Statistical Analysis Plan for the Dose Escalation Phase

Clinical Trial Protocol Identification No.	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	Phase Ib
Investigational Medicinal Product(s)	Avelumab and NHS-IL12 combination
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Statistical Analysis Plan Authors	PPD PPD PPD
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Statistical Analysis Plan Reviewers	PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD

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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.

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3 List of Abbreviations and Definition of Terms

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
AUCτ	Area under the concentration-time curve from time zero to τ hours after dosing
AUC0-∞	Area under the concentration-time curve from time zero extrapolated to infinity
AUC0-∞ /Dose	Dose normalized AUC0-∞
AUC0-t	Area under the concentration-time curve from 0 to last quantifiable concentration
AUC0-t /Dose	Dose normalized AUC0-t
AUCextra	Percentage of AUC0-∞ obtained by extrapolation
AUCτ /Dose	Dose normalized AUCτ
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
BMI	Body Mass Index
BOR	Best Overall Response
Ceoi	Concentration observed immediately at the end of infusion
CI	Confidence Interval
CL	Total body clearance of drug following intravenous administration
CL/f	Apparent total clearance (extravascular)
Clast	Last quantifiable concentration

Cmax	Maximum observed concentration
Cmax/Dose	Dose normalized maximum concentration.
COVID-19	2019 Novel Coronavirus Disease
CPD	Confirmed Progressive Disease
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castrate resistant Prostate Cancer
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
Ctrough	Concentration observed immediately before next dose (corresponding to pre-dose or trough concentration for multiple dosing)
CV	Coefficient of variation
DI	Dose Intensity
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EOT	End Of Treatment
FAS	Full Analysis Set
GeoCV	Geometric coefficient of variation

GeoMean	Geometric mean
GGT	Gamma Glutamyl Transferase
H1	Histamine H1 receptor
HB	Hemoglobin
HR	Heart Rate
IAS	Immunogenicity Analysis Set
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMP	Investigational Medical Product
irAE	Immune Related Adverse Event
irBOR	Immune Related Best Overall Response
irCR	Immune-Related Complete Response
irCPD	Immune-Related Confirmed Progressive Disease
irOR	Immune Related Objective Response
irORR	Immune Related Objective Response rate
irPD	Immune-Related Progressive Disease
irPR	Immune-Related Partial Response
IRR	Infusion-Related Reaction
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
irSD	Immune-Related Stable Disease
irTRAE	Immune-Related Treatment Related Adverse Event
irUPD	Immune-Related Unconfirmed Progressive Disease
IV	Intravenous
LDH	Lactate Dehydrogenase

LLN	Lower limit of normal
LLOQ	Lower Limit of Quantification
logFC	Log fold change from baseline
MAD	Maximum Administred Dose
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MSSO	Maintenance and Support Services Organization
MTD	Maximum Tolerated Dose
N	Number
NC	Not Calculable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not evaluable
Non-CR/Non-PD	Non-Complete Response/Non-Progressive Disease
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCSA	Potentially Clinically Significant Abnormalities
PD	Progressive Disease
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival

PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
q4w	every 4 weeks
QPD	Quantitative Pharmacology and Drug Disposition
QTCF	QT Interval Corrected Using Fridericia's Formula
Racc(AUC)	Accumulation factor for the area under the curve
Racc(Cmax)	Accumulation factor for the maximum concentration
RBC	Red Blood Cell
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
Std	Standard deviation
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Event
t_{last}	Time at which last quantifiable concentration occurs
TLF	Tables, Listings, and Figures

t_{max}	Time of maximum concentration
TNM	Tumor Node Metastasis Classification of Malignant Tumors
TR	Treatment Related
TRAE	Treatment Related Adverse Event
TRIRR	Treatment-Related Infusion-Related Reaction
TTR	Time to Response
ULN	Upper limit of normal
ULOQ	Upper Limit of Quantification
UPD	Unconfirmed Progressive Disease
VZ	Apparent volume of distribution during the terminal phase (intravenous)
VZ/f	Apparent volume of distribution during the terminal phase (extravascular)
WBC	White Blood Cells
WHO	World Health Organization
λz	Terminal rate constant
τ	Dosing interval

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	20 September 2018	PPD	Not applicable-first version
2.0	20 October 2020	PPD	1. CCI [redacted] 2. Section 12.1: added a description for the overview of the impact of COVID-19 events. 3. Section 12.2: added an analysis of COVID-19 related protocol deviations. 4. CCI [redacted] 5. Section 17.1.1: added a listing of COVID-19 related events. 6. Section 17.1: updated the definition of immune-related adverse events and infusion-related reactions (appendix 20.4 added)

5 Purpose of the Statistical Analysis Plan

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for the Dose Escalation phase under protocol MS201781-0031. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR. The analyses of the data for Expansion Cohorts will be specified in a separate SAP.

The SAP is based upon section 8 (Statistics) of the Clinical Trial Protocol (CTP) and protocol amendments and is prepared in compliance with ICH E9.

6 Summary of Clinical Study Features

Study 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 NHS-IL12 and avelumab when given in combination in subjects with metastatic or locally advanced solid tumors. **Secondary** Part A: Dose Escalation • To characterize pharmacokinetic (PK) profiles of avelumab and NHS-IL12 when given in combination • To determine the RP2D of NHS-IL12 and avelumab when given in combination • To evaluate the immunogenicity of combination therapy with NHS-IL12 and avelumab • To evaluate preliminary antitumor activity of combination therapy with NHS-IL12 and avelumab. CCI [redacted]
Study Endpoints	**Primary** **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. **Secondary** **Part A: Dose Escalation** • PK profiles of avelumab and NHS-IL12 • Immunogenicity of avelumab and immunogenicity of NHS-IL12 in combination therapy, as measured by anti-drug 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. CCI [redacted]
Study Design	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 NHS-IL12 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 NHS-IL12 every 4 weeks (q4w) with fixed avelumab dose. Additional subjects may be added to dose level 4 for PK and pharmacodynamic evaluations. The observation period for 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 NHS-IL12 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. In addition to the above NHS-IL12 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 NHS-IL12 at the NHS-IL12 MTD once every 4 weeks, then avelumab at 800 mg once every 2 weeks plus NHS-IL12 at the NHS-IL12 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 NHS-IL12 dose. The avelumab once weekly cohort will enroll up to 6 subjects using the same 3 + 3 rules as outlined. **Definition of DLT** With some exceptions in protocol Section 7.4.1.5, a DLT is defined as any Grade $\geq$ 3 non-hematologic adverse event (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 during the DLT evaluation period 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.
Number of Subjects	Part A: Dose Escalation Approximately 45 subjects.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule	**Avelumab** 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. 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. **NHS-IL12** NHS-IL12 – Dose Escalation: Subjects will receive NHS-IL12 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 NHS-IL12 will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of NHS-IL12 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.
Treatment and Study Duration	The anticipated duration of the whole study including follow-up period is 124 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 protocol Section 6.13.
Study Periods	1. Screening Period (days -28 to -1) 2. Treatment period A single treatment cycle is 28 days long. Avelumab administration will be according to cohort (dose-escalation / avelumab once weekly cohort); NHS-

	IL12 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 NHS-IL12 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) should be treated 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. 3. Follow-up period Subjects without progressive disease and who are not receiving subsequent anti-cancer therapy after the EOT 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 progressive disease 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.
Randomization and Blinding	Not applicable.

7 Sample Size/Randomization

Part A: Dose Escalation

This is a non-randomized dose-escalation study (modified 3 + 3 design). No formal statistical comparison between dose levels will be performed. Summary statistics used to describe the study population may include means, medians, ranges, and appropriate measures of variability; qualitative variables will be summarized by counts and percentages.

Approximately 45 subjects will be enrolled, though the final sample size may vary depending on

the total number of dose levels to be escalated and tested and the subject replacement for DLT evaluations if applicable. Subjects who do not fulfill the treatment and safety requirements during the first 3 weeks after administration in each dose level will be replaced.

A minimum of 12 subjects will be required when only 2 dose levels need to be tested to establish the MTD of avelumab in the combination with NHS-IL12. A maximum of 24 DLT-evaluable subjects will be required when all 4 NHS-IL12 dose levels need to be tested. At each dose level, 3 to 6 subjects will be treated depending on toxicities observed, though all dose levels until MTD determination will ultimately be filled with 6 subjects. Subjects who do not fulfill the treatment and safety requirements during the first 3 weeks after administration in each dose level will be replaced. Another 6 evaluable subjects will be enrolled into the avelumab once weekly cohort. The Sponsor may also choose to open additional avelumab once weekly cohorts at a NHS-IL12 dose level below the MTD. The final sample size may vary depending on the total number of dose levels to be escalated and tested and the subject replacement for DLT evaluations if applicable; therefore, approximately 45 subjects (including non-evaluable subjects) will be enrolled for the escalation phase of the study.

8 Overview of Planned Analyses

This SAP covers the analyses for safety and efficacy at the end of the dose escalation part of the study. Statistical analyses will be performed after the end of study and database lock using cleaned eCRF data as well as external data including pharmacokinetic/pharmacodynamic data, immunogenicity, and biomarkers. 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.

There will be one planned analysis after the end of study for all the dose escalation dose levels. For each dose level, after 3 subjects are treated for 3 weeks, the study data (presented as patient profiles) will be evaluated by a SMC before decision is made to go to the next dose level. No interim analysis is planned for this study but a safety summary with a subset of outputs will be produced .

A further separate SAP for the expansion phase of the study will be developed.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The COVID-19 pandemic was unforeseen at the time of the development of the clinical trial protocol; therefore, analyses related to the COVID-19 pandemic have been added later to the analysis plan.

No changes to the planned analysis of the efficacy endpoints will be performed due to the impact of COVID-19 outbreak.

Instead, additional outputs (summary tables and listings) will be generated to assess potential impacts of COVID-19 on this study and are described in Section 12.1, Section 12.2, and Section 17.1.1.

10 Analysis Sets

Table 1 summarizes the use of the analysis sets in the different analyses.

Table 1 Statistical Analysis by Analysis Set

Analyses	Safety Analysis Set	Full Analysis Set	DLT Analysis Set	PK Analysis Set	Immuno-genicity Analysis Set	BASto* BAScp**
Demographics/ Baseline Characteristics	✓					
Prior and Concomitant Therapies	✓					
Exposure	✓					
Safety	✓					
MTD, DLT			✓			
Efficacy		✓				
Pharmacokinetics				✓		
Immunogenicity					✓	
CCI						✓

*CCI

** CCI

CCI

Number of subjects in each analysis set will be tabulated by dose level and overall. A table by sites will also be provided.

10.1 Screened Analysis Set

The screening analysis set includes all subjects who signed the informed consent form (ICF). The number of screened subjects will be presented.

10.2 Safety Analysis Set (SAF)

All subjects who receive at least 1 dose (complete or incomplete) of any IMP (Avelumab or NHS-IL12). Subjects will be classified according to the dose level of NHS-IL12 and Avelumab actually received.

10.3 Full Analysis Set (FAS)

In this non-randomized study the SAF and FAS are identical.

10.4 DLT Analysis Set (DLT 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.

Subjects will be classified according to the dose level of IMP actually received.

10.5 PK Analysis Set

The PK Analysis Set will consist of all subjects who receive at least one complete dose (at least 90% of planned dose) of Avelumab and NHS-IL12, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration of Avelumab or NHS-IL12. Subjects will be analyzed according to the first dose level of IMP actually received.

The description of important protocol deviations can be found in the Appendix 20.1. The important events affecting PK will be a subset of documented handling error. These events will be checked at latest during the Data Review Meeting and the decision will be taken whether the event is leading to the exclusion from PK set.

All PK analyses will be based on this analysis set.

10.6 Immunogenicity Analysis Set (IAS)

All subjects who complete at least one complete dose (at least 90% of planned dose) of Avelumab or NHS-IL12 and at least 1 valid ADA result for avelumab or NHS-IL12 .

Subjects will be classified according to the dose level of IMP actually received.

CCI [redacted]

CCI [redacted]

10.9 Other Analysis Sets

The following additional analysis sets for Escalation phase are defined in the protocol:

CCI [redacted]

Biomarker Analysis Set for Pharmacogenetics / Pharmacogenomics: All subjects who have provided a whole blood sample prior to any avelumab and NHS-IL12 treatment.

The statistical analysis of selected biomarkers based on these analysis sets will be described in a separate Exploratory Biomarker Analysis SAP.

11 General Specifications for Statistical Analyses

11.1 Data handling after the cut-off date

Not Applicable

11.2 Pooling of centers

Not applicable

11.3 Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values, [n (missing)], mean, median, standard deviation (Std), minimum, maximum and first and third quartile (Q1 and Q3).

For time-to-event variables analysed using Kaplan Meier approach the following statistics will be presented: number of subjects with events, median, minimum, maximum and 95% confidence interval.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

11.4 Definition of baseline

The last available assessment prior to the start of study treatment is defined as "baseline" value or "baseline" assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on treatment day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on treatment day 1 will be considered to have been obtained after study treatment administration.

Subjects who start treatment and discontinue from the study on the same day may have two different sets of data collected on treatment Day 1 (one during study and one in the end of treatment [EOT] visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

11.5 Definition of study treatment day

Treatment day is defined relative to the date of start of treatment. Treatment Day 1 defines the day of first administration of treatment, the day before is defined as Treatment Day –1 (no Treatment day 0 is defined). The Treatment Day X is defined as Date of treatment – Date on first administration of treatment + 1.

11.6 Definition of on-treatment period

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

The date of new anti-cancer therapy after treatment start is collect in eCRF pages "Anti-Cancer Treatment after Discontinuation Details"

11.7 Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age

  Age [years] = (date of given informed consent - date of birth + 1) / 365.25

  In case the day or the day and the month of the date of birth and the date of informed consent is unknown, the following approach will be used:

  In case of missing day: Age [years] = (year/month/01 of given informed consent – year/month/01 of birth + 1) / 365.25

  In case only year of birth is given: Age [years] = (year/01/01 of given informed consent year/01/01 of birth +1) / 365.25

  The integer part of the calculated age will be used for reporting purposes.

- Duration

  Duration will be calculated as Stop Date – Start Date + 1, unless otherwise specified.

  The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event. In general, the reference date will be the date of first dose of study treatment.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g. 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6. However, maximum of available decimal will be kept in ADaM dataset.

All statistical analyses will be performed using SAS® Version 9.2 or higher.

11.8 Presentation of Pharmacokinetic Results

For measurement of NHS-IL12 concentrations, up to 3 analytical methods have been used per sample. For the secondary endpoint analyses described below, Merck Assay ID 1.2.1 will be used, which measures intact NHS-IL12. The results from other methods (Merck Assay IDs 1.1.1 and 2.1.1) will be included in the SDTM.

11.8.1 Presentation of Pharmacokinetic Concentration Data

Pharmacokinetic concentration data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (Std), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant figures
Std:	4 significant figures
CV%:	1 decimal place

For the PK concentration data Ctrough and Ceoi the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM) will be additionally reported with the following conventions:

GeoMean, 95% CI:	3 significant figures
GeoCV%:	1 decimal place

11.8.2 Presentation of Pharmacokinetic Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (Std), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM).

PK parameter C_{max} will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the Study Data Tabulation Model (SDTM) PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant figures
Std:	4 significant figures
CV%, GeoCV%:	1 significant figure

11.9 Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

11.10 Missing data and Imputation rules

All data will be evaluated as observed, and no imputation method for missing values will be used except for the cases described in the sections 11.10.1-11.10.6.

In all subject data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as 'Not Calculable' or 'Not Applicable'. For example, if N=1, the measure of variability (Std) cannot be computed and should be presented as 'NC'.

For PK data to report statistics that are not calculated due to insufficient data 'NC' (for Not Calculable) will be used.

11.10.1 Disease history

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

11.10.2 Adverse Events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

11.10.3 Exposure

- For each treatment, in case the last date of study drug is incomplete the date of last administration of study drug will be taken from the treatment termination eCRF pages.

11.10.4 Last Alive Date

The last alive date will be derived for subjects not known to have died at the analysis cut-off using the latest complete date among the following:

- All subject assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Date last known to be alive collected on the eCRF form "Subject Status / Survival Follow-up"

- Study drug start and end dates
- Date of discontinuation from the "Study Termination" eCRF page (not used if reason for discontinuation is lost to follow-up)

Only dates associated with actual examinations of the subject will be used in the derivation. Dates associated with a technical operation unrelated to subject status such as the date a blood sample was processed will not be used.

11.10.5 Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as day after date of last contact from the CRF survival page
- If the day or both day and month are missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

If the day is missing from the date of last contact it will be imputed to 1st day of the month and year of last contact only if derived from the survival page.

11.10.6 Tumor assessments

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g. X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

11.11 Inferential Methods

Not applicable.

12 Study Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/study discontinuations. Additionally procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

Overall summary of analysis sets will be tabulated using frequency and percentage by dose level (if applicable) and overall based on all the subjects who signed informed consent form (ICF) and entered the study. The number of subjects in SAF analysis will be used as the denominator.

- Number of subjects who signed ICF
- Number of subjects in SAF analysis set
- Number of subjects still on treatment
- Number of subjects who permanently discontinued the study treatment along with the reason will be presented separately for Avelumab and NHS-IL12.
- Reasons off-treatment will be presented as collected on the "NHS-IL12 Termination" and "Avelumab Termination" eCRF page:
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Disease progression
    - Withdrew consent
    - Other
- Number of subjects who discontinued both treatments but are still in follow-up ("Study Termination" eCRF page is not completed)
- Number of subjects with avelumab re-initiation
- Number of subjects with NHS-IL12 re-initiation ("Re-Initiated Nhs-Il12 Termination" eCRF page is completed)
- Number of subjects off-study

  Reasons off-study (as collected on the "Study Termination" eCRF page)
    - Lost to follow-up

- Death
- Withdrew consent
- Other

The listing of subject disposition will include all subjects who signed ICF (i.e. including screening failures).

The listing will include the following information: subject identifier, date of informed consent, continue beyond screening, date and reason for not continuing beyond screening, assigned dose level for Avelumab and NHS-IL12, first treatment date for Avelumab and NHS-IL12, date of last administration and primary reason for permanent treatment termination of NHS-IL12 (as reported on "NHS-IL12 Termination" eCRF page), date of last administration and primary reason for permanent treatment termination of Avelumab (as reported on "Avelumab Termination" eCRF page,), date and reason for study termination (as reported on"Study Termination" eCRF page), flags for the SAF and the DLT set.

A separate listing for reason for EOT due to adverse events (AEs) will be provided. The listing will be restricted to the SAF subjects who are off-treatment due to an AE, and will include the following information: dose level, subject identifier, first / last treatment date of NHS-IL12 or Avelumab, date off-treatment of NHS-IL12 or Avelumab, and the relevant AE system organ classes (SOCs), preferred terms (PTs) and AE relationship to the study treatment.

The indirect impact of COVID-19 will be assessed as follows:

- The number and percentage of participants in pre/during/post COVID-19 study period will be provided:
  - Number of subjects who started treatment prior to the COVID-19 study period
    - Received at least one dose during the COVID-19 study period
    - Discontinued treatment before start of the COVID-19 study period
  - Number of subjects who started treatment during the COVID-19 study period
  - Number of subjects who started treatment posterior to the COVID-19 study period*

    * No participants will be categorized into the "post COVID-19 study period".

The COVID-19 study period is defined as follows:

- The start of COVID-19 study period will be defined by country as the minimum of the date of the first death from COVID-19 occurred in each country (according to the published data by European Centre for Disease Prevention and Control on 26th June 2020) and 11 March 2020 (WHO-start of world-wide pandemic).
- Post-pandemic could be defined as date (1) vaccination is released, (2) WHO declares COVID-19 pandemic over, (3) region-specific calls are made to end social distancing measures with no relevant rise in cases thereafter.

An overview of the COVID-19 impact on the study will also be provided. This will include the number and percentage of participants who meet the following items:

- Potentially affected by COVID-19 (Started during pandemic/Started before pandemic and dosed during pandemic/Started before pandemic and not dosed during pandemic)
- At least one COVID-19 impact
    - At least one adverse event related to COVID-19 (see Section 15.1.1)
    - At least one COVID-19-related protocol deviation
    - At least one missed dose of avelumab
    - At least one missed dose of NHS-IL12
    - At least one dose interruption of avelumab
    - At least one dose interruption of NHS-IL12
    - At least one missed visit
    - At least one missed tumor assessment
    - At least one tele-visit replacing on-site visit
    - Number of participants who permanently discontinued avelumab for any reason related to COVID-19
    - Number of participants who permanently discontinued NHS-IL12 for any reason related to COVID-19
    - Number of participants who discontinued the study for any reason related to COVID-19
    - Number of participants who died for any reason related to COVID-19

A listing of all participants affected by COVID-19 including the outcome to each category of the overview table, the PT and AE number of AEs attributed to COVID-19, and the COVID-19 related protocol deviations will also be provided.

12.2 Protocol Deviations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication.
- Deviation from GCP

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

Subset of these important protocol deviations are clinically important, if leading to the exclusion of a subject from an analysis set.

All important protocol deviations should be documented in CDISC datasets whether identified through sites monitoring, medical review or programming. Important Protocol Deviations to be identified by programming as well as all clinically Important Protocol Deviations need to be listed and described in Appendix 20.1.

Protocol deviations will be listed and summarized by dose level based on the FAS.

Additionally, the COVID-19 related protocol deviations will be described as follows:

- Frequency table per category of important COVID-19 related protocol deviations
- Frequency table per category of non-important COVID-19 related protocol deviations
    - Listing of COVID-19 related protocol deviations

COVID-19-related protocol deviations are identified in the database based on the prefix "COVID-19" reported in the description. Additionally, a flag will be added to the SDTM datasets.

13 Demographics and Other Baseline Characteristics

All the demographics and other baseline characteristics will be summarized on the SAF overall and by dose level.

13.1 Demographics

The demographics and baseline characteristics tables will include descriptive statistics for the following variables:

- Age (in years)
- Age categories: < 65 years, ≥ 65 years (65 – <75 years, 75 – <85 years, >=85 years)
- Sex: Male, Female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not collected
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Height (cm)
- Weight (kg) at baseline

- BMI (kg/m²) at baseline
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1 at baseline
- Nicotine use status
    - Never used
    - Regular user
    - Occasional user
    - Former user
- Duration of nicotine consumption (years) will be derived for nicotine user only: defined as (end date of nicotine consumption – start date of nicotine consumption + 1) / 365.25

  Only month and year will be collected in eCRF. As a result the day will be assumed to be the same for start and end date here. If month and year are missing, no imputation will be performed and if only month is missing, December 31th will be imputed for end date and January 1st will be imputed for start date for concerning the worst case of nicotine consumption. Duration of nicotine consumption will be presented by category:
    - Regular user:<5, 5-<10, ≥10 years
    - Occasional user: <5, 5-<10, ≥10 years
    - Former user: <5, 5-<10, ≥10 years

The listing of demographics and baseline characteristics will include the following information: dose level, subject identifier, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m²) and ECOG performance status at baseline. A separate listing of nicotine consumption will be created.

13.2 Medical History

Medical history will be coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized as the numbers and percentages of subjects by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each subject will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

Listing of medical history data by subject will include coded terms and all the relevant data fields as collected on the "Medical History" eCRF page. This listing will be sorted by dose level, subject identifier and then by start date.

13.3 Hepatitis B and C Serology

The results of the hepatitis B (HBsAg, HBsAb, HBcAb IgG and IgM) and hepatitis C (HCVAb with reflex to HCV RNA) screening tests will be listed.

13.4 Disease History

Disease history is collected on "Disease History" eCRF page. Partial date will be imputed as described in the section 11.10.1.

The disease history table will include descriptive statistics for the following variables:

- Site of primary tumor
  - Lung, not otherwise specified (NOS)
  - Breast, NOS
  - ….
- Time since first diagnosis (years), defined as (the first study treatment date – the date of initial cancer diagnosis)/365.25
- Time since last disease progression (months), defined as (the first study treatment date - the date of last progression of disease)/30.4375
- Tumor Node Metastasis (TNM) Classification of Malignant Tumors at initial diagnosis
  - TX
  - T0
  - N1
  - ….
- TNM at study entry
  - TX
  - T0
  - N1
  - …

Listing of disease history will be provided with all relevant data (as collected on the "Disease History" eCRF page) and derived variables used in the above table.

14 Prior and Concomitant Medications/Procedures

Prior and concomitant anti-cancer therapy / other medications will be coded using the latest available version of WHO Drug Dictionary, and summarized based on the SAF by dose level and overall.

14.1 Prior Anti-Cancer Therapies/Procedures

The prior anti-cancer treatments and procedures are collected under the "Prior anti-cancer drug therapies details", "Prior anti-cancer radiotherapies details" and "Prior anti-cancer surgeries details" eCRF pages.

The overall summary of presence of prior anti-cancer treatments and procedures table will include: the number and percentages of subjects by type of treatment (by dose level and overall):

- subjects with at least one type of prior anti-cancer treatment/procedure
- subjects with at least one prior anti-cancer surgery
- subjects with at least one prior anti-cancer drug therapy
- subjects with at least one prior anti-cancer radiotherapy

For prior anti-cancer drug therapy the following items will be summarized:

- Type of therapy: Anti-PD1 or Anti-PD-L1 / Cytotoxic Therapy / Monoclonal Antibodies Therapy/ Small Molecules / Immunotherapy except Anti-PD-1 or Anti-PD-L1 / Endocrine Therapy/Other
- Intent of therapy: Adjuvant / Neoadjuvant / Metastatic/ Locally advanced
- For Metastatic/ Locally advanced intent, the therapy lines: 1 / 2 / 3 / ≥4
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD)/ Progressive Disease (PD)/ /Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD)/ Not evaluable (NE) / Unknown / Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be extensively detailed with the number and percentage of subjects by the drug class and PT in a separate table. A subject will be counted only once within a given drug class and within a given drug name, even if the subject received the same medication at different times. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class, based on the incidence in the "Overall" column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

The listings of prior anti-cancer treatments and procedures will also be provided:

- listing of prior anti-cancer drug therapies
- listing of prior anti-cancer radiotherapy
- listing of prior anti-cancer surgeries

These will include dose level, subject identifier, and all the relevant collected data-fields on the corresponding eCRF pages (ordered by dose level, subject identifier and therapy start date).

14.2 Previous and Concomitant Medications/Procedures

Previous and concomitant medications are collected on the "Relevant previous medications details" and "Concomitant medications details" eCRF page. Prior and concomitant procedures are collected on the "Concomitant procedures details" eCRF page.

Previous medications are medications, other than study medications and pre-medications for study drug, which are started before first dose date of study treatment.

Concomitant medications are medications, other than study medications and pre-medications for study drug, which started prior to first dose date of study treatment and continued on in on-treatment period as well as those started during the on-treatment period.

Previous medications and Concomitant medications will be summarized separately showing the number of subjects and percentages by drug class and preferred term by dose level and overall. A subject will be counted only once within a given drug class and within a given drug name, even if the subject received the same medication at different times.

The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class, based on the incidence in the "Overall" column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Previous and concomitant medication data will be listed separately. Following variables will be included in the listings: dose level, subject dentifier, and all corresponding collected data-field on the corresponding eCRF page. The listings will be sorted by dose level, subject dentifier, and the start date of the medication.

Prior and concomitant procedures data will be listed from the Concomitant procedures details eCRF page. Dose level, subject identifier, and all collected data-field on the corresponding eCRF page will be included in the Prior and Concomitant Procedure listing. The listings will be sorted by dose level, subject dentifier, and the start date of the procedure.

Premedication data (reported on the "Premedication details" eCRF page) given before the study drug administration will be listed.

14.3 Subsequent Anti-Cancer Therapies/Procedures

Number of subjects received treatment after discontinuation will be summarized as reported on the "Anti-Cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Surgery after Discontinuation Details" eCRF pages.

Number and percentage of subjects with any anti-cancer treatment after discontinuation will be tabulated by dose level and overall based on the data collected from the "Anti-Cancer Treatment Details" eCRF pages, as following:

Type of therapies (as collected in eCRF):

- Anti-PD-1/anti-PD-L1,

- Cytotoxic Therapy,
- Endocrine Therapy,
- Monoclonal Antibodies therapy,
- Small molecules,
- Immunotherapy except Anti-PD-1/anti-PD-L1,
- Other.

Summary statistics will be created for best response across all post study treatments based on the data collected from "Anti-Cancer Treatment Details" eCRF page, i.e. CR / PR / PD / SD / Non-CR/Non-PD / Unknown / Not evaluable / Not applicable.

Anti-cancer treatment after discontinuation will be provided in a listing with data retrieved from "Anti-Cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Surgery after Discontinuation Details" eCRF pages.

15 Treatment Compliance and Exposure

All dosing calculations and summaries, as well as the listings of study drug administration will be based on 'NHS-IL12 Administration' and 'Avelumab Administration' eCRF pages.

For the the dose levels 4 µg/kg, 8 µg/kg, 12 µg/kg, 16.8 µg/kg: Avelumab administered as IV infusion at a dose of 10 mg/kg once every 2 weeks will be administered on Day 1 and Day 15 of each 28-day (4 weeks) cycle. NHS-IL12 will be administered in escalating doses of 2, 4, 8, 12, 16.8 µg/kg at a starting dose level of 4 µg/kg by subcutaneous injection only on Day 1 of each cycle, immediately prior to avelumab infusion.

For the avelumab once weekly cohort: In addition to the above NHS-IL12 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 NHS-IL12 at the NHS-IL12 MTD once every 4 weeks, then avelumab at 800 mg once every 2 weeks plus NHS-IL12 at the NHS-IL12 MTD once every 4 weeks until a criterion for treatment discontinuation has been met.

15.1 Exposure to Study Drug

15.1.1 Avelumab

The actual dose level for avelumab is calculated as actual dose administered/weight (mg/kg). The last available weight of the subject on or prior to the day of dosing will be used. The subjects of the avelumab once weekly cohort will receive avelumab flat dose at 800 mg IV infusion .

The duration of avelumab treatment (in weeks) during the study for a subject will be based on the duration of the cycle of 28 days and is defined as:

Treatment duration (weeks) = (end date of last cycle –first dose date + 1)/7

With the exception of the avelumab once weekly cohort, the end date of last cycle for avelumab is defined as follows:

- if the last dose is given at the day 1 of the cycle then the end date of the last cycle will be the date of the last dose + 28 days -1
- if the last dose is given at the day 15 of the cycle then the end date of the last cycle will be the date of the last dose + 14 days -1

For the subjects in the avelumab once weekly cohort, the end date of last cycle for avelumab is defined as follows :

- if the last dose is given at the day 1 of the cycle then the end date of the last cycle will be the date of the last dose + 28 days -1
- if the last dose is given at the day 8 of the cycle then the end date of the last cycle will be the date of the last dose + 21 days -1
- if the last dose is given at the day 15 of the cycle then the end date of the last cycle will be the date of the last dose + 14 days -1
- if the last dose is given at the day 22 of the cycle then the end date of the last cycle will be the date of the last dose + 7 days -1

The cumulative dose (mg/kg) of avelumab per subject in a time period is the sum of the actual dose levels that the subject received within that period (i.e., total dose administered (mg) / weight (kg)). The last available weight of the subject on or prior to the day of dosing will be used. For the subjects of the avelumab once weekly cohort, the cumulative dose (mg) of avelumab per subject in a time period is the sum of the actual doses that the subject received within that period.

Each cycle for avelumab is defined by a 28-day period. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each subject across all cycles. The dose intensity per cycle (mg/kg/cycle), with the exception of the avelumab once weekly cohort, is defined as

DI (mg/kg/cycle) = Cumulative dose (mg/kg)/[treatment duration (in weeks)/4]

For the subjects in the avelumab once weekly cohort, the dose intensity per cycle (mg/cycle) is defined as

DI (mg/cycle) = Cumulative dose (mg)/[treatment duration (in weeks)/4]

The relative dose intensity (RDI), with the exception of the avelumab once weekly cohort, is defined as the actual dose intensity divided by the planned dose per cycle and expressed in %.

RDI (%) = 100×[DI (mg/kg/cycle)/(planned dose×2) (mg/kg/cycle)]

For the subjects in the avelumab once weekly cohort, the relative dose intensity (RDI) is defined as

RDI (%) = 100×[DI (mg/cycle)/(planned dose×2) (mg/cycle)]

The summary of treatment exposure and compliance for avelumab will include the following information:

- Treatment duration (weeks)
- Total number of infusions received
- Cumulative dose (mg/kg)
- Dose intensity (mg/kg/cycle)
- Relative dose intensity (%)
    - <50%
    - [50% , 65%[
    - [65% , 80%[
    - [80% , 100%]
    - > 100%

15.1.2 NHS-IL12

The actual dose level for NHS-IL12 is calculated as actual dose administered/weight (µg /kg). The last available weight of the subject on or prior to the day of dosing will be used.

The duration of NHS-IL12 treatment (in weeks) during the study for a subject is defined as:

Treatment duration (weeks) = (last dose date –first dose date + 28)/7

The cumulative dose (µg /kg) of NHS-IL12 per subject in a time period is the sum of the actual dose levels that the subject received within that period (i.e., total dose administered (µg) / weight (kg)).

NHS-IL12 will be administered at Day1 of each cycle. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each subject across all cycles. The dose intensity per cycle (µg /kg/cycle) is defined as

DI (µg /kg/cycle) = Cumulative dose (µg /kg)/[treatment duration (in weeks)/4]

The relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose per cycle and expressed in %.

RDI (%) = 100×[DI (µg/kg/cycle)/(planned dose) (µg /kg/cycle)]

The summary of treatment exposure and compliance for NHS-IL12 will include the following information:

- Treatment duration (weeks)
- Total number of infusions received
- Cumulative dose (µg /kg)
- Dose intensity (µg /kg/cycle)
- Relative dose intensity (%)
    - <50%
    - [50% , 65%[
    - [65% , 80%[
    - [80% , 100%]
    - > 100%

15.2 Dose Reductions

Dose reductions of avelumab or NHS-IL12 is defined as actual non-zero dose < 90% of the planned dose.

Number and percentage of subjects with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 / ≥4) will be summarized by dose level.

15.3 Dose Delays

Delays will be derived based on study drug administration date and will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous treatment administration date):

- No delay (including 1 day delay)
- 2-6 days delay
- 7 or more days delay

Number and percentage of subjects with delayed study drug administration and maximum length of delay, i.e. the worst case of delay if subjects have multiple dose delays will be summarized by dose level.

15.4 Infusion rate reductions

Infusion rate reductions of avelumab as recorded on the eCRF will be used for analysis. Number and percentage of subject with at least one infusion rate reduction as well as a breakdown of infusion rate reductions (1 / 2 / ≥3) will be summarized by dose level.

15.5 Dose Interruptions

Drug interruptions of avelumab or NHS-IL12 as recorded on the eCRF will be used for analysis.

The number and percentage of subjects with dose interruptions and the corresponding reasons will be summarized.

16 Endpoint Evaluation

The subsections in this section include specifications for analyzing clinical study endpoints specified in the CTP to meet the study objectives.

16.1 Primary Endpoint Analyses

The primary endpoints of this study are safety endpoints:

- Occurrence, severity, and duration of treatment emergent adverse events (TEAEs) and treatment emergent related adverse events (TRAEs), graded according to the NCI-CTCAE v4.03
- Occurrence of DLTs during the first 3 weeks of treatment in the dose escalation part

The DLT analysis set will be used for the DLT analysis and the SAF for the analysis of TEAEs and TRAEs.

The details of these analyses and respective derivations can be found in section 17.1.

16.2 Secondary Endpoint Analyses

The secondary endpoints for this study are:

- PK profiles of avelumab and NHS-IL12
- Immunogenicity of avelumab and immunogenicity of NHS-IL12 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.

16.2.1 PK Parameters

PK parameters for Avelumab and NHS-IL12 will be listed and summarized by dose level, analyte (Avelumab or NHS-IL12) and cycle/day using standard descriptive statistics, as detailed in section 11.8. The details of the PK outputs will be specified in a separate document.

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set. Any PK concentrations excluded from the PK analysis set will be listed and flagged.

16.2.1.1 PK Concentration Data

Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration. The same applies to the very first pre-dose sample of a multiple dose study.

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data.

In case of concentrations above the upper limit of quantification (ULOQ) the numeric value of the actual ULOQ of the bioanalytical assay may be used for preliminary, draft PK evaluations only. For final evaluations >ULOQ values are not accepted and should be replaced by valid numeric values from dilution measurement.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.".

PK concentrations which are erroneous due to a protocol violation (as defined in the CTP), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing statistical analyses. In this case the rational for exclusion must be provided in the CSR. Any other PK concentrations that appear implausible to the Pharmacokineticist/PKPD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

Tables, Listing and Figures for avelumab and NHS-IL12 concentrations will be specified in a seprate analysis plan.

16.2.1.2 Estimation of Individual PK Parameters

Pharmacokinetic parameters will be calculated by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a Contract Research Organization selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA) will be used to derive PK parameters applying Non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

Tables, Listing and Figures for avelumab and NHS-IL12 PK parameters will be specified in a separate analysis plan.

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[redacted]

The frequency and percentage of subjects in each category for each molecule will be summarized by dose level and overall. A listing will be prepared by dose level for subject IDs ever positive for both molecules.

ADA results for ever positive subjects will be listed by molecule and dose level:

- Overview on ADA status: Subject ID, age, gender, ADA Status, Study Day of Start of ADA response, Duration of ADA immunogenicity response (weeks)
- Listing of ADA and C_{trough} concentrations: Subject ID, Visit and Visit Date, ADA result, Date of last prior avelumab infusion, Days since last avelumab infusion, Date of last available predose drug concentration at or before ADA assessment and corresponding drug concentration
- Listing of all PK concentrations, Subject ID, Visit name and Visit Date, timepoint, observed avelumab serum concentration, Actual date/time; Hours since last avelumab infusion.
- Listing of immunogenicity data and adverse events (AEs): Subject ID, age, gender, study treatment start and stop date, all dates with positive ADA result, AE start date, stop date, preferred term, CTCAE toxicity grade, seriousness, and applicable flags for immune-related adverse event (irAE), infusion related reaction (IRR), serious adverse event (SAE), or reason for permanent treatment discontinuation.

16.2.3 Best Overall Response per RECIST v1.1

16.2.3.1 Confirmed Best Overall Response

Confirmed Best Overall Response will be evaluated according to RECIST v1.1 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 rule.

Complete response = at least two determinations of CR at least 4 weeks apart and before progression. Namely, second determination date of CR – progression date >= at least 4 weeks or at least two determinations of CR without any progression determination.

Partial response = at least two determinations of PR or better at least 4 weeks apart and before progression (and not qualifying for a CR). Namely, second PR or better determination date – progression date >= at least 4 weeks or at least two PR or better determinations without any progression determination.

Stable disease = at least one SD assessment (or better) ≥ 6 weeks after the first study treatment administration and before progression (and not qualifying for CR or PR)

Non-CR/non-PD (for the subjects with non-measurable disease at baseline) = at least one Non-CR/non-PD assessment (or better) ≥ 6 weeks after the first study treatment administration and before progression (and not qualifying for CR or PR)

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

Not Evaluable (NE): all other cases.

Only tumor assessments performed on or before the start of any further anti-cancer therapy (Drug therapy, surgery and radiotherapy other than radiation with palliative intent) will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

The frequency (number and percentage) of subjects with BOR of CR, PR, SD, non-CR/non-PD (applicable only to subjects with non-measurable disease at baseline), PD and not evaluable (NE) will be tabulated. Subjects with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessments
- No post-baseline assessments
- All post-baseline assessments have overall response NE
- New anticancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after Treatment day 1 without further evaluable tumor assessment)
- PD too late (Tumor assessment detecting the PD >12 weeks after Treatment day 1 with no tumor assessment in between)
- Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD of insufficient duration'

Percent change from baseline in sum of longest diameters will be plotted.

16.2.3.2 Objective Response

Objective response (OR) is defined as confirmed CR or PR according to RECIST v1.1. Subjects who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-tumor 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.

Each subject will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of subjects with OR in the analysis set.

ORR will be tabulated by dose level along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

These evaluations will also be presented in data listings with detailed information collected per eCRF pages as well as BOR for all the subjects from the FAS.

16.2.4 Immune-related BOR

Immune-related Best Overall Response (irBOR) 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, according to the following rules (Nishino, 2013)).

- Immune-Related Complete Response (irCR) = at least two determinations of irCR at least 4 weeks apart and before irPD
- Immune-Related Partial Response (irPR) = at least two determinations of irPR or better at least 4 weeks apart and before irPD (and not qualifying for a irCR)
- Immune-Related Stable Disease (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).
- Immune-Related Progressive Disease (irPD) = at least two consecutive determinations of irPD at least 4 weeks apart.

Only tumor assessments performed on or before the start of any further anti-cancer therapy will be considered in the assessment of irBOR.

Immune-related Objective Response (irOR) is defined as irCR or irPR according to irRECIST 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 Full Analysis Set. 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.

CCI [redacted]

- Changes in blood, tumor, and tumor microenvironment biomarkers
- Clinical response (time to response, objective response, duration of response, progression-free survival time, and overall survival time).

CCI

[redacted]

CCI

CCI

16.3.4 Clinical Response

The following parameters will be summarized descriptively by dose level and overall:

- time to response (TTR)
- objective response (described in the section 16.2.3)
- duration of response (DOR)

- progression-free survival time (PFS)

In addition, overall survival time (OS) will also be analysed.

16.3.4.1 Time to Response

Time to response is defined as the time in months from the treatment day 1 to the first documentation of OR as per RECIST v1.1 criteria which is subsequently confirmed. Further details on OR can be found in the section 16.2.3.

TTR will be summarized for the FAS of subjects with a confirmed CR or PR using descriptive statistics.

16.3.4.2 Duration of Response

Duration of response is defined, for subjects with confirmed OR, as the time in months from first documentation of OR to the date of first documentation of PD as per RECIST v1.1 or death due to any cause. If a subject has not had an event (PD or death), DOR is censored. The censoring rules for DOR are the same as described below for PFS.

DOR will be summarized for the FAS of subjects with a confirmed OR using the Kaplan-Meier method. The median event time and 2-sided 95% CI for the median will be provided. If the number of subjects with a confirmed CR or PR is small, the data will only be listed.

16.3.4.3 Progression Free Survival

Progression free survival time is defined as the time (in months) from treatment day 1 to the date of the first documentation of objective PD as per RECIST v1.1 or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last evaluable tumor assessment in the following cases:

- for subjects who do not have an event (PD or death),
- for subjects who started a new anti-cancer therapy prior to an event
- for subjects with an event after two or more missing tumor assessments.

Subjects who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the treatment day 1 unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS and DOR analysis are presented in the Table 4.

Table 4 Outcome and Event Dates for PFS and DOR analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Treatment Day 1	Censored [a]

CCI

[redacted]

CCI

CCI

17 Safety Evaluation

All safety analyses will be performed using the SAF by dose level and overall, unless otherwise stated.

17.1 Adverse Events

Treatment emergent adverse events are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period as defined in Section 11.6.

All analyses described will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings. A separate listing including AEs started after the on-treatment period will also be provided.

- Treatment Related Adverse Events (TRAE): adverse events with relationship to Avelumab and/or NHS-IL12 (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with study treatment").

- Serious Adverse Events (SAEs): serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).

- Adverse Events Leading to Any Treatment Discontinuation: adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with any study drug = Drug withdrawn).

- Adverse Events Leading to Death: adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).

- Immune-Related Adverse Events (irAEs): Immune-Related adverse events (see Appendix 20.4)

- Infusion-Related Reactions (IRRs):IRRs (see Appendix 20.4).

- Cytokine release syndrome (as recorded on the AE eCRF page, Cytokine release syndrome ticked)

The severity of TEAEs/TRAEs will be graded using the NCI-CTCAE, version 4.03. In case a subject has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

TEAEs/TRAEs will be coded according to the latest available version of MedDRA. Unless otherwise specified, AEs will be summarized by number and percentage of subjects by dose level, primary SOC and PT in decreasing frequency. Each subject will be counted only once within each SOC or PT. If a subject experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

17.1.1 All Adverse Events

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of subjects with each of the following by dose level:
    - TEAEs
    - TEAEs, Grade ≥ 3
    - TRAEs (related to any drug, to Avelumab, to NHS-IL12)
    - TRAEs, Grade ≥ 3 (related to any drug, to Avelumab, to NHS-IL12)
    - Serious TEAEs
    - Serious TRAEs (related to any drug, to Avelumab, to NHS-IL12)
    - TEAEs leading to death
    - TRAEs leading to death (related to any drug, to Avelumab, to NHS-IL12)
    - All irAEs
    - irTRAEs (related to Avelumab)
    - All IRRs
    - IRRs TRAE (related to Avelumab)
    - Treatment-emergent Cytokine Release Syndrome AE
    - Cytokine Release Syndrome TRAE (related to NHS-IL12, related to Avelumab)
- Any TEAEs by SOC and PT
- Any TEAEs by SOC and PT and worst grade
- TRAEs by SOC and PT (related, to Avelumab, to NHS-IL12)
- TRAEs by SOC and PT and worst grade (related, to Avelumab, to NHS-IL12)

- TEAEs leading to death by SOC and PT
- TRAEs leading to death by SOC and PT (, to Avelumab, to NHS-IL12)
- TEAEs Excluding SAEs, with Frequency ≥ 5% in any dose level by SOC and PT
- Serious TEAEs, with Frequency ≥ 5% in any dose level by SOC and PT

Evaluation of COVID-19 effect on AEs

The direct effect of COVID-19 for AEs will be assessed via a listing of COVID-19 related AEs including the relevant information. The listing will be generated using the "COVID-19 related terms MedDRA 23.0 update Spreadsheet" (https://www.meddra.org/covid-19-related-terms-meddra-230-update-spreadsheet) or a later version as available from Maintenance and Support Services Organization (MSSO), considering all "search terms for COVID-19-related" = "Y".

17.1.2 Adverse Events Leading to Treatment Discontinuation

The number and percentage of subjects with each of the following events will be presented for TEAEs leading to permanent discontinuation in an overall summary table by dose level:

- TEAEs leading to study drug discontinuation (both drugs, Avelumab, NHS-IL12)
- Avelumab related TEAEs leading to study drug discontinuation (any drug, Avelumab, NHS-IL12)
- NHS-IL12 related TEAEs leading to study drug discontinuation (any drug, Avelumab, NHS-IL12)
- irAEs leading to permanent Avelumab discontinuation
- irAEs leading to permanent NHS-IL12 discontinuation
- IRRs leading to permanent Avelumab discontinuation
- IRRs leading to permanent NHS-IL12 discontinuation
- Cytokine release syndrome TEAEs leading to permanent discontinuation of NHS-IL12
- Cytokine release syndrome TEAEs leading to permanent discontinuation of Avelumab

The following summaries by SOC and PT will be produced:

- TEAEs Leading to Avelumab Permanent Discontinuation by SOC and PT
- TEAEs Leading to NHS-IL12 Permanent Discontinuation by SOC and PT
- TEAEs Leading to Avelumab and NHS-IL12 Permanent Discontinuation by SOC and PT

- Avelumab related AEs Leading to Avelumab Permanent Discontinuation by SOC and PT
- NHS-IL12 related AEs Leading to NHS-IL12 Permanent Discontinuation by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

17.1.3 DLT, Serious Adverse Events and Other Significant Adverse Events

17.1.3.1 DLT

A DLT is defined as Grade >= 3 non-hematologic or Grade >= 4 hematologic AE according to NCI-CTCAE v4.03, occurring in the DLT evaluation period (first 21 days of treatment) that is related to either or both study drugs with some exceptions in protocol section 7.4.1.5. A DLT must be confirmed by the SMC (confirmation is reported in eCRF). The summary of DLT table will include the following variables:

- number and proportion of subjects who experienced a DLT during the DLT evaluation period
- number and proportion of TEAEs experienced by subjects in the DLT Set during the DLT evaluation period.
- number of DLT per subject, 1 /2 /≥3
- DLT by SOC and PT

The number and percentage of subjects who experienced a TEAE during the DLT evaluation period will also be summarized by dose level for the DLT analysis set. A listing of DLT adverse events will include subject identifier, dose level, and all relevant variables from AE eCRF page.

The MTD is defined as the highest dose at which no more than 1 of 6 evaluable subjects experience a DLT. The decision on the MTD will be made by the SMC.

17.1.3.2 Serious Adverse Events

The frequency (number and percentage) of subjects with each of the following will be presented for treatment emergent SAEs by dose level:

- SAEs by SOC and PT
- Related (to Avelumab or NHS-IL12 separately) SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

17.1.3.3 Other Significant Adverse Events

The frequency (number and percentage) of subjects with each of the following will be presented for treatment emergent irAEs, by dose level:

- irAEs leading to death, by SOC and PT
- irAEs, by SOC and PT
- irAEs leading to discontinuation, by SOC and PT
- irAEs, Grade ≥ 3, by SOC and PT
- irAEs by SOC and PT and worst grade
- serious irAEs by SOC and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period. A separate listing of irAEs with onset after the on-treatment period will also be provided.

The frequency (number and percentage) of subjects with each of the following will be presented for treatment emergent IRRs, by dose level:

- IRRs leading to death, by SOC and PT
- IRRs leading to discontinuation, by SOC and PT
- IRRs, by SOC and PT
- IRRs, Grade ≥ 3, by SOC and PT
- Serious IRRs, by SOC and PT

Timing of first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be provided.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

The frequency (number and percentage) of subjects with each of the following will be presented for treatment emergent Cytokine release syndrome, by dose level:

- Cytokine release syndrome leading to death, by SOC and PT
- Cytokine release syndrome Leading to Discontinuation, by SOC and PT
- Cytokine release syndrome, by SOC and PT

- Cytokine release syndrome, Grade ≥ 3, by SOC and PT
- Serious Cytokine release syndrome, by SOC and PT

The listing of all Cytokine release syndrome will also be provided with the relevant information.

Timing of first onset of a CRS (injection 1, infusion 1, infusion 2, injection 2, infusion 3, infusion 4 or later) will be provided.

17.2 Deaths

The frequency (number and percentage) of subjects who died will be tabulated based on information from the "Death" eCRF page by dose level.

All deaths will be tabulated and listed for SAF analysis set. The deaths table will include the following information:

- Number and percentage of subjects who died
    - Primary reason for death
        - Disease progression
        - Adverse event related to study treatment
        - Adverse event not related to study treatment
        - Other
        - Unknown
- Number and percentage of subjects who died within 30 days of the last study treatment administration
    - Primary reason for death
        - Disease progression
        - Adverse event related to study treatment
        - Adverse event not related to study treatment
        - Other
        - Unknown
- Number and percentage of subjects who died within 60 days of the first study treatment administration
    - Primary reason for death
        - Disease progression
        - Adverse event related to study treatment

- Adverse event not related to study treatment
- Other
- Unknown

In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.
- Flag for death within 60 days of first dose of study treatment.

17.3 Clinical Laboratory Evaluation

The laboratory parameters will be presented for SAF.

Laboratory results will be classified by grade according to NCI-CTCAE v4.03 when applicable (Appendix 20.2). 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. For the parameters with both low (below lower limit of normal range) and high (above upper limit of normal range) toxicity grades such as potassium (hypokalemia/ hyperkalemia), the low and high grades will be summarized separately. For the values below normal limit (e.g. hypokalemia) the grade will be set to 0 when summarizing grades above normal limit (e.g. hyperkalemia), and vice versa.

Results for variables that are not gradable according to NCI-CTCAE will be presented as within or outside normal limits (Appendix 20.3). Only subjects with post-baseline laboratory values will be included in these analyses.

17.3.1 Hematology and Clinical Chemistry Parameters

Parameters with CTCAE grade defined

The laboratory toxicities will be tabulated by the worst post-baseline CTCAE grade and the shift from baseline in the CTCAE grade using descriptive statistics (count and percentage) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (i.e. those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

The summary of laboratory parameters by CTCAE grade table will include number and percentage of subjects with grade 1, 2, 3, 4, 3/ 4 and any grade (1 to 4) laboratory abnormalities during on-treatment period.

The shift table will summarize baseline CTCAE grade versus the worst post-baseline CTCAE grade. The worst grade per subject is defined as the highest CTCAE grade during the on-treatment period.

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, i.e.:

- Hematology: absolute lymphocyte count, absolute neutrophil count, hemoglobin, platelet count, white blood cells (WBC)
- Serum Chemistry: ALT (SGPT), AST (SGOT), creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin, amylase, direct bilirubin, gamma glutamyltransferase (GGT), lipase.

Parameters with no CTCAE grade defined

Hematology and chemistry evaluations which cannot be graded per CTCAE will be summarized as:

- Shift from baseline value (low, normal, high) to above normal during on-treatment period
- Shift from baseline value (low, normal, high) to below normal during on-treatment period

In this study, this applies to the following parameters:

- Hematology: hematocrit, red blood cells (RBC) and differential count (lymphocytes, neutrophils, monocytes, eosinophils, basophils)
- Serum Chemistry: lacatate dehydrogenase (LDH) , calcium, chloride, carbon-dioxide, blood urea nitrogen/total urea, creatine kinase.

The laboratory listings (hematology, chemistry) will include all the laboratory parameters as available in the EDC database with the all corresponding relevant information. Scatterplots of the hematology and biochemistry results vs study day will be produced.

Liver Function Elevation and Possible Hy's Law Cases during On-Treatment Period

ALT, AST and Total Bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of subjects with each of the following during the on-treatment period will be summarized overall and by dose level:

- ALT $\geq$ 3×ULN, ALT $\geq$ 5×ULN, ALT $\geq$ 10×ULN, ALT $\geq$ 20×ULN
- AST $\geq$ 3×ULN, AST $\geq$ 5xULN, AST $\geq$ 10×ULN, AST $\geq$ 20×ULN

- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- Total Bilirubin ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a subject with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying peak serum ALT (/ULN) vs peak Total Bilirubin (/ULN) including reference lines at ALT ≥3xULN and bilirubin ≥2xULN. The display will be divided into 4 quadrants by the lines through ALT ≥ 3×ULN and Total Bilirubin ≥2×ULN. The left lower quadrant is then considered normal or insignificant elevations in liver chemistries, the left upper quadrant indicates patients with possible Gilbert's cholestasis; the right upper quadrant are the possible Hy's Law patients; the right lower quadrant is possible Temple's Corollary (patients with ALT ≥ 3 x ULN but not satisfying Hy's Law). Different symbol will be used for different dose level.

17.3.2 Other laboratory parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected data-fields on the eCRF.

- Urinalysis: all urinalysis parameters
- Hormones: free thyroxine and thyroid-stimulating hormone
- Pregnancy test

17.4 Vital Signs

All vital sign parameters will be summarized using descriptive statistics of actual values and changes from baseline for all vital sign assessments from the on-treatment period. End of treatment visit will be summarized separately. The changes computed will be the differences from baseline.

Summary of vital signs will be based on the SAF. The substantial change from baseline regarded as potentially clinically significant will be derived as below and summarized with subject incidence and percentage during the on-treatment period:

- ≥ 10% weight increase
- ≥ 10% weight decreases
- ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg in systolic blood pressure
- ≥ 160 mmHg and increased from baseline ≥ 20 mmHg in systolic blood pressure
- ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg in diastolic blood pressure
- ≥ 110 mmHg and increased from baseline ≥ 10 mmHg in diastolic blood pressure
- ≤ 50 bpm and decrease from baseline ≥ 20 bpm in pulse rate
- ≥ 120 bpm and increase from baseline ≥ 20 bpm in pulse rate

All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

Vital signs maximum change from baseline values will be listed. A separate listing will show Change from Baseline in Abnormal Vital Sign Parameters.

17.5 Other Safety or Tolerability Evaluations

17.5.1 Electrocardiogram (ECG)

Electrocardiogram data will be summarized by visit including change from baseline.

The incidence and percentage of subjects with potentially clinically significant abnormalities (PCSA) for 12-lead Electrocardiogram (Triplicate) parameters will be summarized during the on-treatment period. The PCSA criteria are provided in the Table 5.

Table 5 - Potentially Clinically Significant Abnormalities criteria for ECG

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increased from baseline ≥ 20 bpm
QRS	≥ 120 ms
QTcF absolute	>450 ms >480 ms >500 ms
QTcF change from baseline	Increase: >30 ms >60 ms

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
QTcF change from baseline	decrease: >30 ms >60 ms

QT based on Fridericia's formula (QTcF= QT/RR0.33) will be summarized as collected in eCRF.

Listings of ECG parameters will be provided including the data collected in eCRF and the change from baseline. A separate listing for potentially clinically significant abnormalities will be created.

17.5.2 Eastern Cooperative Oncology Group (ECOG)

The ECOG shift from baseline to highest post-baseline score will be summarized by dose level during the on-treatment period and this analysis will be based on SAF analysis set. Missing category will be included and the number of subjects at each dose level will be used as the denominator.

ECOG performance status will also be presented in a data listing with dose level, subject identifier, and Visits. The listing will be sorted by dose level, subject identifier, and date of assessment.

18 Benefit Risk Assessment

Not Applicable

19 References

Merck KGaA protocol MS201781_0031 version 7.0

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European Centre for Disease Prevention and Control. Data on COVID-19 geographic distribution by country. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide, accessed and downloaded on 26 June 2020.

20 Appendices

20.1 Important Protocol Deviations

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Incl: Signed written informed consent	Informed Consent	Subject did not meet Inclusion Criteria # 1	5.3.1	List if DM.RFICDTC is missing or if DM.RFICDTC > Earliest date of SV.SVSTDTC. Medical Review Required
Incl: 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.	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 3	5.3.1	Medical Review Required
Incl: Adequate hematological function as defined below: a. White blood cells (WBC) count ≥ 3.0 × 109/L b. Absolute neutrophil count ≥ 1.5 × 109/L c. Lymphocyte count ≥ 0.5 × 109/L d. Platelet count ≥ 100 × 109/L e. Hemoglobin ≥ 9 g/dL (may have been transfused)	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 6	5.3.1	List if at least one parameter is out of the range before 1st dose. Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Incl: 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 ≤ 2.5 × ULN c. Alanine aminotransferase (ALT) levels ≤ 2.5 × ULN d. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 but less than 3 × ULN	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 7	5.3.1	List if at least one parameter is out of the range before 1st dose. Medical Review Required
Incl: Adequate renal function as defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 8	5.3.1	List if creatinine clearance is out of the range before 1st dose. Medical Review Required
Excl: Concurrent treatment with a nonpermitted drug/intervention	Eligibility and Entry Criteria	Subject met Exclusion Criteria #1	5.3.2	Medical Review Required
Excl: Any prior treatment with any form of IL-12	Eligibility and Entry Criteria	Subject met Exclusion Criteria #2	5.3.2	Medical Review Required
Excl: Prior organ transplantation, including allogeneic stem-cell transplantation	Eligibility and Entry Criteria	Subject met Exclusion Criteria #5	5.3.2	Medical Review Required
Excl: Previous malignant disease (other than the indication for this study) within the last 5 years	Eligibility and Entry	Subject met Exclusion Criteria #6	5.3.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
	Criteria			
Excl: Significant acute or chronic infections requiring systemic therapy	Eligibility and Entry Criteria	Subject met Exclusion Criteria #7	5.3.2	Medical Review Required
Excl: Active or history of autoimmune disease that might deteriorate when receiving an immunostimulatory agent.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #8	5.3.2	Medical Review Required
Excl: Persisting toxicity related to prior therapy of Grade > 1	Eligibility and Entry Criteria	Subject met Exclusion Criteria #11	5.3.2	Medical Review Required
Excl: Uncontrolled intercurrent illness	Eligibility and Entry Criteria	Subject met Exclusion Criteria #14	5.3.2	Medical Review Required
Excl: 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.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #16	5.3.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Excl: Administration of a live vaccine within 30 days prior to study entry	Eligibility and Entry Criteria	Subject met Exclusion Criteria #19	5.3.2	Medical Review Required
Excl: 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	Eligibility and Entry Criteria	Subject met Exclusion Criteria #20	5.3.2	Medical Review Required
Excl: History of congenital or active mmunodeficiency, with the exception of acquired treatment-related hypogammaglobulinemia requiring periodic IV immunoglobulin infusion.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #22	5.3.2	Medical Review Required
Participation in another treatment trial	Concomitant Medication	Subject participated in another clinical study	5.5.1	Medical Review Required
If the administration of a prohibited concomitant medication becomes necessary during the study, the subject will be withdrawn from study treatment.	Concomitant Medication	Subject received a prohibited concomitant medication	5.5.1	Medical Review Required
Other Prohibited Interventions	Concomitant Medication	Subject received a prohibited concomitant procedure	6.5.3	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
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	Eligibility and Entry Criteria		5.5.1	Medical Review Required
Occurrence of pregnancy	Serious Adverse Event	Subject became pregnant but continued on treatment	5.5.1	List subjects with positive pregnancy test and study drug administrtion after the start date. Medical Review Required
Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or study integrity	IP Compliance	Subject had a noncompliance deemed to compromise safety / study integrity	5.5.1	Medical Review Required
Incorrect IMP dose: dose doesn't correspond to the dose level planned dose	IP Compliance	Subject received incorrect study treatment dose	6.2.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Noncompliance: subject missing > 1 cycle of study treatment for nonmedical reasons (the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons)	IP Compliance	Subject missed > 1 cycle of study treatment for nonmedical reasons	6.9	List subjects with >28 days between 2 consequent administrations. Medical Review Required

20.2 NCI-CTCAE v4.03 Grades for Laboratory Parameters

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology							
Erythrocytes (10E12/L)	No						
Ery. Mean Corpuscular Hemoglobin (pg/cell)	No						
Ery. Mean Corpuscular HGB Concentration (g/L)	No						
Ery. Mean Corpuscular Volume (fL)	No						
Hemoglobin (g/L) High	Yes	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Hemoglobin (g/L) Low	Yes	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL;	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9	Hgb <8.0 g/dL; <4.9 mmol/L; <80	Life-threatening consequences;	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			<LLN - 6.2 mmol/L; <LLN - 100 g/L	mmol/L; <100 - 80g/L	g/L; transfusion indicated	urgent intervention indicated	
Leukocytes (10E9/L) Low	Yes	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Leukocytes (10E9/L) High	Yes	Leukocytosis			>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Lymphocytes (10E9/L) High	Yes	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Lymphocytes (10E9/L) Low	Yes	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocytes/Leukocytes (%)	No						
Neutrophils (10E9/L)	Yes	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Neutrophils/Leukocytes (%)	No						
Monocytes (%)	No						
Reticulocytes/Erythrocytes (%)	No						
Reticulocytes (10E9/L)	No						
Eosinophils (%)	No						
Basophils (%)	No						
Hematocrit (%)	No						
Platelet (10E9/L)	Yes	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L	-
RBC morphology	No						

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Biochemistry							
Creatinine (umol/L)	Yes	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Alanine Aminotransferase (U/L)	Yes	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate Aminotransferase (U/L)	Yes	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Gamma Glutamyl Transferase (U/L)	Yes	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Total Bilirubin (umol/L)	Yes	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Direct Bilirubin (umol/L)	Yes	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Cholesterol (mmol/L)	Yes	Cholesterol high	>ULN - 300 mg/dL;	>300 - 400 mg/dL;	>400 - 500 mg/dL; >10.34	>500 mg/dL; >12.92	-

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	- 12.92 mmol/L	mmol/L	
Lipase (IU/L)	Yes	Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Amylase (IU/L)	Yes	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Total Protein (G/L)	No						
Albumin (g/L)	Yes	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase (IU/L)	Yes	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Glucose (mmol/L) High	Yes	Hyperglycemia	Fasting glucose value >ULN	Fasting glucose value >8.9 -	>13.9 - 27.8 mmol/L; hospitalization	>27.8 mmol/L; life-threatening	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			- 8.9 mmol/L	13.9 mmol/L	indicated	consequences	
Glucose (mmol/L) Low	Yes	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L; life-threatening consequences; seizures	Death
Blood Urea Nitrogen (mmol/L)	No						
Uric Acid (umol/L)	Yes	Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Sodium (mmol/L) High	Yes	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium (mmol/L) Low	Yes	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Potassium (mmol/L) High	Yes	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Potassium (mmol/L) Low	Yes	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Chloride (mmol/L)	No						
Calcium (mmol/L)	No						
Magnesium (mmol/L) High	Yes	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Magnesium (mmol/L) Low	Yes	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Carbon Dioxide (mmol/L)	No						
Creatine Kinase (IU/L)	No						
Lactate Dehydrogenase (IU/L)	No						
Phosphate (mmol/L)	Yes	Hypophosphatemia	<LLN - 0.8 mmol/L	<0.8 - 0.6 mmol/L	<0.6 - 0.3 mmol/L	<0.3 mmol/L;	
Urea (mmol/L)	No						
C-Reactive Protein	No						
Serum electrophoresis protein pattern	No						
Triglyceride (mmol/L)	Yes	Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death

20.3 Worst Values for Non Gradable Laboratory Parameters

Category	Parameter	Abnormal value to be considered
Hematology	Erythrocytes	Low
	Ery. Mean Corpuscular Hemoglobin	Low
	Ery. Mean Corpuscular HGB Concentration	Low
	Ery. Mean Corpuscular Volume	Low and High
	Reticulocytes	Low and High
	Reticulocytes/Erythrocytes	Low and High
	Hematocrit	Low
	Basophils	High
	Eosinophils	High
	Monocytes	High
	Lymphocytes/Leukocytes	Low and High
	Neutrophils/Leukocytes	Low and High
	RBC morphology	Any Abnormalities
Biochemistry	Blood Urea Nitrogen	High
	Urea	High
	Creatine Kinase	High
	Lactate Dehydrogenase	High
	Carbon Dioxide	Low and High
	Creatinine	High

	Chloride	High
	C-Reactive Protein	High
	Serum electrophoresis protein pattern	Any Abnormalities

20.4 Description of the Case Definition for Assessment of Immune-Related AEs and IRRs

Immune-Related Adverse Events

Immune-related adverse events (irAEs) will be identified programmatically. AEs which satisfy all of the following criteria will be flagged as immune-related:

1) The AE preferred term matches a preferred term on the list of pre-selected MedDRA terms.

2) The AE onset occurs after the first study drug administration and no more than 90 days after last dose.

3) On the AE eCRF page, the question "Were Corticosteroids, Immunosuppresants, or hormonal therapy (e.g. Thyroid) applied?" has the answer "Yes" selected.

4) On the AE eCRF page, either:

a. The question "Does any of the following provide a clear etiology for the event?" has the answer "No" selected, indicating that the AE is not attributable to underlying cancer disease/PD, prior or concomitant medications/procedures, nor another medical condition such as an infection or pre-existing disease.

OR

b. The AE eCRF indicates that a biopsy was performed and the question "Is the histopathology/biopsy consistent with an immune-mediated event?" has the answer "Yes" selected.

In the case that criteria (1) through (3) are met, and entries for condition (4) are missing, the following rules will be applied:

- If the answer to "Does any of the following provide a clear etiology for the event?" (4a) is missing, the event will be considered as irAE (irrespective of biopsy results).
- If the answer to "Is the histopathology/biopsy consistent with an immune-mediated event?" (4b) is missing, or if no biopsy was performed, and condition (4a) is not satisfied (i.e. "Yes" is selected as the answer to the question "Does any of the following provide a clear etiology for the event?"), the event will be considered as a non-irAE.

IRRs

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to Table 9.

Table 9 Criteria for infusion related reactions

Infusion related reactions	**Reactions - Considered when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date):** • Infusion related reaction • Drug hypersensitivity • Anaphylactic reaction • Hypersensitivity • Type 1 hypersensitivity **Signs and Symptoms - occurring on the day of study drug infusion (during or after the infusion) and resolved with end date within 2 days after onset** • Pyrexia • Chills • Flushing • Hypotension • Dyspnoea • Wheezing • Back pain • Abdominal pain • Urticaria

ELECTRONIC SIGNATURES

Document: ctp-ms201781-0031-sap-main-body-v2-0

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Business Approval	22-Oct-2020 07:37
PPD	Task Completed (Approval eSign): Approved	Technical Approval	22-Oct-2020 14:16

Integrated Analysis Plan

Clinical Study Protocol Identification No.	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.
Study Phase	Phase Ib
Investigational Medicinal Product(s)	Avelumab and NHS-IL12 combination
Clinical Study Protocol Version	26 April 2019 /Version 7.0
Integrated Analysis Plan Author	**Coordinating Author** PPD Merck PPD PPD PPD **Function** / **Author(s) / Data Analyst(s)** PPD PPD PPD P
Integrated Analysis Plan Date and Version	20 October 2020 / Final 2.0
Integrated Analysis Plan Reviewers	**Function** / **Name** PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD

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Approval Page

Integrated Analysis Plan: MS201781-0031

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.

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Approval of the IAP by all Merck Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval within Eldorado, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADA	Anti-Drug Antibody
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
BOR	Best Overall Response
CDISC	Clinical Data Interchange Standards Consortium
Ceoi	Concentration observed immediately at the end of infusion
CI	Confidence Interval
C_{max}	Maximum serum concentration observed postdose
COVID-19	2019 Novel Coronavirus Disease
CR	Complete Response
CRC	Colorectal carcinoma
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerized Tomography
Ctrough	Concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
DBL	Data Base Lock
DI	Dose Intensity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire Core instrument
EOT	End of Treatment
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HIV	Human Immunodeficiency Virus
HRQOL	Health Related Quality of Life

IAP	Integrated Analysis Plan
IAS	Immunogenicity Analysis Set
IC	Immune Cells
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICP	Immune Cells Present
irAE	Immune-Related Adverse Event
CCI	[redacted]
irCR	Immune-related Complete Response
irOR	Immune-related Objective Response
CCI	[redacted]
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
CCI	[redacted]
IRRs	Infusion-Related Reactions
irSD	Immune-related Stable Disease
LLOQ	Lower Limit Of Quantification of the assay
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
MSSO	Maintenance and Support Services Organization
NC	Not Calculable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHS-IL12	M9241
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
OR	Objective Response
OS	Overall Survival
PCSA	Potentially Clinically Significant Abnormalities
PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PFS	Progression Free Survival

PGIS	Patient Global Impression of Severity
PT	Preferred Term
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-Reported Outcome
Q1	25th Percentile
Q3	75th Percentile
QLQ-CR29	EORTC Colorectal Cancer Module
QLQ-NMIBC24	EORTC Non-Muscle Invasive Bladder Cancer Module
QLQ-RCC10	EORTC Renal Cell Carcinoma Module
RBC	Red Blood Cells
RCC	Renal Cell Carcinoma
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TC	Tumor Cells
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
TNM	Tumor Node Metastasis
TRAE	Treatment-Related Adverse Event
UC	Urothelial Carcinoma
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
WHO	World Health Organization

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	21OCT2019	PPD	Not Applicable
2.0	20OCT2020	PPD	1. Further to the futility analysis, it has been decided to stop the study earlier. Hence, the sensitivity, subgroup and exploratory analyses of the efficacy criteria as well as the analysis of patient reported outcomes were removed. 2. Section 8.2: updated the categorizations for PD-L1 expression level at Baseline. 3. Section 11.1: added item ethnicity (Japanese, Non-Japanese). 4. Section 10.1: added a description for the overview of the impact of COVID-19 events. 5. Section 10.2.1: added an analysis of COVID-19 related protocol deviations. 6. Section 15.1.1: added a listing of COVID-19 related events. 7. Minor corrections in Section 16.2. 8. Appendix 18.3: table updated (added previously omitted parameter).

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for the expansion cohorts under protocol MS201781-0031. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 8 (Statistics) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments, with the exception of exploratory exposure-QTc analyses, which will be described and reported separately. Details of the futility and Safety Monitoring Committee (SMC) analyses for review of the participants' safety without formal statistical analysis are provided in sections 6.1 and 6.2.

5 Objectives and Endpoints

Please find below the Summary of the study expansion objectives and corresponding endpoints according to the protocol version 7/Global Amendment 6.0.

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
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	Confirmed BOR by Investigator assessment according to RECIST v1.1 by selected tumor type	14.1
To evaluate the safety and tolerability of combination therapy with avelumab and M9241 at the RP2D.	Occurrence, severity, and duration of TEAEs and TRAEs, graded according to the NCI-CTCAE v4.03.	15.1.1
Secondary		
To characterize PK profiles of avelumab and M9241 at the RP2D when given in combination	PK profiles of avelumab and M9241	16.1
To evaluate the immunogenicity of combination therapy with avelumab and M9241	Immunogenicity of avelumab and immunogenicity of M9241 in combination therapy, as measured by anti-drug antibody (ADA) assays.	16.1
To evaluate antitumor activity of combination therapy with avelumab and M9241 in selected solid tumor types.	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 duration of response (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	14.2, 14.3, 14.4

CCI [redacted]

Objectives	Endpoints (Outcome Measures)	IAP section
To assess symptom severity via patient-reported outcome (PRO) measures.	Change from Baseline of patient-reported outcomes disease-related symptoms and physical functioning concepts from the European Organisation for Research and Treatment of Cancer (EORTC) item bank.	Not performed (see Section 3)

The analyses of the endpoints will be described in the respective sections for efficacy, safety or other endpoints, regardless if the endpoint is a primary endpoint or not.

6 Overview of Planned Analyses

The following analyses are planned in the protocol:

- Futility analysis after Stage 1 of the urothelial carcinoma (UC) expansion cohort (data will be presented to the SMC). For UC cohort Stage 2 SMC review will be when 50% of patient in stage 2 are enrolled

- For indications other than UC, SMC review at the latest when 50% of each cohort (ie, 15 to 20 subjects enrolled) of the expansion part

- Safety and efficacy analyses at the end of each cohort (approximately 4 months after start of treatment of the last participant of each cohort which corresponds to 2 sequential radiographic disease evaluations)

- Safety and efficacy analysis at the end of the dose expansion part (after Data Base Lock (DBL))

This IAP covers the analyses planned for the expansion cohorts for efficacy and safety based on the data cut-off (see also section 9 Data handling after cut-off date) when applicable. Statistical analyses will be performed using cleaned eCRF data gained until a clinical cut-off date which is determined for each cohort.

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

Safety and efficacy analysis at the end of the dose expansion part of the study are covered. Statistical analyses will be performed after the end of study and DBL using cleaned eCRF data as well as external data including pharmacokinetic/pharmacodynamic data, immunogenicity, and biomarkers. The end of study is defined as 1 year after the last participant receives the last dose of protocol treatment, or the last participant dies, whichever comes first.

6.1 Futility Analysis

The UC expansion cohort entails a 2-stage design. During Stage 1 (single-arm), 16 participants will be enrolled and treated with combination therapy. At the end of this stage a futility analysis will be

performed by treatment arm for the primary efficacy endpoint confirmed BOR. If 3 or more responders are observed, an open-label randomized (1:1) controlled part (Stage 2) will be initiated.

The clinical cut-off date will be determined based on the treatment period for the 16 participants enrolled on the UC expansion cohort stage 1 after 4 months after start of treatment of the last participant or alternatively after the third responder be observed and after all of 16 participants have been completed the cycle 1 safety assessments (what happens later).

6.2 SMC Analysis

Safety data will be evaluated by an SMC at predefined time points in the SMC charter. For the expansion cohorts, the SMC will review the emerging safety profile and reconvene, for UC cohort after the first 16 participants in expansion phase have been dosed and when 50% for stage 2 has been enrolled, and for the remaining cohorts when 50% of each cohort (ie, 15 to 20 participants) has been enrolled. Further details are described in the SMC charter.

The clinical cut-off date will be determined based on the number of participants dosed in each cohort.

6.3 End of Cohort Analysis

For each expansion cohort, an end of cohort analysis is planned approximately 4 months after start of treatment of the last participant of each cohort. These analyses are planned after 2 sequential radiographic disease evaluations are available from all subjects.

The clinical cut-off date will be determined based on the treatment period for each cohort and after 2 sequential radiographic disease evaluations are available from all participants.

6.4 Final Analysis

All final, planned analyses identified in the Clinical Study Protocol and in this IAP will be performed only after the last participant has completed the follow-up period of the study with all study data in-house, all data queries resolved, and the database locked.

A data review meeting will be held prior to database lock.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The statistical methods as described in the protocol version 7/Global Amendment 6.0 were adopted.

Additionally, the COVID-19 pandemic was unforeseen at the time of the development of the clinical trial protocol; therefore, analyses related to the COVID-19 pandemic have been added later to the analysis plan.

No changes to the planned analysis of the efficacy endpoints will be performed due to the impact of COVID-19 outbreak.

Instead, additional outputs (summary tables and listings) will be generated to assess potential impacts of COVID-19 on this study and are described in Section 10.1, Section 10.2.1, and Section 15.1.1.

Finally, an unplanned interim analysis has been performed on the 16 participants enrolled and dosed in the stage 1 UC expansion cohort. This analysis was intended for internal planning purposes and performed prior to the futility analysis.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants who are dosed on the study despite not satisfying the inclusion criteria;
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn;
- Participants who receive the wrong treatment or an incorrect dose;
- Participants who receive an excluded concomitant medication.
- Deviation from Good Clinical Practice (GCP)

All important protocol deviations will be documented in the Clinical Trial Management System (CTMS) and in the Study Data Tabulation Model (SDTM) datasets, whether identified through site monitoring, medical review, or data management programming.

Important Protocol Deviations are specified in Appendix 18.1, and will be listed and summarized by cohort and overall based on the FAS.

8.2 Definition of Analysis Populations and Subgroups

This section describes the analysis populations of participants whose data will be included in the analyses described in this IAP.

Screened Analysis Set (SCR)

The screening analysis set includes all participants who signed the informed consent form (ICF). The number of screened participants will be presented.

Safety Analysis Set (SAF)

The Safety analysis set will include all participants who receive at least 1 dose of any study treatment. Analyses performed on the Safety analysis set will consider participants as treated according to the predefined protocol treatment arms.

Full Analysis Set (FAS)

The Full analysis set will include all participants for renal cell carcinoma (RCC), colorectal carcinoma (CRC), Non-Small Cell Lung Cancer (NSCLC) and UC stage 1 cohorts who receive at least 1 dose of any study treatment. For UC stage 2 cohort will include all participants who were randomized. Analyses performed on the FAS will consider participants as treated according to the predefined protocol treatment arms for RCC, CRC, NSCLC and UC stage 1 cohorts and for UC stage 2 cohort will consider participants according to the treatment assigned at randomization as per the intent-to-treat principle.

PK Analysis Set

The PK Analysis Set will consist of all participants who receive at least one complete dose (at least 90% of planned dose) of avelumab or NHS-IL12, have no important protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration of avelumab or NHS-IL12. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed according to the first dose level of IMP actually received.

All PK analyses will be based on this analysis set.

Immunogenicity Analysis Set (IAS)

All participants who receive at least one complete dose (at least 90% of planned dose) of avelumab or NHS-IL12 and at least 1 valid ADA result for avelumab or NHS-IL12.

CCI [redacted]

Table 1 Statistical Analysis by Analysis Set

Analyses	Safety Analysis Set	Full Analysis Set	PK Analysis Set	Immunogenicity Analysis Set
Demographics/ Baseline Characteristics		✓		
Prior and Concomitant Therapies		✓		
Exposure	✓			
Safety	✓			
Efficacy		✓		
Pharmacokinetics			✓	
Immunogenicity				✓
PRO		✓		
PD-L1 subgroup description	✓			

Analyses	Safety Analysis Set	Full Analysis Set	PK Analysis Set	Immunogenicity Analysis Set
CCI [redacted]				

Number of participants in each analysis set will be tabulated by cohort and overall. A table by sites will also be provided.

Subgroup definition

The following subgroups will be defined:

CCI [redacted]

CCI [redacted]

9 General Specifications for Data Analyses

Study intervention groups

The RCC, CRC, NSCLC and UC stage 1 cohorts are a unique group that receive a combination therapy with avelumab and M9241.

The UC stage 2 study intervention groups are defined and labelled as study intervention (combination therapy with avelumab and M9241) or avelumab weekly induction monotherapy.

Exposure analyses for UC cohort stage 2 will be presented separately for the two study intervention groups.

Study participants, demographics, previous or concomitant medications/procedures and safety analysis will be presented separately by study cohort and by treatment group (only for UC cohort Stage 2). Additionally, for UC cohort the results will be displayed by combination therapy (Stage 1 + Stage 2 combination therapy group) and UC cohort overall (Stage 1 + Stage 2).

Data handling after cut-off date

Data after cut-off do not undergo the cleaning process and not included in the SDTM package nor in the analysis.

Significance level

All statistical tests mentioned in this IAP are to be regarded as exploratory. All statistical tests comparing study intervention groups will be performed two-sided. If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise stated in this IAP.

Except for the tests described in Section 14, p-values will not be produced.

Presentation of continuous and qualitative variables

Continuous variables (non-PK) will be summarized using descriptive statistics, i.e.

- number of participants, number of participants with non-missing values,
- mean, standard deviation,
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum.

If there are no missing values this should be indicated by a 0.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of participants in each cohort of the analysis population of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

For time-to-event variables analyzed using Kaplan Meier approach, the following statistics will be presented: number of participants with events, median, minimum, maximum and 95% CI.

Definition of baseline

The last available assessment prior to the start of study treatment is defined as "baseline" value or "baseline" assessment for safety and efficacy analyses, even for randomization part for the stage 2 UC cohort. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on treatment day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an

unscheduled assessment on treatment day 1 will be considered to have been obtained after study treatment administration.

Participants who start treatment and discontinue from the study on the same day may have two different sets of data collected on treatment Day 1 (one during study and one in the end of treatment [EOT] visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Definition of change from baseline

Change from baseline = visit value – baseline value

Percent Change from Baseline = 100 * (visit value – baseline value) / baseline value

Definition of study treatment day

Treatment day is defined relative to the date of start of treatment. Treatment Day 1 defines the day of first administration of treatment, the day before is defined as Treatment Day –1 (no Treatment day 0 is defined). The Treatment Day X is defined as Date of treatment – Date on first administration of treatment + 1.

Definition of on-treatment period

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

The date of new anti-cancer therapy after treatment start is collected in eCRF pages "Anti-Cancer Treatment after Discontinuation Details" and "Radiotherapy After Discontinuation Details". 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 are considered anti-cancer therapy.

Definition of duration

Duration will be calculated as Stop Date – Start Date + 1, unless otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event. In general, the reference date will be the date of first dose of study treatment, even for randomization part for the stage 2 UC cohort.

Definition of age

Age [years] = (date of given informed consent - date of birth + 1) / 365.25

In case the day or the day and the month of the date of birth and the date of informed consent is unknown, the following approach will be used:

In case of missing day: Age [years] = (year/month/01 of given informed consent – year/month/01 of birth + 1) / 365.25

In case only year of birth is given: Age [years] = (year/01/01 of given informed consent year/01/01 of birth +1) / 365.25

The integer part of the calculated age will be used for reporting purposes.

Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data

Unless otherwise specified (Section 13, 15, 16 and 17), all data will be evaluated as observed, and no imputation method for missing values will be used.

Missing statistics, e.g. when they cannot be calculated, should be presented as 'Not Calculable' or 'Not Applicable'. For example, if N=1, the measure of variability (Std) cannot be computed and should be presented as 'NC'.

For PK data, 'ND' (for Not Determined) will be used to report statistics that are not calculated due to insufficient data.

- **Disease history**

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

- **Adverse Events**

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

  Unknown AE relationship to avelumab and/or NHS-IL12 (i.e. no answer to the question "Relationship with study treatment") will be considered as Relationship with study treatment = Related.

- **Exposure**

  For each treatment, in case the last date of study drug is incomplete the date of last administration of study drug will be taken from the treatment termination eCRF pages.

- **Last Alive Date**

The last alive date will be derived for participants not known to have died at the analysis cut-off using the latest complete date among the following:

- All participant assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Date last known to be alive collected on the eCRF form "Subject Status / Survival Follow-up"
- Study drug start and end dates
- Date of discontinuation from the "Study Termination" eCRF page (not used if reason for discontinuation is lost to follow-up)

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used.

- **Death date**

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as day after date of last contact from the eCRF survival page
- If the day or both day and month are missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

If the day is missing from the date of last contact, it will be imputed to 1st day of the month and year of last contact only if derived from the survival page.

- **Tumor assessments**

All investigation dates (e.g. X-ray, computerized tomography (CT) scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g. X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

- **Missing questionnaires items**

Unless otherwise specified, all HRQOL questionnaires will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual.

PGIS

No imputation will be applied to Patient Global Impression of Severity (PGIS). Number and percentage of missing questionnaires will be summarized.

EORTC QLQ-C30

For the EORTC QLQ-C30 selected items collected, if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which are present for that respondent (Fayers, et al., 2001).

QLQ-NMIBC24

No imputation will be applied to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Non-Muscle Invasive Bladder Cancer Module (QLQ-NMIBC24) due to selected items only will be collected. Number and percentage of missing questionnaires and missing items will be summarized.

NSCLC-SAQ

No imputation will be applied to the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) due to selected items only will be collected. Number and percentage of missing questionnaires and missing items will be summarized.

QLQ-CR29

No imputation will be applied to the EORTC Colorectal Cancer Module (QLQ-CR29) due to selected items only will be collected. Number and percentage of missing questionnaires and missing items will be summarized.

QLQ-RCC10

No imputation will be applied to the EORTC Renal Cell Carcinoma Module (QLQ-RCC10) due to selected items only will be collected. Number and percentage of missing questionnaires and missing items will be summarized.

- **Missing questionnaires forms**

No imputation on missing questionnaires will be applied.

In HRQOL summary tables over-time the total of missing and non-missing observations at each time-point will be displayed.

Softwares

The estimation of PK parameters will be performed using the validated software tool Phoenix®/WinNonlin 6.3® (or later). All other statistical analyses will be performed using SAS® Version 9.4 or higher, or R, Version 2.10.1 or higher.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

Overall summary of analysis sets will be tabulated using frequency and percentage by cohort, by treatment group (only for UC cohort Stage 2) and overall based on all the participants who signed informed consent form (ICF) and entered the study. The number of participants in SAF analysis in each cohort will be used as the denominator.

- Number of participants who signed ICF
- Number of participants in SAF analysis set
- Number of participants randomized (only applicable for Stage 2 UC cohort)

- Number of participants who at least receive one study treatment administration
- Number of participants still on treatment
- Number of participants who permanently discontinued the study treatment along with the reason will be presented separately for avelumab and NHS-IL12.
- Reasons off-treatment will be presented as collected on the "NHS-IL12 Termination" and "Avelumab Termination" eCRF page:
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Disease progression
    - Withdrew consent
    - Other
- Number of participants who discontinued both treatments but are still in follow-up ("Study Termination" eCRF page is not completed)
- Number of subjects with avelumab re-initiation
- Number of subjects with NHS-IL12 re-initiation ("Re-Initiated Nhs-Il12 Termination" eCRF page is completed)
- Number of participants off-study
    - Reasons off-study (as collected on the "Study Termination" eCRF page)
        - Lost to follow-up
        - Death
        - Withdrew consent
        - Other

The listing of subject disposition will include all participants who signed ICF (i.e. including screening failures).

The listing will include the following information: subject identifier, date of informed consent, continue beyond screening, date and reason for not continuing beyond screening, cohort, first treatment date for avelumab and NHS-IL12, date of last administration and primary reason for permanent treatment termination of NHS-IL12 (as reported on "NHS-IL12 Termination" eCRF page), date of last administration and primary reason for permanent treatment termination of avelumab (as reported on "Avelumab Termination" eCRF page,), date and reason for study termination (as reported on "Study Termination" eCRF page), flag for the SAF set.

A separate listing for reason for EOT due to adverse events (AEs) will be provided. The listing will be restricted to the SAF participants who are off-treatment due to an AE, and will include the following information: cohort, subject identifier, first / last treatment date of NHS-IL12 or avelumab, date off-treatment of NHS-IL12 or avelumab, and the relevant AE system organ classes (SOCs), preferred terms (PTs), AE relationship to the study treatment, AE grade and AE seriousness. This listing will include all subjects with AEs with "Drug withdrawn" in avelumab or NHS-IL12 actions taken (as reported on "Adverse Events Details" eCRF page)

The indirect impact of COVID-19 will be assessed as follows:

- The number and percentage of participants in pre/during/post COVID-19 study period will be provided:
    - Number of subjects who started treatment prior to the COVID-19 study period
        - Received at least one dose during the COVID-19 study period
        - Discontinued treatment before start of the COVID-19 study period
    - Number of subjects who started treatment during the COVID-19 study period
    - Number of subjects who started treatment posterior to the COVID-19 study period*

      * No participants will be categorized into the "post COVID-19 study period".

The COVID-19 study period is defined as follows:

- The start of COVID-19 study period will be defined by country as the minimum of the date of the first death from COVID-19 occurred in each country (according to the published data by European Centre for Disease Prevention and Control on 26th June 2020) and 11 March 2020 (WHO-start of world-wide pandemic).
- Post-pandemic could be defined as date (1) vaccination is released, (2) WHO declares COVID-19 pandemic over, (3) region-specific calls are made to end social distancing measures with no relevant rise in cases thereafter.

An overview of the COVID-19 impact on the study will also be provided. This will include the number and percentage of participants who meet the following items:

- Potentially affected by COVID-19 (Started during pandemic/Started before pandemic and dosed during pandemic/Started before pandemic and not dosed during pandemic)
- At least one COVID-19 impact
    - At least one adverse event related to COVID-19 (see Section 15.1.1)
    - At least one COVID-19-related protocol deviation
    - At least one missed dose of avelumab
    - At least one missed dose of NHS-IL12
    - At least one dose interruption of avelumab
    - At least one dose interruption of NHS-IL12

- At least one missed visit
- At least one missed tumor assessment
- At least one tele-visit replacing on-site visit
- Number of participants who permanently discontinued avelumab for any reason related to COVID-19
- Number of participants who permanently discontinued NHS-IL12 for any reason related to COVID-19
- Number of participants who discontinued the study for any reason related to COVID-19
- Number of participants who died for any reason related to COVID-19

A listing of all participants affected by COVID-19 including the outcome to each category of the overview table, the PT and AE number of AEs attributed to COVID-19, and the COVID-19 related protocol deviations will also be provided.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided:

- Frequency table per category of important protocol deviations
- Listing of important protocol deviations

Additionally, the COVID-19 related protocol deviations will be described as follows:

- Frequency table per category of important COVID-19 related protocol deviations
- Frequency table per category of non-important COVID-19 related protocol deviations
  - Listing of COVID-19 related protocol deviations

COVID-19-related protocol deviations are identified in the database based on the prefix "COVID-19" reported in the description. Additionally, a flag will be added to the SDTM datasets.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

All criteria/reasons leading to the exclusion of a participant from an Analysis Population should be summarized and listed (see section 8.2).

11 Demographics and Other Baseline Characteristics

All the demographics and other baseline characteristics will be summarized on the FAS overall, by study cohort.

11.1 Demographics

The demographics and baseline characteristics tables will include descriptive statistics for the following variables:

- Age (in years)
- Age categories: < 65 years, ≥ 65 years (65 – <75 years, 75 – <85 years, >=85 years)
- Sex: Male, Female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not collected
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino; Japanese, Not Japanese
- Height (cm)
- Weight (kg) at baseline
- BMI (kg/m^2) at baseline
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1 at baseline

Nicotine consumption will be described separately and will include descriptive statistics for the following variables:

- Nicotine use status
  - Never used
  - Regular user
  - Occasional user
  - Former user
- Duration of nicotine consumption (years) will be derived for nicotine user only: defined as (end date of nicotine consumption – start date of nicotine consumption + 1) / 365.25
- Only month and year will be collected in eCRF. As a result the day will be assumed to be the same for start and end date here. If month and year are missing, no imputation will be performed and if only month is missing, December 31th will be imputed for end date and January 1st will be imputed for start date for concerning the worst case of nicotine consumption. Duration of nicotine consumption will be presented by category:
  - Regular user:<5, 5-<10, ≥10 years
  - Occasional user: <5, 5-<10, ≥10 years
  - Former user: <5, 5-<10, ≥10 years

The listing of demographics and baseline characteristics will include the following information: study cohort, subject identifier, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2) and ECOG performance status at baseline. A separate listing of nicotine consumption will be created.

11.2 Medical History

Medical history will be coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized as the numbers and percentages of participants by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

Listing of medical history data by participant will include coded terms and all the relevant data fields as collected on the "Medical History" eCRF page. This listing will be sorted by study cohort, subject identifier and then by start date.

11.3 Hepatitis B and C Serology

The results of the hepatitis B (HBsAg, HBsAb, HBcAb IgG and IgM), hepatitis C (HCVAb with reflex to HCV RNA) and human immunodeficiency virus (HIV) screening tests will be listed.

11.4 Disease History

Disease history is collected on "Urothelial Carcinoma Diagnosis", "NSCL Cancer Diagnosis", "Colorectal Cancer Diagnosis" and "Renal Cell Carcinoma Diagnosis" eCRF pages. Partial date will be imputed as described in the section 11.10.1.

The disease history table will include descriptive statistics for the following variables:

- Tumor sub-type
    - Renal pelvis
    - Ureter….
- Time since first diagnosis (years), defined as (the first study treatment date – the date of initial cancer diagnosis)/365.25
- Time since first metastatic disease diagnosis (years), defined as (the first study treatment date – the date of first occurrence of metastatic disease)/365.25
- Time since last disease progression (months), defined as (the first study treatment date - the date of last progression of disease)/30.4375
- Tumor Node Metastasis (TNM) Classification of Malignant Tumors at initial diagnosis
    - TX
    - T0
    - N1
    - ….

- TNM at study entry
    - TX
    - T0
    - N1
    - …

Listing of disease history will be provided with all relevant data (as collected on the "Urothelial Carcinoma Diagnosis", "NSCL Cancer Diagnosis", "Colorectal Cancer Diagnosis" and "Renal Cell Carcinoma Diagnosis" eCRF pages) and derived variables used in the above table.

Additionally, listings of screening tumor biopsy and liquid biopsy data will be provided (as collected on the "Screening Tumor Biopsy" and "Liquid Biopsy" eCRF pages).

12 Previous or Concomitant Medications/Procedures

Prior and concomitant anti-cancer therapy / other medications will be coded using the latest available version of WHO Drug Dictionary and summarized based on the FAS by cohort and overall.

12.1 Prior Anti-Cancer Therapies/Procedures

The prior anti-cancer treatments and procedures are collected under the "Prior anti-cancer drug therapies details", "Prior anti-cancer radiotherapies details" and "Prior anti-cancer surgeries details" eCRF pages.

The overall summary of presence of prior anti-cancer treatments and procedures table will include: the number and percentages of participants by type of treatment (by dose level and overall):

- participants with at least one type of prior anti-cancer treatment/procedure
- participants with at least one prior anti-cancer surgery
- participants with at least one prior anti-cancer drug therapy
- participants with at least one prior anti-cancer drug therapy for metastatic disease
- participants with at least one prior anti-cancer radiotherapy

For prior anti-cancer drug therapy, the following items will be summarized:

- Type of therapy: Anti-PD1 or Anti-PD-L1 / Cytotoxic Therapy / Monoclonal Antibodies Therapy/ Small Molecules / Immunotherapy except Anti-PD-1 or Anti-PD-L1 / Endocrine Therapy/Other
- Intent of therapy: Adjuvant / Neoadjuvant / Metastatic/ Locally advanced
- For Metastatic/ Locally advanced intent, the therapy lines: 1 / 2 / 3 / ≥4
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD)/ Progressive Disease (PD)/ /Non-Complete Response/Non-Progressive Disease (Non-CR/Non-

PD)/ Not evaluable (NE) / Unknown / Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be extensively detailed with the number and percentage of participants by the drug class and PT in a separate table. A participant will be counted only once within a given drug class and within a given drug name, even if the participant received the same medication at different times. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class, based on the incidence in the "Overall" column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

The listings of prior anti-cancer treatments and procedures will also be provided:

- listing of prior anti-cancer drug therapies
- listing of prior anti-cancer radiotherapy
- listing of prior anti-cancer surgeries

These will include study cohort, subject identifier, and all the relevant collected data-fields on the corresponding eCRF pages (ordered by study cohort, subject identifier and therapy start date).

12.2 Previous and Concomitant Medications/Procedures

Previous and concomitant medications are collected on the "Relevant previous medications details" and "Concomitant medications details" eCRF page. Prior and concomitant procedures are collected on the "Concomitant procedures details" eCRF page.

Previous medications are medications, other than study medications and pre-medications for study drug, which are started before first dose date of study treatment.

Concomitant medications are medications, other than study medications and pre-medications for study drug, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period.

Previous medications and Concomitant medications will be summarized separately showing the number of participants and percentages by drug class and preferred term by dose level and overall. A participant will be counted only once within a given drug class and within a given drug name, even if the participant received the same medication at different times.

The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class, based on the incidence in the "Overall" column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Previous and concomitant medication data will be listed separately. Following variables will be included in the listings: study cohort, subject identifier, and all corresponding collected data-field

on the corresponding eCRF page. The listings will be sorted by study cohort, subject identifier, and the start date of the medication.

Prior and concomitant procedures data will be listed from the "Concomitant procedures details" eCRF page. Study cohort, subject identifier, and all collected data-field on the corresponding eCRF page will be included in the Prior and Concomitant Procedure listing. The listings will be sorted by study cohort, subject identifier, and the start date of the procedure.

Premedication data (reported on the "Premedication details" eCRF page) given before the study drug administration will be listed.

12.3 Subsequent Anti-Cancer Therapies/Procedures

Number of participants received treatment after discontinuation will be summarized as reported on the "Anti-Cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Surgery after Discontinuation Details" eCRF pages.

Number and percentage of participants with any anti-cancer treatment after discontinuation will be tabulated by cohort and overall based on the data collected from the "Anti-Cancer Treatment Details" eCRF pages, as following:

- Type of therapies (as collected in eCRF):
- Anti-PD-1/anti-PD-L1,
- Cytotoxic Therapy,
- Endocrine Therapy,
- Monoclonal Antibodies therapy,
- Small molecules,
- Immunotherapy except Anti-PD-1/anti-PD-L1,
- Other.

Summary statistics will be created for best response across all post study treatments based on the data collected from "Anti-Cancer Treatment Details" eCRF page, i.e. CR / PR / PD / SD / Non-CR/Non-PD / Unknown / Not evaluable / Not applicable.

Anti-cancer treatment after discontinuation will be provided in a listing with data retrieved from "Anti-Cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Surgery after Discontinuation Details" eCRF pages.

13 Study intervention Compliance and Exposure

All dosing calculations and summaries, as well as the listings of study drug administration will be based on 'NHS-IL12 Administration' and 'Avelumab Administration' eCRF pages.

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 participants 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.

13.1 Exposure to Study Drug

13.1.1 Avelumab

The calculations described on this point will use all information before treatment re-initiation. Treatment re-initiation will be listed.

The actual dose level for avelumab is 800 mg.

The duration of avelumab treatment (in weeks) during the study for a participant will be based on the duration of the cycle of 28 days and is defined as:

Treatment duration (weeks) = (end date of last cycle –first dose date + 1)/7

The end date of last cycle for avelumab is defined as follows:

- if the last dose is given at the day 1 of the cycle then the end date of the last cycle will be the date of the last dose + 28 days -1
- if the last dose is given at the day 8 of the cycle then the end date of the last cycle will be the date of the last dose + 21 days -1 (only applicable for the first 3 cycles)
- if the last dose is given at the day 15 of the cycle then the end date of the last cycle will be the date of the last dose + 14 days -1
- if the last dose is given at the day 22 of the cycle then the end date of the last cycle will be the date of the last dose + 7 days -1 (only applicable for the first 3 cycles)

The cumulative dose (mg/kg) of avelumab per participant in a time period is the sum of the actual dose that the participant received within that period.

The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each participant across all cycles. The dose intensity per cycle (mg/cycle) is defined as

DI (mg/cycle) = Cumulative dose (mg)/[treatment duration (in weeks)/4]

The relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose per cycle and expressed in %.

RDI (%) = 100×[DI (mg/cycle)/(planned dose×2) (mg/cycle)]

The planned 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 summary of treatment exposure and compliance for avelumab will include the following information:

- Treatment duration (weeks)
- Total number of infusions received
- Cumulative dose (mg))
- Dose intensity (mg/cycle)
- Relative dose intensity (%)
    - <50%
    - [50%, 65%[
    - [65%, 80%[
    - [80%, 100%]
    - > 100%

13.1.2 NHS-IL12

The actual dose for NHS-IL12 is calculated as actual dose administered/weight (µg /kg). The last available weight of the participant on or prior to the day of dosing will be used.

The duration of NHS-IL12 treatment (in weeks) during the study for a participant is defined as:

Treatment duration (weeks) = (last dose date –first dose date + 28)/7

The cumulative dose (µg /kg) of NHS-IL12 per participant in a time period is the sum of the actual dose levels that the participant received within that period (i.e., total dose administered (µg) / weight (kg)).

NHS-IL12 will be administered at Day1 of each cycle. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each participant across all cycles. The dose intensity per cycle (µg /kg/cycle) is defined as

DI (µg /kg/cycle) = Cumulative dose (µg /kg)/[treatment duration (in weeks)/4]

The relative RDI is defined as the actual dose intensity divided by the planned dose per cycle and expressed in %.

RDI (%) = 100×[DI (µg/kg/cycle)/(planned dose) (µg /kg/cycle)]

The summary of treatment exposure and compliance for NHS-IL12 will include the following information:

- Treatment duration (weeks)
- Total number of infusions received
- Cumulative dose (µg /kg)
- Dose intensity (µg /kg/cycle)
- Relative dose intensity (%)
    - <50%
    - [50%, 65%[
    - [65%, 80%[
    - [80%, 100%]
    - > 100%

13.2 Dose Reductions

Dose reductions of avelumab or NHS-IL12 is defined as actual non-zero dose < 90% of the planned dose.

Number and percentage of participants with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 / ≥4) will be summarized by cohort.

13.3 Dose Delays

Delays will be derived based on study drug administration date and will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous treatment administration date):

- No delay (including 1day delay)
- 2-6 days delay
- 7 or more days delay

Number and percentage of participants with delayed study drug administration and maximum length of delay, i.e. the worst case of delay if participants have multiple dose delays will be summarized by cohort.

13.4 Infusion rate reductions

Infusion rate reductions of avelumab as recorded on the eCRF will be used for analysis. Number and percentage of participant with at least one infusion rate reduction as well as a breakdown of infusion rate reductions (1 / 2 / ≥3) will be summarized by cohort.

13.5 Dose Interruptions

Drug interruptions of avelumab or NHS-IL12 as recorded on the eCRF will be used for analysis.

The number and percentage of participants with dose interruptions and the corresponding reasons will be summarized by cohort.

14 Efficacy Analyses

The subsections in this section include specifications for analyzing clinical study endpoints for efficacy as specified in the Clinical Study Protocol to meet the study objectives.

Efficacy analysis will be summarized on the FAS overall, by study cohort and by treatment group (only for UC cohort Stage 2). Additionally, for UC cohort the results will be displayed by combination therapy (Stage 1 + Stage 2 combination therapy group).

14.1 Primary Endpoint: confirmed BOR

The primary efficacy endpoint is the confirmed BOR by Investigator assessment according to RECIST v1.1 by selected tumor type.

Confirmed Best Overall Response will be evaluated according to RECIST v1.1 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 rule.

- Complete response = at least two determinations of CR at least 4 weeks apart and before progression. Namely, second determination date of CR – progression date >= at least 4 weeks or at least two determinations of CR without any progression determination.
- Partial response = at least two determinations of PR or better at least 4 weeks apart and before progression (and not qualifying for a CR). Namely, second PR or better determination date – progression date >= at least 4 weeks or at least two PR or better determinations without any progression determination.
- Stable disease = at least one SD assessment (or better) ≥ 6 weeks after the first study treatment administration and before progression (and not qualifying for CR or PR)
- Non-CR/non-PD (for the participants with non-measurable disease at baseline) = at least one Non-CR/non-PD assessment (or better) ≥ 6 weeks after the first study treatment administration and before progression (and not qualifying for CR or PR)
- Progressive Disease = PD <= 16 weeks after the first study treatment administration (and not qualifying for CR, PR, SD, or non-CR/non-PD).
- Not Evaluable (NE): all other cases.

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met.

Objective Response (OR) is defined as a confirmed BOR of complete response (CR) or partial response (PR) according to RECIST v1.1.

Only tumor assessments performed on or before the start of any further anti-cancer therapy (Drug therapy, surgery and radiotherapy other than radiation with palliative intent) will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease

progression. 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 are considered anti-cancer therapy.

The frequency (number and percentage) of participants with confirmed responses (defined as confirmed CR or confirmed PR) will be summarized by study cohort. The ORR will be determined as the proportion of participants with a confirmed BOR of PR or CR. Participants with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessments
- No post-baseline assessments
- All post-baseline assessments have overall response NE
- New anticancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after Treatment day 1 without further evaluable tumor assessment)
- PD too late (Tumor assessment detecting the PD >12 weeks after Treatment day 1 with no tumor assessment in between)
- Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD of insufficient duration'

Percent change from baseline in sum of longest diameters will be plotted.

14.1.1 Primary Objective: Analysis of the primary endpoint confirmed BOR

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Confirmed Best Overall Response (BOR)			
Primary (FAS)	The confirmed BOR will be determined as the proportion of subjects with a confirmed CR or confirmed PR.	The frequency (number and percentage) of subjects with confirmed responses (defined as confirmed CR or confirmed PR) will be summarized by study cohort. For UC cohort will be summarized by stage and for stage 2 by treatment group. In stage 2 odds ratio will be displayed for treatment comparison. Additional for UC cohort Stage 1 and Stage 2 combination therapy group will be displayed together. Response rate with CI (Clopper-Pearson)	Participants with missing data are considered as non-responders

14.2 Secondary Endpoint: PFS time

Progression free survival time is defined as the time (in months) from treatment day 1 to the date of the first documentation of objective PD as per RECIST v1.1 or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last evaluable tumor assessment in the following cases:

- for participants who do not have an event (PD or death),
- for participants who started a new anti-cancer therapy prior to an event
- for participants with an event after two or more missing tumor assessments.

Participants who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the treatment day 1 unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

14.2.1 Secondary Objective: Analysis of the secondary endpoint PFS time

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Progression Free Survival (PFS)			
Secondary (FAS)	time from treatment day 1 to the date of the first documentation of objective PD as per RECIST v1.1 or death due to any cause, whichever occurs first.	Kaplan-Meier estimates (product-limit estimates) will be presented by study cohort together with a summary of associated statistics (median time, 6-, 12-, 18-, 24-month rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 95% confidence intervals. The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982). For UC cohort PFS results will be summarized by stage and for stage 2 by treatment group. In stage 2 hazard ratio will be displayed for treatment comparison. Additional for UC cohort Stage 1 and Stage 2 combination therapy group will be displayed together.	Model based

Analyses of progression free survival time: additional information

The censoring and event date options to be considered for the PFS and DOR analyses are presented in the Table 2.

Table 2 Outcome and Event Dates for PFS and DOR analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Treatment Day 1	Censored [a]

Scenario	Date of event/censoring	Outcome
If the last tumor assessment is beyond 6 months from the first dose: Progression or death ≤ 12 weeks after last tumor assessment or ≤ 12 weeks after treatment day 1	Date of progression or death	Event
If the last tumor assessment is within 6 months from the first dose: Progression or death ≤ 8 weeks after last tumor assessment or ≤ 8 weeks after treatment day 1	Date of progression or death	Event
If the last tumor assessment is beyond 6 months from the first dose: Progression or death > 12 weeks after the last tumor assessment	Date of last evaluable assessment	Censored
If the last tumor assessment is within 6 months from the first dose: Progression or death > 8 weeks after the last tumor assessment	Date of last evaluable assessment	Censored
No progression	Date of last evaluable assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last evaluable assessment before anti-cancer therapy is given	Censored
[a] However if the subject dies ≤12 weeks after treatment day 1 the death is an event with date on death date		

PFS (months) = [date of event or censoring – treatment day 1 +1]/30.4375

PFS will be summarized by dose level using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CIs for each median will be provided. Kaplan-Meier plots will also be provided.

The PFS time or censoring time and the reasons for censoring will also be presented in a participant listing.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by study cohort. Reasons for censoring will be summarized according to the categories in Table 3 following the hierarchy shown.

Table 3. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than 8 (or 12 if beyond 6 months from the first dose of study treatment) weeks after last adequate post-baseline tumor assessment/ date of first dose of study treatment (see here also Table 2)	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Subject refused further FU]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any tumor evaluation after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] more than 8 (or 12) weeks after last adequate tumor assessment (see here also Table 2).

14.3 Secondary Endpoint: OS time

Overall survival (in months) is defined as the time from treatment day 1 to the date of death due to any cause. Participants known to be alive will be censored at date as specified in section 9 "last alive date" considerations.

OS (months) = [date of death or censoring – treatment day 1 +1]/30.4375

OS will be summarized and presented as PFS.

Frequency (number and percentage) of participants with event and censoring reasons will be presented by dose level. Censoring reasons are as follows:

- Ongoing in the study without an event

- Withdrawal of consent
- Lost to follow-up

The OS time or censoring time and the reasons for censoring will also be presented in a participant listing.

14.4 Secondary Endpoint: Duration of response

Duration of response is defined, for participants with confirmed OR, as the time in months from first documentation of OR to the date of first documentation of PD as per RECIST v1.1 or death due to any cause. If a participant has not had an event (PD or death), DOR is censored. The censoring rules for DOR are the same as described below for PFS.

DOR will be summarized for the FAS of participants with a confirmed OR using the Kaplan-Meier method. The median event time and 2-sided 95% CI for the median will be provided. If the number of participants with a confirmed CR or PR is small, the data will only be listed.

15 Safety Analyses

All safety analyses will be performed using the SAF by study cohort and overall, unless otherwise stated.

15.1 Adverse Events

Definitions

Treatment-emergent adverse events: those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period as defined in Section 9.

Treatment Related Adverse Events (TRAE): adverse events with relationship to avelumab and/or NHS-IL12 (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator.

Serious Adverse Events (SAEs): serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).

Adverse Events Leading to Any Treatment Discontinuation: adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with any study drug = Drug withdrawn).

Adverse Events Leading to Death: adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).

Immune-Related Adverse Events (irAEs): Immune-Related adverse events (please refer to the section 18.4)

Infusion-Related Reactions (IRRs): IRRs (please refer to the section 18.4).

CCI [redacted]

CCI [redacted]

Missing data handling

Missing data imputation is described in Section 9.

15.1.1 All Adverse Events

Unless otherwise stated, adverse events will be displayed in terms of frequency tables: by study cohort, primary SOC and PT in decreasing frequency.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per participant, using preferred term as event category and primary system organ class (SOC).

If an adverse event is reported for a given participant more than once during study intervention, the worst severity and the worst relationship to study intervention will be tabulated.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following by study cohort and overall:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - CCI [redacted]
  - CCI [redacted]
  - Serious TEAEs
  - CCI [redacted]
  - TEAEs leading to death
  - CCI [redacted]
  - All irAEs
  - CCI [redacted]
  - All IRRs
  - CCI [redacted]
  - Any Infusion-Related Reaction Leading to Death

- Any Infusion-Related Reaction Grade >=3
- Any Serious Infusion-Related Reaction
- Any Immune-Related Reaction
- Any Immune-Related Reaction Leading to Death
- Any Immune-Related Reaction Grade >=3
- Any Serious Immune-Related Reaction
- CCI
- CCI
- CCI
- CCI
- CCI

- Any TEAEs by SOC and PT
- Any TEAEs by SOC and PT and worst grade
- CCI
- CCI
- TEAEs leading to death by SOC and PT
- CCI
- TEAEs Excluding SAEs, with Frequency ≥ 5% in any dose level by SOC and PT
- Serious TEAEs, with Frequency ≥ 5% in any dose level by SOC and PT

Evaluation of COVID-19 effect on AEs

The direct effect of COVID-19 for AEs will be assessed via a listing of COVID-19 related AEs including the relevant information. The listing will be generated using the "COVID-19 related terms MedDRA 23.0 update Spreadsheet" (https://www.meddra.org/covid-19-related-terms-meddra-230-update-spreadsheet) or a later version as available from Maintenance and Support Services Organization (MSSO), considering all "search terms for COVID-19-related" = "Y".

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

The number and percentage of participants with each of the following events will be presented for TEAEs leading to permanent discontinuation in an overall summary table by study cohort and overall:

- TEAEs leading to study drug discontinuation (both drugs, avelumab, NHS-IL12)
- Avelumab related TEAEs leading to study drug discontinuation (any drug, avelumab, NHS-IL12)
- NHS-IL12 related TEAEs leading to study drug discontinuation (any drug, avelumab, NHS-IL12)
- irAEs leading to permanent avelumab discontinuation
- IRRs leading to permanent avelumab discontinuation
- Cytokine release syndrome TEAEs leading to permanent discontinuation of NHS-IL12
- Cytokine release syndrome TEAEs leading to permanent discontinuation of avelumab

The following summaries by SOC and PT will be produced:

- TEAEs Leading to avelumab Permanent Discontinuation by SOC and PT
- TEAEs Leading to NHS-IL12 Permanent Discontinuation by SOC and PT
- TEAEs Leading to avelumab and NHS-IL12 Permanent Discontinuation by SOC and PT
- Avelumab related AEs Leading to avelumab Permanent Discontinuation by SOC and PT
- NHS-IL12 related AEs Leading to NHS-IL12 Permanent Discontinuation by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

The frequency (number and percentage) of participants who died will be tabulated based on information from the "Death" eCRF page by study cohort and overall.

- All deaths will be tabulated and listed for SAF analysis set. The deaths table will include the following information:
    - Number and percentage of participants who died

- Primary reason for death
  - Disease progression
  - Adverse event related to study treatment
  - Adverse event not related to study treatment
  - Other
  - Unknown

- Number and percentage of participants who died within 30 days of the last study treatment administration
  - Primary reason for death
    - Disease progression
    - Adverse event related to study treatment
    - Adverse event not related to study treatment
    - Other
    - Unknown
- Number and percentage of participants who died within 60 days of the first study treatment administration
  - Primary reason for death
    - Disease progression
    - Adverse event related to study treatment
    - Adverse event not related to study treatment
    - Other
    - Unknown

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (study treatment received, date of first / last administration, study cohort) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.
- Flag for death within 60 days of first dose of study treatment.

15.2.2 Serious Adverse Events

The frequency (number and percentage) of participants with each of the following will be presented for treatment emergent SAEs by dose level:

- SAEs by SOC and PT
- Related (to avelumab or NHS-IL12 separately) SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

15.2.3 Other Significant Adverse Events

The frequency (number and percentage) of participants with each of the following will be presented for treatment emergent irAEs, by study cohort and overall:

- irAEs leading to death, by SOC and PT
- irAEs, by SOC and PT
- irAEs leading to discontinuation, by SOC and PT
- irAEs, Grade $\geq$ 3, by SOC and PT
- irAEs by SOC and PT and worst grade
- serious irAEs by SOC and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period. A separate listing of irAEs with onset after the on-treatment period will also be provided.

The frequency (number and percentage) of participants with each of the following will be presented for treatment emergent IRRs, by study cohort and overall:

- IRRs leading to death, by SOC and PT
- IRRs leading to discontinuation, by SOC and PT
- IRRs, by SOC and PT
- IRRs, Grade $\geq$ 3, by SOC and PT
- Serious IRRs, by SOC and PT

Timing of first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be provided.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

CCI

- CCI
- CCI
- CCI
- CCI
- CCI

CCI

15.3 Clinical Laboratory Evaluation

The laboratory parameters will be presented for SAF.

Laboratory results will be classified by grade according to NCI-CTCAE v4.03 when applicable (Appendix 18.2). 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. For the parameters with both low (below lower limit of normal range) and high (above upper limit of normal range) toxicity grades such as potassium (hypokalemia/ hyperkalemia), the low and high grades will be summarized separately. For the values below normal limit (e.g. hypokalemia) the grade will be set to 0 when summarizing grades above normal limit (e.g. hyperkalemia), and vice versa.

Results for variables that are not gradable according to NCI-CTCAE will be presented as below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges) (Appendix 18.3). Only participants with post-baseline laboratory values will be included in these analyses.

The worst on-treatment grade (i.e. on or after first study intervention administration and within 60 days after last study intervention administration) will be summarized considering only participants with post baseline laboratory samples: Laboratory tests by NCI-CTC grade (0, 1, 2, 3, 4, any).

Quantitative data will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time.

The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High). The number of participants with clinical laboratory values below, within, or above normal ranges at baseline compared to endpoint will be tabulated for each test by study intervention. Shift tables of baseline versus endpoint (as well as the worst value at any post-baseline visit) will be presented. Abnormalities classified according to NCI-CTCAE toxicity grading will be described using the worst grade. In case of missing data at the end of the treatment period, the last known post-baseline value will be carried forward.

15.3.1 Hematology and Clinical Chemistry Parameters

Parameters with CTCAE grade defined

The laboratory toxicities will be tabulated by the worst post-baseline CTCAE grade and the shift from baseline in the CTCAE grade using descriptive statistics (count and percentage) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for CTCAE grading (i.e. those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).

The summary of laboratory parameters by CTCAE grade table will include number and percentage of participants with grade 1, 2, 3, 4, 3/ 4 and any grade (1 to 4) laboratory abnormalities during on-treatment period.

The shift table will summarize baseline CTCAE grade versus the worst post-baseline CTCAE grade. The worst grade per participant is defined as the highest CTCAE grade during the on-treatment period.

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE available in 18.2 NCI-CTCAE v4.03 Grades for Laboratory Parameters

Parameters with no CTCAE grade defined

Hematology and chemistry evaluations which cannot be graded per CTCAE will be summarized as:

- Shift from baseline value (low, normal, high) to above normal during on-treatment period
- Shift from baseline value (low, normal, high) to below normal during on-treatment period

In this study, this applies to the parameters available in section 18.3 Worst Values for Non Gradable Laboratory Parameters.

The laboratory listings (hematology, chemistry) will include all the laboratory parameters as available in the EDC database with the all corresponding relevant information. Scatterplots of the hematology and biochemistry results vs study day will be produced.

Liver Function Elevation and Possible Hy's Law Cases during On-Treatment Period

ALT, AST and Total Bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized overall and by dose level:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- Total Bilirubin ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying peak serum ALT (/ULN) vs peak Total Bilirubin (/ULN) including reference lines at ALT ≥3×ULN and bilirubin ≥ 2×ULN. The display will be divided into 4 quadrants by the lines through ALT ≥ 3×ULN and Total Bilirubin ≥ 2×ULN. The left lower quadrant is then considered normal or insignificant elevations in liver chemistries, the left upper quadrant indicates participants with possible Gilbert's cholestasis; the right upper quadrant are the possible Hy's Law participants; the right lower quadrant is possible Temple's Corollary (participants with ALT ≥ 3 × ULN but not satisfying Hy's Law). Different symbol will be used for different dose level.

15.3.2 Other laboratory parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected data-fields on the eCRF.

- Urinalysis: all urinalysis parameters
- Hormones: free thyroxine, thyroid-stimulating hormone, adrenocorticotropic hormone, anti-nuclear antibody and rheumatoid factor.

- Pregnancy test

15.4 Vital Signs

All vital sign parameters will be summarized using descriptive statistics of actual values and changes from baseline for all vital sign assessments from the on-treatment period. End of treatment visit will be summarized separately. The changes computed will be the differences from baseline.

Summary of vital signs will be based on the SAF. The substantial change from baseline regarded as potentially clinically significant will be derived as below and summarized with participant incidence and percentage during the on-treatment period:

- ≥ 10% weight increase
- ≥ 10% weight decreases
- ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg in systolic blood pressure
- ≥ 160 mmHg and increased from baseline ≥ 20 mmHg in systolic blood pressure
- ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg in diastolic blood pressure
- ≥ 110 mmHg and increased from baseline ≥ 10 mmHg in diastolic blood pressure
- ≤ 50 bpm and decrease from baseline ≥ 20 bpm in pulse rate
- ≥ 120 bpm and increase from baseline ≥ 20 bpm in pulse rate

All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

Vital signs maximum change from baseline values will be listed. A separate listing will show Change from Baseline in Abnormal Vital Sign Parameters.

15.5 Other Safety or Tolerability Evaluations

ECG

Electrocardiogram data will be summarized by visit including change from baseline.

The incidence and percentage of participants with potentially clinically significant abnormalities (PCSA) for 12-lead Electrocardiogram (Triplicate) parameters will be summarized during the on-treatment period. The PCSA criteria are provided in the Table 4 based on the centrally-read ECGs.

Table 4 - Potentially Clinically Significant Abnormalities criteria for ECG

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increased from baseline ≥ 20 bpm

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
QTcF absolute	>450 ms >480 ms >500 ms
QTcF change from baseline	Increase: >30 ms >60 ms
QTcF change from baseline	decrease: >30 ms >60 ms

QT based on Fridericia's formula (QTcF= QT/RR0.33) will be summarized as collected in eCRF.

Listings of ECG parameters will be provided including the centrally-read ECG data collected in eCRF and the change from baseline. A separate listing for potentially clinically significant abnormalities will be created based on the centrally-read ECGs. Additionally, locally read ECG data will be provided in a separate listing.

Eastern Cooperative Oncology Group (ECOG)

The ECOG shift from baseline to highest post-baseline score will be summarized by study cohort during the on-treatment period and this analysis will be based on SAF analysis set. Missing category will be included and the number of participants at each dose level will be used as the denominator.

ECOG performance status will also be presented in a data listing with cohort, subject identifier, and Visits. The listing will be sorted by dose level, subject identifier, and date of assessment.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

PK evaluation will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set.

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics of PK concentrations at the end of infusion (C_{eoi}) and trough concentrations (C_{trough}) will additionally show the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM).

Descriptive statistics will only be calculated for N>2 in which a measurement of < lower limit of quantification of the assay (LLOQ) represents a valid measurement.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD	4 significant digits
CV%, GeoCV%:	1 decimal place

16.1.2 General Specifications for PK Concentration and PK Parameter Data

Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration. The same applies to the pre-dose (trough) sample of a multiple dose study.

Pre-dose samples which have been taken after the subsequent dosing will be reported as protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations.

Values below the LLOQ will be taken as zero for summary statistics of PK concentration data and for graphical presentations. It is expected that samples with concentrations above the upper limit of quantification (ULOQ) will be diluted and retested.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A subject who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

Samples that are collected outside the specified time windows specified in the clinical study protocol (CSP) will be excluded from the concentration summary and mean concentration plots.

PK concentrations which are erroneous due to a protocol violation (as defined in the CSP), sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion must be provided in the CSR. Any implausible data will be documented in the CSR.

Any PK concentrations excluded from summary statistics will be included in subject listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific SDTM and ADaM data sets.

16.1.3 Presentation of PK Concentration and PK Parameter Data

16.1.3.1 Listings and Tables

The following PK tables will be produced for both analytes (avelumab and NHS-IL12) based on PK Analysis Set:

- Individual concentrations with descriptive statistics by cohort, analyte, cycle, day and time
- Trough concentrations (C_{trough}) will be listed and summarized by cohort, analyte, cycle and day, using standard descriptive statistics
- For avelumab only, the concentrations at end of infusion (Ceoi) will be listed and summarized by cohort, cycle and day, using standard descriptive statistics
- For M9241, the concentration at 1 hour (end of avelumab infusion)
- Concentration at Day 2 (24 hour)

The following additional PK Listings will be produced based on the Safety Analysis Set:

- PK Sampling date, actual time, nominal time, deviation from time and concentration by cohort, subject and analyte sorted chronological

16.1.3.2 Graphical Summaries and Individual plots (PK Analysis Set)

The following figures will be produced for both analytes (avelumab and M9241) based on PK Analysis Set:

- Overlaid both analytes individual concentration versus time plots; linear and semi-log; using the actual time points for all subjects
- Individual concentration versus time plots; linear and semi-log; using the actual time points for all subjects by cohort and analyte
- Mean concentration time plots; linear with standard deviation and semi-log; using scheduled (nominal) time points by cohort and analyte

- Overlaid both analytes mean concentration time plots; linear with standard deviation and semi-log; using scheduled (nominal) time points by cohort
- Individual C_{trough} values will be plotted against actual time points on a linear scale, for all subjects by cohort and analyte
- Mean C_{trough} ±SD values will be plotted on a linear scale by cohort and analyte
- Median C_{trough} values will be plotted on a linear scale by cohort and analyte
- Mean C_{trough} ±SD values within a treatment phase cycle will be plotted on a linear scale; overlay of all cycles by cohort and analyte;
- Individual 24 hour concentration values will be plotted against actual time points on a linear scale, for all subjects by cohort and analyte
- Mean 24 hour concentration ±SD values will be plotted on a linear scale by cohort and analyte
- Median 24 hour concentration values will be plotted on a linear scale by cohort and analyte

For avelumab only, the following figures will be produced based on PK Analysis Set:

- Individual avelumab C_{eoi} values will be plotted against actual time points on a linear scale, for all subjects by cohort
- Mean avelumab C_{eoi} ±SD values will be plotted on a linear scale by cohort
- Median avelumab C_{eoi} values will be plotted on a linear scale by cohort

For M9241, the following figures will be produced based on PK Analysis Set:

- Individual M9241 1 hour concentration values will be plotted against actual time points on a linear scale, for all subjects by cohort
- Mean M9241 1 hour concentration ±SD values will be plotted on a linear scale by cohort
- Median M9241 1 hour values will be plotted on a linear scale by cohort

16.2 Immunogenicity Evaluation

Samples for avelumab anti-drug antibody (ADA) and M9241 ADA will be measured in all subjects that receive combination therapy (M9241 and avelumab) and avelumab ADA in UC subjects that undergo avelumab weekly induction monotherapy alone.

Anti-M9241 and anti-avelumab antibodies will be assessed by specific methods. The algorithm for classification of antibody status is given in Table 5.

Table 5. Algorithm for Independent Derivation of Avelumab and M9241 ADA Results

SDTM raw data			ADaM
Screening Result	**Confirmatory Result**	**Titer Result**	**ADA result**
Negative	NA, NR, or Negative	NA	Negative
NR	NA	NA	NR
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NR	Positive-TNR

ADaM = analysis data model, NR = not reportable, NA = not applicable, SDTM = study data tabulation model, TNR = titer not reportable, ADA = anti-drug antibody.

Subjects will be characterized into different ADA categories independently for both methods based on criteria in Table 6.

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[redacted]

The impact on the respective pharmacokinetics of M9241 ADA and avelumab by anti-M9241 and avelumab ADA will be assessed. For each drug, M9241 and avelumab, ever-positive subjects versus never-positive subjects will be descriptively summarized by study cohort.

C_{trough} measurements in anti-M9241 or anti-avelumab antibodies ever-positive subjects with valid results on the same nominal day will be descriptively summarized by nominal day for the positive results vs negative results. Median Ctrough will be plotted vs nominal day. Mean Ctrough (±SD) will be plotted vs nominal day.

C_{trough} measurements in anti-M9241 or anti-avelumab antibodies ever-positive subjects with valid results on the same nominal day will be graphed by nominal day as box plots for the positive results and negative results.

Due to the small sample size – no comparison between two treatment groups for UC cohort at Stage 2 will be done.

The anti-avelumab antibodies rate; median time to detection of anti-avelumab antibodies; median duration of anti-avelumab antibodies positivity in months, and the numbers of doses (before/after first detection of anti-avelumab antibodies and total) received in patients with treatment-emergent anti-avelumab antibodies will be summarized by study cohort, by treatment group (only for UC cohort Stage 2) and overall.

The anti-M9241 antibodies rate; median time to detection of anti-M9241 antibodies; median duration of anti-M9241 antibodies positivity in months, and the numbers of doses (before/after first detection of anti-M9241 antibodies and total) received in patients with treatment-emergent anti-M9241 antibodies will be summarized by study cohort and overall.

16.2.1 Avelumab Immunogenicity Incidence and Characterization

Immunogenicity samples were collected prior to study treatment start, prior to dosing at regular intervals while on treatment, and at post-treatment follow-up visits (see Table 7). Samples collected after the last dose of study treatment (e.g. safety follow-up visit) will be included in the analysis.

CCI [redacted]

Testing for ADA was conducted using a tiered assay approach. If the sample was confirmed positive for ADA, it was subsequently analyzed to determine the titer and neutralizing antibody (nAb). The ADA results will be derived based on the algorithm in Table 8. Negative, number, or

positive-Titer Not Reportable (TNR) are valid results; number and positive-TNR are positive results.

CCI

[redacted]

Subjects with ever positive ADA results will be assigned to the following Status Groups for listing preparation based on the categories defined in Table 5:

Avelumab ADA Status Groups:

All subjects who have at least one positive ADA result will be assigned to one of the following ADA status groups for purposes of display in some TLFs. The three groups are mutually exclusive:

- Pre-existing (including treatment-boosted)
- Transient treatment-emergent
- Persistent treatment-emergent

Start of immunogenicity response and duration of response are defined as follows:

Avelumab Start of Immunogenicity Response

For subjects with any positive ADA (nAb) response, the date of the first assessment with positive ADA (nAb) result will be considered as start date of ADA (nAb) response.

Time to onset (weeks) of ADA response will be calculated as:

(Date of first positive ADA assessment – start date of avelumab treatment + 1) / 7

Note: If the first positive is prior to the start of treatment, the formula is revised to: (Date of first positive assessment – start date of avelumab treatment) / 7

16.3 M9241 (IL-12) Immunogenicity Evaluation

Samples for Anti-M9241 will be measured in all subjects that receive combination therapy. To evaluate the potential effect of Anti-M9241 on M9241 PK, M9241 drug concentration in serum will be measured using the optimized intact IL-12 assay. Anti-M9241 ever-positive subjects and Anti-M9241 never-positive subjects will be descriptively summarized by study cohort, by treatment group (only for UC cohort Stage 2) . No comparison between the 2 treatment groups for UC cohort Stage 2 will be done.

The Anti-M9241 rate; median time to detection of Anti-M9241; median duration of Anti-M9241 positivity in months, and the numbers of doses (before/after first detection of Anti-M9241 and total) received in patients with treatment-emergent Anti-M9241 will be summarized by study cohort, by treatment group (only for UC cohort Stage 2) and overall. No comparison between the 2 treatment groups for UC cohort Stage 2 will be done.

16.3.1 M9241 Immunogenicity Incidence and Characterization

Immunogenicity samples were collected prior to study treatment start, prior to dosing at regular intervals while on treatment, and at post-treatment follow-up visits (see Table 10). Samples collected after the last dose of study treatment (e.g. safety follow-up visit) will be included in the analysis

Table 10: M9241 Immunogenicity Sampling Schedule

• Study	• Sampling Schedule per Protocol
• MS201781-031	• Predose* (Prior to study treatment start); Prior to dosing on nominal Study Days 15, Predose cycles 2, 3 and 4, then Predose every three cycles stating with cycle 7. A final sample should be taken 30+5 days after last treatment during safety follow up

*Predose is prior to M9241 administration. Samples should be collected as close to the start of infusion as possible and within 2 hours prior to administration

Testing for Anti-M9241 was conducted using a tiered assay approach. If the sample was confirmed positive for Anti-M9241, it was subsequently analyzed to determine the titer. The Anti-M9241 results will be derived based on the algorithm in Table 11. Negative, number, or positive-Titer Not Reportable (TNR) are valid results; number and positive-TNR are positive results.

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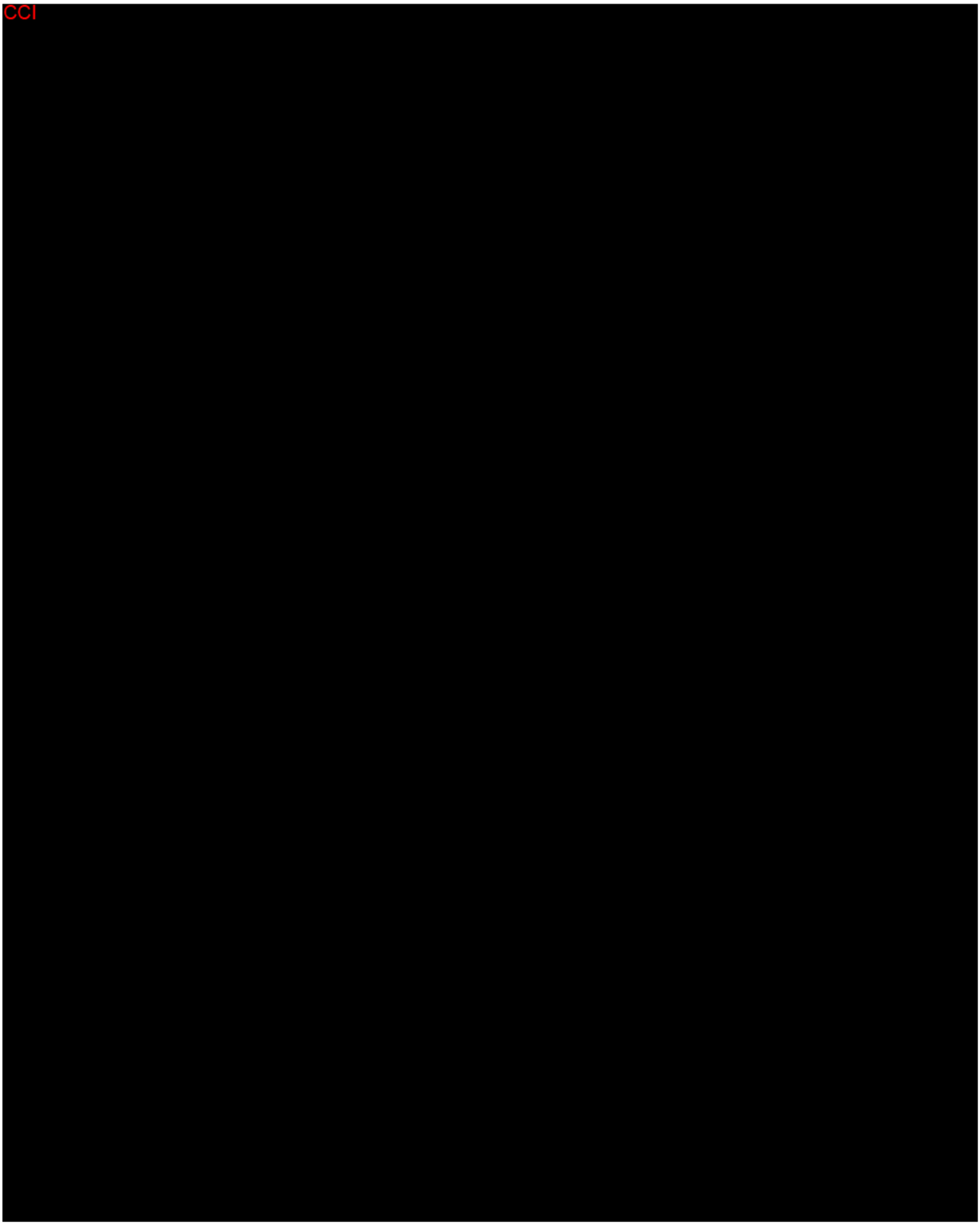
Subjects will be characterized into different categories based on the criteria in 12.

CCI



Subjects with ever positive Anti-M9241 results will be assigned to the following Status Groups for listing preparation based on the categories defined in Table 8:

Anti-M9241 Status Groups:

All subjects who have at least one positive Anti-M9241 result will be assigned to one of the following Anti-M9241 status groups for purposes of display in some TLFs. The three groups are mutually exclusive:

- Pre-existing (including treatment-boosted)
- Transient treatment-emergent
- Persistent treatment-emergent

Start of immunogenicity response and duration of response are defined as follows:

Anti-M9241 Start of Immunogenicity Response

For subjects with any positive Anti-M9241 (nAb) response, the date of the first assessment with positive

Time to onset (weeks) of Anti-M9241 response will be calculated as:

(Date of first positive Anti-M9241 assessment – start date of M9241 treatment + 1) / 7

Note: If the first positive is prior to the start of treatment, the formula is revised to: (Date of first positive assessment – start date of M9241 treatment) / 7

CCI [redacted]

17 References

Merck KGaA protocol MS201781_0031 version 7.0

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18 Appendices

18.1 Important Protocol Deviations

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Incl: Signed written informed consent	Informed Consent	Subject did not meet Inclusion Criteria # 1	5.3.1	List if DM.RFICDTC is missing or if DM.RFICDTC > Earliest date of SV.SVSTDTC. Medical Review Required
Incl: 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.	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 3	5.3.1	Medical Review Required
Incl: Adequate hematological function as defined below: a. White blood cells (WBC) count ≥ 3.0 × 109/L b. Absolute neutrophil count ≥ 1.5 × 109/L c. Lymphocyte count ≥ 0.5 × 109/L d. Platelet count ≥ 100 × 109/L	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 6	5.3.1	List if at least one parameter is out of the range before 1st dose. Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
e. Hemoglobin ≥ 9 g/dL (may have been transfused)				
Incl: 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 ≤ 2.5 × ULN c. Alanine aminotransferase (ALT) levels ≤ 2.5 × ULN d. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 but less than 3 × ULN	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 7	5.3.1	List if at least one parameter is out of the range before 1st dose. Medical Review Required
Incl: Adequate renal function as defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula	Eligibility and Entry Criteria	Subject did not meet Inclusion Criteria # 8	5.3.1	List if creatinine clearance is out of the range before 1st dose. Medical Review Required
Excl: Concurrent treatment with a nonpermitted drug/intervention	Eligibility and Entry Criteria	Subject met Exclusion Criteria #1	5.3.2	Medical Review Required
Excl: Any prior treatment with any form of IL-12	Eligibility and Entry Criteria	Subject met Exclusion Criteria #2	5.3.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Excl: Prior organ transplantation, including allogeneic stem-cell transplantation	Eligibility and Entry Criteria	Subject met Exclusion Criteria #5	5.3.2	Medical Review Required
Excl: Previous malignant disease (other than the indication for this study) within the last 5 years	Eligibility and Entry Criteria	Subject met Exclusion Criteria #6	5.3.2	Medical Review Required
Excl: Significant acute or chronic infections requiring systemic therapy	Eligibility and Entry Criteria	Subject met Exclusion Criteria #7	5.3.2	Medical Review Required
Excl: Active or history of autoimmune disease that might deteriorate when receiving an immunostimulatory agent.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #8	5.3.2	Medical Review Required
Excl: Persisting toxicity related to prior therapy of Grade > 1	Eligibility and Entry Criteria	Subject met Exclusion Criteria #11	5.3.2	Medical Review Required
Excl: Uncontrolled intercurrent illness	Eligibility and Entry Criteria	Subject met Exclusion Criteria #14	5.3.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Excl: 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.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #16	5.3.2	Medical Review Required
Excl: Administration of a live vaccine within 30 days prior to study entry	Eligibility and Entry Criteria	Subject met Exclusion Criteria #19	5.3.2	Medical Review Required
Excl: 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	Eligibility and Entry Criteria	Subject met Exclusion Criteria #20	5.3.2	Medical Review Required
Excl: History of congenital or active mmunodeficiency, with the exception of acquired treatment-related hypogammaglobulinemia requiring periodic IV immunoglobulin infusion.	Eligibility and Entry Criteria	Subject met Exclusion Criteria #22	5.3.2	Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Participation in another treatment trial	Concomitant Medication	Subject participated in another clinical study	5.5.1	Medical Review Required
If the administration of a prohibited concomitant medication becomes necessary during the study, the subject will be withdrawn from study treatment.	Concomitant Medication	Subject received a prohibited concomitant medication	5.5.1	Medical Review Required
Other Prohibited Interventions	Concomitant Medication	Subject received a prohibited concomitant procedure	6.5.3	Medical Review Required
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	Eligibility and Entry Criteria		5.5.1	Medical Review Required
Occurrence of pregnancy	Serious Adverse Event	Subject became pregnant but continued on treatment	5.5.1	List subjects with positive pregnancy test and study drug administrtion after the start date. Medical Review Required

Protocol Reference Text	Protocol Deviation Category	Description of Protocol Deviation	Protocol Section	Method of Identification (Programmable vs Medical Review)
Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or study integrity	IP Compliance	Subject had a noncompliance deemed to compromise safety / study integrity	5.5.1	Medical Review Required
Incorrect IMP dose: dose doesn't correspond to the dose level planned dose	IP Compliance	Subject received incorrect study treatment dose	6.2.2	Medical Review Required
Noncompliance: subject missing > 1 cycle of study treatment for nonmedical reasons (the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons)	IP Compliance	Subject missed > 1 cycle of study treatment for nonmedical reasons	6.9	List subjects with >28 days between 2 consequent administrations. Medical Review Required

18.2 NCI-CTCAE v4.03 Grades for Laboratory Parameters

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology							
Ery. Mean Corpuscular Hemoglobin (pg/cell)	No						
Ery. Mean Corpuscular HGB Concentration (g/L)	No						
Ery. Mean Corpuscular Volume (fL)	No						
Hemoglobin (g/L) High	Yes	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Hemoglobin (g/L) Low	Yes	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L;	Life-threatening consequences; urgent	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			mmol/L; <LLN - 100 g/L	mmol/L; <100 - 80g/L	transfusion indicated	intervention indicated	
Leukocytes (10E9/L) Low	Yes	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Leukocytes (10E9/L) High	Yes	Leukocytosis			>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Lymphocytes (10E9/L) High	Yes	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Lymphocytes (10E9/L) Low	Yes	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Lymphocytes/Leukocytes (%)	No						

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils (10E9/L)	Yes	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Neutrophils/Leukocytes (%)	No						
Monocytes (%)	No						
Reticulocytes/Erythrocytes (%)	No						
Reticulocytes (10E9/L)	No						
Eosinophils (%)	No						
Basophils (%)	No						
Hematocrit (%)	No						
Platelet (10E9/L)	Yes	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L	-
RBC count	No						
RBC morphology	No						

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Biochemistry							
Creatinine (umol/L)	Yes	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Alanine Aminotransferase (U/L)	Yes	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate Aminotransferase (U/L)	Yes	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Gamma Glutamyl Transferase (U/L)	Yes	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Total Bilirubin (umol/L)	Yes	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Cholesterol (mmol/L)	Yes	Cholesterol high	>ULN - 300 mg/dL; >ULN -	>300 - 400 mg/dL; >7.75 -	>400 - 500 mg/dL; >10.34 -	>500 mg/dL; >12.92 mmol/L	-

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			7.75 mmol/L	10.34 mmol/L	12.92 mmol/L		
Lipase (IU/L)	Yes	Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Amylase (IU/L)	Yes	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Total Protein (G/L)	No						
Albumin (g/L)	Yes	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase (IU/L)	Yes	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Glucose (mmol/L) High	Yes	Hyperglycemia	Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L; hospitalization indicated	>27.8 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glucose (mmol/L) Low	Yes	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L; life-threatening consequences; seizures	Death
Blood Urea Nitrogen (mmol/L)	No						
Uric Acid (umol/L)	Yes	Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Sodium (mmol/L) High	Yes	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Sodium (mmol/L) Low	Yes	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Potassium (mmol/L) High	Yes	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Potassium (mmol/L) Low	Yes	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Chloride (mmol/L)	No						
Calcium (mmol/L)	No						
Magnesium (mmol/L) High	Yes	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Magnesium (mmol/L) Low	Yes	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
						threatening consequences	
Creatine Kinase (IU/L)	No						
Lactate Dehydrogenase (IU/L)	No						
Phosphate (mmol/L)	Yes	Hypophosphatemia	<LLN - 0.8 mmol/L	<0.8 - 0.6 mmol/L	<0.6 - 0.3 mmol/L	<0.3 mmol/L;	
Urea Nitrogen	No						
Urea (mmol/L)	No						
C-Reactive Protein	No						
Serum electrophoresis protein pattern	No						
Triglyceride (mmol/L)	Yes	Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death

Note: fasting glucose status is not collected on eCRF and worst case approach will be used, any glucose values will be used with the same limits

18.3 Worst Values for Non Gradable Laboratory Parameters

Category	Parameter	Abnormal value to be considered
Hematology	Ery. Mean Corpuscular Hemoglobin	Low
	Ery. Mean Corpuscular HGB Concentration	Low
	Ery. Mean Corpuscular Volume	Low and High
	Erythrocytes	Low
	Reticulocytes	Low and High
	Reticulocytes/Erythrocytes	Low and High
	Hematocrit	Low
	Basophils	High
	Eosinophils	High
	Monocytes	High
	Lymphocytes	Low and High
	Neutrophils	Low and High
	RBC count	Low
	RBC morphology	Any Abnormalities
Biochemistry	Blood Urea Nitrogen	High
	Urea Nitrogen	High
	Creatine Kinase	High
	Lactate Dehydrogenase	High
	Creatinine	High
	Chloride	High
	C-Reactive Protein	High
	Serum electrophoresis protein pattern	Any Abnormalities

18.4 Description of the Case Definition for Assessment of Immune-Related AEs and IRRs

Immune-Related Adverse Events

Immune-related adverse events (irAEs) will be identified programmatically. AEs which satisfy all of the following criteria will be flagged as immune-related:

1) The AE preferred term matches a preferred term on the list of pre-selected MedDRA terms.

2) The AE onset occurs after the first study drug administration and no more than 90 days after last dose.

3) On the AE eCRF page, the question "Were Corticosteroids, Immunosuppresants, or hormonal therapy (e.g. Thyroid) applied?" has the answer "Yes" selected.

4) On the AE eCRF page, either:

a. The question "Does any of the following provide a clear etiology for the event?" has the answer "No" selected, indicating that the AE is not attributable to underlying cancer disease/PD, prior or concomitant medications/procedures, nor another medical condition such as an infection or pre-existing disease.

OR

b. The AE eCRF indicates that a biopsy was performed and the question "Is the histopathology/biopsy consistent with an immune-mediated event?" has the answer "Yes" selected.

In the case that criteria (1) through (3) are met, and entries for condition (4) are missing, the following rules will be applied:

- If the answer to "Does any of the following provide a clear etiology for the event?" (4a) is missing, the event will be considered as irAE (irrespective of biopsy results).
- If the answer to "Is the histopathology/biopsy consistent with an immune-mediated event?" (4b) is missing, or if no biopsy was performed, and condition (4a) is not satisfied (i.e. "Yes" is selected as the answer to the question "Does any of the following provide a clear etiology for the event?"), the event will be considered as a non-irAE.

IRRs

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to **Table** .

Table 9 Criteria for infusion related reactions

Infusion related reactions	**Reactions - Considered when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date):** • Infusion related reaction • Drug hypersensitivity • Anaphylactic reaction • Hypersensitivity • Type 1 hypersensitivity **Signs and Symptoms - occurring on the day of study drug infusion (during or after the infusion) and resolved with end date within 2 days after onset** • Pyrexia • Chills • Flushing • Hypotension • Dyspnoea • Wheezing • Back pain • Abdominal pain • Urticaria

ELECTRONIC SIGNATURES

Document: ctp-ms201781-0031-sap-expansion-v2-0

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Business Approval	22-Oct-2020 07:45
PPD	Task Completed (Approval eSign): Approved	Technical Approval	22-Oct-2020 14:15