor archival material must be suitable for biomarker assessment (refer to the Central Laboratory Manual/Flowchart for details). On fresh biopsy, if a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor.

5. At least 1 unidimensional radiographically measurable lesion based on RECIST v1.1
6. ECOG PS of 0 to 1 at Screening
7. Estimated life expectancy of more than 12 weeks
8. Adequate hematological function as defined below:
    a. WBC count $\geq 3.0 \times 10^9$/L
    b. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    c. Lymphocyte count $\geq 0.5 \times 10^9$/L
    d. Platelet count $\geq 100 \times 10^9$/L
    e. Hemoglobin $\geq 9$ g/dL (may have been transfused)
9. Adequate hepatic function as defined below:
    a. A total bilirubin level $\leq 1.5 \times$ the ULN range
    b. AST levels $\leq 3 \times$ ULN
    c. ALT levels $\leq 3 \times$ ULN
    d. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 but less than $3 \times$ ULN
    e. For subjects with liver involvement in their tumor, AST $\leq 5.0 \times$ ULN, ALT $\leq 5.0 \times$ ULN, and bilirubin $\leq 3.0$ is acceptable
10. Adequate renal function as defined by an estimated creatinine clearance $\geq$ 30 mL/min according to the Cockcroft-Gault formula
11. Negative blood pregnancy test at Screening for women of childbearing potential. For the purposes of this study, women of childbearing potential are defined as all female subjects after puberty unless they are postmenopausal for at least 1 year, are surgically sterile or are sexually inactive.
12. Highly effective contraception (ie, methods with a failure rate of less than 1% per year) must be used before the start of treatment, for the duration of the study treatment, and for at least 50 days after stopping study treatment for both men and women if the risk of conception exists. The effects of avelumab and M9241 on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, as defined in Appendix I

### 5.3.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following criteria (applicable to all subjects, including all expansion cohorts, unless noted otherwise):

1. Concurrent treatment with a nonpermitted drug/intervention (listed below)
    a. Anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug

within 4 weeks or 5 half-lives, whichever is shorter, prior to start of study treatment, or not recovered from AE related to such therapies, with the following exceptions:

i. Palliative radiotherapy delivered in a normal organ-sparing technique is permitted (concurrently or within pretreatment period as described in Section 6.5.3)
ii. Erythropoietin, darbepoetin-α, and granulocyte colony-stimulating factor are permitted
iii. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted

b. Major surgery (as deemed by Investigator) for any reason (except diagnostic biopsy), within 4 weeks prior to start of study treatment, or not fully recovered from surgery within 4 weeks prior to start of study treatment
c. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before start of study treatment, with the following exceptions:
   i. Subjects with adrenal insufficiency, may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily
   ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) is permitted
   iii. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to ≤ 10 mg prednisone daily

2. Any prior treatment with any form of IL-12
3. For the NSCLC, CRC, and UC expansion cohorts, prior therapy with any antibody / drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anticytotoxic T lymphocyte antigen-4 (CTLA-4) antibody is prohibited
4. Intolerance to checkpoint inhibitor therapy, as defined by the occurrence of an AE requiring drug discontinuation
5. Active or history of primary or metastatic central nervous system tumors
6. Prior organ transplantation, including allogeneic stem-cell transplantation
7. Previous malignant disease (other than the indication for this study) within the last 5 years (except adequately treated nonmelanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the subject was deemed to have been cured with no additional therapy required or anticipated to be required
8. Significant acute or chronic infections requiring systemic therapy including, among others:
   a. History of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
   b. Hepatitis B or C infection (hepatitis B virus [HBV] surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive hepatitis C virus [HCV] antibody with reflex to positive HCV ribonucleic acid [RNA]). Subjects with history of infection must have PCR documentation that infection is cleared

c. Active tuberculosis (history of exposure or history of positive tuberculosis test with presence of clinical symptoms, physical, or radiographic findings)

9. Active or history of autoimmune disease that might deteriorate when receiving an immune-stimulatory agent. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible if they are stable on other medical treatment and do not fulfill exclusion criterion 15
10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), or uncontrolled asthma (ie, 3 or more features of partially controlled asthma)
11. History of allergic reaction to methotrexate (trace methotrexate may be present in M9241 as a part of the manufacturing process) or history of severe hypersensitivity reaction to any other ingredient of the study drug(s) and / or their excipients. Since M9241 contains sucrose as an excipient, subjects suffering from hereditary fructose intolerance are also excluded
12. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v4.03 with the following exceptions:
    a. Neuropathy Grade ≤ 2 is acceptable
    b. All grades of alopecia are acceptable
    c. Endocrine dysfunction on replacement therapy is acceptable
13. Pregnancy or lactation
14. Known alcohol or drug abuse as deemed by the Investigator
15. Uncontrolled intercurrent illness including, but not limited to:
    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mm Hg or lower)
    b. Uncontrolled active infection
    c. Uncontrolled diabetes (eg, glycosylated hemoglobin ≥ 8%)
16. Clinically significant (or 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 (eg, inflammatory bowel disease, current severe acute or chronic colitis) or chronic medical conditions (including laboratory abnormalities) that in the opinion of the Investigator might impair the subject's tolerance of study treatment or interpretation of study results
18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements
19. Legal incapacity or limited legal capacity
20. Administration of a live vaccine within 30 days prior to study entry
21. Any subject with possible area of ongoing necrosis (non-disease related), such as active ulcer, non-healing wound, or intercurrent bone fracture that may be at risk of delayed healing due to protocol therapy
22. Oxygen saturation < 90% at rest, known pulmonary fibrosis, or active interstitial lung disease

23. History of congenital or active immunodeficiency, with the exception of acquired treatment-related hypogammaglobulinemia requiring periodic IV immunoglobulin infusion

## 5.4 Criteria for Initiation of Study Treatment

This is an open-label study. Subjects who provide written informed consent and who meet all relevant eligibility criteria will receive open-label avelumab in combination with M9241 at the appropriate dose level or be randomized to receive combination therapy or avelumab weekly induction monotherapy (Stage 2 UC expansion cohort only).

## 5.5 Criteria for Subject Withdrawal

### 5.5.1 Withdrawal from Study Therapy

A subject must be withdrawn from study treatment if any of the following occur:

- Subject withdrew consent
- Subject lost to follow-up
- Participation in another clinical study
- Any events that unacceptably endanger the safety of the subject.
- In case of disease progression per RECIST v1.1, the subject will be withdrawn from study treatment; however, treatment may continue if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and there is no unacceptable toxicity. The decision to continue treatment should be discussed with the Medical Monitor and documented in the study records.
- If the administration of a prohibited concomitant medication as specified in Section 6.5 becomes necessary during the study, the subject will be withdrawn from study treatment (the Sponsor may be contacted to confirm whether study treatment must be discontinued prior to doing so).
- Subjects enrolled in dose-levels 2 through 4 experiencing DLTs as described in Section 7.4.1.5 will be allowed to step down 1 dose level of M9241 and continue treatment provided the subject has no concurrent AE requiring discontinuation. If the subject experiences a DLT at the lower dose level, the subject should be discontinued from further treatment with M9241. Subjects who come off treatment must be followed on study until resolution of toxicity and until disease progression.
- 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 prior to treatment completion
- Occurrence of AEs, resulting in the discontinuation of the study drug being desired or considered necessary by the Investigator and/or the subject (if applicable)
- Occurrence of pregnancy

- Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or study integrity (see Section 6.9).

Refer to the Schedules of Assessments for data to be collected at the time of discontinuation of treatment. Subjects will be followed for survival and AEs as specified in the Schedules of Assessments.

Subjects who do not fulfill the treatment and safety requirements during the first 3 weeks after administration in each dose level of the dose-escalation part of the study will be replaced.

### 5.5.2 Withdrawal from the Study

Subjects may withdraw from the study at any time without giving a reason.

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

- Subject withdrew consent
- Lost to follow-up
- Death

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

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

## 5.6 Premature Termination of the Study

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of the IMPs.

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

## 5.7 Definition of End of Study

The end of study is defined as 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first. Following termination of the study, there may be allowance for subjects to enter a rollover study, expanded access, or other mechanism for study drug access as appropriate.

# 6 Investigational Medicinal Product and Other Drugs Used in the Study

The term "investigational medicinal product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical study, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

In this study, the term "investigational medicinal product" refers to avelumab and M9241, which are the IMPs used in this study. The term "study treatment" refers to the combination of avelumab and M9241.

## 6.1 Description of the Investigational Medicinal Product

### 6.1.1 Avelumab

Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentration of 20 mg/mL in European pharmacopeia and United States pharmacopeia type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure. Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20). For administration, avelumab drug concentrate must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed.

### 6.1.2 M9241

M9241 is supplied in single-use glass vials with an extractable volume of 1.0 mL sealed with a rubber septum. M9241 is formulated as a 1.5 mg/mL citrate buffered solution containing Polysorbate 20 and L-arginine as stabilizers and sodium chloride as an isotonicity agent. M9241 is ready-to-use; no special medication preparation is needed prior to administration; however, for doses below 300 µg, a dilution with 0.9% sodium chloride injection is required.

## 6.2 Dosage and Administration

Each treatment cycle is of 28 days; treatment cycles will continue until the end of treatment.

### 6.2.1 Avelumab

With the exception of the avelumab once weekly cohort, subjects in the dose-escalation part of the study will receive avelumab 10 mg/kg IV infusion at time 0 over approximately 1 hour every 2 weeks on Day 1 and Day 15 of each cycle. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

Subjects in the avelumab once weekly cohort will receive avelumab at 800 mg IV infusion at time 0 over approximately 1 hour once weekly for the first 12 weeks, then 800 mg once every 2 weeks thereafter.

Subjects in the expansion cohorts will receive avelumab weekly induction monotherapy: avelumab 800 mg once weekly for the first 12 weeks, then avelumab at 800 mg once every 2 weeks until any criterion for treatment discontinuation is met (Section 5.5.1).

In order to mitigate infusion-related reactions, subjects will receive pretreatment with histamine H1 receptor blockers and acetaminophen prior to avelumab infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is recommended prior to the first 4 infusions of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate. Premedication may be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions.

### 6.2.2 M9241

In the Dose-escalation part of the study, M9241 will be administered in escalating doses of 2, 4, 8, 12, 16.8 µg/kg (Figure 1) at a starting dose level of 4 µg/kg by SC injection at time (up to -20 minutes) relative to the start of avelumab infusion (time 0), q4w on Day 1 of each cycle. The dose of M9241 will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of M9241 used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.

#### 6.2.2.1 M9241 Dose Escalation

The study will follow a 3+3 dose-escalation scheme at predefined dose levels as shown in Table 10.

**Table 10 Dose Escalation Schedule**

| Dose Level | Avelumab | M9241 (µg/kg) |
|---|---|---|
| -1 | 10 (mg/kg) once every 2 weeks | 2 once every 4 weeks |
| 1 | 10 (mg/kg) once every 2 weeks | 4 once every 4 weeks |
| 2 | 10 (mg/kg) once every 2 weeks | 8 once every 4 weeks |
| 3 | 10 (mg/kg) once every 2 weeks | 12 once every 4 weeks |
| 4 | 10 (mg/kg) once every 2 weeks | 16.8 once every 4 weeks |
| X | Up to 20 mg/kg once every 2 weeks | To be determined |
| WD | 800 mg weekly for 12 weeks then 800 mg every 2 weeks thereafter | MTD |

MTD = maximum-tolerated dose; WD = weekly avelumab dosing.

#### 6.2.2.2 M9241 Expansion Cohorts

Based on review of available safety, PK, and pharmacodynamics data, the M9241 dose for the expansion cohorts will be 16.8 µg/kg once every 4 weeks (Section 3.6.4).

### 6.2.3 Modification of Treatment Administration

Depending on the results of ongoing PK studies of avelumab and M9241, dose level "X" may be opened, with a higher dose of avelumab of up to 20 mg/kg (the highest dose tested in EMR100070-001, which did not reach MTD), paired with a safe and tolerable dose of M9241 as determined by the study Sponsor and the SMC.

If DLT is demonstrated at dose level 1, the dose of M9241 will either be reduced by 50% (2 µg/kg, dose level -1), or the drug administration schedule may be changed to stagger the timing of M9241 and avelumab such that there is a 7-day gap between each drug dose. This decision will be made based on available PK/pharmacodynamic data. This decision would be made by the Sponsor in conjunction with the SMC. If dose level -1 is opened and determined to be the MTD, this cohort may be expanded to 12 subjects. In the event of a dose schedule change, a protocol amendment would be submitted.

If an ADR requiring drug discontinuation can be specifically assigned to only 1 drug, it may be permitted to resume treatment with the other drug, only after discussion with the Medical Monitor.

Cytokine-release syndrome, infusion-related reactions, and irAEs should be handled according to the guidelines provided in Sections 6.5.4.1, 6.5.4.2, and 6.5.4.3, respectively.

**Adverse Drug Reactions requiring avelumab discontinuation**

The following ADRs (see Section 7.4.1.1) require permanent treatment discontinuation or treatment modification of avelumab:

- Any Grade 4 ADRs: Permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.
- Any Grade 3 ADRs:
  - Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate
  - Permanently discontinue avelumab if toxicity does not resolve to Grade $\leq$ 1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

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

**Adverse Drug Reactions requiring M9241 discontinuation**

Subjects will be removed from treatment if they meet one of the following criteria:

- Any Grade 4 ADRs: permanently discontinue M9241 except for laboratory values out of normal range that do not have any clinical correlate.
- Any Grade 3 ADRs:

- Withhold M9241 except for laboratory values out of normal range that do not have any clinical correlate.

- Permanently discontinue M9241 if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

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

## 6.3 Assignment to Treatment Groups

All eligible subjects will be assigned to receive open-label avelumab in combination with M9241 or be randomized to receive combination therapy or avelumab weekly induction monotherapy (Stage 2 UC expansion cohort only). Subjects will be assigned to treatment sequentially. During dose-escalation, the next dose level will be open for enrollment only after the DLTs in the current dose level have been fully evaluated by the SMC and a formal SMC decision to proceed to the next dose level has been documented.

### 6.3.1 Study Intervention Assignment

- Before the study is initiated, the telephone number and call-in directions for the Interactive Web Response System (IWRS) and/or the log-in information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each subject. The site will record the study intervention assignment in the applicable eCRF.
- After confirmation of a subject's eligibility, the IWRS will be used to assign unique subject numbers.

For the UC expansion cohort (Stage 2 only):

- After confirmation of a subject's eligibility for the UC expansion cohort (Stage 2) and prior to study intervention administration in the Expansion Phase, subjects will be centrally allocated to either study intervention (combination therapy) or avelumab weekly induction monotherapy in a 1:1 ratio, using IWRS and per a computer-generated randomization list.

## 6.4 Noninvestigational Medicinal Products to be Used

In order to mitigate infusion-related reactions, subjects will receive pretreatment with histamine H1 receptor blockers and acetaminophen prior to avelumab infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is recommended prior to the first 4 infusions of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate. Premedication may be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions.

As with all monoclonal antibody therapies, there is a risk of allergic reaction. 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 must be observed for 2 hours post infusion for potential infusion-related reactions. Refer to the guidelines for handling of infusion-related reaction in Section 6.5.4.2.

## 6.5 Concomitant Medications and Therapies

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

### 6.5.1 Permitted Medicines

- Any medications (other than those specifically excluded by the clinical study protocol) that are considered necessary to protect subject welfare and will not interfere with the study drugs may be given administered at the Investigator's discretion, including those for the management of symptoms associated with the administration of avelumab or M9241 as required. These might include narcotic or other analgesics, antiemetics, antihistamines, diuretics, or antianxiety medications.

- Drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms.

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

- Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.

### 6.5.2 Prohibited Medicines

As mentioned in the exclusion criteria in Section 5.3.2, subjects must not have had any anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, and targeted small molecule therapy with the following exceptions: palliative radiotherapy delivered in a normal organ-sparing technique [within 2 weeks before the start of study treatment or within pretreatment period], erythropoietin, darbepoetin-α, and granulocyte colony-stimulating factor, which are permitted), major surgery, or received another investigational agent within 4 weeks or 5 half-lives, whichever is shorter, before the start of study treatment.

The following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of immune-related adverse events [irAEs]), or other experimental pharmaceutical products.

- Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Administration of a live vaccine within 30 days prior to study entry.
- Growth factors (granulocyte macrophage colony stimulating factor). Exception: Erythropoietin, darbepoetin-α, and granulocyte colony-stimulating factor are permitted may be prescribed at the Investigator's discretion.
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).

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

### 6.5.3 Other Interventions

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

- Major surgery (excluding prior diagnostic biopsy)
- Subjects should not abuse alcohol or other drugs during the study
- Radiotherapy with the exception of palliative radiotherapy delivered in a normal organ-sparing technique

The assessment of PD will be made according to RECIST v1.1 and not based on the necessity for palliative bone-directed radiotherapy.

### 6.5.4 Special Precautions

Prior to the first administration of M9241, educational material may be given to and verbally reviewed with each participating subject, communicating the clinical signs and symptoms associated with potential CRS, the importance of vigilance and monitoring of these symptoms, and instruction on seeking medical advice and/or attention with occurrence of these symptoms.

For both the dose escalation (including the avelumab once weekly cohort) and the expansion cohorts, for Cycle 1 on days of avelumab infusion, vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) will be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. If vital signs are not stable after 2 hours then continue monitoring every 15 minutes (± 5 minutes) until stable on 2 consecutive repeated measurements. Otherwise, subsequent vital signs should be taken every 60 minutes (± 10 minutes) (or more often as clinically indicated) at 3 and 4 hours after the start of infusion. After Cycle 1, vital signs should be collected for the dose escalation and expansion cohorts as described in Section 7.4.4.1 and according to the Schedules of Assessments.

In the dose escalation part of the study, for Cycle 1, subjects will have daily evaluations (no more than 24 hours apart) with interval history and physical examination for at least 48 hours and up to 72 hours following drug infusion. For 5 days following drug administration, subjects will remain local to the study center or specified satellite center expert in monitoring, recognizing, and treating potential CRS.

In the expansion cohorts, daily evaluations are not required in Cycle 1. For 5 days following the first drug administration in Cycle 1, subjects must remain local to any medical center expert in monitoring, recognizing, and treating potential CRS.

As a routine precaution, subjects enrolled in this study must be observed for 2 hours post infusion for at least the first 4 drug administrations (except for conditions defined in Section 6.5.4), in an area with resuscitation equipment and emergency agents. At all times during avelumab and M9241 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.

The treatment recommendations for CRS and infusion-related reactions according to the NCI are as outlined in Sections 6.5.4.1 and 6.5.4.2, 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 or anti-neutrophil cytoplasmic antibodies. See Section 6.5.4.3 for details on the management of irAEs.

### 6.5.4.1 Management of Cytokine Release Syndrome

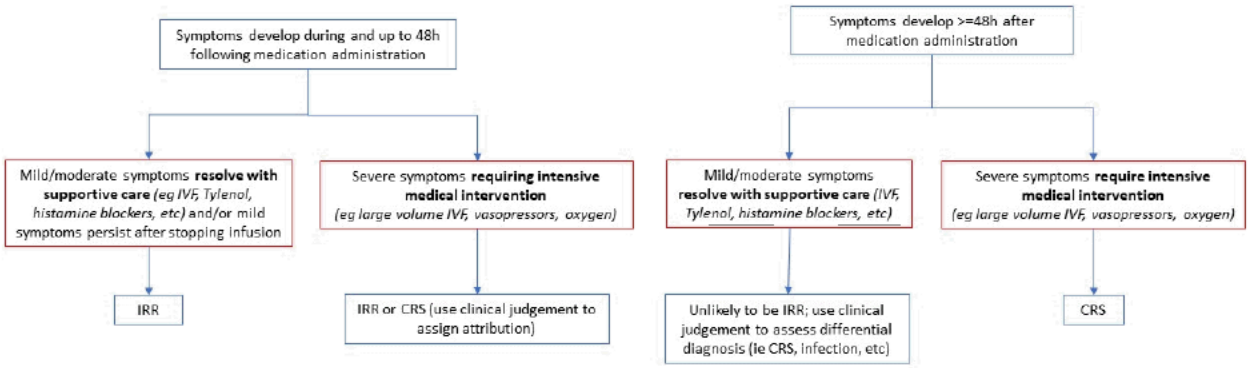
Symptoms of CRS are described in Table 11. Medical management of symptomatic cytokine release is supportive and should follow local standard of care. Algorithms to assess an infusion-related reaction versus CRS and for management of CRS is suggested in Figure 5 and Figure 6.

**Table 11 Clinical Signs and Symptoms Associated with Cytokine Release Syndrome**

| Organ System | Symptoms |
|---|---|
| Constitutional | Fever + rigors , malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache |
| Skin | Rash |
| Gastrointestinal | Nausea, vomiting, diarrhea |
| Respiratory | Tachypnea, hypoxemia |
| Cardiovascular | Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late) |
| Coagulation | Elevated D-dimer, hypofibrinogenemia + bleeding |
| Renal | Azotemia |
| Hepatic | Transaminitis, hyperbilirubinemia |
| Neurologic | Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures |

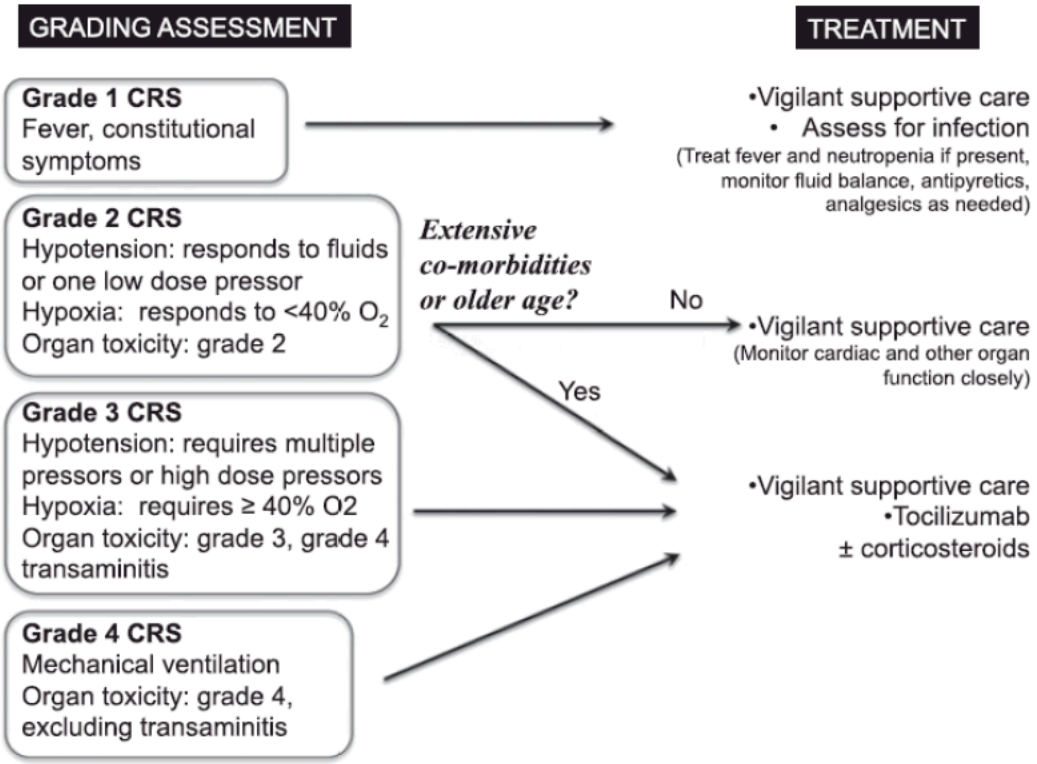
Source: Lee 2014.

**Figure 5 Algorithm to Assess Infusion Related Reaction versus Cytokine Release Syndrome**




CRS=Cytokine Release Syndrome; IRR=infusion-related reaction; IVF: intravenous fluid resuscitation.

**Figure 6** **Algorithm for Management of Cytokine Release Syndrome**




Source: Lee 2014.
CRS=Cytokine Release Syndrome

### 6.5.4.2 Management of Infusion Related Reactions

In order to mitigate infusion-related reactions, subjects have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence / severity of prior infusion reactions.

Symptoms of infusion-related reactions include pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of symptoms should follow the guidelines set forth in Table 12.

**Table 12 Treatment Modification for Symptoms of Infusion-Related Reactions Associated with Avelumab**

| NCI-CTCAE Grade | Treatment Modification for Avelumab |
|---|---|
| **Grade 1 – mild**<br>• 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**<br>• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for 24 hours | • Temporarily discontinue avelumab infusion<br>• 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**<br>• Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae<br>• Grade 4: Life-threatening consequences; urgent intervention indicated | • Stop the avelumab infusion immediately and disconnect infusion tubing from the subject<br>• 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.

### 6.5.4.3 Management of 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

Management of specific irAE should follow the guidelines set forth in Table 13.

## Table 13 Management of Immune-Related Adverse Events

| Gastrointestinal irAEs | | |
|---|---|---|
| **Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Diarrhea: < 4 stools/day over Baseline<br>Colitis: asymptomatic | Continue avelumab therapy<br>Symptomatic treatment (eg, loperamide) | Close monitoring for worsening symptoms<br>Educate subject to report worsening immediately<br>If worsens:<br>Treat as Grade 2, 3 or 4 |
| **Grade 2**<br>Diarrhea: 4 to 6 stools per day over Baseline; iv fluids indicated < 24 hours; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | Withhold avelumab therapy<br>Symptomatic treatment | If improves to Grade ≤ 1: Resume avelumab therapy<br>If persists > 5 to 7 days or recurs:<br>Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; iv fluids ≥ 24 hours; interfering with ADL<br>Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs<br>Grade 4: life-threatening, perforation | Withhold avelumab for Grade 3<br>Permanently discontinue avelumab for Grade 4 or recurrent Grade 3.<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider lower endoscopy | If improves:<br>Continue steroids until Grade ≤ 1, then taper over at least 1 month, resume avelumab therapy following steroids taper (for initial Grade 3).<br>If worsens, persists > 3 to 5 days, or recurs after improvement:<br>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 v4.03)** | **Initial Management** | **Follow-up Management** |
| **Grade 1 to 2**<br>Covering ≤ 30% body surface area | Continue avelumab therapy<br>Symptomatic therapy (eg, antihistamines, topical steroids) | If Grade 2 persists > 1 to 2 weeks or recurs:<br>Withhold avelumab therapy<br>Consider skin biopsy<br>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<br>If worsens: Treat as Grade 3 to 4 |

| | | |
|---|---|---|
| **Grade 3 to 4**<br>Grade 3: Covering > 30% body surface area;<br>Grade 4: life threatening consequences | Withhold avelumab for Grade 3.<br>Permanently discontinue for Grade 4 or recurrent Grade 3<br>Consider skin biopsy<br>Dermatology consult<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). |
| **Pulmonary irAEs** | | |
| **Grade of Pneumonitis (NCI-CTCAE v4.03)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Radiographic changes only | Consider withholding avelumab therapy<br>Monitor for symptoms every 2 to 3 days<br>Consider Pulmonary and Infectious Disease consults | Re-assess at least every 3 weeks<br>If worsens:<br>Treat as Grade 2 or Grade 3 to 4 |
| **Grade 2**<br>Mild to moderate new symptoms | Withhold avelumab therapy<br>Pulmonary and Infectious Disease consults<br>Monitor symptoms daily, consider hospitalization<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | Re-assess every 1 to 3 days<br>If improves:<br>When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, then resume avelumab therapy following steroids taper<br>If not improving after 2 weeks or worsening or for recurring Grade 2:<br>Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Grade 3: Severe new symptoms; New / worsening hypoxia;<br>Grade 4: life-threatening | Permanently discontinue avelumab therapy<br>Hospitalize<br>Pulmonary and Infectious Disease consults<br>1.0 to 2.0 mg/kg/day prednisone equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | If improves to Grade ≤ 1:<br>Taper steroids over at least 6 weeks<br>If not improving after 48 hours or worsening:<br>Add additional immunosuppression (eg, infliximab, cyclophosphamide, iv immunoglobulin, or mycophenolate mofetil) |

| **Hepatic irAEs** | | |
|---|---|---|
| **Grade of Liver Test Elevation (NCI-CTCAE v4.03)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 × ULN | Continue avelumab therapy | Continue liver function monitoring<br>If worsens:<br>Treat as Grade 2 or 3 to 4 |
| **Grade 2**<br>AST or ALT > 3.0 to ≤ 5 × ULN and / or total bilirubin > 1.5 to ≤ 3 × ULN | Withhold avelumab therapy<br>Increase frequency of monitoring to every 3 days | If returns to Grade ≤ 1:<br>Resume routine monitoring; resume avelumab therapy.<br>If elevation persists > 5 to 7 days or worsens:<br>If worsens: Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>AST or ALT > 5 × ULN and / or total bilirubin > 3 × ULN | Permanently discontinue avelumab therapy<br>Increase frequency of monitoring to every 1 to 2 days<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consult gastroenterologist/ hepatologist<br>Consider obtaining MRI / CT scan of liver and liver biopsy if clinically warranted (for study sites in Germany, only MRI is to be used) | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month<br>If does not improve in > 3 to 5 days, worsens or rebounds:<br>Add mycophenolate mofetil 1 gram (g) twice daily<br>If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines |
| **Renal irAEs** | | |
| **Grade of Creatinine Increased (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Creatinine increased > ULN to 1.5 × ULN | Continue avelumab therapy | Continue renal function monitoring<br>If worsens:<br>Treat as Grade 2 to 3 or 4 |
| **Grade 2 to 3**<br>Creatinine increased > 1.5 and ≤ 6 × ULN | Withhold avelumab therapy<br>Increase frequency of monitoring to every 3 days<br>1.0 to 2.0 mg/kg/day prednisone or equivalent. | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper.<br>If worsens:<br>Treat as Grade 4. |

| | | |
|---|---|---|
| | Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy | |
| **Grade 4**<br>Creatinine increased > 6 × ULN | Permanently discontinue avelumab therapy<br>Monitor creatinine daily<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy<br>Nephrology consult | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month, |
| **Cardiac irAEs** | | |
| **Myocarditis** | **Initial Management** | **Follow-up Management** |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | Withhold avelumab therapy<br>Hospitalize<br>In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management<br>Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.<br>Guideline based supportive treatment as per cardiology consult.[a]<br>Consider myocardial biopsy if recommended per cardiology consult. | If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.<br>If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. |
| Immune-mediated myocarditis | Permanently discontinue avelumab.<br>Guideline based supportive treatment as appropriate as per cardiology consult.[a]<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections. | Once improving, taper steroids over at least 1 month.<br>If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A) |
| a Local guidelines, or eg, ESC or AHA guidelines<br>ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines | | |

AHA guidelines website: http://professional heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

**Endocrine irAEs**

| Endocrine Disorder | Initial Management | Follow-up Management |
|---|---|---|
| **Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)** | Continue avelumab therapy<br>Endocrinology consult if needed<br>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.<br>Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis) | Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate |
| **Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)** | Withhold avelumab therapy<br>Consider hospitalization<br>Endocrinology consult<br>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.<br>Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis) | Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).<br>Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate |
| **Hypopituitarism / Hypophysitis (secondary endocrinopathies)** | If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) :<br>• 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)<br>• hormone replacement/ suppressive therapy as appropriate | Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).<br>In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.<br>Continue hormone replacement/ suppression therapy as appropriate. |

| | | |
|---|---|---|
| | • Perform pituitary MRI and visual field examination as indicated<br>**If hypophysitis confirmed:**<br>• Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month<br>• 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.<br>• Add prophylactic antibiotics for opportunistic infections. | |
| **Other irAEs (not described above)** | | |
| **Grade of other irAEs (NCI-CTCAE v4)** | **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<br>If irAE is confirmed, treat as Grade 2 or 3 irAE |
| **Grade 2 irAE or first occurrence of Grade 3 irAE** | Withhold avelumab therapy<br>1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month and resume avelumab therapy following steroids taper |
| **Recurrence of same Grade 3 irAEs** | Permanently discontinue avelumab therapy<br>1 to 2 mg/kg/day<br>prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |

| | | |
|---|---|---|
| **Grade 4** | Permanently discontinue avelumab therapy<br>1.0 to 2.0 mg/kg/day<br>prednisone or equivalent and/or other immunosuppressant as needed<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult. | If improves to Grade ≤ 1:<br>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**<br>**Persistent Grade 2 or 3 irAE lasting 12 weeks or longer** | Permanently discontinue avelumab therapy<br>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 of the Investigational Medicinal Product

### Avelumab

Avelumab is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. Avelumab will be packed in boxes containing a suitable number of vials. The information on the label 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.

### M9241

M9241 is formulated as a 1.5 mg/mL solution and is supplied by the Sponsor in single-use glass vials with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. M9241 will be packed in boxes containing a suitable number of vials. The information on the study drug will be in accordance with approved submission documents.

M9241 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

CCI

[redacted]

CCI [redacted]

## 6.8 Investigational Medicinal Product Accountability

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

- Upon receipt of IMPs, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range
  - The inventory of IMP provided for the clinical study and prepared at the site
  - The use of each dose by each subject
  - The disposition (including return, if applicable) of any unused IMPs
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMPs prepared at the site), and the individual subject study numbers.

The study site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMPs must not be discarded or used for any purpose other than the present study. No IMPs that are dispensed to a subject may be re-dispensed to a different subject.

The Sponsor's Medical Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the study site.

## 6.9 Assessment of Investigational Medicinal Product Compliance

In this study, subjects will receive avelumab in combination with M9241 or avelumab monotherapy (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 study treatment for nonmedical reasons (see Section 5.5.1). 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 Blinding

This is an open-label study; therefore, no blinding will be performed.

## 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 non-serious), must be reported to the Sponsor's Global Patient Safety department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

There are no known symptoms of avelumab and M9241 overdose to date. There is no established treatment for overdose with avelumab or M9241. The Investigator should use clinical judgment to manage any overdose considering the presenting symptoms and standard evaluation results.

## 6.13 Medical Care of Subjects after End of Study

After a subject has completed the study or has withdrawn early, usual treatment will be administered, if required, in accordance with the study site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs. Upon withdrawal from the study, subjects may receive whatever care they and their physicians agree upon. Following termination of the study, there may be allowance for subjects to enter a rollover study, expanded access, or other mechanism for study drug access as appropriate.

# 7 Study Procedures and Assessments

## 7.1 Schedule of Assessments

Prior to performing any study assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

Complete Schedules of Assessments are provided for the dose-escalation part of the study and expansion cohorts (Schedules of Assessments). Every effort should be made to perform assessments as close as possible to the scheduled time points.

### 7.1.1 Screening Period (Day -28 to Day -1)

Based on the findings obtained during the Screening Period (see the appropriate Schedules of Assessments), the Investigator will decide whether the subject is eligible for the study. At the earliest timepoint during screening when eligibility of the subject for the treatment has been verified, for women of childbearing potential and men, highly effective contraception (Appendix I) must be immediately commenced preventing a pregnancy during treatment. According to the highly effective contraception method used, treatment must not be started until the timepoint when the contraception method can be considered effective.

Assessments performed as part of routine medical care (eg, clinical laboratory assessments) prior to written informed consent for the study may be used as screening assessments provided they are within 28 days of the first dose.

### 7.1.2 Treatment Period

For this protocol, a treatment cycle is defined as 28 days. Avelumab administration will be according to cohort (ie, either biweekly or once weekly); M9241 will be administered only on Day 1 of each cycle, immediately prior to avelumab infusion. Subjects in this study will receive combination therapy with avelumab and M9241 or avelumab weekly induction monotherapy until 1 or more of the criteria in Section 5.5.1 is met.

#### 7.1.2.1 Treatment Period for Dose Escalation

Subjects will be asked to visit the investigational site according to the appropriate Schedules of Assessments in order to receive study treatment and for study assessments to be performed. Time windows as per the Schedules of Assessments are permitted for all study procedures; however, treatment schedules should be strictly adhered to, returning to the target date even if the previous schedule was off.

The following instructions should be followed:

- Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then according to instructions in the appropriate Schedules of Assessments)
- On Day 1 of each treatment cycle, M9241 and avelumab should not be administered until the predose bioanalytical and biomarkers sample collection has been completed (see the appropriate Schedules of Assessments)
- On days when M9241 is administered, it should be administered immediately prior to avelumab infusion
- Bioanalytical and biomarker assessment blood samples should be collected according to the appropriate Schedules of Assessments. Every effort should be made to collect samples per the

scheduled timepoint and within the specified windows. Exact sampling time should be recorded. A protocol deviation is captured only if the sample is not collected

#### 7.1.2.2 Treatment Period for Expansion Cohorts

Subjects will be asked to visit the investigational site according to the appropriate Schedules of Assessments in order to receive study treatment and for study assessments to be performed. Time windows as per the Schedules of Assessments are permitted for all study procedures; however, treatment schedules should be strictly adhered to, returning to the target date even if the previous schedule was off.

The following instructions should be followed:

- For subjects in the expansion cohorts, PRO assessments will be performed according to the appropriate Schedules of Assessments. Whenever possible the PRO assessment (physical functioning and disease related symptom from the EORTC item bank) should be completed by the subject prior to a health care intervention of any nature, regardless of whether it is study-related or not. This sequencing is important to reduce measurement bias as the subject assessment should reflect subject impressions up to Visit X; any intervention administered on Visit X would be captured in subsequent assessment. Any intervention on Visit X may bias the subject responses positively or negatively and no longer be an accurate reflection of subject impressions leading up to Visit X. A protocol deviation occurs only when study-related interventions occur PRIOR to the PRO assessments, other than vital signs, demographics and clinical history information
- Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and/or infusion), and then according to instructions in the appropriate Schedules of Assessments
- ECGs should be performed according to the appropriate Schedules of Assessments, prior to treatment (on treatment days), and prior to blood sample collection, such that the blood sample is collected at the planned time. See Section 7.4.4.2 for additional details
- On Day 1 of each treatment cycle, M9241 and avelumab should not be administered until the predose bioanalytical and biomarkers sample collection has been completed (see the appropriate Schedules of Assessments)
- On days when M9241 is administered, it should be administered immediately prior to avelumab infusion.
- Baseline tumor biopsy or archival tumor tissue is required for subjects in the CRC, NSCLC, RCC, and UC expansion cohorts at Stage 2 and is highly recommended for UC expansion cohort at Stage 1.
- An on-treatment tumor biopsy is required for subjects in the CRC and RCC expansion cohorts (see the appropriate Schedules of Assessments). On-treatment biopsies for the NSCLC and UC cohorts are optional. The on-treatment biopsy should occur on Cycle 3 Day 4 (± 1 day)
- Bioanalytical and biomarker assessment blood samples should be collected according to the appropriate Schedules of Assessments. Every effort should be made to collect samples per the

scheduled timepoint and within the specified windows. Exact sampling time should be recorded. A protocol deviation is captured only if the sample is not collected

### 7.1.3 End of Treatment (Within 7 Days of Decision to Discontinue)

All subjects must undergo an End-of-Treatment visit after discontinuation of IMP for any reason. This visit should be performed on the day of or within 7 days after the decision to discontinue IMP but before any new antineoplastic therapy is started (if possible), whichever occurs earlier (see the appropriate Schedules of Assessments). If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment within 30 / 50 days of last treatment (see below) or they will be unable to return within 30 / 50 days of last treatment, assessments associated with the 30 / 50-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit; however pregnancy testing needs to continue per the appropriate Schedules of Assessments.

### 7.1.4 Safety Follow-Up

**30 / 50-Day Safety Follow-Up Assessments:**

A Safety Follow-up visit is scheduled 30 days after the last IMP administration for the dose-escalation and 50 days after the last IMP administration for the expansion cohorts but before any new antineoplastic therapy is started, if possible, whichever occurs earlier. If it is known to the Investigator at the time of the End-of-Treatment visit that the subject will start new treatment or they will be unable to return to the clinic prior to the scheduled 30 / 50-Day Safety Follow-up visit, assessments associated with the 30 / 50-Day Safety Follow-up visit may be conducted at End-of-Treatment visit. The 30 / 50-Day Safety Follow-up visit will comprise a full assessment for safety, immunogenicity, PRO assessment (expansion cohorts only), and tumor response as appropriate (see the appropriate Schedules of Assessments).

**90-Day Safety Follow-Up Assessments:**

Documentation of AEs: After the 30 / 50-day Safety Follow-Up Visit, all SAEs and all treatment related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment related non-serious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

### 7.1.5 Long-Term Follow-Up (Every 3 Months)

Subjects without PD and who are not receiving subsequent anticancer therapy after the End-of-Treatment Visit will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, until PD according to RECIST v1.1.

Long-term follow-up for survival (every 3 months starting after completion of the 90-Day Safety Follow-Up Visit) will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first.

## 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
- Ethnicity.

### 7.2.2 Diagnosis of Tumor

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

- Detailed history of the tumor including histopathological diagnosis, grading, and staging in accordance with the International Union Against Cancer TNM Classification at diagnosis
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy, chemotherapy, and immunotherapy)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current cancer signs and symptoms and side effects from current and/or previous anticancer treatments
- Current cancer disease status
- HER2 status if available (gastric/gastroesophageal junction cancer only)
- Smoking history
- EGFR-activating mutation or ALK re-arrangement status or other (as appropriate)
- Human papilloma virus status (head and neck squamous cell carcinoma only)
- MSI status for subjects in the CRC expansion cohort (see Section 5.3.1.2)

In NSCLC expansion cohort PD-L1 expression (defined as < 50% tumor proportion score determined using PD-L1 IHC 22C3 pharmDx test or an equivalent FDA-approved PD-L1 test) and absence of EGFR activating mutation or ALK re-arrangement (see Section 5.3.1.2).

### 7.2.3 Medical History

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

- Past and concomitant non-malignant diseases and treatments
- All medications taken and procedures carried out within 30 days prior to Screening.

For the study entry, all the subjects must fulfill all inclusion criteria described in Section 5.3.1.1 or Section 5.3.1.2, as applicable, 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 (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed according to the appropriate Schedules of Assessments. See Section 7.4.4.1 for additional details regarding on-treatment vital signs collection.

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.

Body weight and height will be recorded.

### 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory [for study sites in countries with radiation exposure control for subjects, only MRI may 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; other regions as specifically required for specific tumor indications) will be performed within 28 days prior to study treatment start in order to document the Baseline status of the tumor disease using RECIST v1.1 (Eisenhauer 2009) target and non-target lesions, however, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the Screening CT / MRI does not need to be performed.

A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks. In subjects with UC this scan is only necessary if clinically indicated. Thereafter, brain CT / MRI scan should be done if clinically indicated by development of new specific symptoms.

A bone scan should be done at Screening as clinically indicated. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.

### 7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening and subsequently according to the appropriate Schedules of Assessments. Electrocardiograms 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 (see Section 7.4.4.2 for additional treatment phase details).

### 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 study, but will also help to make sure that each enrolled subject fulfills all the study entry criteria and does not meet any of the study exclusion criteria for laboratory parameters as listed in Section 5.3. Detailed description of laboratory assessments is provided in Section 7.4.3.

## 7.3 Efficacy Assessments

The tumor response assessment will be performed as listed according to the appropriate Schedules of Assessments. This should include a complete assessment of all target and non-target lesions for subjects with solid tumors. This assessment will be performed by CT or MRI. In general, lesions detected during Screening need to be followed using the same methodology and preferably the same equipment at subsequent tumor assessment visits.

The efficacy endpoints for this study have been mentioned below:

- **Clinical endpoints:** BOR, time to response, DOR, and PFS time per Investigator assessment according to RECIST v1.1 (Eisenhauer 2009) and immune-related RECIST (irRECIST; Bohnsack 2014). Overall survival time will also be determined.
- **Surrogate endpoints:** Not applicable.

Subjects without PD and who are not receiving subsequent anticancer therapy after the End-of-Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of study and then every 12 weeks thereafter, and for survival for the first year then every 6 months thereafter until PD according to RECIST v1.1. The survival follow-up will continue until up to 1 year after the last subject receives the last dose of protocol treatment, or the last subject dies, whichever comes first. Under some circumstances, subjects may not be followed for this entire time, eg, in the case of enrollment into a rollover study or early Sponsor termination of the study.

### 7.3.1 Immune-Related Response Criteria

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at Baseline and throughout the study. All measurements should be recorded in metric notation.

Overall tumor assessment per timepoint will be derived from tumor response assessments obtained for measured lesions, non-target lesions, and new lesions (Appendix III).

Below is a summary of immune-related RECIST (irRECIST; for more comprehensive information, refer to Bohnsack 2014).

1. Total measured tumor burden: Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the TMTB, and one combined assessment provided.

2. New Measurable Lesions: In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non-measurable tumor burden, but do not get measured.

3. irPR if no Target Lesions: If new measurable lesions appear in subjects with no target lesions at Baseline, irPD will be assessed. That irPD timepoint will be considered a new Baseline, and all subsequent timepoints will be compared with it for response assessment. An assessment of irPR is possible if the TMTB of new measurable lesions decreases by $\geq$ 30% compared with the first irPD documentation.

4. Non-Target Lesions: In alignment with RECIST 1.1, Baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

## 7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting, and analysis of Baseline medical conditions, AEs, physical examination findings including vital signs, laboratory tests, ECOG PS, and 12-lead ECGs.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

## 7.4.1 Adverse Events

### 7.4.1.1 Adverse Event Definitions

**Adverse Event**

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical study associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign, or clinically significant laboratory abnormality or worsening of a preexisting condition or abnormality is considered an AE. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to Baseline or stabilization of event. Progressive disease will be captured as an efficacy endpoint and therefore is not regarded as an AE.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE, v4.03 (publication date: 14 June 2010); a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death.

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets 1 of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will

not be recorded as a separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then may be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to IMPs (including any other non-IMPs, radiation therapy, etc) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, study procedures.

**Unrelated:** Not reasonably related to the IMPs. AE could not medically (pharmacologically/clinically) be attributed to the IMPs under study in this clinical study protocol. Only events clearly not related (disease progression, environmental, unrelated trauma, etc.) should be categorized as unrelated to the study treatment.

**Related:** Reasonably related (ie, any toxicities considered related, probably related, or possibly related) to the IMPs. The AE could medically (pharmacologically / clinically) be attributed to the IMPs under study in this clinical study protocol.

**Abnormal Laboratory Findings and Other Abnormal Investigational Findings**

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (eg, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

**Adverse Drug Reaction**

An ADR is defined in this study as any AE suspected to be related to study treatment by the Investigator and / or Sponsor.

**Serious Adverse Events**

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

- Results in death
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is otherwise considered to be medically important (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of

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

For the purposes of reporting any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

**Events that Do Not Meet the Definition of an SAE**

Elective hospitalizations to administer, or to simplify study procedures or treatment (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, 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 study visit that do not worsen in severity or frequency during the study are defined as Baseline medical conditions, and are not to be considered AEs.

**AE/SAEs Observed in Association with Disease Progression**

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

**Adverse Events of Special Interest**

Given the intended mechanism of action of avelumab, particular attention will be given to AEs that may follow the enhanced T-cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis. Any Grade ≥ 3 AE that is suspected to be a potential irAE will be considered as an AESI.

Cytokine release syndrome, regardless of grade, will be considered as an AE of special interest (AESI). Fever within the first 5 days following administration of M9241, without other clinical signs and symptoms of CRS, is not classified as an AESI. Continuous or daily fevers extending beyond 5 days are considered an AESI.

### 7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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

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

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

### 7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues through the study's Safety Follow-Up Visit. After this visit, all SAEs and all treatment related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment related non-serious AEs.

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

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

**Serious Adverse Events**

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

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

Relevant pages from the eCRF may be provided in parallel (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Medical Monitor; although, in exceptional circumstances, the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

**Adverse Events of Special Interest**

Serious AESIs must be reported in an expedited manner as SAEs as outlined above. Other non-serious AESIs must be reported on the AESI Report Form as per normal reporting timelines.

### 7.4.1.5 Dose-Limiting Toxicities

A DLT is defined as any Grade $\geq 3$ non-hematologic AE or any Grade $\geq 4$ hematologic AE according to the NCI-CTCAE v4.03, occurring during the DLT observation period that is related to either or both study drugs as determined by the Investigator or Sponsor at any dose and judged not to be related to the underlying disease or any previous or concomitant medication. A DLT must be confirmed by the SMC. Study accrual will be halted, pending discussions with the SMC and the study Sponsor, if there is an occurrence of a Grade 5 toxicity by the NCI-CTCAE v4.03 attributable to the treatment regimen or if the MTD is exceeded in dose level 1.

The following **treatment-related** AEs are exceptions to the aforementioned DLT definition:

- Grade $\geq 3$ thrombocytopenia **with** medically concerning bleeding will be defined as a DLT.
- Any Grade 4 neutropenia of $< 5$ days duration will **not** be considered a DLT.
- Any Grade 3 autoimmune thyroid-related toxicity that doesn't clinically resolve to $\leq$ Grade 2 within 7 days of initiating therapy will be defined as a DLT.
- Grade 3 infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management will **not** be considered a DLT.
- Grade 3 diarrhea or skin toxicity that resolves to Grade $\leq 1$ in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated will **not** be considered a DLT.
- Transient ($\leq 48$ hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, nausea, emesis, and diarrhea are **not** DLTs.
- Other single laboratory values out of normal range that have no clinical correlate, and resolve to Grade $\leq 1$ or to baseline within 7 days with adequate medical management are **not** DLTs.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor is **not** a DLT.

- A TEAE that in the opinion of the SMC is of potential clinical significance such that further dose-escalation would expose subjects to unacceptable risk will be considered a DLT.

The observation period for DLTs refers to the first 3 weeks after IMPs for all dose cohorts and for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD. Subjects will be considered evaluable for dose-escalation decisions if they have completed the minimum safety evaluations (hematology, chemistry, and clinical assessments) after the combination administration during the DLT observation period and have received at least 1 injection of M9241 and 2 infusions of avelumab. Subjects who are not evaluable for DLT during this time for any reason other than a DLT will be replaced.

The SMC will review the safety data on a regular basis. The SMC will decide on relevant DLTs for protocol criteria and will decide by consensus on dose-escalation, dose de-escalation, or suspension of enrollment and / or declaration of the MTD. Data of Subjects 1 through 3 in each cohort will be used to make dose-escalation decisions (ie, if 0/3 DLTs then next cohort will be opened), though safety data from Subjects 4 through 6, as it becomes available, will be reviewed at the next SMC meeting. In the event that DLTs occur in Subjects 4 through 6 of a lower dose level cohort after a higher dose level has been opened, the data will be reviewed by the Sponsor and the SMC to determine the best course of action for currently enrolling subjects at the highest dose level.

Any event meeting the above definition of a DLT must be recorded in the eCRF within 24 hours after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs as outlined in Section 7.4.1.4. A DLT not meeting SAE criteria must be reported through the DLT Assessment Report Form within 24 hours after becoming aware of the event.

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

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

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the IEC / IRB that approved the study.

In accordance with ICH GCP, the Sponsor / designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's / IRB's approval / favorable opinion to continue the trial". In particular and in line with respective regulations, the Sponsor / designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions"). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor / designee will provide appropriate Safety Reports directly to the concerned lead IEC / IRB and will maintain records of

these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC / IRB of any Safety Reports provided by the Sponsor / designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs / suspected unexpected serious adverse reactions / safety issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

#### 7.4.1.7 Monitoring of Subjects with Adverse Events

All AEs will be recorded and assessed continuously throughout the study (see Section 7.4.1.3) and assessed for final outcome at the Safety Follow-Up Visit. After this visit, all SAEs and all treatment related nonserious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". At 90 days following the last treatment, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs. Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

### 7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to IMP (eg, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page / section of the eCRF for both pregnancies in female subjects and pregnancies in female partners of male subjects. The Investigator must notify the Sponsor / designee in an expedited manner (within a maximum of 24 hours after becoming aware of the event) of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the study.

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

Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

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

### 7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests (Table 14), following the timing noted in the appropriate Schedules of Assessments. All samples should be clearly identified.

The Sponsor should receive a list of laboratory normal ranges before shipment of study drug. Any change in laboratory normal ranges during the study should be forwarded to Sponsor.

**Table 14** **Required Laboratory Panel Tests**

| Full Chemistry | Hematology |
|---|---|
| Albumin | Absolute lymphocyte count |
| Alkaline phosphatase[a] | Absolute neutrophil count |
| Alanine aminotransferase[a] | Hematocrit |
| Amylase | Hemoglobin |
| Aspartate aminotransferase[a] | Platelet count |
| Gamma glutamyltransferase | RBC |
| Blood urea nitrogen/Total urea[a] | WBC and differential count |
| Calcium[a] | RBC morphology[b] |
| Chloride[a] | Reticulocytes[b] |
| Cholesterol | Mean corpuscular hemoglobin |
| Creatine kinase | Mean corpuscular volume |
| Creatinine[a] | Mean corpuscular hemoglobin concentration |
| C-reactive protein | |
| Glucose[a] | **Hemostaseology** |
| Lactate dehydrogenase | Activated partial thromboplastin time |
| Lipase | Prothrombin time (international normalized ratio) |
| Phosphorus/Phosphates[a] | |
| Magnesium[a] | **Urinalysis[c]**<br>**Full:** protein content[d], albumin<br>**Basic (dipstick)**: protein content only[d] |
| Potassium[a] | |
| Serum electrophoresis[b] | |
| Sodium[a] | |
| Total bilirubin[a] | |
| Total protein | **Totality of binding ADA** |
| Uric acid | |
| Triglycerides | |
| | |
| **Hormone** | |
| Follicle-stimulating hormone (screening only if applicable), TSH, and T4. | |

ADA = antidrug antibody; RBC = red blood cell; T4 = Free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a Core serum chemistries.

b Only if clinically indicated.

c Urinalysis does not have to be performed for subjects with urothelial cancers.

d If urinalysis is positive for protein, sediment will also be evaluated.

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

### 7.4.4.1 Vital Signs and Physical Examinations

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 appropriate Schedules of Assessments and documented in the eCRF. Results of the physical examination including any abnormalities will be documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

Vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) should be assessed predose (within 15 minutes [± 5 minutes] of injection and / or infusion), and then every 15 minutes (± 5 minutes) from the start of avelumab infusion for at least 2 hours. If vital signs are not stable after 2 hours then continue monitoring every 15 minutes (± 5 minutes) until stable on 2 consecutive repeated measurements. Otherwise, subsequent vital signs should be taken every 60 minutes (± 10 minutes) (or more often as clinically indicated) at 3 and 4 hours after the start of infusion.

If there are no clinically significant changes in vital signs during the first 2 avelumab infusions, then the vital signs schedule for subsequent infusions will be predose, every 15 minutes during the infusion, and then at 90 minutes, 2 hours, and 3 hours from the start of infusion. After Cycle 2, if a patient has not had any infusion-related reaction, then vital sign monitoring is only required for 1 hour post infusion. If in a subsequent cycle the subject experiences an infusion-related reaction, then the original 2-hour schedule should be resumed.

### 7.4.4.2 12-Lead Electrocardiograms

Subjects will have 12-lead ECGs as indicated in the Schedules of Assessments.

Electrocardiograms 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.

All ECG assessments should be performed prior to dosing (on dosing days) and prior to blood sample collection, such that the blood sample is collected at the planned time.

**For expansion cohorts:** On treatment triplicate ECGs will be performed on Day 1 of Cycle 1 and Cycle 2 predose (within 4 hours before avelumab infusion and before M9241 dose) and Day 2 of Cycle 1 and Cycle 2. Specifically, 3 consecutive 12 lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates) with digital upload for centralized analysis. Central over-read will be performed when all pre-specified triplicate ECGs from a given cohort are collected. One (the first) of the 3 ECGs is read locally at the time

of acquisition. In addition to prespecified triplicate timepoints above, if a subject experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (> 500 msec), the ECGs should be re-evaluated by a qualified person at the study site for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Other ECGs (specifically at Screening, at the End-of-Treatment and Safety Follow-up visits are single, locally read ECGs.

#### 7.4.4.3 Other Safety Assessments

All newly diagnosed or worsening conditions, signs, and symptoms observed since Screening, whether related to IMP 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 at the visits as indicated in the appropriate Schedules of Assessments. Results of the most recent pregnancy test should be available prior to the next dosing of IMP. Subjects that are postmenopausal (age-related amenorrhea ≥ 12 consecutive months or follicle-stimulating hormone > 40 mIU/mL), or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

### 7.5 Pharmacokinetics

Samples for PK assessments will be collected as per the appropriate Schedules of Assessments. Refer to the Central Laboratory Manual/Flowchart for specifics regarding sample collection, storage and shipping.

Serum samples will be analyzed by a validated immunoassay to quantitate avelumab concentration.

Serum samples will be analyzed by a validated immunoassay to quantitate M9241 concentration. Samples may be further tested in qualified or validated PK characterization assays.

The PK and ADA samples for M9241 and avelumab collected at the same predose time points may be used interchangeably (PK with ADA, avelumab with M9241) if the dedicated sample has insufficient quantity as the subjects will have consented to all collections and tests. In Part A, the Screening ADA sample is considered to be interchangeable with the Day 1 predose PK sample.

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## 7.8 Total Blood Collection for Clinical Assessments

The total amount of blood taken during the first 8 weeks of the trial will not exceed the total of 500 mL and during the first 85 days will not exceed the total of 650 mL.

## 7.9 Other Assessments

For the dose-expansion cohorts, PROs will be collected to evaluate the change from Baseline of specific disease-related symptoms and physical functioning.

The following PRO assessments will be conducted:

**Applied to all cohorts:**

- Physical Functioning Scale form the EORTC QLQ-C30 instrument, consisting of 5 items
- PGIS, a single, global item assessing the subject's perception of overall symptom severity.

**Applied only to respective specific cohorts (selected from the EORTC item bank):**

- UC disease-related symptoms
  - Urinary symptoms (5 items); malaise (1 item); bloating and flatulence (2 items); pain (1 item)
- NSCLC disease-related symptoms
  - Cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 item)
- CRC disease-related symptoms
  - Fatigue (3 items); appetite loss (1 item); pain (3 items); diarrhea (1 item)
- RCC disease-related symptoms
  - Pain (2 items); flank swelling (1 item); fatigue (3 items); sleep (1 item); diarrhea (1 item); appetite loss (1 item).

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## 8.2 Randomization

Only applicable for Stage 2 of the UC expansion cohort in Part B: After confirmation of a subject's eligibility, subjects will be randomly assigned to one of the 2 treatment arms in a 1:1 ratio according to an unstratified block randomization technique. For further details, see Section 6.3.

## 8.3 Endpoints

### 8.3.1 Primary Endpoints

#### 8.3.1.1 Part A: Dose Escalation

- Occurrence, severity, and duration of TEAEs and TRAEs, graded according to the NCI-CTCAE v4.03
- Occurrence of DLTs during the first 3 weeks of treatment.

#### 8.3.1.2 Part B: Expansion Cohorts

- Confirmed BOR by Investigator assessment according to RECIST v1.1 by selected tumor type.
- Occurrence, severity, and duration of TEAEs and TRAEs, graded according to the NCI-CTCAE v4.03.

### 8.3.2 Secondary Endpoints

#### 8.3.2.1 Part A: Dose Escalation

- PK profiles of avelumab and M9241
- Immunogenicity of avelumab and immunogenicity of M9241 in combination therapy, as measured by ADA assays
- Confirmed BOR according to RECIST v1.1
- Immune-related BOR using the irRECIST, derived from RECIST v1.1.

### 8.3.2.2 Part B: Expansion Cohorts

- PFS time, defined as the time (in months) from first treatment day to the date of the first documentation of objective PD as per RECIST v1.1, as assessed by the Investigator, or death due to any cause, whichever occurs first
- OS time, defined as the time from first treatment day to the date of death due to any cause
- DOR, defined for subjects with an objective response (OR), as the time from first documentation of OR to the date of first documentation of PD as per RECIST v1.1 (assessments by the Investigator) or death due to any cause
- PK profiles of avelumab and M9241
- Immunogenicity of avelumab and immunogenicity of M9241 in combination therapy, as measured by ADA assays.

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## 8.4 Analysis Sets

The following analysis sets will be defined in this study:

**DLT Analysis Set:** All subjects with data used for implementing the dose-escalation schedule. These subjects will have received all study treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.

**Safety Analysis Set:** All subjects who receive at least 1 dose of any study treatment.

**Full Analysis Set:**

- Part A and Part B (RCC, CRC, NSCLC, UC Stage 1): All subjects who receive at least 1 dose of any study treatment
- Part B (UC Stage 2): All subjects who were randomized. Subjects will be classified according to the treatment assigned at randomization as per the intent-to-treat principle.

**PK Analysis Set:** All subjects who complete at least 1 administration of avelumab and/or M9241, and who provide at least 1 sample with a measurable concentration of avelumab or M9241.

**Immunogenicity (ADA) Analysis Set:** All subjects who complete at least 1 administration of avelumab and/or M9241, and who have at least 1 valid ADA result for avelumab or M9241.

**Biomarker Analysis Set for PD-L1 Target Occupancy:** All subjects who received at least 1 administration of avelumab and M9241 and have provided a blood sample prior to any avelumab and M9241 treatment and at least 1 post-treatment blood sample.

**Biomarker Analysis Set for Genetic Markers in Tumor Tissue:** All subjects who received at least 1 administration of avelumab and M9241 and have provided at least a tumor sample prior to any avelumab and M9241 treatment.

**Biomarker Analysis Set for Pharmacogenetics / Pharmacogenomics:** All subjects who have provided a whole blood or tumor sample.

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## 8.5.2 Analysis of Primary Endpoints

### 8.5.2.1 Part A: Dose Escalation Adverse Events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

The incidence of TEAEs regardless of attribution and AEs defined as related to the study treatment will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to avelumab and M9241. Adverse events (serious and non-serious) will be considered TEAEs when emerging in the on-treatment period 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.

### 8.5.2.2 Part A: Dose Escalation Maximum-Tolerated Dose Determination

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

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

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

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

### 8.5.2.3 Part A: Dose Escalation and Part B: Expansion Cohorts Confirmed Best Overall Response per RECIST 1.1

Best Overall Response will be evaluated according to RECIST v1.1 (Eisenhauer 2009) based on the Investigator's assessment of disease at different evaluation time points from the first study administration date until documented disease progression, according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart and before progression
- PR = at least two determinations of PR or better at least 4 weeks apart and before progression (and not qualifying for a CR)
- SD = at least one SD assessment (or better) $\geq$ 6 weeks after the first study treatment administration and before progression (and not qualifying for CR or PR).

- PD = progression ≤ 12 weeks after the first study treatment administration (and not qualifying for CR, PR, or SD).

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

Objective Response (OR) is defined as CR or PR according to RECIST v1.1 as described above. Subjects who do not have an on-treatment radiographic tumor assessment due to early progression, who receive antitumor treatments other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR.

For the expansion cohorts, the primary analysis of the BOR will be conducted in the FAS, defined as all treated subjects who had measurable disease at baseline according to Investigator assessment. The number and proportion of confirmed responses (defined as confirmed CR or confirmed PR) will be tabulated. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR.

The analysis of the BOR for the dose-escalation (secondary endpoint) will be conducted in the Full Analysis Set. The ORR, defined as the proportion of subjects with BOR of PR or CR will be tabulated by dose level and overall. The 2-sided 95% Clopper-Pearson CI will be constructed.

### 8.5.3 Analysis of Secondary Endpoints

#### 8.5.3.1 Pharmacokinetic Profile

Pharmacokinetic parameters for avelumab and M9241 will be evaluated according to standard non-compartmental analysis by the PK/ pharmacodynamic data processing group of QPD, Merck Serono, Darmstadt, Germany, using the validated software tool Phoenix/WinNonlin 6.3 (or later). The PK parameters listed below will be calculated using the actual time elapsed from dosing (or using scheduled time if actual time is not available).

The following PK parameters will be estimated and reported for the PK analysis set (see Table 2, Table 4, or Table 7 as appropriate for time points) for avelumab and M9241 during the dose-escalation part of the study:

| | | |
|---|---|---|
| $AUC_{0-t}$ | – | AUC from time of dosing to the time of the last observation |
| $AUC_{0-\infty}$ | – | AUC from time of dosing extrapolated to infinity.<br>$AUC_{0-\infty} = AUC_{0-t} + AUC_{extra}$, where $AUC_{extra} = C_{last\ pred}/\lambda z$ |
| $AUC_{tau}$ | – | AUC from the time of dosing to the length of a dosing interval tau |
| $\Lambda z$ | – | Terminal elimination rate constant |
| $C_{max}$ | – | Maximum serum concentration observed post-dose |

$C_{min}$ – Minimum serum concentration observed post-dose

$t_{max}$ – Time to reach maximum concentration $C_{max}$

$t_{1/2}$ – Apparent terminal half-life, calculated by $\ln 2/\lambda z$

The following PK parameters will be measured for avelumab and M9241 (for combination therapy only) during the expansion part of the study:

$C_{max}$ – Maximum serum concentration observed post-dose (for M9241)

$C_{eoi}$ – Concentration at end of infusion (for avelumab)

$C_{trough}$ – Trough serum concentration (for both avelumab and M9241)

The calculation of the AUCs will be performed using the mixed log-linear trapezoidal method (linear up, log down). Extrapolated areas will always be computed using the predicted last concentration that is estimated using the linear regression from terminal rate constant determination.

PK concentrations below LLOQ are taken as zero for descriptive statistics. PK concentrations below LLOQ, which are before the last quantifiable data point, will be taken as zero for calculating the AUC.

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

### 8.5.3.2 Immunogenicity of Avelumab and M9241

Subjects will be characterized into different categories, independently for each molecule, based on the criteria in Table 15.

**Table 15 Subject Characterization Based on ADA Results**

| Category | Definition | Subject at Risk (Denominator for Incidence) |
|---|---|---|
| Never positive | No positive results at any time point | Number of subjects with at least one valid result at any time point |
| Ever positive | At least one positive result at any time point | Number of subjects with at least one valid result at any time point |
| Pre-existing | A positive ADA result prior to treatment with avelumab | Number of subjects with valid baseline result |
| Treatment boosted | A positive ADA result prior to treatment with avelumab and the titer ≥ 8 × baseline titer while on avelumab treatment | Number of subjects with valid baseline and at least one valid post-baseline result |
| Treatment emergent | Not positive prior to treatment with avelumab and with at least one positive post-baseline result | Number of subjects with at least one valid post-baseline result and without positive baseline results (including missing, NR) |
| Transient positive | If treatment emergent subjects have (a single positive evaluation, or duration between first and last positive result < 16 weeks) and last assessment not positive. | Number of subjects with at least one valid post-baseline result and without positive baseline results (including missing, NR) |
| Persistent positive | If treatment emergent subjects have duration between first and last positive result ≥ 16 weeks or a positive evaluation at the last assessment | Number of subjects with at least one valid post-baseline result and without positive baseline results (including missing, NR) |

ADA = antidrug antibody; NR = not reportable.

Listings of TEAEs for ADA ever-positive subjects will include flags for those characterized as IRRs and / or irAEs.

For expansion cohorts, efficacy listings will be prepared for ADA ever-positive subjects by cohort.

Listings of drug concentration in serum will be prepared for ADA ever-positive subjects.

### 8.5.3.3 Efficacy Endpoints

#### 8.5.3.3.1 Clinical Response

The following parameters will be calculated using Investigator's assessment of tumors per RECIST v1.1 criteria:

- Time to response and DOR (for subjects with OR)
- PFS time.

In addition, OS time will be calculated for all subjects. The analysis of these parameters will be conducted in the Full Analysis Set.

#### 8.5.3.3.2 Immune-Related BOR Using the irRECIST.

Immune-related Best Overall Response will be derived based on reported lesion responses at different evaluation time points from the first study treatment administration until immune-related disease progression per irRECIST (Nishino 2013) according to the following rules:

- irCR = at least two determinations of irCR at least 4 weeks apart and before irPD
- irPR = at least two determinations of irPR or better at least 4 weeks apart and before irPD (and not qualifying for a irCR)
- irSD = at least one irSD assessment (or better) $\geq$ 6 weeks after the first study treatment administration and before irPD (and not qualifying for irCR or irPR).
- irPD = at least two consecutive determinations of irPD at least 4 weeks apart.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of irBOR.

Immune-related Objective Response (irOR) is defined as irCR or irPR according to irRECIST from the first study treatment administration until irPD or death due to any cause. Both irCR and irPR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for immune-related response are first met. Also, irPD must be confirmed by a second, consecutive assessment at least 4 weeks apart. Immune-related OR rate (irORR) is the proportion of subjects with irOR in the analysis set.

The analysis of the irBOR will be conducted in the FAS. The irORR will be tabulated by dose level and overall. The 2-sided 95% Clopper-Pearson CI will be constructed.

The response at each scheduled tumor assessment and the irBOR will be listed for each subject.

### 8.5.4 Analysis of Safety and Other Endpoints

The extent of exposure to avelumab and M9241 will be characterized by duration (weeks), number of administrations, cumulative dose (µg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), and number of dose delays.

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

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

#### 8.5.4.1 Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-study grades after the first study treatment will be summarized. Shifts in toxicity grading from first treatment to highest grade will be displayed. Results for variables that are gradable according to

NCI-CTCAE will be presented as within or outside normal limits. Only subjects with post-baseline laboratory values will be included in these analyses.

#### 8.5.4.2 Physical Examination, Including Vital Signs and 12-lead Electrocardiogram

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure), 12-lead ECG, and ECOG recorded according to the appropriate Schedules of Assessments will be presented.

Further details will be provided in the SAP based on current safety experience applying the latest version of Medical Dictionary for Regulatory Activities.

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#### 8.5.4.4 Correlation of Immune Endpoints and Gene Mutations and Expression with Clinical Outcomes

Selected biomarker parameters will be compared with the clinical outcomes of the subjects.

Spearman's rank correlation coefficient will be calculated for the numeric parameters. Logistic models will be used to describe the association between the biomarkers and the objective response.

Details of the statistical analysis of the association of these parameters will be presented in the SAP.

#### 8.5.4.5 Correlation of Soluble Factor Levels and TRAEs

The association of the soluble factor levels (cytokines and soluble PD-L1) with the occurrence of TRAE will be studied using logistic models.

Details of the statistical analysis of the association of these parameters will be presented in the SAP.

## 8.6 Interim and Additional Planned Analyses

### 8.6.1 Part A: Dose Escalation

For each cohort, after 3 subjects are treated for 3 weeks, the study data will be evaluated by a SMC before decision is made to go to the next dose level.

No interim analyses are planned.

### 8.6.2 Part B: Expansion Cohorts

After Stage 1 of the UC expansion cohort, a futility analysis will be performed.

In general, for the expansion cohorts, individual cohort analyses are planned approximately 4 months after start of treatment of the last subject of each cohort. These analyses are planned after 2 sequential radiographic disease evaluations are available from all subjects. However, further unplanned analyses may also be performed. Safety data will be evaluated by an SMC at predefined time points (Section 2.5).

# 9 Ethical and Regulatory Aspects

## 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the study.

According to the United States Code of Federal Regulations Part 54.2 (e), for studies 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 an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the study and for 12 months following completion of the study.

## 9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and 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 a designate will inform the subject verbally of all pertinent aspects of the study, using language chosen so that the

information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the study and sign the Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject (legal representative) and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived 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 Informed Consent Form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each study subject and obtain new written consent for continued participation in the study. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

A specific second Informed Consent Form has to be signed by subjects for germline pharmacogenetic / pharmacogenomic (PGt) analysis. This consent form confirms the subject's agreement to allow the use of their samples for the purpose of germline PGt analyses. If the subject is in agreement with this portion of the study, this written Informed Consent Form must also be obtained before any activities related to the PGt assessments are carried out. It must be signed and personally dated by the subject and by the Investigator/person designated by the Investigator to conduct the informed consent discussion.

## 9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the study as well as in the clinical study database. All subject data collected in the study will be stored under the appropriate subject number. Only the Investigator will be able to link study data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Medical Monitor, audits, and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

After the end of the study, samples will be stored at a Sponsor's designated biorepository under the supervision of Sponsor.

## 9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during study participation in order to provide clinical study subjects with a way of identifying themselves as participating in a clinical study and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical study 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, they will answer any questions. Any subsequent action (eg, unblinding) will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor or designated CRO will provide the appropriate means to contact a Sponsor/CRO 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/CRO physician to assist with the medical emergency.

## 9.5 Clinical Study Insurance and Compensation to Subjects

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

## 9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, this clinical study protocol will be submitted together with its associated documents (eg, Informed Consent Form) to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor electronic Trial Master File.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the study, the clinical study protocol version, and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

## 9.7 Health Authorities

The clinical study protocol and any applicable documentation (eg, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site. In the EU countries, the Sponsor commits to provide a dose justification summary prior to the enrollment of subjects in expansion cohorts (Part A of the study will be conducted in the US only). The dose justification will be based on the available safety, PK, and pharmacodynamic data obtained from subjects at all available dose levels upon MTD determination. These results will be submitted as a Voluntary Harmonization Procedure (VHP) substantial amendment for approval by the respective national competent authorities before the first subject may be enrolled in the expansion cohorts.

# 10 Study Management

## 10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical study protocol in a complete, accurate, legible, and timely manner. The data in the eCRF shall be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the study.

## 10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the study. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification, ie, the Sponsor study number for this clinical study, and subject number
- Dates for entry into the study (informed consent) and visits to the site

- Any medical examinations and clinical findings predefined in this clinical study protocol
- All AEs
- Date that the subject left the study including any reason for early withdrawal from the study or IMP (if applicable).

All documents containing source data must be filed including, but not limited to, CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Medical Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Medical Monitor and kept in a safe place at the site.

## 10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary. The file must be available for review by the Medical Monitor, during Sponsor audits, and for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

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 study will be monitored in accordance with the ICH GCP and any other applicable regulations. The Medical Monitor will perform visits to the study site at regular intervals.

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

## 10.5 Changes to the Clinical Study Protocol

Changes to the clinical study protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the study requires additional informed consent prior to implementation following the process as described in Section 9.2.

## 10.6 Clinical Study Report and Publication Policy

### 10.6.1 Clinical Study Report

After completion of the study, a clinical study report will be written by the Sponsor/designee in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

### 10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from the study site. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. 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 review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on ClinicalTrials.gov is planned and will occur 12 months after the last clinic visit of the final study subject or another appropriate date to meet applicable requirements.

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# 12 Appendices

# Appendix I Contraceptive Guidance and Woman of Childbearing Potential

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A women of childbearing potential is not:

1. Premenarchal

2. A premenopausal female with 1 of the following:

    * Documented hysterectomy

    * Documented bilateral salpingectomy

    * Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female

* A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

* A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.

* A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Birth control methods considered as highly effective:

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

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal, injectable)
- Progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4].

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

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

[3] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential study subject 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 study and the preferred and usual lifestyle of the subject.

# Appendix II ECOG Performance Status

| ECOG Performance Status[a] | |
|---|---|
| Grade | ECOG |
| 0 | Fully active, able to carry on all predisease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, 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 |

[a] Oken 1982.

# Appendix III Immune-Related RECIST Assessment Classifications

## irRECIST Overall Tumor Assessment

| TMTB | | | | | |
|---|---|---|---|---|---|
| Assessment based on TMTB of Measured Lesions | Target Lesions | New Measured Lesions[a] | Non-Target Lesions | New Non-Measured Lesions[a] | Overall Tumor Assessment |
| irCR | irCR | irCR | Absent at BL/irCR | No | irCR |
| | irCR | irCR | irNN | Yes, No | irPR |
| | irCR | irCR | Absent at BL/irCR, irNN | Yes | irPR |
| | irCR | irCR | irNE | Yes, No | irPR |
| | irCR | irCR | irPD | Yes, No | irPD |
| | irCR | irCR | Absent at BL/irCR irNN, irNE | Unequivocal Progression | irPD |
| | irCR | None | Absent at BL/irCR | No | irCR |
| | irCR | None | irNN | Yes, No | irPR |
| | irCR | None | irNE | Yes, No | irPR |
| | irCR | None | Absent at BL/irCR | Yes | irPR |
| | irCR | None | irPD | Yes/No | irPD |
| | irCR | None | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | None | irCR | irCR | No | irCR |
| | None | irCR | irNN | Yes, No | irPR |
| | None | irCR | irNE | Yes, No | irPR |
| | None | irCR | irPD | Yes, No | irPD |
| | None | irCR | None | No | irCR |
| | None | irCR | None | Yes | irPR |
| | None | irCR | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| irPR | irPR | irPR | Absent at BL/irCR, irNN, irNE | Yes, No | irPR |
| | irPR | irPR | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | irPR | None | Absent at BL/irCR, irNN, irNE | Yes, No | irPR |
| | irPR | None | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | None | irPR | Absent at BL/irCR, irNN, irNE | Yes, No | irPR* |
| | None | irPR | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |

| TMTB | | | | | |
|---|---|---|---|---|---|
| **Assessment based on TMTB of Measured Lesions** | **Target Lesions** | **New Measured Lesions[a]** | **Non-Target Lesions** | **New Non-Measured Lesions[a]** | **Overall Tumor Assessment** |
| irSD | irSD | irSD | Absent at BL/irCR, irNN, irNE | Yes, No | irSD |
| | irSD | irSD | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | irSD | None | Absent at BL/irCR, irNN, irNE | Yes, No | irSD |
| | irSD | None | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | None | irSD | Absent at BL/irCR, irNN, irNE | Yes, No | irSD |
| | None | irSD | irCR, irNN, irNE | Unequivocal Progression | irPD |
| irPD | irPD | irPD | Absent at BL/irCR, irNN or irNE | Yes, No, Unequivocal Progression | irPD |
| | irPD | None | Absent at BL/irCR, irNN or irNE | Yes, No, Unequivocal Progression | irPD |
| | None | irPD | irCR, irNN, irNE, or None | Yes, No, Unequivocal Progression | irPD |
| irNE | irNE, irSD or None | irNE | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | irNE | irNE, irSD or None | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | irNE, irSD or None | irNE | Absent at BL/irCR, irNN, irNE | Yes, No | irNE |
| | irNE | irNE, irSD or None | Absent at BL/irCR, irNN, irNE | Yes, No | irNE |
| N/A | None | None | irCR | No | irCR |
| | None | None | irCR | Yes | irNN |
| | None | None | Absent at BL/irCR, irNN, irNE | Unequivocal Progression | irPD |
| | None | None | irNN | Yes, No | irNN |
| | None | None | irPD | Yes, No | irPD |
| | None | None | irNE | Yes, No | irNE |
| | None | None | None | No | irND |
| | None | None | None | Yes | irNN |
| Any | Any | Any | irPD | Yes, No | irPD |

BL = baseline; irCR = immune-related complete response; irNE = immune-related not evaluable; irNN = non irCR /non irPD; irPD = immune-related progressive disease; irPR = immune-related partial disease; irSD = immune-related stable disease; N/A = not applicable.

a When there is no disease at baseline, but there is at least one new measurable lesion at a post-baseline timepoint, the overall tumor assessment is irPD at that timepoint, and any assessment is possible at subsequent timepoints - irCR, irPR, irSD, irPD, or irNE. In addition, when there is no disease at baseline, but there are one or more new non-measurable lesions at a post-baseline timepoint, the overall tumor assessment is irNN at that timepoint, and the possible assessments at subsequent timepoints are irCR, irNN, irPD, or NE.

NOTE: Worsening of non-target and/or new non-measured lesions must be massive to drive an overall irPD by itself.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial. All measurements should be recorded in metric notation.

# Appendix IV Signature Pages and Responsible Persons for the Study

## Signature Page – Protocol Lead

| | |
|---|---|
| **Trial Title:** | A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors |
| **IND Number:** | CCI |
| **EudraCT Number** | 2017-002212-13 |
| **Clinical Trial Protocol Date / Version:** | 22 July 2019 / Version 8.0, Amendment 7.0 |

**Protocol Lead responsible for designing the clinical study:**

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

| | |
|---|---|
| Name, academic degree: | PPD |
| Function / Title: | Medical Director, PPD |
| Institution: | Merck KGaA |
| Address: | Frankfurter Strasse 250, Postcode: F135/201, 64293 Darmstadt, Germany |
| Telephone number: | PPD |
| E-mail address: | PPD |

## Signature Page – Coordinating Investigator

| | |
|---|---|
| **Trial Title** | A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors |
| **IND Number** | CCI |
| **EudraCT Number** | 2017-002212-13 |
| **Clinical Trial Protocol Date / Version** | 22 July2019 / Version 8.0, Amendment 7.0 |
| **Coordinating Investigator** | PPD |

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

PPD _____ PPD _____

Signature Date of Signature

| | |
|---|---|
| Name, academic degree: | PPD |
| Function / Title: | PPD |
| Institution: | National Cancer Institute |
| Address: | PPD |
| Telephone number: | PPD |
| Fax number: | |
| E-mail address: | |

## Signature Page – Principal Investigator

| | |
|---|---|
| **Trial Title** | A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors |
| CCI [redacted] | [redacted] |
| **EudraCT Number** | 2017-002212-13 |
| **Clinical Trial Protocol Date / Version** | 22 July2019 / Version 8.0, Amendment 7.0 |
| **Center Number** | |
| **Principal Investigator** | |

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

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

## Sponsor Responsible Persons not Named on the Cover Page

| | |
|---|---|
| Name, academic degree: | PPD |
| Function / Title: | PPD |
| Institution: | Merck KGaA |
| Address: | Frankfurter Strasse 250, Postcode: F135/201, 64293 Darmstadt, Germany |
| Telephone number: | PPD |
| E-mail address: | PPD |

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

# Appendix V Protocol Amendment History

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

## Changes from Version 6.0 (Global) to Version 7.0 Included in the Amendment

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Minor editorial and document formatting revisions. | Minor, therefore have not been summarized. |
| Synopsis, Methodology | Added details of addition of Stage 2 design and avelumab weekly induction monotherapy. | To include new design and treatment in Stage 2 UC expansion cohort. |
| Synopsis, Key Inclusion Criteria for Expansion Cohort; 5.3.1.2 Inclusion Criteria for Expansion Cohorts | Updated inclusion criteria for UC cohort | To add additional inclusion criteria for subjects who received prior adjuvant/neoadjuvant chemotherapy. |
| Synopsis, Planned number of subjects | Updated to 170 subjects planned. | To update the planned number of subjects after addition of 2-stage design for the UC cohort. |
| Synopsis, Pharmacokinetics; 8.5.3.1 Pharmacokinetic Profile | Specified PK parameters to be measured during the dose-escalation and dose expansion parts of the study. | To clarify PK parameters to be measured during the dose-escalation and expansion parts of the study. |
| Synopsis, Key Inclusion Criteria for Expansion Cohorts; Section 5.3.1.2, Inclusion Criteria for Expansion Cohorts; Section 3.4 Study Rationale | Added criterion to urothelial carcinoma (UC) cohort. | To add subjects in UC cohort should not have been previously treated with anti-PD-1/PD-L1 agents. |
| Synopsis, Statistical Methods, Part B: Expansion Cohorts; 3.5 Rationale for Study Design; 5.1 Overall Study Design and Plan; 5.2 Discussion of Study Design | Added 2-stage design to the UC expansion cohort. | To add details of the 2-stage design to the UC expansion cohort. |
| Synopsis, Statistical Methods, Part B: Expansion Cohorts; 8.6.2 Part B: Expansion Cohort | Updated text regarding analyses to be performed throughout the study. | To add planned individual cohort analyses. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Schedule of Assessments, Table 1 (Part A), Table 3 (Part A), Table 5 (Part B), and Table 7 (Part B) | Footnotes were updated/added as follows:<br>-Table 1: Added in footnote h brain CT/MRI scans are only necessary if clinically indicated for subjects with UC.<br>-Tables 1 and 3 (Part A): To specify that Screening laboratory samples can be used as Day 1, Cycle 1 samples if drawn within 1 week prior to the Day 1, Cycle 1 visit. Added urinalysis does not have to be performed in the UC cohort.<br>-Table 5 (Part B): To clarify in footnote f ECGs to be performed for the M9241/avelumab combination cohorts and avelumab weekly induction monotherapy cohort and to correct footnotes k (concomitant medications) and l (adverse events) to 50-day Safety Follow-Up Visit for Part B of the study. To correct footnote j with regards to ECG evaluations. Added urinalysis does not have to be performed in the UC cohort.<br>- Table 6 (Part B): Added urinalysis does not have to be performed in the UC cohort.<br>-Table 7 (Part B): To clarify PK and ADA is collected for those receiving combination therapy only. Added footnote b to specify timing of procedures. | Table 1: To clarify brain CT/MRI scans for subjects with UC.<br>Tables 1 and 3 (Part A): To potentially reduce the burden on subjects to have to repeat Day 1, Cycle 1 blood draws if recently done.<br>Table 5 (Part B): To provide clarity on ECG evaluations and correct for ECGs after Cycle 3.<br>Tables 5 and 7 (Part B): To provide clarity to the study staff and Investigators. To clarify timing of procedures.<br>Tables 1, 3, 5, and 6: To clarify urinalysis is not required for the UC cohort. |
| 2.4 Study Coordination / Monitoring | Removed gene expression profiling. | To correct sentence as this is included as biomarker analyses. |
| 2.5 Safety Monitoring Committee | Updated text regarding SMC review. | To update Safety Monitoring Committee review for UC expansion cohorts. |
| 3.4 Study Rationale | Added details for the UC expansion cohort. | To include rationale for the 2-stage design for the UC expansion cohort. |
| 3.6.4 Dose for Expansion Cohorts; 3.7 Known and Potential Risks and Benefits to Human Subjects | A definition of Cytokine Release Syndrome (Section 3.6.4) and a summary of data (Sections 3.6.4 and 3.7) was added from the dose-escalation part of the study. | To provide information for Investigators regarding cytokine release syndrome data from the dose-escalation part of the study. |
| 3.6.4 Dose for Expansion Cohorts | Added text regarding the avelumab monotherapy arm. | To add justification for the inclusion of the avelumab monotherapy arm. |
| 5.3.2 Exclusion Criteria | Added exclusion criterion as it appeared in previous version(s) of the protocol. | To exclude subjects with active tuberculosis |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.4 Criteria for Initiation of Study Treatment; 8.2 Randomization | Added randomization text. | To add randomization details for Stage 2 of UC expansion cohort. |
| 6.3 Assignment to Treatment | Added details for Stage 2 UC expansion cohort and new section. | To add study intervention assignment details following addition of randomized part of Stage 2 UC expansion cohort. |
| 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline | Deleted text regarding brain CT / MRI scans. | To remove cohorts not applicable to protocol. |
| CCI [redacted] | [redacted] | [redacted] |
| 8.4 Analysis Sets | Amended text following new 2-stage designed in UC cohort. | To update Full Analysis Set for Part B, UC Stage 2. To remove efficacy analysis set in line with the avelumab program. |
| 9.3 Subject Identification and Privacy | To delete subject registration text | To remove text which is not applicable |
| Appendix I Contraceptive Guidance and Woman of Childbearing Potential | Added mandatory text. | To update with Merck mandatory protocol text regarding women of childbearing potential. |

## Changes from Version 6.0 (Global) to Version 6.1 Included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.5 Safety Monitoring Committee | Specified that the SMC will review emerging safety profile and reconvene after the first 16 patients in expansion phase have been dosed | Added at request of the VHP |
| 5.1 Overall Study Design and Plan | Added statement that there would be a waiting period of at least 24 hours between the dosing of the first 16 subjects in the expansion phase | Added at the request of VHP. |

## Changes from Version 5.0 (Global) to Version 6.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Editorial changes, including deletion of repetitive language, and document formatting revisions to reduce redundancy and potential for internal discrepancies | Do not affect the understanding, interpretation, or conduct of the protocol; therefore, have not been summarized |
| Synopsis – Primary objective – Dose escalation | Updated the objectives regarding RP2D to account for new avelumab weekly dosing regimen | To account for new avelumab weekly dosing regimen |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis – Secondary objectives – Dose escalation<br>4.1.1 Part A: Dose Escalation<br>4.2.1 Part A: Dose Escalation | | |
| Synopsis – CCI [redacted] | CCI [redacted] | CCI [redacted] |
| Synopsis – Methodology – Part A Dose Escalation<br>5.1 Overall Study Design and Plan | Added statement that Part A of the study would be performed only in the US | For clarification |
| Synopsis – Methodology – Part A Dose Escalation<br>Synopsis – Investigational Medicinal Product: dose/mode of administration/ dosing schedule<br>Synopsis – Planned study and treatment duration per subject<br>3 Background Information (throughout)<br>5.1 Overall Study Design and Plan<br>6.2.1 Avelumab<br>7.1.2 Treatment Period<br>7.1.2.1 Treatment Period for Dose Escalation | Added language for avelumab once weekly dose escalation cohort and modified treatment language to avoid inconsistencies and added Schedule of Assessments for avelumab once weekly dosing | To explore avelumab once weekly dose |
| Synopsis – Methodology – Part A Dose Escalation<br>5.1 Overall Study Design and Plan | Added statement that dose level 4 could be expanded | To allow for more subjects in dose level 4 for PK and pharmaco-dynamic investigations |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis – Methodology – Part B Expansion cohorts | Added treatment doses to be used for expansion cohorts | To provide Investigators dosing regimens to be used for expansion cohorts |
| Synopsis – Methodology – Part B Expansion<br>5.1 Overall Study Design and Plan<br>9.7 Health Authorities | Added language to specify that in the EU countries participating in the VHP the Sponsor commits to submit a substantial amendment providing complete analysis of the available safety and PK / pharmacodynamics data to justify the recommended dose | Requirement of the VHP Regulatory Authority |
| Synopsis - Planned number of subjects<br>Synopsis – Statistical methods: Part A: Dose Escalation<br>8.1 CCI<br>Part A: Dose escalation | Updated approximate number of subjects for the dose escalation | To account for new avelumab once weekly cohort |
| Synopsis – Inclusion Criteria<br>5.3.1.1 Inclusion Criteria for Dose Escalation<br>5.3.1.2 Inclusion Criteria for Expansion Cohorts | Change period for highly effective contraception from 30 days to 50 days after stopping study treatment | To provide extra safety margin |
| Synopsis – Inclusion Criteria (all cohorts except as noted for individual expansion cohorts)<br>5.3.1.1 Inclusion Criteria for Dose Escalation: | Added statement allowing subjects for whom standard therapy is not acceptable | To provide greater flexibility and not deny opportunity to receive treatment |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts | Added statement that if a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor | To avoid over burdening subjects |
| Synopsis –Inclusion Criteria for Expansion Cohorts<br>5.3.1.2 Inclusion Criteria for Expansion Cohorts: | Modified text to allow for subjects in expansion cohorts to have ALT/AST ($\leq 3 \times$ ULN) | To conform with CTCAE Grade 1 |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – NSCLC first - line cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added that never / former light smoker (< 15 pack years) squamous cell carcinoma subjects (per local standard of care), require EGFR and ALK testing if status is unknown<br>Also added statement that the cohort would not be opened for enrollment in Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom | Provide additional guidance to Investigators |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis – Key Inclusion Criteria for Expansion Cohorts<br>5.3.1.2 Inclusion Criteria for Expansion Cohorts: | Added statement that for VHP-participating countries, CRC second-line subjects must have exhausted or be ineligible or intolerant for other chemotherapies | To be in accordance with treatment guidelines in VHP-participating countries |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – RCC cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added statement that a fresh tumor biopsy is required for enrollment. If a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor.<br>Also added statement that in France, in addition to having received checkpoint inhibitor therapy, subjects should have already received recommended local standard therapy per the discretion of the Investigator | Provide additional guidance for investigators |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria<br>6.5. Prohibited Medicines | Added that granulocyte colony-stimulating factor is permitted. | Provide greater flexibility for treatment options for subjects |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria<br>6.5.2 Prohibited Medicines | Modified language lengthening washout for prior therapies | To provide extra safety margin |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria | Added language to require subject to be stable on medication and specify that they should not meet Exclusion criterion 15 | To provide clarity and additional guidance to Investigators |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria | Specified in exclusion criterion 11 that subjects with hereditary fructose intolerance will be ineligible | To provide additional guidance to Investigators |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria | Deleted tuberculosis from exclusion criteria | For consistency with other protocols in the avelumab program |
| Synopsis<br>5.1 Overall Study Design and Plan | Changed wording of duration of treatment for subjects with CR from "should" to "may" be treated for up to 24 months | Standard is 12 months treatment – language allows for more without mandating if Investigator believes more treatment would be beneficial |
| 1.1 Schedules of Assessments | Added physical examination to Cycle 1 Day 1, changed the Safety follow-up visit for the expansion cohorts to 50 days after last study drug administration, and added pregnancy testing text to EoT and Safety Follow-up visits | To provide additional safety information through a longer follow-up period and as an extra safety precaution |
| 1.1 Schedules of Assessments | Updated and added new Schedules of Assessments and footnotes to account for new schedules and to refer to text body for specifics | To account for the avelumab once weekly schedules and for additional guidance to Investigators |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.5 Safety Monitoring Committee | Added language stating the SMC will review data from the expansion cohorts | Added at request of the French RA |
| 3.6.4 Dose for Expansion Cohorts | Added new section describing the RP2D | To provide and justify study treatment doses for the expansion cohorts |
| 5.1 Overall Study Design and Plan | Added statement that there would be no waiting period between subjects in the Expansion cohorts | Safety of the infusions will have been established |
| 5.1 Overall Study Design and Plan | Updated study duration to 222 weeks | Due to added cohorts and recruitment realities |
| 5.3 Selection of Study Population | Added statement that for subjects in Germany, a legal representative is not applicable | Due to German regulatory requirements |
| 5.7 Definition of End of Study | Added language allowing subjects to possibly enter a rollover study | To possibly provide access to study treatment after end of the study |
| 6.2.1 Avelumab | Added the dose of avelumab to be used for the expansion cohorts | To provide Investigators avelumab dose to be used for expansion cohorts |
| 6.2.2.1 NHS-IL12 Dose Escalation | Table 10 updated to reflect avelumab weekly dosing | Updated to reflect avelumab weekly dosing |
| 6.2.2.2 NHS-IL12 Expansion Cohorts | Added new section with the NHS-IL12 dose to be used for the expansion cohorts | To provide Investigators NHS-IL12 dose to be used for expansion cohorts |
| 6.2.3 Modification of Treatment Administration | Modified text regarding ADRs requiring avelumab discontinuation | Updated in accordance with latest avelumab safety information and for consistency with other avelumab program protocols |
| 6.2.3 Modification of Treatment Administration | Modified text regarding ADRs requiring NHS-IL12 discontinuation | Updated in accordance with latest NHS-IL12 safety information |
| 6.5.4 Special Precautions | Text was modified updated for better readability | |
| 6.5.4.2 Management of Infusion Related Reactions | Modified text regarding infusion-related reactions to be consistent with latest IB | Modified to be consistent with the latest avelumab IB |
| 6.5.4.3 Management of Immune-related Adverse Events | Added text to be compatible with latest IB | To be compatible and in alignment with latest avelumab IB |
| 6.5.4.4 Management of Severe Hypersensitivity Reactions and Flu Like Symptoms | Deleted section | To be compatible and in alignment with latest avelumab IB |
| 6.12 Treatment of Overdose | Changed definition of avelumab overdose from 5% to 10% of calculated dose | For alignment with other avelumab program protocols |
| 7.1.1 Screening Period (Day -28 to Day -1) | Added statement allowing assessments as part of routine medical care obtained prior to signing informed consent to be used for screening | To avoid duplication and undue burden for subjects |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.1.1 Screening Period (Day -28 to Day -1) | Added statement regarding the start of highly effective contraception | To provide additional guidance to Investigators |
| 7.1.3 End of Treatment (Within 7 Days of Decision to Discontinue)<br>7.1.4 Safety Follow-Up | Changed the Safety follow-up visit for the expansion cohorts to 50 days after last study drug administration and added statement regarding pregnancy testing continuing according to schedule of assessments | To provide additional safety information through a longer follow-up period |
| 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline | Added statement that for study sites in countries with radiation exposure control for subjects, only MRI may be used and changed baseline assessment from within 18 days to within 28 days | For compliance with country-specific regulations |
| 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline | Added statement that bone metastases identified at screening should be followed at subsequent assessments | For clarification and internal consistency |
| 7.3.1 Modified Immune-Related Response Criteria | Added new section for irRECIST | Added to allow for immune-related response assessments and endpoints |
| 7.4.1.1 Adverse Event Definitions | Added definition for ADR and updated adverse events of special interest | For additional clarification and in accordance with latest avelumab safety information and for consistency with other avelumab program protocols |
| 7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities | Deleted Grade $\geq$ 3 infusion related reactions | Error correction and to be in alignment with other protocols in the avelumab program |
| 7.4.3 Clinical Laboratory Assessments – Table 14 | Updated Table and deleted ACTH | Updated to be in alignment with the avelumab program |
| 7.4.4 Vital Signs, Physical Examinations, and Other Assessments | Updated and expanded safety assessments sections to provide additional guidance and deleted blood volumes | To provide additional guidance |
| 7.6.1 Part A: Dose Escalation Biomarkers Assessments | Added additional information regarding tumor samples requirements | To provide additional information and instruct to investigators |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments | Modified language regarding pharmacogenetics and biopsy samples | To provide additional guidance to Investigators |
| 8.4 Analysis Sets | Updated PK and immunogenicity analysis sets | To provide greater specificity |
| 8.5.3.2 Immunogenicity of Avelumab and NHS-IL12 | Modified language to be consistent with the SAP | To be consistent with the SAP |
| 9.3 Subject Identification and Privacy | Deleted text regarding duration of storage of blood and tissue samples | For alignment with other studies in the program and avoid discrepancies with informed consent |

## Changes from Version 5.1 (Belgium, Czech Republic, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom) to Version 6.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Editorial changes, including deletion of repetitive language, and document formatting revisions to reduce redundancy and potential for internal discrepancies | Do not affect the understanding, interpretation, or conduct of the protocol; therefore, have not been summarized |
| Synopsis – Primary objective – Dose escalation<br>Synopsis – Secondary objectives – Dose escalation<br>4.1.1 Part A: Dose Escalation<br>4.2.1 Part A: Dose Escalation | Updated the objectives regarding RP2D to account for new avelumab weekly dosing regimen | To account for new avelumab weekly dosing regimen |
| CCI [redacted] | CCI [redacted] | CCI [redacted] |
| Synopsis – Methodology – Part A Dose Escalation<br>Synopsis – Investigational Medicinal Product: dose/mode of administration/ dosing schedule<br>Synopsis – Planned study and treatment duration per subject:<br>3 Background Information (throughout)<br>5.1 Overall Study Design and Plan<br>6.2.1 Avelumab<br>7.1.2 Treatment Period<br>7.1.2.1 Treatment Period for Dose Escalation | Added language for avelumab once weekly dose escalation cohort and modified treatment language to avoid inconsistencies and added Schedule of Assessments for avelumab once weekly dosing | To explore avelumab once weekly dose |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis – Methodology – Part A Dose Escalation<br>5.1 Overall Study Design and Plan | Added statement that dose level 4 could be expanded | To allow for more subjects in dose level 4 for PK and pharmaco-dynamic investigations |
| Synopsis – Methodology – Expansion cohorts | Added treatment doses to be used for expansion cohorts | To provide Investigators dosing regimens to be used for expansion cohorts |
| Synopsis - Planned number of subjects<br>Synopsis – Statistical methods: Part A: Dose Escalation<br>8.1 CCI<br>Part A: Dose escalation | Updated approximate number of subjects for the dose escalation | To account for new avelumab once weekly cohort |
| Synopsis – Inclusion Criteria<br>5.3.1.1 Inclusion Criteria for Dose Escalation: | Added statement allowing subjects for whom standard therapy is not acceptable | To provide greater flexibility and not deny opportunity to receive treatment |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts | Added statement that if a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor | To avoid over burdening subjects |
| Synopsis – Inclusion Criteria<br>5.3.1.2 Inclusion Criteria for Expansion Cohorts: | Modified text to allow for subjects in expansion cohorts to have ALT/AST ($\leq 3 \times$ ULN) | To conform with CTCAE Grade 1 |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – NSCLC first - line cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added France to the list of countries that would not enroll subject for this cohort | Provide additional guidance to Investigators |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts<br>5.3.1.2 Inclusion Criteria for Expansion Cohorts: | Added statement that for VHP-participating countries, CRC second-line subjects must have exhausted or be ineligible or intolerant for other chemotherapies | To be in accordance with treatment guidelines in VHP-participating countries |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – RCC cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added statement that a fresh tumor biopsy is required for enrollment. If a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor. | Provide additional guidance for investigators |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Also added statement that in France, in addition to having received checkpoint inhibitor therapy, subjects should have already received recommended local standard therapy per the discretion of the Investigator | |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria<br>6.5.2 Prohibited Medicines | Added that granulocyte colony-stimulating factor is permitted. | Provide greater flexibility for treatment options for subjects |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria<br>6.5.2 Prohibited Medicines | Modified language lengthening washout for prior therapies | To provide extra safety margin |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria | Deleted tuberculosis from exclusion criteria | For consistency with other protocols in the avelumab program |
| Synopsis<br>5.1 Overall Study Design and Plan | Changed wording of duration of treatment for subjects with CR from "should" to "may" be treated for up to 24 months | Standard is 12 months treatment – language allows for more without mandating if Investigator believes more treatment would be beneficial |
| 1.1 Schedules of Assessments | Updated Schedules of Assessments and footnotes to account for new schedules and to refer to text body for specifics | To account for the avelumab once weekly schedules and for additional guidance to Investigators |
| 2.5 Safety Monitoring Committee | Added language stating the SMC will review data from the expansion cohorts | Added at request of the French RA |
| 3.6.4 Dose for Expansion Cohorts | Added new section describing the RP2D | To provide and justify study treatment doses for the expansion cohorts |
| 5.3 Selection of Study Population | Added statement that for subjects in Germany, a legal representative is not applicable | Due to German regulatory requirements |
| 5.7 Definition of End of Study | Added language allowing subjects to possibly enter a rollover study | To possibly provide access to study treatment after end of the study |
| 6.2.1 Avelumab | Added the dose of avelumab to be used for the expansion cohorts | To provide Investigators avelumab dose to be used for expansion cohorts |
| 6.2.2.1 NHS-IL12 Dose Escalation | Table 10 updated to reflect avelumab weekly dosing | Updated to reflect avelumab weekly dosing |
| 6.2.2.2 NHS-IL12 Expansion Cohorts | Added new section with the NHS-IL12 dose to be used for the expansion cohorts | To provide Investigators NHS-IL12 dose to be used for expansion cohorts |
| 6.2.3 Modification of Treatment Administration | Modified text regarding ADRs requiring avelumab discontinuation | Updated in accordance with latest avelumab safety information and for consistency with other avelumab program protocols |
| 6.2.3 Modification of Treatment Administration | Modified text regarding ADRs requiring NHS-IL12 discontinuation | Updated in accordance with latest NHS-IL12 safety information |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.5.4.2 Management of Infusion Related Reactions | Modified text regarding infusion-related reactions to be consistent with latest IB | Modified to be consistent with the latest avelumab IB |
| 6.5.4.3 Management of Immune-related Adverse Events | Added text to be compatible with latest IB | To be compatible and in alignment with latest avelumab IB |
| 6.5.4.4 Management of Severe Hypersensitivity Reactions and Flu Like Symptoms | Deleted section | To be compatible and in alignment with latest avelumab IB |
| 6.12 Treatment of Overdose | Changed definition of avelumab overdose from 5% to 10% of calculated dose | For alignment with other avelumab program protocols |
| 7.1.1 Screening Period (Day -28 to Day -1) | Added statement allowing assessments as part of routine medical care obtained prior to signing informed consent to be used for screening | To avoid duplication and undue burden for subjects |
| 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline | Added statement that for study sites in countries with radiation exposure control for subjects, only MRI may be used and changed baseline assessment from within 18 days to within 28 days | For compliance with country-specific regulations |
| 7.2.5 CT or MRI Scans for Tumor Assessment at Baseline | Added statement that bone metastases identified at screening should be followed at subsequent assessments | For clarification and internal consistency |
| 7.3.1 Modified Immune-Related Response Criteria | Added new section for irRECIST | Added to allow for immune-related response assessments and endpoints |
| 7.4.1.1 Adverse Event Definitions | Added definition for ADR and updated adverse events of special | For additional clarification and in accordance with latest avelumab safety information and for consistency with other avelumab program protocols |
| 7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities | Deleted Grade $\geq$ 3 infusion related reactions | Error correction and to be in alignment with other protocols in the avelumab program |
| 7.4.3 Clinical Laboratory Assessments – Table 14 | Updated Table and deleted ACTH | Updated to be in alignment with the avelumab program |
| 7.4.4 Vital Signs, Physical Examinations, and Other Assessments | Updated and expanded safety assessments sections to provide additional guidance and deleted blood volumes | To provide additional guidance |
| 7.6.1 Part A: Dose Escalation Biomarkers Assessments | Added additional information regarding tumor samples requirements | To provide additional information and instruct to investigators |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments | Modified language regarding pharmacogenetics and biopsy samples | To provide additional guidance to Investigators |
| 8.4 Analysis Sets | Updated PK and immunogenicity analysis sets | To provide greater specificity |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.5.3.2 Immunogenicity of Avelumab and NHS-IL12 | Modified language to be consistent with the SAP | To be consistent with the SAP |
| 9.3 Subject Identification and Privacy | Deleted text regarding duration of storage of blood and tissue samples | For alignment with other studies in the program and avoid discrepancies with informed consent |

## Changes from Version 5.2 (US only) to Version 6.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Minor editorial and document formatting revisions | Minor; therefore, have not been summarized |
| Synopsis – Methodology – Expansion cohorts | Added treatment doses to be used for expansion cohorts | To provide Investigators dosing regimens to be used for expansion cohorts |
| Synopsis<br>5.1 Overall Study Design and Plan | Changed wording of duration of treatment for subjects with CR from "should" to "may" be treated for up to 24 months | Standard is 12 months treatment – language allows for more without mandating if Investigator believes more treatment would be beneficial |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts | Added statement that if a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor | To avoid over burdening subjects |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – NSCLC first - line cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added France to the list of countries that would not enroll subject for this cohort | Provide additional guidance to Investigators |
| Synopsis – Key Inclusion Criteria for Expansion Cohorts – RCC cohort<br>5.3.1.1 Inclusion Criteria for Expansion Cohorts: | Added statement that a fresh tumor biopsy is required for enrollment. If a subject has 2 separate biopsy attempts in which usable tissue is not obtained, enrollment may be possible after discussion with the Medical Monitor.<br>Also added statement that in France, in addition to having received checkpoint inhibitor therapy, subjects should have already received recommended local standard therapy per the discretion of the Investigator | Provide additional guidance for investigators |
| Synopsis – Exclusion Criteria<br>5.3.2 Exclusion Criteria<br>6.5.2 Prohibited Medicines | Added that granulocyte colony-stimulating factor is permitted. | Provide greater flexibility for treatment options for subjects |
| 2.5 Safety Monitoring Committee | Added language stating the SMC will review data from the expansion cohorts | Added at request of the French RA |
| 3.6.4 Dose for Expansion Cohorts | Added new section describing the RP2D | To provide and justify study treatment doses for the expansion cohorts |
| 5.3 Selection of Study Population | Added statement that for subjects in Germany, a legal representative is not applicable | Due to German regulatory requirements |
| 6.2.1 Avelumab | Added the dose of avelumab to be used for the expansion cohorts | To provide Investigators avelumab dose to be used for expansion cohorts |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.2.2.2 NHS-IL12 Expansion Cohorts | Added new section with the NHS-IL12 dose to be used for the expansion cohorts | To provide Investigators NHS-IL12 dose to be used for expansion cohorts |
| 6.5.2 Prohibited Medicines | Modified language lengthening washout for prior therapies | For consistency with statement in exclusion criteria |
| 7.1.1 Screening Period (Day -28 to Day -1) | Added statement allowing assessments as part of routine medical care obtained prior to signing informed consent to be used for screening | To avoid duplication and undue burden for subjects |
| 7.4.3 Clinical Laboratory Assessments – Table 14 | Updated Table and deleted ACTH | Updated to be in alignment with the avelumab program |
| 7.6.2 Part B: Expansion Cohorts Biomarkers Assessments | Modified language regarding pharmacogenetics and biopsy samples | To provide additional guidance to Investigators |
| 9.3 Subject Identification and Privacy | Deleted text regarding duration of storage of blood and tissue samples | For alignment with other studies in the program and avoid discrepancies with informed consent |

## Changes from Version 4.0 to Version 5.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>Synopsis<br>Signature pages | Added EudraCT number | Study will now include sites in the EU |
| Synopsis – Study centers / county | Added number of study centers to be included in the study | Was not included previously as prior to expansion, was a singe center study |
| Synopsis – Planned study period | Updated the last subject out | |
| Synopsis – Trial registry<br>2 Sponsor, Investigators and Study Administrative Structure | Updated language in the trial registries | New registries due to expansion of study to EU and other countries |
| Synopsis - Objectives | Updated objectives to account for expansion cohorts | To account for expansion cohorts |
| Synopsis - Methodology | Updated language in the methodology describing the study | To account for new expansion cohorts |
| Synopsis – Planned number of subjects | Updated planned number of subjects to be enrolled in the study | To account for subjects in the new expansion cohorts |
| Synopsis – Primary endpoints<br>8.3.1.1 Part A: Dose Escalation<br>8.3.1.2 Part B: Expansion Cohorts | Updated primary endpoints | To account for new expansion cohorts |
| Synopsis – Secondary endpoints<br>8.3.2.1 Part A: Dose Escalation<br>8.3.2.2 Part B: Expansion Cohorts | Updated secondary endpoints and deleted PK parameters | To account for new expansion cohorts – deleted PK parameters to avoid redundancy |
| CCI [redacted] | CCI [redacted] | CCI [redacted] |
| Synopsis - Pharmacokinetics | Deleted reference to comparing PK profiles across cycles | |
| Synopsis - Pharmacokinetics | Clarified that ADAs for each molecule will be determined | Changed for better clarity |
| CCI [redacted] | CCI [redacted] | CCI [redacted] |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis – Other assessments<br>7.6.2 Part B: Expansion Cohorts Biomarkers Assessments | Added biomarker assessments for the expansion cohorts | To account for new expansion cohorts |
| Synopsis – Inclusion criteria | Updated inclusion criteria to account for new expansion cohorts | To account for new expansion cohorts |
| Synopsis – Inclusion criteria<br>5.3.1.1 Inclusion Criteria for Dose Escalation: | Updated contraception language to reduce post-treatment requirement from 60 days to 30 days | Changed for consistency with latest safety and PK information and current IB |
| Synopsis – Key exclusion criteria<br>5.3.2 Exclusion Criteria (Applicable to all Subjects, Including all Expansion Cohorts) | Modified language to allow palliative radiotherapy delivered in a normal organ-sparing technique | To not be too restrictive |
| Synopsis – Exclusion criteria<br>5.3.2 Exclusion Criteria | Added new exclusion criterion for the NSCLC, CRC and UC cohorts that previous immune checkpoint inhibitor therapy is not permitted | To account for specific exclusion criteria in the new expansion cohorts |
| Synopsis – Investigational Medicinal Product: dose/mode of administration/ dosing schedule<br>6.2.1 Avelumab | Updated language regarding avelumab premedication requirements | Updated due to accumulating safety information on avelumab and infusion-related reactions |
| Synopsis – Investigational Medicinal Product: dose/mode of administration/ dosing schedule | Added new language for NHS-IL12 administration for the expansion cohorts and clarified that dose reductions for NHS-IL12 are permitted | To account for treatment in the new expansion cohorts at the RP2D |
| Synopsis – Planned study and treatment duration per subject: | Modified treatment discontinuation language and added new language providing continued treatment for subjects with clinical responses | To address and internal inconsistency and to provide new guidance for Investigators allowing continued treatment for subjects who may benefit |
| Synopsis – Statistical methods | Provided justification for the number of subjects in the expansion cohorts | Updated to account for the new expansion cohorts |
| Table 2 | Clarified EOI (1h) abbreviation | For better clarity |
| Table 3 and Table 4 | Added new Schedule of Assessments Tables for the expansion cohorts | To provide schedule of assessments for new expansion cohorts |
| 2.1 Investigational Sites | Updated information on study sites | To account for expansion to new |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | | sites due to addition of expansion cohorts |
| 2.2 Coordinating Investigator | Updated section for the Coordinating Investigator | Updated due to study becoming multicenter and to be in accordance with new template language |
| 2.5 Safety Monitoring Committee | Clarified that the SMC will monitor safety data throughout the duration of the study | Added language for greater clarity |
| 3 Background Information | Added statement regarding new expansion cohorts | To introduce and account for new expansion cohorts |
| 3.2.1 Supporting Clinical Data for Avelumab | Modified language to refer to the IB for updated information on current studies | To refer to the current IB to account for new and ongoing studies |
| 3.2.1 Supporting Clinical Data for Avelumab | Modified language to refer to the IB for updated information on current studies | To refer to the current IB to account for new and ongoing studies |
| 3.2.1 Supporting Clinical Data for Avelumab | Updated avelumab clinical efficacy section with new information | Updated due to new information on avelumab efficacy in several indications |
| 3.4 Study Rationale | Updated study rationale to provide rationales for the expansion cohorts | To provide rationales for the expansion cohorts |
| 3.5 Rationale for Study Design | Updated the rationale for the study design and added language stipulating that dose reductions of NHS-IL12 are allowed | To account for new expansion cohorts |
| 3.5.1 Rationale for Endpoints | Added rationale for the primary endpoint for the expansion cohorts | To provide rationale for BOR as the primary endpoint for the expansion cohorts |
| 4.1 Primary Objectives | Updated primary objectives to account for expansion cohorts | To account for expansion cohorts |
| 4.2 Secondary Objectives | Updated secondary objectives to account for expansion cohorts | To account for expansion cohorts |
| 4.3 CCI [redacted] | [redacted] | [redacted] |
| 5.1 Overall Study Design and Plan | Updated study design to include the expansion cohorts | To account for expansion cohorts |
| 5.1 Overall Study Design and Plan | Updated and corrected the treatment duration | To correct internal contradiction of when subjects must discontinue treatment and to allow treatment to continue passed initial PD and provide guidance on treatment for subjects with response |
| 5.2 Discussion of Study Design | Updated the discussion of the study design to account for the expansion cohorts | Updated to account for the expansion cohorts |
| 5.3.1.1 Inclusion Criteria for Dose Escalation: | Updated contraception language to reduce post-treatment requirement from 60 days to 30 days | Changed for consistency with latest safety and PK information and current IB |
| 5.3.1.2 Inclusion Criteria for Expansion Cohorts: | Added new section of inclusion criteria for the expansion cohorts | To provide inclusion criteria for the expansion cohorts |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.5.1 Withdrawal from Study Therapy | Updated language to account for expansion cohorts and specified the subjects within the dose-escalation could be replaced | Modified in order to account for the expansion cohorts |
| 6.2.4 Modification of Treatment Administration | Added bullet point providing allowance for continuing therapy in subjects with asymptomatic Grade ≥ 3 lipase or amylase elevation | To give up-to-date guidance to Investigators and allow subjects who may benefit to continue treatment |
| 6.2.4 Modification of Treatment Administration | Added bullet providing reference to individual sections for how to manage cytokine-release syndrome, infusion-related reactions, irAEs and hypersensitivity reactions | To give up-to-date guidance to Investigators and allow subjects who may benefit to continue treatment |
| 6.5.2 Prohibited Medicines | Modified language to allow palliative radiotherapy delivered in a normal organ-sparing technique | To not be too restrictive |
| 6.5.3 Other Interventions | Modified language to allow palliative radiotherapy delivered in a normal organ-sparing technique | To not be too restrictive |
| 6.4 Noninvestigational Medicinal Products to be Used | Added language mandating premedication for the first 4 avelumab infusions only and then according to any infusion reactions thereafter | Updated in oreder to provide latest guidance to Investigators for avelumab premedication |
| 6.5.4 Special Precautions | Modified language regarding stopping avelumab treatment in case of Grade ≥ 2 hypersensitivity, inflammatory response, or infusion-related reaction. | To be in accordance with current guidance on management of possible infusion reactions and to give Investigators more flexibility |
| 6.5.4.2 Management of Infusion Related Reactions– Table 9 | Updated Table 9 to delete total infusion time not to exceed 120 minutes | To be in accordance with current guidance on management of possible infusion reactions to give Investigators more flexibility |
| 6.5.4.3 Management of Immune-related Adverse Events | Updated Table providing latest guidance for management of possible immune-related AEs | To give Investigators current guidance on management of possible irAEs |
| 7.1 Schedule of Assessments | Updated language to account for escalation cohorts | Updated language to account for expansion cohorts |
| 7.1.1 Screening Period (Day -28 to Day -1) | Added information regarding tumor samples for expansion cohorts | To account for expansion cohorts |
| 7.1.2 Treatment Period | Updated language to allow subjects to continue treatment beyond initial assessment of PD | Updated to correct internal contradiction that subjects may continue treatment beyond initial assessment of disease progression |
| 7.1.2.2 Treatment Period for Expansion Cohorts | Added new section for treatment period for the expansion cohorts | Added section to account for treatment period for expansion cohorts |
| 7.2.2 Diagnosis of Tumor | Added MSI status for CRC expansion cohort and PD-L1 expression and EGFR and ALK status for NSCLC expansion cohort | To have better understanding of tumor baseline characteristics versus response |
| 7.2.4 Vital Signs and Physical Examination | Added guidance for the collection of vital signs from treatment cycle 2 onwards for the | To provide guidance to Investigators and decrease the |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | expansion cohorts | intensity of mandatory vital sign collection for the expansion cohorts |
| 7.2.6 Cardiac Assessments | Added ECGs for the expansion cohorts | To provide guidance for ECGs for the expansion cohorts |
| 7.3 Efficacy Assessments | Modified language to change from irRC to iorRECIST | Changed to use updated immune-response criteria and to align programmatically |
| 7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities | Updated to be in compliance with new template and guidelines | Updated due to new guidelines |
| 7.5 Pharmacokinetics | Updated blood volumes to account for the expansion cohorts | Updated to account for escalation cohorts |
| 7.5 Pharmacokinetics | CCI [redacted] | CCI [redacted] |
| 7.7 CCI [redacted] | CCI [redacted] | CCI [redacted] |
| 7.7 CCI [redacted] | CCI [redacted] | CCI [redacted] |
| 7.8 Total Blood Collection for Clinical Assessments | Updated blood volumes to be collects to account for expansion cohorts | Updated to account for expansion cohorts |
| 8.1 CCI [redacted] | Added justifications for numbers of subjects in the expansion cohorts | To provide justification and power estimates for the number of subjects in the expansion cohorts |
| 8.3.2.1 Part A: Dose Escalation<br>8.3.2.2 Part B: Expansion Cohorts | Updated secondary endpoints and deleted PK parameters | To account for new expansion cohorts – deleted PK parameters to avoid redundancy |
| 8.4 Analysis Sets | Corrected the Immunogenicity Analysis Set and added Efficacy analysis set | Top correct mistake in the original text and account for expansion cohorts |
| 8.5.2.3 Part A: Dose Escalation and Part B: Expansion Cohorts Confirmed Best Overall Response per RECIST 1.1 | Updated analysis of the primary endpoints to include the BOR for the expansion cohorts | Updated to account for the expansion cohorts |
| 8.5.3.1 Pharmacokinetic Profile | Deleted reference to comparing PK profiles across cycles | To provide updated analysis plan |
| 8.5.3.2 Immunogenicity of Avelumab and NHS-IL12 | Added new text regarding the reporting of ADAs | To provide updated analysis plan |
| 8.6.2 Part B: Expansion Cohorts | Added new section for expansion cohorts interim analyses | To account for the expansion cohorts |

## Changes from Version 3.0 to Version 4.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1-1 | Added visit windows to the Schedule of Assessments | For clarity and internal document consistency |
| Table 1-1 Footnote "a: | Corrected on-treatment visit window to -3 / +1 days | To provide more flexibility and for programmatic consistency |
| Table 1-2 | Deleted blood samples for immune-monitoring biomarkers at Cycle 1 Day 2, 3, and 8 timepoints and added footnote that in the event of an irAE requiring steroid treatment, a sample for immune-monitoring should be collected, prior to steroid treatment, though sample is not required | To be less burdensome for subjects and to provide extra guidance to Investigators |
| Table 1-2 | Added superscript and footnote for PK, Soluble factors, and target occupancy indicating optional sample on Cycle 1 Days 17, 22 and 25 and Cycles 3 and 4 on Day 3 | To be less burdensome for subjects and to provide extra guidance to Investigators |
| 5.1 Overall Trial Design and Plan | Deleted statement that subjects must stay on dose they were assigned | Subjects in Cohorts 2 through 4 will now be able to de-escalate 1 dose level |
| 5.1 Overall Trial Design and Plan | Added statement that subjects in Cohorts 2 through 4 who experience a DLT will be allowed to continue treatment at 1 dose level lower | To allow subjects who may benefit to continue treatment |
| 5.5.1 Withdrawal from Trial Treatment | Deleted statement that subjects in Dose levels 2 through 4 must discontinue if they experience a DLT and added statement that they will be allowed to continue treatment at 1 dose level lower | To allow subjects who may benefit to continue treatment |
| 6.5.4.3 Immune-Related Adverse Events – Table 6-4 | Made correction in management of Cardiac irAEs (Myocarditis) | To correct error that suggested to hospitalize only in the presence of life-threatening cardiac decompensation |
| 7.1.2 Treatment Period | Modified language describing the treatment period (deleting bullet lists of all assessments) | To conform with protocol template instructions and to minimize the chance of discrepancies between text and Schedule of Assessments |
| 7.1.3 End of Treatment (Within 7 Days of Decision to Discontinue) | Modified language describing the treatment period (deleting bullet lists of all assessments) | To conform with protocol template instructions and to minimize the chance of discrepancies between text and Schedule of Assessments |
| 7.1.4 Safety Follow-Up | Modified language describing the treatment period (deleting bullet lists of all assessments) | To conform with protocol template instructions and to minimize the chance of discrepancies between text and Schedule of Assessments |
| 7.5 Pharmacokinetics<br>7.7 Immunogenicity Analysis | Corrected serum sample storage language | To provide proper guidance to investigators and site staff for storage of serum samples |
| 7.6 Biomarkers | Updated blood volume to be collected at Cycle 1 as a result of the deletion of samples | Decreased volume due to deletion of samples for immune- |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | for immune-monitoring biomarkers at Cycle 1 Day 2, 3, and 8 | monitoring biomarkers at Cycle 1 Day 2, 3, and 8 |
| 7.7 Immunogenicity Analysis | Added statement specifying that predose serum samples may be used interchangeably for PK and ADA analyses | To allow greater flexibility for serum sample analysis |
| 7.8 Total Blood Collection for Clinical Assessments | Updated total blood volume to be collected at Cycle 1 as a result of the deletion of samples for immune-monitoring biomarkers at Cycle 1 Day 2, 3, and 8 | Decreased volume due to deletion of samples for immune-monitoring biomarkers at Cycle 1 Day 2, 3, and 8 |
| Sponsor Responsible Persons not Named on the Cover Page | Updated the Biostatistician | Updated due to change in personnel |

## Changes from Version 2.0 to Version 3.0 included in the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>Trial center/country | Text modification | Make an administrative change to update the number of sites. |
| Synopsis Pharmacogenetics | Text modification | Add language regarding pharmacogenetic assessments to address clinically relevant germline findings. |
| 2.1<br>Investigational Sites | Text modification | Make an administrative change to update the number of sites. |
| 6.2.4<br>Modification of Treatment Administration, Adverse Drug Reactions requiring avelumab discontinuation | Text modification | Resolve discrepancy between Section 6.2.4 (Modification of Treatment Administration) and Section 7.4.1.5 (Dose-Limiting Toxicities) to clarify Grade 3 adverse drug reactions which require treatment discontinuation. |
| 6.2.4<br>Modification of Treatment Administration, Adverse Drug Reactions requiring avelumab discontinuation | Text modification | Resolve discrepancy between Section 6.2.4 (Modification of Treatment Administration) and Section 7.4.1.5 (Dose-Limiting Toxicities) to clarify Grade 3 adverse drug reactions which require treatment discontinuation. |
| Table 6-3 | Table modification | Clarify that the total infusion time of avelumab must not exceed 120 minutes is applicable to Grade 2 infusion-related reactions, as well as Grade 1, and that the 120 minutes refers only to the time that avelumab is actively being infused. |
| Table 6-3 | Table modification | Clarify that the total infusion time of avelumab must not exceed 120 minutes is applicable to Grade 2 infusion-related reactions, as well as Grade 1, and that the 120 minutes refers only to the time that avelumab is actively being infused. |
| 7.6<br>Biomarkers | Text modification | Add language regarding pharmacogenetic assessments to address clinically relevant germline findings. |

## Changes from Version 1.0 to Version 2.0 included in the Amendment:

| Section | Change | Brief Rationale |
|---|---|---|
| Synopsis Inclusion Criteria<br>Section 5.3.1 Inclusion Criteria | Text modification | Revise the eligibility criterion regarding prior therapy to express the following: Subjects must be refractory to, or intolerant of established therapy known to provide clinical benefit for their condition, ie, subjects must not be candidates for regimens known to provide clinical benefit. |
| 6.2.4 Modification of treatment administration Adverse Drug Reactions requiring avelumab discontinuation | Text modification | Correct a typographical error about continuing avelumab treatment in the case of change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days. |
| 6.2.4 Modification of treatment administration Adverse Drug Reactions requiring NHS-IL12 discontinuation | Text addition | List criteria for treatment delay with NHS-IL12. Additionally, specify the duration of treatment delay (usually7 days) that results in a subject being discontinued from study treatment, and, if in cycle 1, listed as a DLT event. |
| 7.4.1.1 Adverse Event Definition | Text modification | Update definitions for "unrelated" and "related" adverse event. |