Phase I Dose Escalation - Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS100070-0306
Title	Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma
Trial Phase	I/II
Investigational Medicinal Product(s)	Avelumab
Clinical Trial Protocol Version	15 September 2017 / Version 2.0

Integrated Analysis Plan Author

Coordinating Author	
PPD , EMD Serono	PPD

Function	Author(s) / Data Analyst(s)
PPD , EMD Serono	PPD
PPD	
PPD , Merck	PPD

Integrated Analysis Plan Date and Version	22 June 2021 / Version 2.0

Integrated Analysis Plan Reviewers

Function	Name
PPD	
PPD , EMD Serono	PPD
PPD Merck	PPD
PPD , Merck	PPD
PPD , Merck	PPD
PPD EMD Serono	PPD
PPD Merck	PPD
PPD , PPD	PPD
PPD , Merck	PPD

Approver Page

Integrated Analysis Plan: MS100070-0306

Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma

Merck responsible

PPD , PPD

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

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADA	Antidrug antibody
AE(s)	Adverse event(s)
AUC	Area under the serum concentration-time curve
AUC_{0-t}	Area under the serum concentration-time curve from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero (dosing time) extrapolated to infinity
AUC_{τ}	Area under the serum concentration-time curve over the dosing interval from T_1=0 h to T_2=336 h
BMI	Body mass index
BOR	Best overall response
BSA	Body surface area
C_{EOI}	Concentration at the end of the infusion
CI	Confidence Interval
C_{max}	Maximum serum concentration observed postdose
CIPD	Clinically Important Protocol Deviations
CL	Total body clearance
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTMS	Clinical Trial Management System
CTP	Clinical trial protocol
C_{trough}	Minimum serum postdose trough concentration
CV	Coefficient of variation
DI	Dose intensity
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form

eDISH	Evaluation of drug-induced serious hepatoxicity
EOT	End of treatment
FAS	Full analysis set
GCP	Good Clinical Practice
GeoMean	Geometric mean
IAP	Integrated analysis plan
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IPD	Important protocol deviation
CCI	CCI
LLOQ	Lower limit of quantification
Max	Maximum
Min	Minimum
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NR	No result
OR	Objective response
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death ligand 1
PFS	Progression-free survival

PK	Pharmacokinetic(s)
PP	Per protocol
PR	Partial response
PT	Preferred Term
RBC	Red blood cell
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended phase 2 dose
SAE(s)	Serious adverse event(s)
SDTM	Study data tabulation model
SCR	Screening analysis set
SD	Stable disease
SD	Standard deviation
SMC	Safety Monitoring Committee
SOC	System organ class
SOLD	Sum of longest diameters
t_{last}	Last PK sample at which the concentration is at or above the lower limit of quantification
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TNR	Titer no result
TTR	Time to response
ULN	Upper limit of normal
V_Z	Apparent volume of distribution during the terminal phase
λ_z	Terminal first order (elimination) rate constant
τ	Dosing interval

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	18 December 2017	PPD	NA First Version
2.0	22 June 2021	PPD	Background: the avelumab EMA PIP has been modified and evaluation of avelumab monotherapy in pediatric patient has been terminiated after Phase I of this study. Therefore, analysis of Phase II data will not be completed. The analyses described have been modified according to the needs of the Phase I reporting. All changes implemented in the IAP are listed below: • Section 6: Update trigger for Final Analysis to occur after all subjects have withdrawn from the trial, rather than 1 year after last End of Treatment visit • Section 7: Update to drop inclusion of analysis of gestational age and weight at birth; remove text indicating efficacy analysis will not be performed for Phase I • Section 8.2: Add specifics regarding tumor category subgroup analysis; specify all efficacy analyses will be performed overall and by tumor category • Section 9: Update text for last-alive date to match current IAP language • Section 10.1: Update disposition table to count subjects treated, rather than subjects enrolled; update disposition table to remove study "completion" category, include death and progressive disease as reason for study discontinuation; remove table of subjects by region and site • Section 10.2.2: Added section to specify COVID-19 protocol deviation listing • Section 11.1: Removal of gestational age, pooled geographic region, birth weight from demographics table • Section 11.2: Update to specify medical history details will be listed only. • Section 11.3: Update to remove site of primary tumor and add tumor category to disease history table • Section 11.4: Update to include all prior anti-cancer treatments on a single listing, rather than have three separate listings • Section12: Update to remove prior medications table; include prior medications in concomitant medication listing • Section 13: Sections for and analyses of partial doses, infusion rate reductions, and infusion interruptions removed • Section 14.1: Added details regarding analysis of objective response; updated listings to include tumor assessment and reason for overall response of NE to a single listing, rather than separate listings • Section 14.2 and 14.3: Update to clarify that the analyses will not be conducted if no responders are observed • Section 14.4: Update to analyze PFS in weeks, not months; update to provide details on PFS analysis (add Kaplan meier estimates)

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			CCI • Section 15.1: Update to specify that Analyses of DLTs is per SMC assessment • Section 15.3.3: Update to drop listing of irAEs outside the on-treatment period; removal of table of IRRs leading to withdrawal of study treatment • Section 15.4.1: Removal of summary statistics analysis of laboratory values; removal of liver function test table; removal of eDISH plot; removal of shift to worst grade table; removal of shift to worst value table • Section 15.5: Removal of vital signs summary statistics table • Section 15.6: Removal of ECG analyses. A listing only will be produced. • Section 15.6.1: Removal of change from baseline table for quality of life assessments • Section 16.1: Specify handling of samples collected outside of the specified time windows; • Section 16.1.2: Specify use of PK analysis set; update to definitions of PK parameters to provide additional details • Section 16.1.2.2: addition of section to describe planned PK outputs • Section 16.2: Update to produce only one listing for immunogenicity data • Section 16.3: Update to display biomarkers as box plots, rather than using summary statistics; drop summary of cytokines and circulating proteins • Section 16.4: Update to listing description to drop flags for ADA status

4 Purpose of the Integrated Analysis Plan (IAP)

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for Phase I, the dose-finding portion, of protocol MS100070-0306. 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 trial protocol and protocol amendments and is prepared in compliance with International Council for Harmonisation (ICH) E9.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To evaluate the safety and tolerability of avelumab	Primary Endpoint • Occurrence and severity of treatment-emergent adverse events (TEAEs) ≥ Grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Secondary Endpoints • Vital signs (including blood pressure and heart rate) • Occurrence and severity of TEAEs, AEs of special interest, and treatment-related AEs, and incidence of laboratory abnormalities as graded by NCI-CTCAE version 4.03	• 15.2 Adverse Events • 15.5 Vital Signs • 15.2 Adverse Events
	To determine the recommended Phase II dose (RP2D) of avelumab in pediatric subjects 0 to < 18 years of age with solid tumors and lymphoma	Primary Endpoint • Dose limiting toxicities (DLTs) to determine RP2D	15.1 Dose-Limiting Toxicities
Secondary Objective	To assess antitumor activity of avelumab by determining the ORR according to RECIST 1.1 and as adjudicated by the Investigator in pediatric subjects with solid tumors and lymphoma treated with avelumab	Secondary Endpoint • Confirmed BOR according to RECIST 1.1 and as adjudicated by the Investigator	14.1 Confirmed Best Overall Response
	To assess progression-free survival (PFS) based on Investigator assessments, duration of response (DOR), time to response (TTR), and overall survival (OS)	Secondary Endpoint: • DOR, TTR, PFS per RECIST 1.1 and as adjudicated by the Investigator and OS	• 14.2 Duration of Response • 14.3 Time to Response • 14.4 Progression Free Survival • 14.5 Overall Survival
	To characterize the pharmacokinetics (PK) of avelumab	Secondary Endpoint: • Single- and multiple-dose PK profiles of avelumab (ie, C_{max}, AUC, $t_{1/2}$, and C_{trough}, as data permit)	16.1 Pharmacokinetics
	To assess the immunogenicity of avelumab	Secondary Endpoint: • Immunogenicity as measured by avelumab anti-drug antibodies (ADA), including neutralizing antibodies (nAbs)	16.2 Immunogenicity
	To evaluate programmed death ligand (PD-L1) expression; tumor infiltrating T-cell activity; T-cell population; and T-cell, B-cell and NK-cell numbers in tumor tissue at Baseline and at confirmed progression (if tumor tissue is obtained)	Secondary Endpoint: • Assessment of tumor PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers at Baseline and at confirmed progression (if tumor tissue is obtained)	16.3 Biomarkers

	Objective	Endpoint	IAP section
	To measure changes in vaccination-related antibody concentrations (diphtheria, tetanus, and pneumococcal conjugate)	Secondary Endpoint: • Vaccination-related antibody concentrations	16.4 Vaccination-related antibody concentrations
[redacted]			

6 Overview of Planned Analyses

This document covers the avelumab standards for analyses of efficacy and safety. There are no interim analyses for efficacy planned for this trial, but ad hoc interim analyses may be conducted if necessary. There will be periodic safety review by the safety monitoring committee (SMC). The SMC will be responsible for reviewing the safety data and output containing the following information:

- The number and proportion of subjects in the DLT Analysis Set who experienced a DLT during the DLT evaluation period (first two cycles or 28 days of study treatment)
- The number and proportion of TEAEs experienced by subjects in the DLT Analysis Set during the DLT evaluation period
- The number and proportion of TEAEs $\geq$ Grade 3 experienced by subjects in the DLT Analysis Set during the DLT evaluation period.

The SMC will also review patient profiles.

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed after the last subject has completed his or her end of treatment visit or has been transferred off the trial, and all study data is in-house, all data queries are resolved, and the database is locked.

Statistical analyses will be performed using cleaned eCRF data as well as external data including laboratory data.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods specified in this document are in accordance with protocol version 2.0 (dated 15 September 2017).

The PK Analysis Set definition in this IAP is slightly modified from the protocol. The protocol defines the PK Analysis Set as all subjects who complete at least 1 administration of avelumab and who provide at least 1 sample with measurable concentrations of avelumab (at least 1 predose and 2 postdose from 2 or more treatment cycles). In the IAP, we remove the specification in parentheses as the PK analysis will include any PK data obtained, and it is not necessary for a subject to have 1 predose and 2 post dose concentrations.

The immunogenicity analysis set definition in this IAP is slightly modified from the protocol. The protocol defines the immunogenicity analysis set as all subjects who complete at least 1 administration of avelumab, and who have provided a blood sample prior to any avelumab treatment and at least 1 post-treatment sample. In this IAP, we are only including subjects who have received any dose of avelumab and have at least one valid ADA result (including negative, positive-titer no result (TNR)). This change prevents exclusion of subjects with a missing baseline sample.

The wording of the PK, Immunogenicity, and Biomarker analysis sets is slightly modified from saying "subjects who complete at least 1 administration of avelumab" to "subjects who receive any dose of avelumab". This is to clarify that subjects that receive any amount of study medication can be included in these analysis sets including those who do not complete the full dose.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations (IPDs) 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.

IPDs 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 a significantly incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from Good Clinical Practice (GCP).

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

- IPDs as defined above
- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

All IPDs will be documented in the study data tabulation model (SDTM) datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set (SCR)

The screening analysis set includes all subjects who signed the informed consent.

Full Analysis Set (FAS)

The full analysis set (FAS) will include all enrolled subjects who receive any dose of avelumab.

Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all enrolled subjects who were administered any dose of avelumab. Analyses performed on the safety set will consider subjects as treated. In this non-randomized study, the FAS and the SAF will be identical.

Dose Limiting Toxicity (DLT) Analysis Set

The DLT analysis set includes all subjects who meet either of the following criteria:

- Have received 100% of all planned doses of treatment during the DLT evaluation period (first 2 cycles of treatment) and have been followed for at least 28 days
- Have stopped treatment because of a DLT in the DLT evaluation period

Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will consist of all subjects who receive at least one dose of avelumab, have no important protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration. Subjects will be analyzed according to the actual treatment they received. All PK analyses will be based on this analysis set.

Immunogenicity Analysis Set

The immunogenicity analysis set will include all subjects who receive any dose of avelumab and who have at least one valid ADA result (including negative, positive-TNR).

Biomarker Analysis Set

Biomarker analysis set will include all subjects who receive any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments.

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

Table 1 Statistical Analysis by Analysis Set

Analyses	Screening Analysis Set	Full Analysis Set	Safety Analysis Set	DLT Analysis Set	PK Analysis Set	Immunogenicity Analysis Set	Biomarker Analysis Set
Baseline Characteristics	✓	✓	✓				
Prior and Concomitant Therapies		✓	✓				
Compliance and Exposure			✓				
Primary Endpoint			✓	✓			
Secondary Endpoint		✓			✓	✓	✓
CCI							
Safety			✓				

CCI

9 General Specifications for Data Analyses

Throughout this document "start date" is the date of first dose of study treatment.

Data handling after cut-off date:

Data after the cut-off may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

Pooling of centers:

Because of the high number of participating centers and the anticipated small number of subjects treated in each center data will be pooled across centers, and the factor center will not be considered in statistical models or for subgroup analyses.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

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

Qualitative variables will be summarized by 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.

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 study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

If both central and local labs are collected in the study, the baseline will be derived based only on the central lab collected data.

Subjects who start treatment and discontinue from the study on the same day may have two different sets of data collected on study 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.

Baseline for HR and QT/QTc assessments will be derived from the visit where both HR and QT are not missing. QTcF will be derived based on HR and QT.

Definition of study day:

Study day is defined relative to the date of start of treatment. Study day 1 defines the day of first administration with avelumab, the day before is defined as study day –1 (no study day 0 is defined).

Definition of on-treatment period:

The 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 drug therapy after start date is derived as outlined in Section 12.1.

Definition of duration:

Duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first dose of study drug + 1).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

Standard derivations and reporting conventions:

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

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

Demographic and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case only year and month of birth are given: Age [years]: (year/month of given informed consent – year/month of birth) / 12
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

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

- BMI (kg/m^2) = weight (kg)/[height (m)]^2.

- BSA (m^2) = ([height (cm) × weight (kg)] / 3600)$^{0.5}$ (1)

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. 6.1 to 6.4 will be rounded to an integer of 6, and 6.5 to 6.9 will be rounded to an integer of 7.

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 (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

Handling of missing data and imputation rules:

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

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 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND'.

Disease history:

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, 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.
- For all imputed disease history dates, the imputed date will be set equal to the maximum of the imputed date as specified above and the subject's date of birth.

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.
- For all imputed AE start dates, the imputed date will be set equal to the maximum of the imputed date as specified above and the subject's date of birth.
- 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. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.

Prior and concomitant medications:

Incomplete prior/concomitant medication start dates will be imputed as follows:

- If the medication start date is missing completely, then the medication start date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication start date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication start date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- For all imputed prior/concomitant start dates, the imputed date will be set equal to the maximum of the imputed date as specified above and the subject's date of birth.
- 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 medication stop date will not be imputed.

In case an imputed medication start date is later than the medication stop date, it will be replaced by the medication stop date.

Subsequent anti-cancer therapy

Incomplete subsequent anti-cancer therapy start dates will be imputed as follows:

- If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.
- If both day and month are missing, no imputation will be performed.

Exposure:

- In case the study drug start date is missing, no imputation will be performed.
- 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.

Date of last contact:

The date of last contact 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 on disposition eCRF pages (do not use 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. Assessment dates after the cut-off date will not be applied to derive the last contact date.

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
- If the day or both day and month is 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, computed 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 than 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.

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

10 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.

10.1 Disposition of Subjects and Discontinuations

The following will be summarized overall and by dose level.

The percentages below will be calculated based on the number of subjects in the FAS.

- Total number of subjects screened
- Number of subjects who screen failed prior to enrollment overall and by reason for screen failure
- Number and percentage of treated subjects in the following populations:
  - FAS
  - Safety analysis set

  - DLT analysis set
  - Immunogenicity analysis set
  - PK analysis set
  - Biomarker analysis set
- Number of treated subjects
- Number of subjects that received no treatment
- Number and percentage of subjects still on treatment
- Number and percentage of subjects who discontinued treatment overall and per reason of treatment discontinuation
- Number and percentage of subjects who discontinued the treatment but are still in follow-up
- Number and percentage of subjects who re-initiated avelumab treatment and discontinued treatment after re-initiation
- Number and percentage of subjects who discontinued the trial overall and by the main reason for discontinuation

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations (IPDs)

Important protocol deviations (IPDs) 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 enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study intervention or an incorrect dose
- Participants that receive an excluded concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)
- Any other protocol deviation 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 will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

All important protocol deviations are captured in SDTM datasets, whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside of this IAP document.

IPDs will be listed for all subjects in the FAS.

IPDs will be determined for all subjects by either medical review processes or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol.

The complete list of IPDs is maintained by the medical team in the Clinical Trial Management System (CTMS) and will be finalized prior to database lock.

10.2.2 Protocol Deviations Related to the COVID-19 Pandemic

Protocol deviations that are identified as being caused by the impact of the COVID-19 pandemic, such as those resulting from illness, changes in local regulations, or changes by subject behavior, will be documented in CTMS and flagged accordingly by site monitors. All COVID-19 related protocol deviations are captured in SDTM datasets, regardless of whether the deviation is classified as "Important" or "Minor".

A listing of protocol deviations related to the COVID-19 pandemic will be prepared. The listing will include all such protocol deviations reported, including non-important deviations.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented for the FAS by dose level and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized using the following information from the 'Demographics' eCRF page.

- Demographic characteristics
  - Sex: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not collected at this site
  - Ethnic origin: Hispanic or Latino (Yes/No), Japanese (Yes/No)
  - Age (years)

- Age categories :
  - < 1 year
  - 1 - 12 years
  - > 12 years
- Geographic Region (as applicable):
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- European Economic Area (EEA): Yes or No
- Lansky Performance Status
- Karnofsky Performance Status

- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)
  - Body Surface Area (BSA) (m^2)

Site codes will be used for the determination of the subject's geographic region.

The listing of demographics and baseline characteristics will include the following information: subject identifier, dose level, age, sex, race, ethnicity, height (cm), weight (kg), gestational age, BMI (kg/m^2), BSA (m^2), Karnofsky and Lansky performance status.

11.2 Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the "Medical History" eCRF page. Medical history details for subjects in the Full Analysis Set will be provided in a listing.

11.3 Disease Characteristics

Information on disease characteristics collected on the "Disease History" eCRF page and the "Cohort" eCRF page will be summarized along with tumor category (see Section 8.2) and PD-L1 expression status as assessed by a central lab. Summary statistics will be presented for:

- PD-L1 expression status (positive/negative) at cut-offs 1%, 5%, 25%, 50%, 80%
- Type of primary tumor (solid tumor/lymphoma)Tumor category (soft tissue/bone sarcoma, GI, CNS)
- Time since initial cancer diagnosis (months), defined as (start date of study treatment – date of initial cancer diagnosis)/30.4375
- Time since metastatic disease (months), defined as (start date of study treatment – date of metastatic disease)/30.4375
- Stage at initial diagnosis
- TNM classification at initial diagnosis
- Stage at study entry
- TNM classification at study entry

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

11.4 Prior Anti-Cancer Therapies

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details" eCRF pages.

The number and percentage of subjects in each of the following anti-cancer therapy categories will be tabulated:

- Subjects with at least one type of prior anti-cancer treatment
- Subjects with at least one prior anti-cancer drug therapy
- Subjects with at least one prior anti-cancer radiotherapy
- Subjects with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows:

- Number and percentage of subjects with at least one prior anti-cancer drug therapy
- Number and percentage of subjects with number of any prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / ≥4
- Number and percentage of subjects with number of prior anti-cancer therapy regimens for metastatic disease: missing / 1 / 2 / 3 / ≥4
- Type of prior anti-cancer therapy: Cytotoxic / Endocrine / Monoclonal Antibodies / Targeted / Immunotherapy / Other
- Intent of Therapy: Metastatic / Non metastatic

- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Non-complete Response/Non-Progressive Disease (Non-CR /Non-PD) / Progressive Disease (PD) / Not Evaluable / Unknown.

Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be summarized based on the number and percentage of subjects by the drug class and preferred term within each regimen number. A subject will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

A listing of prior anti-cancer treatments and procedures will also be provided. This listing will include the subject identification number, and all the relevant collected data-fields on the corresponding eCRF pages:

- Prior anti-cancer drug therapies
- Prior anti-cancer radiotherapy
- Prior anti-cancer surgeries

12 Prior or Concomitant Medications/Procedures

Concomitant medications are medications, other than study medications, which started prior to first dose date of study treatment and continued into the on-treatment period as well as those started during the on-treatment period. **Prior 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 will be summarized from the "Concomitant Medications Details" eCRF page.

In cases where the date values do not allow unequivocal allocation of a medication to concomitant (as opposed to prior) medication the medication will be considered as concomitant medication.

Summary of concomitant medications will include the number and percentage of subjects by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A subject will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category.

A listing of prior and concomitant medications will be created with the relevant information collected on the "Concomitant Medications Details" eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be summarized. A listing of concurrent procedures will be created with the relevant information collected on the "Concomitant Procedures Details" eCRF page.

12.1 Subsequent Anti-Cancer Therapies/Procedures

Subsequent anti-cancer treatment will be provided in a data listing with data retrieved from "Anti-Cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details", and "Surgery after Discontinuation" eCRF pages. The earliest date of start of new anti-cancer *drug* therapy will be used for the definition of the on-treatment period; the earliest date of new anti-cancer therapy will be used for censoring for efficacy analyses.

Number and percentage of subjects with any subsequent anti-cancer treatment will be tabulated overall and by type of therapy based on the data collected from the "Anti-Cancer Treatment after Discontinuation" eCRF page.

Summary statistics will be created for best response across all post study treatments based on the data collected from "Systemic Anti-Cancer Treatment after Discontinuation Details" eCRF page.

13 Treatment Compliance and Exposure

The following analyses will be performed based on the SAF by dose level.
All dosing calculations and summaries will be based on the 'Avelumab Administration' eCRF page. A listing of study drug administration will be created with the information collected on the 'Avelumab Administration' eCRF page.

The derivations below are provided for the following:

- Avelumab administered as a 1-hour IV infusion at a dose of xx mg/kg once every 2 weeks in 2-week cycles

The dose level, denoted as "xx" will be determined from the dose escalation process. Analysis of exposure will be based on the calculated actual dose levels (total dose / weight).

13.1 Exposure to Study Drug

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

Treatment duration (weeks) = (last dose date –first dose date + 14)/7

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)).

Each cycle for avelumab is defined by a 2-week 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) is defined as

DI (mg/kg/cycle) = Cumulative dose (mg/kg)/[duration of therapy (in weeks)/2]

The relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose as specified in the protocol per cycle, denoted in the formula below as "xx", and expressed in %. The dose level will be determined via the escalation process.

RDI (%) = 100×[DI (mg/kg/cycle)/ xx (mg/kg)]

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 (%)

A listing of study treatment administration will be provided and will include subject identifier, age, study day, start date and time of the infusion as well as the kit number.

13.2 Partial Doses

According to the protocol, preplanned dose reductions are not allowed for avelumab. Any interruptions in delivering the planned dose that resulted in an actual non-zero dose less than the planned dose will be shown in the listing of study drug administration details.

13.3 Dose Delays

Dose delays (i.e. doses given greater than 14 days from the previous administration) will be shown on the listing of study drug administration details.

13.4 Infusion Rate Reductions

Infusion rate reductions as recorded on the eCRF will be identified as a dose modification in the listing of study drug administration details.

13.5 Infusion interruptions

Infusion interruptions, as recorded on the eCRF, will be shown on the listing of study drug administration details.

14 Efficacy Analyses

Analysis sets: *FAS*

14.1 Confirmed Best Overall Response per RECIST v1.1 (Secondary Endpoint)

Confirmed **best overall response (BOR)** will be assessed based on reported overall timepoint responses at different evaluation time points from the start date of study treatment until documented disease progression, according to the following rules according to RECIST 1.1:

- CR = at least two determinations of CR at least 4 weeks apart
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR)
- SD (applicable only to subjects with measurable disease at baseline) = at least one SD assessment (or better) $\geq$ 6 weeks after start date of study treatment (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to subjects with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) $\geq$ 6 weeks after date of randomization and before progression (and not qualifying for CR or PR).
- PD = progression $\leq$ 12 weeks after start date of study treatment (and not qualifying for CR, PR, non-CR/non-PD or SD).
- Not Evaluable (NE): all other cases.

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

Objective Response (OR) is defined as a confirmed BOR of CR or PR according to RECIST 1.1. Subjects who do not have an on-treatment 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).

The frequency (number) of subjects with BOR of CR, PR, SD, non-CR/non-PD (applicable only to subjects with non-measurable disease at baseline), PD, and NE will be tabulated. The confirmed Objective Response Rate by treatment group will be calculated 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).

Subject's individual tumor assessments and BOR will be included in a listing. Additionally, for subjects with BOR of NE, the reason for having NE status will be included in the listing. The following reasons will be used:

- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anticancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after start date of study treatment without further evaluable tumor assessment)
- PD too late (>12 weeks after start date of study treatment)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

14.2 Duration of Response per RECIST v1.1 (Secondary Endpoint)

Duration of Response (DOR) is defined, for subjects with a confirmed objective response, as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause. If a subject has not had an event (PD or death), DOR is censored at the date of last adequate tumor assessment.

DOR (months) = [date of event or censoring– first date of OR +1]/30.4375

The censoring and event date options to be considered for the duration of response (DOR) analysis are presented in Table 2. DOR will be analyzed based on subjects in the FAS overall and by dose level with confirmed OR according to RECIST 1.1.

A swimlane plot indicating the time to and duration of response in months for each subject in the FAS will be provided. The plot will be color coded by dose level and will include symbols indicating the time of response (CR or PR) as well as time of progressive disease and end of treatment. If the subject has an ongoing response, this will be indicated.

A listing including subject ID, dose level, age, PD-L1 expression status, tumor type, the number of infusions, date of first objective response, date of event (PD or death), last tumor assessment date, duration of response (months), censoring status, and the event or censoring description will be provided.

In the absence of responders, these outputs will not be produced.

14.3 Time to Response per RECIST v1.1 (Secondary Endpoint)

Time to response (TTR) is defined, for subjects with an objective response, as the time from the start date of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR will be analyzed based on subjects in the FAS by dose level and overall with confirmed OR.

TTR (in weeks) = (first date of OR – start date of study treatment +1)/7

TTR will be summarized in the swimlane plot described in Section 14.2 and included in a subject data listing. In the absence of responders, these outputs will not be produced.

14.4 Progression Free Survival per RECIST v1.1 (Secondary Endpoint)

The PFS time, according to the RECIST 1.1, is defined as the time from the start date of study treatment until the first documentation of PD or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects who start a new anti-cancer therapy prior to an event or 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 start date of study treatment unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

PFS time (in weeks) is defined as:
(date of PD or death - date of the first dose of study treatment + 1)/7 (weeks).

Specific censoring rules are defined in Table 2.

Table 2 Outcome and event dates for PFS and DOR analyses

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

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

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

Censoring reasons will be listed according to the categories in Table 3 following the hierarchy shown.

Table 3 PFS censoring reasons and hierarchy

Hierarchy	Condition	Censoring Reason
1	No baseline assessment	No baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than 12 weeks after last adequate post-baseline tumor assessment	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 EPOCH after screening says patient 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 12 weeks after last adequate tumor assessment.

Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics including the median survival time with two-sided 95% CIs. In particular, the

progression-free survival rate at 4, 8, 12, and 24 weeks will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (4) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (5) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of subjects with an event (progressive disease or death) will be presented.

A listing including subject ID, dose level, age, first and last dosing date, date of event (PD or death), the PFS time or censoring time, and the reasons for censoring will be provided.

14.5 Overall Survival (Secondary Endpoint)

Overall survival (OS) time is defined as the time from date of first dose of study drug to the date of death due to any cause. Subjects last known to be alive will be censored at date of last contact.

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

The date of last contact will be determined as specified in section 9.

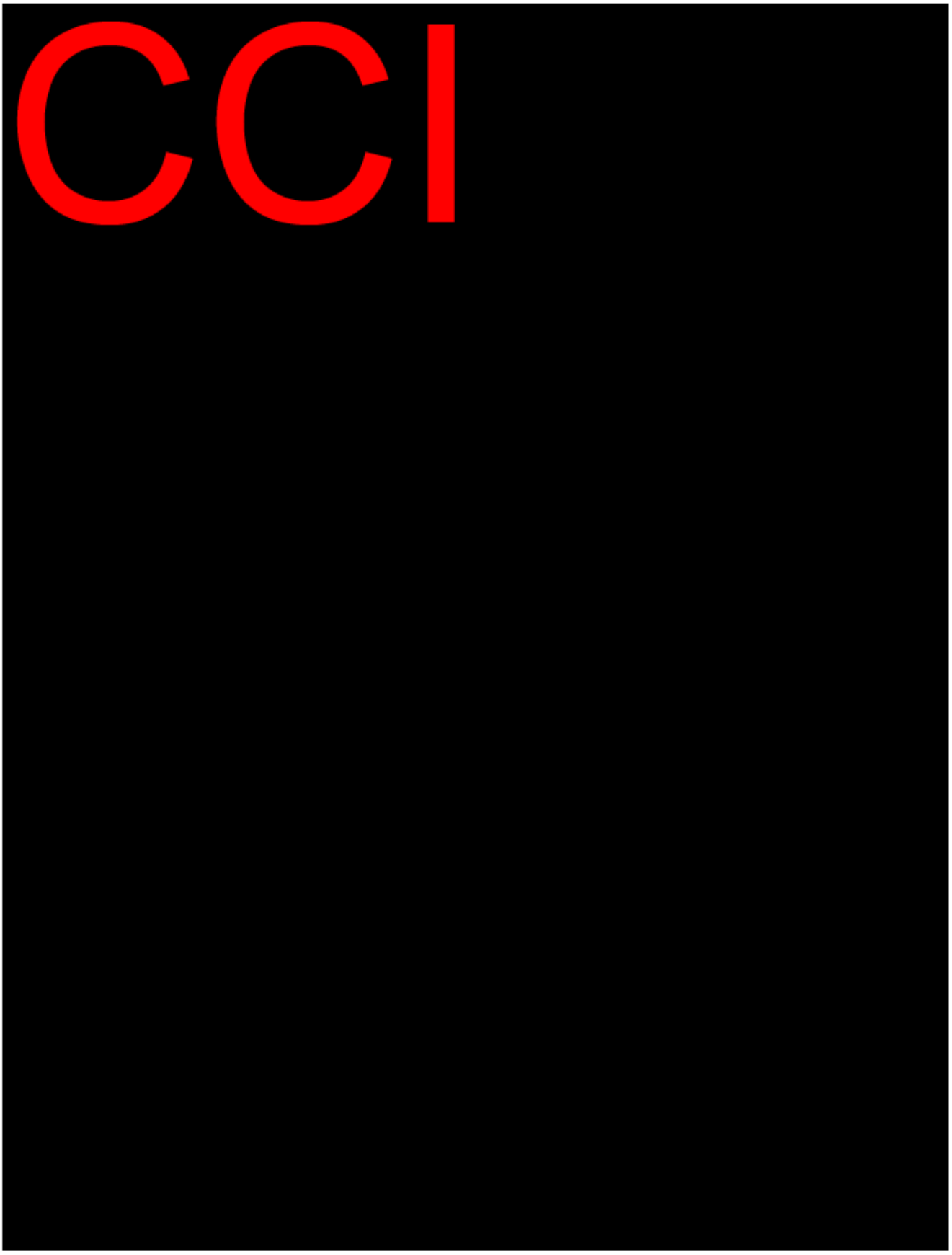
Censoring reasons are as follows:

- Alive
- Withdrawal of consent
- Lost to follow-up

Lost to follow-up will include subjects that the investigator states were lost to follow-up prior to the analysis cut-off as well as subjects with a last contact date > 13 weeks prior to the analysis cut-off date. (13 weeks is based on the assessment schedule of every 12 weeks for survival follow-up interval + 1 week window.)

Analysis of OS will be analogous to the analysis of PFS, with Kaplan-Meier estimates of the survival rate produced for 2, 4, 6, 8, 10, and 12 months after treatment start.

A listing including subject ID, dose level, age, PD-L1 expression status, tumor type, sex, race, first and last dosing date, the overall survival time or censoring time, and the event or censoring description will be provided.


CCI

14.7 Tumor Shrinkage

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- [(Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline] × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy, as:

- Minimum of [(sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline] × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created overall with dose level indicated by varying colors. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each subject with measurable disease at baseline and at least one valid post-baseline assessment. In addition, the percent change from baseline for

sum of diameters will be displayed against time (weeks) in a line/spider plot. The lines of the plot will be color coded according to dose level. Markers for end of treatment, new lesion, non-target PD, death, and start subsequent anti-cancer treatment will be included in the plot.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

All safety analyses are performed using the SAF unless otherwise stated.

15.1 Dose-Limiting Toxicities (Primary Endpoint - Phase I)

Analysis Set: DLT

The primary endpoint of the Phase 1 study is the incidence of DLTs occurring during the DLT evaluation period (28-day period, first 2 cycles of treatment) in order to determine the RP2D. DLTs are collected on the "Adverse Events Details" form on the eCRF and are recorded as the answer ("Yes" or "No") to "Is this adverse event a dose limiting toxicity?" A DLT is defined as a toxicity of interest judged to be related to avelumab by the investigator and/or the SMC using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Per the NCI-CTCAE, a DLT is defined as any of the following toxicities at any dose level and judged to be related to the study drug by the investigator and/or the SMC:

- Grade 4 neutropenia for more than 7 days
- Grade $\geq$ 3 febrile neutropenic infection
- Grade $\geq$ 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia for more than 7 days
- Grade 4 anemia
- Any Grade $\geq$ 3 toxicity, except for the following:
    - Transient ($\leq$ 72 hours) grade 3 flu-like symptoms or fever, which is controlled with medical management
    - Transient ($\leq$ 72 hours) grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to grade $\leq$ 1 or to baseline
    - Grade 3 diarrhea or Grade 3 skin toxicity that resolves to Grade $\leq$ 1 in less than 7 days after medical management (eg immunosuppressant treatment) has been initated

- Grade ≥ 3 amylase or lipase abnormality that is not associated with clinical manifestations of pancreatitis
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Single laboratory values out of normal range that are unlikely related to study drug according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 or Baseline within 7 days with adequate medical management

- Inability to complete at least 2 infusions of avelumab during the DLT observation period due to treatment-related toxicity

While the rules for adjudicating DLTs are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period, may be defined as a DLT after consultation between Sponsor and Investigator, based on the emerging safety profile. DLTs may be identified by the site investigator or by the SMC. Analyses of DLTs will be conducted as per the SMC assessment.

The DLT summary table will present the following for the DLT analysis set:

- the number and percentage of subjects who experienced a DLT during the DLT evaluation period with corresponding two-sided exact Clopper-Pearson (3) 95% confidence intervals (CIs)
- the number and percentage of subjects who experienced a TEAE during the DLT evaluation period with corresponding two-sided exact Clopper-Pearson (3) 95% CIs
- the number and percentage of subjects who experienced a TEAE grade ≥ 3 during the DLT evaluation period with corresponding two-sided exactClopper-Pearson (3) 95% CIs
- DLTs during the DLT evaluation period by SOC and PT

There will be no imputation of missing data for the DLT variable. A flag on the Adverse Events listing will indicate if a given AE was determined to be a DLT, per the SMC.

The maximum tolerated dose (MTD) is defined as the highest dose tested of avelumab associated with the occurrence of DLTs within the DLT evaluation period in <33% of subjects, provided that a higher dose of avelumab was tested and had an associated DLT rate ≥ 33%. If the DLT rate within the DLT evaluation period is < 33% for all tested dose levels, then the MTD will not have been reached. If the starting dose level is confirmed as safe, this dose will be selected as the RP2D if it provides similar exposure in children to those in adults. If exposure is not adequate, a decision can be made to escalate to a dose level up to 20 mg/kg.

Dose escalation/de-escalation rules will follow the modified toxicity probability interval (mTPI) method described in Section 5.1.1.1.1 of the CTP. The mTPI method relies on a statistical probability algorithm to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability rate (pT =

0.3), using all subjects treated in prior and current cohorts at the same dose level to determine whether future cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. The detailed dose-finding rules based on the mTPI are illustrated below in Table 5.

Table 5 **Detailed Dose Re-Escalation/De-Escalation Scheme**

	Number of Subjects Treated at Current Dose											
Number of DLTs	1	2	3	4	5	6	7	8	9	10	11	12
0	NA	NA	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	S	E
3			DU	DU	D	D	S	S	S	S	S	S
4				DU	DU	DU	D	D	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S
6						DU	DU	DU	DU	DU	DU	D
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E = Escalate to the next higher dose, or if current dose level is DL1, stay on DL1. Escalation to DL2 is allowed if exposure at DL1 is not adequate.
S = Stay at the current dose.
D = De-escalate to the next lower dose level.
DU = De-escalate to the next lower dose level; the current dose is unacceptably toxic.
Targeted DLT rate at MTD = 33%.

15.2 Adverse Events (Primary and Secondary Endpoints - Phase I)

Treatment emergent adverse events (TEAEs) 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 9.

TEAEs of grade ≥ 3 are a primary endpoint for the study. The analysis is described below in section 15.2.1. Secondary endpoints related to adverse events for this study include the following:

- Occurrence and severity of TEAEs (See section 15.2.1 for a description of the analysis.)
- AEs of special interest including immune-related adverse events and infusion related reactions (See section 15.3.3 for a description of the analysis)
- Study drug related adverse events. (See section 15.2.1 for a description of the analysis.)

All analyses described **Error! Reference source not found.**in Section 15.2 and 15.3 will be based o n 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.

The following categories of TEAEs are defined for reporting:

- **Related Adverse Events (secondary endpoint):** adverse events with relationship to study drug (as recorded on the AE eCRF page, Relationship with study drug = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with Avelumab").
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = 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).
- **TEAEs of Special Interest (secondary endpoint)**
    - **Immune Related Adverse Events (irAE):** For SMC meetings, potential irAEs will be identified according to a pre-specified search list of MedDRA PTs, documented in a version-controlled repository maintained by the Sponsor. For the final analysis, immune related adverse events according to case definition classified by medical review. Details are included in Table 10 in Appendix I.
    - **Infusion Related Reactions (IRR)**: IRRs are identified based on a list of MedDRA PTs. The detailed criteria of the timing relationship to infusion are specified in Table 11 in Appendix I.

Unless otherwise specified, AEs will be summarized by number and percentage of subjects with the AE in the category of interest as described above by dose level, primary system organ class (SOC) and preferred term (PT) in decreasing frequency for the total column.

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.

15.2.1 All Adverse Events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per subject, using the latest version of MedDRA PT as event category and MedDRA primary SOC body term as Body System category.

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.

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
  - Related TEAEs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs, Grade ≥ 3 (primary endpoint)
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to permanent treatment discontinuation
  - Related TEAEs leading to permanent treatment discontinuation
  - TEAEs leading to death
  - Related TEAEs leading to death
  - Treatment-emergent irAEs
  - Treatment-emergent IRRs
  - Related treatment-emergent IRRs
- TEAEs by SOC and PT and worst grade (secondary endpoint)
- Related TEAEs by SOC and PT and worst grade (secondary endpoint)
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

15.2.2 Adverse Events Leading to Treatment Discontinuation

The frequency (number and percentage) of subjects with each of the following will be presented for TEAEs leading to permanent discontinuation (drug withdrawal), by dose level:

- TEAEs leading to discontinuation of avelumab by SOC and PT

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

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

15.3.1 Deaths

The frequency (number and percentage) of subjects who died, who died within 30 days after last dose of study treatment, and who died within 60 days after first dose of study treatment as well as

the primary reason for death, will be tabulated based on information from the "Death" and "Subject Status/Survival Follow-Up" eCRFs, by dose level.

- All Deaths
- Deaths within 30 days after last dose of study drug
- Deaths within 60 days after first dose of study drug
- Primary Reason for Death
  - Disease progression
  - Event related to Avelumab
  - Event not related to Avelumab
  - 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

15.3.2 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 SAEs by SOC and PT

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

15.3.3 Other Significant Adverse Events

An overall summary of treatment emergent irAEs table will include the frequency (number and percentage) of subjects with each of the following treatment emergent irAEs by dose level:

- irAEs
- Serious irAEs
- irAEs, Grade ≥ 3
- irAEs leading to permanent treatment discontinuation
- irAEs leading to death

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

TheA listing of all irAEs will be provided with the relevant information, including whether there was a clear etiology for the event and whether a biopsy showed histopathology consistent with an immune-related event.

An overall summary of infusion related reactions (IRRs) table will include the frequency (number and percentage) of subjects with each of the following treatment emergent IRRs by dose level:

- IRRs
- Serious IRRs
- IRRs, Grade ≥ 3
- IRRs leading to permanent treatment discontinuation
- IRRs leading to death
- Timing related to first onset of IRR

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

- IRRs, by PT and worst toxicity grade

The listing of all IRRs will also be provided with the relevant information collected from the "Adverse Event Details" eCRF page.

15.4 Clinical Laboratory Evaluation

15.4.1 Hematology and Chemistry Parameters

Treatment emergent laboratory assessments are any sample collected after the first dose of study treatment administration and within 30 days from the last study treatment administration.

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

The worst on-treatment grade (i.e. on or after first study treatment administration and within 30 days after last study treatment administration) will be summarized considering only subjects with post baseline laboratory samples: Laboratory tests by NCI-CTCAE grade (0, 1, 2, 3, 4, any).

Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 are a secondary endpoint for this study and will be described by dose level using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 800/mm^3$
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq 1500/mm^3$

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected Calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 – serum albumin [g/L]).

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) 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.

A listing of all TBILI, ALT, AST and ALP values for subjects with a post-baseline TBILI $\geq$ 2×ULN, ALT$\geq$ 3×ULN or AST $\geq$ 3×ULN will be provided.

Parameters with NCI-CTCAE grades available (secondary endpoint):

The laboratory toxicities will be tabulated using descriptive statistics (number of subjects and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of subjects evaluable for CTCAE grading (i.e., those subjects 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 the on-treatment period – (worst case)

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

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilitubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

15.4.2 Other Laboratory Parameters

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

- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (internationalized normalized ratio) (INR).
- Urinalysis: macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, microscopic evaluation
- Other parameters: hormone (thyroid stimulating hormone (TSH) and free thyroxine (T4)) and totality of binding ADA
- Pregnancy test
- Bone growth assessments (bone density, T-score, Z-score, bone age, insulin-like growth factor (IGF)-1, IGF binding protein-3, 25-hydroxy vitamin D, luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone)

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each subject. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology and chemistry values. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included in the listing.

For all tests not mentioned above but present in the clinical data, a listing of subjects with at least one result for the relevant test will be provided.

15.5 Vital Signs (Secondary Endpoint)

A subject data listing will present all vital sign information collected on the eCRF.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECG

All ECG assessments will be listed.

15.6.2 Quality of Life

Quality of life is assessed at the Screening, Cycle 1, Cycle 2, Cycle 3 visit and every visit until the End of Treatment visit, as well as the safety follow-up visit 30 days after last treatment. The Lansky performance scale will be used to assess subject's quality of life for those $\leq$ 16 years of age, and the Karnofsky performance scale will be used for subjects > 16 years of age. Both scales assess quality of life using a rating from 0-100, with 0 being a low quality of life and 100 being a high quality of life. Listings including all quality of life data will be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics (Secondary Endpoint)

Analysis Set: PK analysis set

16.1.1 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.

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data. 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 questionable due to a protocol deviation (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 a statistical analyses. In this case the rational for exclusion must be provided in the Clinical Study Report (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 Clinical Study Report (CSR).

Based on Table 2 (Schedule of Assessments – Pharmacokinetic and Antidrug Antibody Sampling) of the CSP, the timepoint window for the EOI and 3-hour samples is ± 30 minutes. Samples that are collected outside the specified time windows will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean concentration plots.

Serum avelumab PK concentration data will be listed and summarized by dose level, day and nominal time using standard descriptive statistics including the number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max).

Individual concentration-time profiles showing all subjects by dose level will be created using the actual time points and the numeric concentration data. Arithmetic mean concentration-time profiles by dose level/cohort will be provided using scheduled (nominal) time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean plots will include SD error bars when plotted on a linear scale.

16.1.1.1 Presentation of PK Concentration data

PK concentration data will be descriptively summarized by using: N, Mean, SD, CV%, Min, Median, and 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/PD concentration data:

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

16.1.2 Estimation of Individual PK Parameters

Population: PK Analysis Set

Pharmacokinetic parameters will be calculated by the PK/PD Processing Group of QPD, Merck, Darmstadt, Germany, or by a CRO 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, given with a precision of 14 significant digits or the SAS format Best12. 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.

Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program PPD ® version 6.3, or higher PPD .

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters if appropriate.

PK parameters will be listed and summarized by dose level, cycle, and day (if applicable) using standard descriptive statistics.

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set. The mean concentration-time profiles and PK parameter plots will be plotted using the PK Analysis Set and the individual participant concentration-time profiles will use the Safety Analysis Set. Any PK concentrations excluded from the PK analysis set will be listed and flagged.

The following avelumab PK parameters will be calculated where appropriate:

Symbol	Definition
AUC_{τ}	The area under the concentration-time curve (AUC) over the dosing interval (τ) from T_1=0 h to T_2=336 h (i.e. 14 days). Calculated using the mixed log linear trapezoidal rule (linear up, log down). For single dose, AUCτ is calculated as a partial area with the defined time range. In multiple dose profiles AUC_{τ} is calculated at steady state from one pre-dose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_{τ} will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL.
AUC_{τ} /Dose	The Dose normalized AUC over the interval from T_1=0 h to T_2=336 h. Normalized using actual dose, using the formula AUC_{τ}/Dose. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL/mg.
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down). This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL.

Symbol	Definition
AUC_{0-t} /Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula AUC_{0-t} /Dose. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL/mg.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$ This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL.
$AUC_{0-\infty}$ /Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalised using actual dose, using the formula $AUC_{0-\infty}$ /Dose. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg.h/mL/mg.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. AUCextra = (extrapolated area/$AUC_{0-\infty}$)*100. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = %.
C_{EOI}	Concentration at the end of infusion. Unit = µg/mL.
CL	The total body clearance of drug following intravenous administration. CL = $Dose_{i.v}$ /$AUC_{0-\infty}$. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = L/h.
C_{max}	Maximum observed concentration. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = µg/mL.
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing). Unit = µg/mL.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$ This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = h.
V_Z	The apparent volume of distribution during the terminal phase following intravenous administration. $V_Z = Dose/(AUC_{0-\infty}*\lambda_z)$ following dosing in Cycle 1, Day 1 only. Unit = L.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve. This parameter is calculated following dosing in Cycle 1, Day 1 only. Unit = 1/h.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression ($\lambda_{z\,low}$, $\lambda_{z\,upp}$) to determine λ_z.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq,adj) for calculation of λ_z.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. PPD best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The coefficient of determination (Rsq,adj) should be ≥0.8000 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g.CL, and V_z etc.) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

Partial areas AUC_τ should be calculated using the scheduled dosing interval, as defined in the CTP. The actual dosing interval calculated from CRF time data should not be used. The following rules apply when calculating the partial area AUC_τ within the observed time interval fromT_1 to T_2:

- If either T_1 or T_2 falls within the time range in which samples were taken, but does not coincide with an observed data point, then a linear or logarithmic interpolation is performed to estimate the corresponding concentration value. Whether a linear or logarithmic interpolation is used will depend on the method of AUC calculation e.g. linear up log down.
- If the end time of the interval (T_2) occurs after the last measurable concentration and the terminal regression (λ_z) is estimable, then λ_z is used to estimate the concentration at time T_2. The log trapezoidal rule will be used to calculate the area from the last observation time to the end time of the partial area (T_2). If λ_z cannot be estimated the partial area will not be calculated.

Concentrations <LLOQ, which are before the last quantifiable data point, will be taken as zero for calculating the AUC. 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.

The PPD Core Output will be provided in a separate listing.

16.1.2.1 Presentation of PK Parameter data

PK parameter data will be descriptively summarized using: N, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95%

confidence interval for the GeoMean (lower confidence interval (LCI) 95% GeoMean, upper confidence interval (UCI) 95% GeoMean).

PK parameters C_{max}, C_{EOI} and C_{trough} 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 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 digits
SD:	4 significant digits
CV%, GeoCV%:	1 decimal place

16.1.2.2 Planned Avelumab PK Outputs

The following listings and summary statistics of avelumab PK concentration and parameter data will be provided, where data permit:

- Individual values and summary of avelumab serum concentrations (µg/mL) by dose level, cycle, day, and scheduled time point
- Individual values and summary of single dose PK parameters for avelumab by dose
- Individual values and summary of avelumab C_{EOI} and C_{trough} by dose level
- Summary of avelumab serum concentrations (µg/mL) by dose level, cycle, day, and scheduled time point, stratified by weight (<10 kg or ≥10 kg)
- Summary statistics of single dose PK parameters for avelumab, stratified by weight (<10 kg or ≥10 kg)
- Summary statistics of C_{EOI} and C_{trough} by dose level, stratified by weight (<10 kg or ≥10 kg)
- Individual serum concentration-time course (linear and semi-logarithmic scales) by phase, dose level/cohort, cycle, and day, using actual time points (where available)
- Arithmetic mean serum concentration-time course on both linear (±SD) and semi-logarithmic scales using scheduled time points – with all dose levels overlaid on the same plot for the single dose in Cycle 1, stratifield by weight (<10 kg or ≥10 kg)
- Arithmetic mean trough concentration-time course will be plotted on linear (±SD) scale using scheduled time points – with all dose levels overlaid, stratifield by weight (<10 kg or ≥10 kg)

Dose proportionality (if appropriate) will be presented graphically as follows:

- Boxplots for dose-normalized PK parameters (AUC/Dose, C_{max}/Dose and C_{EOI}/Dose) by dose level, stratifield by weight (<10 kg or ≥10 kg).

- Scatter Plot of individual AUC, C_{max}, and C_{EOI} versus Dose on a log-log scale. A linear regression may also be overlaid.

16.1.3 Population PK Analysis

The population PK analysis plan will be specified in a separate document.

16.2 Immunogenicity (Secondary Endpoint)

Analysis Set: Immunogenicity analysis set

Blood samples for ADA analysis will be collected predose (within 2 hours prior to study treatment) during Cycles 1, 2, 3, 5, 7, 13, 19, 25, and every 6 cycles thereafter for as long as the subject is receiving study treatment; and at the 30-day Safety Follow-up Visit. If the sample is positive for ADA, it will be re-analyzed to determine the titer and tested for neutralizing capacity. The ADA results will be derived based on the algorithm in Table 6. Subjects will be characterized into different ADA categories based on criteria in Table 7.

Table 6 Algorithm for the Derivation of ADA Results

Sample Screen Result in SDTM	Confirmatory Result in SDTM	Titer Result in SDTM	ADA Result in ADaM
Negative	NA	NA	Negative
NR	NA	NA	NR
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NR	Positive-TNR

NR = no result, NA = not applicable, TNR = titer no result.
Negative, number, or positive-TNR are valid results, while number and positive-TNR are considered as positive.

Table 7 **Subjects Characterized based on ADA Results**

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

Samples with a reportable ADA titer will also be tested in the neutralizing antibody (nAb) assay. NAb results are Positive or Negative in a single assay and only derived when not performed because ADA negative (see Table 8). Subjects will be characterized into different nAb categories based on the criteria in Table 9. For nAb, treatment-boosted is not applicable since no titer result.

Table 8 **Algorithm for the Derivation of nAb Results**

ADA Confirmatory Result in SDTM	nAb Result in SDTM	Derived nAb Result in ADaM
Negative	NA	Negative
NR	NA	NR
NA	NA	Negative
Positive	NR	NR
Positive	Positive	Positive
Positive	Negative	Negative

ADA = antidrug antibody, NA = not applicable, nAb = neutralizing antibody, NR = no result.
Positive or Negative are considered valid results.

Table 9 Subjects Characterized based on nAb Results

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

ADA = antidrug antibody, nAb = neutralizing antibody, NR = no result.

The frequency and percentage of each ADA and nAb category will be presented in tables by dose level and overall.

A listing will be prepared for all ADA ever-positive subjects including the following details: subject ID, dose level, age, gender, ADA Status, Study Day of Start of ADA response, Duration of ADA immunogenicity response (weeks), nAb Status, Study Day of Start of nAb response, Duration of nAb immunogenicity response (weeks)

16.3 Biomarkers (Secondary and CCI Endpoints)

Analysis Set: Biomarker analysis set

Blood samples for mandatory biomarker assessments will be collected at Cycles 1, 3, and 7, and again the the end of treatment visit. CCI

The following are defined as secondary biomarker endpoints:

- Tumor PD-L1 Expression
- Tumor-infiltrating T-cell activity (if fresh tumor samples are available)
- Circulating T-cell number at baseline and confirmed progression
- Circulating B-cell number at baseline and confirmed progression
- Circulating NK-cell number at baseline and confirmed progression

Tumor-infiltrating T-cell activity will be summarized at each scheduled assessment using box plots.

CCI

A data listing including all biomarker information collected will be provided.

16.4 Vaccination-related Antibody Concentrations (Secondary Endpoint)

Analysis Set: Safety analysis set

Blood samples to assess levels of vaccination-related antibody concentrations will be collected pre dose, at Cycle 7, and at the end of treatment visit. Vaccination-related antibody concentration values will be provided in a listing by dose level.

17 References

1. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098. PMID 3657876

2. Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

3. Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.

4. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982; 38:29-41.

5. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons 1980.

18 Appendices

Appendix I Description of the Case Review for Assessment of Immune-Related AEs and Definition of Infusion Related Reactions

In order to thoroughly and consistently analyze potential immune-mediated adverse events (AEs), a two-level approach is proposed including:

1. A MedDRA Preferred Term (PT) query is proposed for each event category (i.e., immune-mediated rash, colitis, pneumonitis, hepatitis, nephritis and renal dysfunction, endocrinopathies and other immune-mediated adverse reactions).

2. AEs identified by the MedDRA PT queries will then be medically reviewed using pre-defined case definitions for immune-mediated adverse reactions.

Level 1:

To identify potentially immune-mediated AEs, the MedDRA PT queries will be used to search for AEs of interest in the clinical database. The proposed event categories such as:

Immune-mediated rash, Immune-mediated colitis, Immune-mediated pneumonitis, Immune-mediated hepatitis, Immune-mediated nephritis and renal dysfunction, Immune-mediated endocrinopathies (Thyroid disorders: Hypothyroidism, Hyperthyroidism, and Thyroiditis), Immune-mediated endocrinopathies (Adrenal insufficiency, Immune-mediated endocrinopathies (Type 1 Diabetes Mellitus), Immune-mediated endocrinopathies (Pituitary dysfunction), Immune-mediated endocrinopathies (Hypogonadism), Other immune-mediated adverse events. Further details e.g. MeDDRA PT queries are regularly updated based on the current MeDRA version.

In order to standardize the MedDRA PT queries as much as possible, High Level Terms (HLT) and Standardized MedDRA Queries (SMQ) will be used whenever a choice, that is considered reflective of the events of interest, is available.

Level 2:

In a second level (medical review), the potential immune-mediated AEs identified from the search performed at Level 1, will be reviewed by qualified medical personnel to determine whether the AE meets the criteria (case definition) for an immune-mediated adverse reaction based on the following algorithm:

Table 10 Algorithm for immune-related adverse reactions

Criteria	Description
Onset	AE onset after 1st avelumab administration until up to 90 days after last dose
Duration	AE does not spontaneously resolve (i.e., without corticosteroids/ immunosuppressant treatment) within 7 days after onset
Immunosuppressive therapy	AE treated with corticosteroid or other immunosuppressant therapy. *For endocrinopathies only*: AE required hormone replacement* and /or (corticosteroid or other immunosuppressive therapy)
Etiology	No other clear etiology or Histopathology/biopsy consistent with immune-mediated event
All criteria listed in the left column need to be fulfilled for an event to meet the case definition of immune-mediated reaction.	
*Hormone replacement will be evaluated for specific endocrinopathy disorders only as follows: • Thyroid disorders (HLT): Thyroid therapy (ATC codes (H03A, H03B)) • Diabetes mellitus (including hyperglycaemia): Insulin (ATC code A10A)	

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to Table 11.

Table 11 Criteria for infusion related reactions

Infusion related reactions	**Reactions - Considered when onset is on the day of avelumab infusion (during or after the infusion) or the day after the avelumab infusion (irrespective of resolution date):** • Infusion related reaction • Drug hypersensitivity • Anaphylactic reaction • Hypersensitivity • Type 1 hypersensitivity **Signs and Symptoms - occurring on the day of avelumab 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-ms100070-0306-iap-v2

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	23-Jun-2021 15:22